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The lower limb flexion reflex in humans

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Abstract

The flexion or flexor reflex (FR) recorded in the lower limbs in humans (LLFR) is a widely investigated neurophysiological tool. It is a polysynaptic and multisegmental spinal response that produces a withdrawal of the stimulated limb and resembles (having several features in common) the hind-paw FR in animals. The FR, in both animals and humans, is mediated by a complex circuitry modulated at spinal and supraspinal level.

At rest, the LLFR (usually obtained by stimulating the sural/tibial nerve and by recording from the biceps femoris/tibial anterior muscle) appears as a double burst composed of an early, inconstantly present component, called the RII reflex, and a late, larger and stable component, called the RIII reflex.

Numerous studies have shown that the afferents mediating the RII reflex are conveyed by large-diameter, low-threshold, non-nociceptive A-beta fibers, and those mediating the RIII reflex by small-diameter, high-threshold nociceptive A-delta fibers. However, several afferents, including nociceptive and non-nociceptive fibers from skin and muscles, have been found to contribute to LLFR activation.

Since the threshold of the RIII reflex has been shown to correspond to the pain threshold and the size of the reflex to be related to the level of pain perception, it has been suggested that the RIII reflex might constitute a useful tool to investigate pain processing at spinal and supraspinal level, pharmacological modulation and pathological pain conditions.

As stated in EFNS guidelines, the RIII reflex is the most widely used of all the nociceptive reflexes, and appears to be the most reliable in the assessment of treatment efficacy. However, the RIII reflex use in the clinical evaluation of neuropathic pain is still limited.

In addition to its nocifensive function, the LLFR seems to be linked to posture and locomotion. This may be explained by the fact that its neuronal circuitry, made up of a complex pool of interneurons, is interposed in motor control and, during movements, receives both peripheral afferents (flexion reflex afferents, FRAs) and descending commands, forming a multisensorial feedback mechanism and projecting the output to motoneurons. LLFR excitability, mediated by this complex circuitry, is finely modulated in a state- and phase-dependent manner, rather as we observe in the FR in animal models.

Several studies have demonstrated that LLFR excitability may be influenced by numerous physiological conditions (menstrual cycle, stress, attention, sleep and so on) and pathological states (spinal lesions, spasticity, Wallenberg's syndrome, fibromyalgia, headaches and so on). Finally, the LLFR is modulated by several drugs and neurotransmitters.

Abbreviations: A, adrenaline; CH, cluster headache; CNS, central nervous system; CPH, chronic paroxysmal hemicrania; CPT, cold pressor test; CTTH, chronic tension-type headache; DNICs, diffuse noxious inhibitory controls; EMG, electromyography, electromyographic; FM, fibromyalgia; LLFR, lower limb flexion reflex; FR, flexion or flexor reflex; FRAs, flexion reflex afferents; HNCS, heterotopic noxious conditioning stimulation; IBS, irritable bowel syndrome; IFT, interferential therapy; MCS, motor cortex stimulation; NA, noradrenaline; NFR, nociceptive flexion reflex; NRM, nucleus raphe magnus; NSAIDs, non-steroidal anti-inflammatory drugs; PAG, periacqueductal gray; PECs, piezo-electric currents; PLMs, periodic limb movements; RRF, reflex receptive field; TENS, transcutaneous electrical nerve stimulation; T_p/T_r, pain threshold/reflex threshold ratio; VIP, vasoactive intestinal peptide; WDR, wide dynamic range; WS, whiplash syndrome

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In summary, study of the LLFR in humans has proved to be an interesting functional window onto the spinal and supraspinal mechanisms of pain processing and onto the spinal neural control mechanisms operating during posture and locomotion.

Keywords: Flexion reflex; Flexor reflex; Withdrawal reflex; Flexor reflex afferents

Contents

1. Introduction

The *flexion reflex* (FR), also known as the flexor reflex or withdrawal reflex, is a polysynaptic and multisegmental spinal reflex that induces a complex flexion synergy of the stimulated limb. The mechanical response is a rapid withdrawal movement that constitutes a protective mechanism against possible limb damage.

Whereas this reflex has been poorly investigated in the upper limb, the lower limb flexion reflex (LLFR) in humans and the hind-paw FR in animals have been widely investigated and represent a useful window onto CNS function.

At the beginning of the last century, Sherrington (1910) carried out an extensive study of limb reflexes in animal models and detected a characteristically ipsilateral limb flexion associated with a contralateral limb extension. He observed that the movement was often associated with flight responses in the unaffected limbs. This whole reflex pattern was named the flexion reflex. Later, in 1948, Kugelberg used electromyographic techniques to ascertain which afferent fiber types were involved in eliciting the LLFR in humans. In 1960, Hagbarth systematically investigated the reflex response in a number of extensor and flexor muscles as a function of stimulation site. In the same year, Kugelberg et al. (1960) reported systematic observations of reflex patterns after stimulation at different locations. Similarly, Grimby (1963) studied the different reflex responses induced by stimulation of the medial and distal sole and the plantar surface of the heel.

Shahani and Young (1971) investigated in detail the influence of stimulus intensity on the latencies and sizes of flexor reflexes evoked by stimulation under the sole of the foot. Hugon (1973) distinguished two excitatory components having latencies of 40–60 ms (RII) and 85–120 ms (RIII) and explained these as due to activation of different cutaneous group A-fiber afferents (A-beta and A-delta, respectively). Ertekin et al. (1975) later demonstrated that the conduction velocity of the RIII reflex in humans was within the range of the nociceptive A-delta fibers.

An oscillating sequence composed of a silent period interposed between the RII and RIII reflexes was later rigorously demonstrated by Meinck et al. (1981).

Since the first observation of a strong correlation between the pain intensity stimulus-response curve and the reflex size stimulus-response curve (Willer et al., 1977), several researchers (see elsewhere in the text) have used the flexion reflex as an ''objective'' measure of experimental pain in humans in order to investigate several aspects of pain processing, and pain pathways at spinal and supraspinal level, to assess the role of various neurotransmitters involved in pain control, and to study the pathophysiology of clinical syndromes characterized by chronic pain or by altered pain perception.

EFNS guidelines recommended the RIII reflex as the most reliable nociceptive reflex for assessing treatment efficacy. However, its use in the clinical evaluation of neuropathic pain is still limited.

Paralleling the nociception studies, the FR has also been used as a neural window onto the spinal mechanisms activated during locomotion in animals (Jankowska et al., 1967a,b; Lundberg, 1969, 1979; Grillner, 1981; Schomburg et al., 1998) and, more recently, in humans, too (Rossi and Decchi, 1994; Andersen et al., 2001; Spaich et al., 2004). In fact, in addition to its nocifensive function, the LLFR may be linked to posture and locomotion. This two-fold significance of the LLFR can be attributed to the fact that the interneuronal network mediating the withdrawal responses is, itself, modulated by the transmission of descending motor commands to the target motoneurons.

Recent findings relating to FR circuitry organization and development have given new insight into the development of sensorimotor integration at spinal level (Levinsson et al., 1999; Petersson et al., 2003).

The purpose of this study is to review the methodology, physiology and clinical application of the LLFR technique in order to provide a framework that might allow better recognition and understanding of the full spectrum of the LLFR phenomenon in humans. Furthermore, to fill in gaps where data in humans is lacking, we also review a number of studies of the FR in animal models.

2. Methodology

The LLFR can easily be obtained in the lower limb and recorded using standard electromyography (EMG) equipment (Fig. 1). The surface electrodes used for nerve conduction studies can be used for stimulating the nerves and for recording from the muscles. Several stimulus and recording sites have been used to evoke the LLFR in humans. The most common technique is stimulation of the sural nerve at lateral malleolus

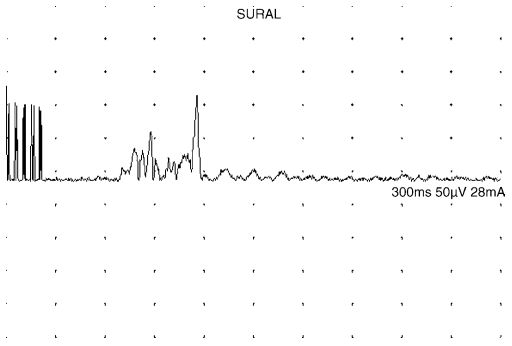

Fig. 1. EMG recording of the flexion reflex response in the short head of the biceps femoris muscle of a healthy adult, elicited after painful electrical stimulation of the sural nerve. The sural nerve was stimulated behind the right lateral malleolus with a 20 ms train of five 1 ms square-wave pulses (perceived as a single stimulus) through surface electrodes (AgCl). Willer's staircase method (Willer, 1977) was used to evaluate the RIII threshold (T_r). The T_r was defined as the stimulation intensity generating stable reflex responses over a series of 20 stimuli. The intensity of stimulation was fixed at $1.2T_r$.

level with recording from the ipsilateral brevis head of the biceps femoris muscle (Willer, 1977, 1983, 1990; Sandrini et al., 1993a). However, other stimulus/recording configurations such as stimulation of the tibialis, plantar or digital foot nerves and recording from the tibialis anterior (Kugelberg et al., 1960; Grimby, 1963; Shahani and Young, 1969, 1971; Dimitrijevic, 1973; Dowman, 1991) or small foot muscles (Kugelberg et al., 1960; Willer, 1977; Jenner and Stephens, 1982) have been used as well. The recordings are usually made in the sitting position, and subjects should be seated in a comfortable armchair with their lower limbs positioned so as to achieve complete muscle relaxation, with the knee flexed at 130° and the ankle at 90° (Sandrini et al., 1993a). However, numerous studies have evaluated the LLFR in the supine and standing positions, as well as during gait and cyclic movements (Rossi and Decchi, 1994; McCrea, 2001; Andersen et al., 1995a; Spaich et al., 2004).

2.1. Stimulus parameters

There is general agreement that a train of impulses is the most suitable stimulus for elicitation of the LLFR (Hagbarth, 1960; Kugelberg et al., 1960; Shahani and Young, 1971; Dimitrijevic, 1973; Meinck et al., 1981), whereas the single pulse seems to be less effective in evoking a stable response, frequently leading to habituation of the reflex, particularly when it is repeated at short intervals (Dimitrijevic and Nathan, 1970; Faganel, 1970). Tørring et al. (1981) systematically investigated some parameters of the stimulus. They found that five rectangular pulses with a duration of 0.5 ms each and an interval of 1 ms was the most efficacious method for elicitation of the LLFR. Meinck et al. (1985a) preferred a duration of 0.1 ms for each pulse, because of possible impairment of the stability of the stimulus effects as a result of susceptibility to irregular repetitive firing in response to a longer lasting stimulus, well known from sensory nerve fibers (Vallbo, 1964; Stampfli and Hille, 1976). In many studies the duration used for the single pulse is 1 ms (Willer, 1977, 1990; Sandrini et al., 1993a; Bouhassira et al., 1993; Arendt-Nielsen et al., 1994) and a train of five electrical pulses delivered at a stimulus frequency of 200 or 300 Hz (with 20–25 ms duration) has been demonstrated to be the most efficacious paradigm to evoke the EMG responses of the LLFR (Dimitrijevic and Nathan, 1968; Dimitrijevic, 1973; Willer, 1977, 1990; Meinck et al., 1985a; Sandrini et al., 1986a,b,c, 1993a). In fact, the reduction of the stimulus efficiency at higher pulse frequencies is most probably due to the relative and absolute refractory periods of peripheral nerve fibers, which significantly reduce the amplitude of the sensory nerve compound potential at elevated pulse frequencies (Buchthal and Rosenfalck, 1965; Tackmann et al., 1974). The train stimulation is usually delivered randomly every 5–15 s to avoid habituation (Sandrini et al., 1993a). The stimulus intensity used to evoke the LLFR varies among laboratories, and it is usually expressed as a multiple of the reflex threshold (see below).

Only a few authors have reported the possibility of eliciting the LLFR by means of radiant laser stimulation, possibly a weak stimulus type (Burke et al., 1971; Willer et al., 1979a; Campbell et al., 1991).

2.2. Pattern response

The pattern of muscle recruitment evoked closely depends on the stimulation site. The muscles activated to withdraw the limb from a noxious stimulus are determined by the location at which the stimulus is applied, so that the movement generated is directly away from the noxious source (Eklund et al., 1959; Kugelberg et al., 1960; Hagbarth, 1960; Hagbarth and Finer, 1963; Schouenborg and Kalliomäki, 1990; Schouenborg et al., 1994). It should be considered that, although the term "flexion" reflex was used to indicate a single reflex response involving excitation of all the flexor muscles in a limb with concomitant inhibition of the extensors, the LLFR is in fact organized to produced the most appropriate withdrawal movement depending on the site at which the stimulus is applied, which could require extensors to act as the primary movers (Schouenborg, 2002; Clarke and Harris, 2004).

Stimulation of the sural nerve, with the subject in sitting or supine position, provokes a response characterized by a flexion of the hip and knee joint (frequently combined with an adduction and rotation of the limb). After stimulation of the tibial nerve, a flexion of the hip and knee and dorsiflexion of the ankle due to a contraction of the tibial muscle is observed. Peroneal nerve stimulation provokes flexion of the hip and knee as well, but in this case, a plantar flexion instead of dorsiflexion of the ankle occurs (Kugelberg et al., 1960; Meinck et al., 1981). Furthermore, stimulation of the skin at the heel excites the ankle extensor muscles (Hagbarth, 1952; Megirian, 1962; Wilson, 1963; Clarke and Harris, 2004). Extensor activity in the rectus femoris is also often seen after stimulation of the anterior region of the thigh (Rothwell, 1987).

In earlier studies on the FR in human leg muscles, the ipsilateral reflex patterns were mostly described as consisting of a double burst of EMG activity (Pedersen, 1954; Grimby, 1963; Shahani and Young, 1971), also known as RII and RIII reflexes

(Hagbarth, 1960; Hugon, 1973) and clearly recorded at rest from the posterior biceps femoris and tibialis anterior after sural or tibial nerve stimulation (Hagbarth, 1960; Shahani and Young, 1971; Hugon, 1973). However, an oscillating sequence of inhibitory and facilitatory phases has also been described (Hagbarth, 1960; Meinck et al., 1981). In fact, in a voluntarily pre-contracted muscle, inhibition of the muscular activity before the excitatory reflex burst is seen (Kugelberg et al., 1960; Brown and Kukulka, 1993; Shahani and Young, 1971). This inhibitory period is often termed the silent period. A further silent period may occur following the secondary excitatory burst, possibly continuing as a dampened oscillation for up to 1 s (Meinck et al., 1981).

2.3. Reflex threshold

The threshold of the LLFR has been investigated using different methodologies. The RII reflex which is a less stable and poorly investigated response is elicited at low non-nociceptive stimulation intensity (Hagbarth and Finer, 1963; Hugon, 1973; Danzinger et al., 1998a). The RII component, depending on the measurement strategy used, may or may not be observed, and, indeed, is not seen in all subjects (Hugon, 1973; Willer, 1977). The electrical threshold of the RII is significantly below the pain threshold and corresponds to two- to three-fold the detection threshold (Sandrini et al., 1986a; Ellrich and Treede, 1998).

On the contrary, the RIII reflex, a widely investigated and ever-present response, is considered to correspond to the intensity of the stimulus (six- to seven-fold the detection threshold) that evokes a stable response at a rate of 60–90% after 20 stimuli according to the ''staircase'' method proposed by Willer (Willer, 1977, 1990; Sandrini et al., 1993a). In order to avoid possible circadian fluctuation of RIII reflex thresholds (Sandrini et al., 1986a), it has been suggested that RIII measurements should be performed at a regular time of day (e.g., between 9 and 11 a.m.) (Sandrini et al., 1993a). However, a variety of methods to measure LLFR thresholds have been used in different laboratories (Hagbarth, 1960; Kugelberg et al., 1960; Grimby, 1963; Shahani and Young, 1971; Merskey, 1979; Meinck et al., 1981; Dowman, 1991; Bouhassira et al., 1994).

In several studies, a close relationship between pain and the threshold of the RIII reflex in humans has been observed (Willer, 1977; Bromm and Treede, 1980; Chan and Dallaire, 1989; Dowman, 1991, 1993). The demonstration of a high correlation between the pain threshold and RIII reflex threshold, the pain intensity stimulus-response curve and the reflex size stimulus-response curve (Willer et al., 1984; De Broucker and Willer, 1985; Chan and Dallaire, 1989; Dowman, 1991, 1993) led to the suggestion that the RIII component of the flexion reflex might be used as an ''objective'' measure of experimental pain in humans (Willer, 1990; Garcia-Larrea and Mauguiere, 1990). Since the method has been standardized, allowing greater reproducibility, numerous clinical studies have been conducted on the RIII reflex and pain mechanism (Willer et al., 1987; Willer and Harrewyn, 1987; Arendt-Nielsen et al., 1994; Sandrini et al., 1986a,d, 1992a,b). Most notably, the RIII reflex has been used in pharmacological studies to assess the analgesic properties of opioid and non-opioid drugs (Willer et al., 1985, 1989b; Willer and Harrewyn, 1987; Piletta et al., 1991).

However, some studies have revealed that in certain conditions, which include hypnosis (Danzinger et al., 1998a), voluntary muscle contraction (Rossi and Decchi, 1994; Rossi et al., 1996), and cervical spinal cordotomy (Garcia-Larrea et al., 1993), pain perception can be dissociated from the RIII reflex threshold and size. This suggests the involvement of several supraspinal strategies in modulating this reflex.

Whereas the threshold of the tactile component of the LLFR, namely the RII reflex, has not been fully investigated, the threshold of the RIII reflex has been shown to be particularly affected by a variety of physiological factors including circadian rhythm, distraction, sex, obesity, menstrual cycle, sleep, cardiac cycle, age, gastric and rectal distension, and stimulation site (Willer et al., 1981; Tassorelli et al., 2002; Sandrini et al., 1986a, 1989, 1993a, 2001; Bouhassira et al., 1994, 1998; Edwards et al., 2001).

Several reflex parameters including the reflex threshold, onset latency, amplitude, area, area under the recruitment curve, and maximal (tolerated) response have been widely used (Willer, 1990; Sandrini et al., 1993a; Skljarevski and Ramadan, 2002). Most studies used rectification and averaging of traces to improve quantitative assessment of the EMG reflex activity in comparison to baseline.

2.4. Habituation

It has been shown that repetitive electrical stimulation induces a gradual decrease of the LLFR (mainly of the RIII component), a phenomenon also known as ''habituation'' (Shahani and Young, 1971; Fuhrer, 1972, 1976; Dimitrijevic et al., 1972; Granat et al., 1991). The same phenomenon was earlier observed for the flexion reflex evoked in rats (Griffin and Pearson, 1967).

Habituation occurs more frequently at low than at high stimulus intensities (Dimitrijevic et al., 1972). Furthermore, habituation has been observed at a stimulation frequency of 0.3–1 Hz and represents an adaptive behavior to repetitive inputs (Dimitrijevic and Nathan, 1970). Higher stimulation frequencies, on the other hand, induce facilitation or dishabituation of the reflex rather than inhibition (Arendt-Nielsen et al., 1994; Fuhrer, 1973).

The degree of habituation is highly dependent on the interstimulus interval (ISI) as detected by Fuhrer (1972, 1973, 1976), who did not find habituation using an ISI of 25 s (at the same stimulus intensity) in spinal cord-injured subjects, but did observe it at an ISI of 5 s.

2.5. Temporal summation

Arendt-Nielsen et al. (1994) demonstrated temporal summation of the second component of the LLFR (RIII reflex) when a train of electrical pulses was repeated at a frequency of 2 Hz (Fig. 2). This experimental model is the human

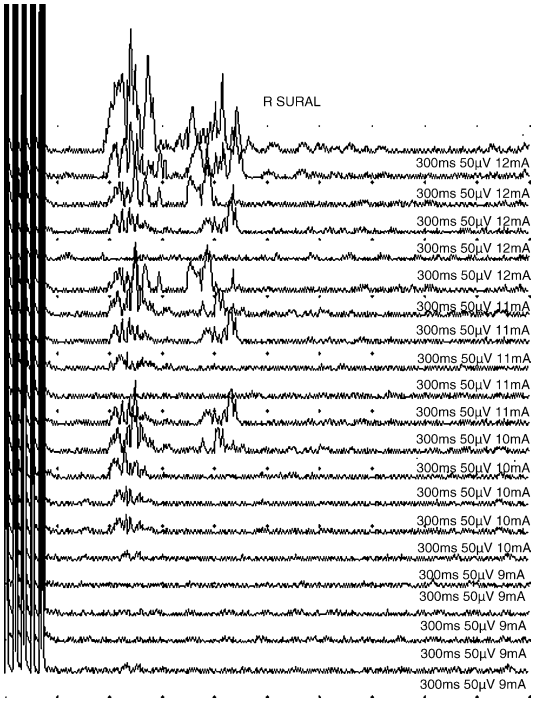

Fig. 2. Temporal summation of the flexion reflex in a healthy adult. The stimulus was repeated at a frequency of 2 Hz, as described by Arendt-Nielsen et al. (1994). The current intensity was increased (in 1 mA steps) to the point at which summation of the RIII (full arrow) could be detected. The RII (tactile) and RIII (nociceptive) components of the flexion reflex are clearly evident in the figure.

counterpart of the wind-up phenomenon in experimental animals (Price, 1972), which involves facilitation of the nociceptive flexion reflex. Wind up of the FR in animals causes a prolonged increase in the excitability of dorsal horn neurons, mainly secondary to C afferent fiber activity (see Herrero et al., 2000) and involving the wide dynamic range (WDR) neurons located in the deep dorsal horn (Schouenborg and Sjolund, 1983). This observation led to the suggestion that there is a causal relationship between wind up and the hyperexcitability of spinal cord nociceptive neurons observed after peripheral damage and known as ''central sensitization'' (Woolf, 1983).

As the RIII component in humans is presumably due to A-delta activation (see later in the text) (Ertekin et al., 1975; Boureau et al., 1978a,b; Wiesenfeld-Hallin et al., 1984; Rossi and Decchi, 1994; Rossi et al., 1996), with C-fibers making a contribution (Gronroos and Pertovaara, 1993; Andersen et al., 1994; Schomburg et al., 2000), it has been hypothesized that the temporal summation of the RIII in humans following repeated electrical stimulation is due mainly to A-delta fiber inputs or to a summation of both A-delta and C-fiber inputs (Arendt-Nielsen et al., 1995; Serrao et al., 2004). This second possibility is supported by evidence that in animals, in addition to C-fibers (in which wind up is more pronounced), the A-delta fibers, too, can induce temporal summation of the nociceptive reflexes (Herrero and Cervero, 1996; Weng et al., 1998; Clarke et al., 2002; Kimura et al., 2005).

Recently, this method in humans has proved to be a useful quantitative measure of temporal summation in pharmacological and clinical studies (Arendt-Nielsen et al., 1994, 1995; Peterson-Felix et al., 1995; Poulsen et al., 1995; Guirimand et al., 1999, 2000; Serrao et al., 2004; Bajaj et al., 2005) and promises to become, in the near future, an interesting tool for studying pain plasticity processes in pathological conditions.

3. Physiology

3.1. Functional significance

In normal subjects the lower limb flexion reflex (LLFR) behaves like a nociceptive withdrawal reflex and is accompanied by a sensation of pricking, short-lasting pain at the point of stimulation. In accordance with Sherrington's early description, its classical function may be ''to withdraw the limb from contact with injurious agents'' (Sherrington, 1910). Thus, the concept postulated by Kugelberg et al. (1960) that the LLFR is a defensive response and a motor reaction for withdrawing the extremity from the source of injury is generally accepted.

In line with this, the LLFR, mainly the RIII component, has been widely used to investigate several aspects of pain processing. The LLFR is interesting because it allows the quantification and objective assessment of pain thresholds in humans (Willer, 1983; Sandrini et al., 1993a,b). Indeed, in normal subjects a close correlation exists between the threshold of the reflex and the subjective pain threshold (Willer, 1977). The LLFR also allows investigation of pain pathways at spinal and at supraspinal level, and makes it possible to assess the role of various neurotransmitters involved in pain control (Sandrini et al., 1993a,b). Finally, the LLFR can be used to study the pathophysiology of clinical syndromes characterized by chronic pain or by altered pain perception.

However, it should be considered that since these early investigations (Kugelberg et al., 1960; Grimby, 1963), other authors have observed a reflex more complex than the simple stereotyped LLFR; in fact, they found a more ''flexible'' reflex and different response patterns depending on the intensity or location of the electrical stimulation. Thus, there is growing evidence that the LLFR, in addition to its protective function, is also part of a more complex motor function. Interneurons mediating these polysynaptic reflex pathways are involved in the transmission of descending motor commands to the target motoneurons and seem to be part of complex neural networks involved in locomotor, movement and postural activities (Jankowska et al., 1967a,b; Lundberg, 1969, 1979; Forssberg et al., 1977; Baldissera et al., 1981; Zehr and Stein, 1999; Duysens et al., 1990a,b, 1992; Rossi and Decchi, 1994; Rossignol and Dubuc, 1994; Schomburg et al., 1998; Burke, 1999; Andersen et al., 2001; Spaich et al., 2004).

When elicited at rest in a sitting and relaxed condition, the LLFR is composed of two bursts of electromyographic (EMG) activity separated by a silent period and followed by movement-related responses.

This oscillating sequence seems to have functional significance. The first flexion burst, or RII reflex (Hugon, 1973), elicited at lower intensity and due to ''tactile'' inputs,

was assumed to initiate or facilitate withdrawal of the foot from the irritating stimulus (Hagbarth and Finer, 1963); in fact, this activation is insufficient to cause a movement. The late burst, called the RIII reflex or nociceptive flexion reflex (NFR) (Hugon, 1973; Willer, 1977), elicited at highest intensity and due to "nociceptive" inputs, represents a coordinated avoidance response that modulates the mechanical effects of the initial burst of neuromuscular activity (Meinck et al., 1981). The silent period observed between the two EMG bursts seems to be part of the reflex pattern, probably counteracting the preceding EMG activity in the same muscle and possibly also in its synergist, and the current EMG activity in the agonists (Meinck et al., 1981).

The LLFR involves coordinated muscle contractions at multiple joint levels. As flexor muscles of the stimulated limb contract, the extensor muscles of the limb are inhibited. However, an extension instead of a flexion can occur, depending on the stimulus site. Furthermore, when the LLFR stimulation is of high intensity, it can be accompanied by a response in the contralateral extensor muscles named crossed extension reflex (Sherrington, 1910), which determines a more efficacious withdrawal of the limb from the noxious source and preserves balance.

The LLFR can be induced by heterosegmentary stimulation (Gozariu et al., 1997), which may be explained by the existence of a propriospinal system responsible for ascending and descending intersegmentary neuronal interaction (Syrovegin et al., 2000).

3.2. Flexion reflex afferents (FRAs)

As mentioned above, the reflex activity consists of two responses recorded from all lower limb flexors (Hagbarth, 1960). The reason for the two-component reflex pattern is the stimulation of different cutaneous afferent fibers, which conduct impulses at different velocities (Shahani, 1970; Dimitrijevic, 1973; Ertekin et al., 1975; Meinck et al., 1981). Hugon (1973) identified an early, inconstantly present reflex response with a lower reflex threshold and a latency of 40–60 ms and a component evoked at a higher threshold with a latency of 85–120 ms (termed RAII and RAIII; Hugon, 1973).

However, several researchers reported the appearance of the RII and RIII components in the lower limbs (mainly in the biceps femoralis or tibialis anterior muscles) with latencies in ranges of 56–65 ms for the RII (Meinck et al., 1985a,b; Danzinger et al., 1998a; Ellrich et al., 2000) and of 85–120, 90–130, 90–180 ms (Hugon, 1973; Willer, 1977, 1990; Sandrini et al., 1993a,b; Bouhassira et al., 1993, 2003) for the RIII. These components are clearly recorded in all flexor muscles of the lower limb and after both sural and tibial nerve stimulation (Hugon, 1973) and the differential threshold persists at low levels of pre-innervation (Meinck et al., 1985a).

After the EMG reflexes come the movement-related responses. These are limb withdrawals and, according to previous studies (Duysens et al., 1992; Zehr et al., 1997; Skljarevski and Ramadan, 2002; Spaich et al., 2004), are expected to occur in a time windows of 125–300 ms.

The RII and RIII evoked reflexes reflect activity in cutaneous afferent group A-fibers (A-beta and A-delta, RII and RIII reflexes, respectively) (Kugelberg, 1948; Shahani, 1970; Hugon, 1973). A conduction velocity of 37–45 m/s corresponding to the group II fiber activity has been estimated for the afferents mediating the RII reflex (Meinck et al., 1981; Ellrich and Treede, 1998).

Conversely, several studies estimating the conduction velocity of the afferent fibers have shown that the RIII reflex in humans is mediated by the A-delta fibers (Ertekin et al., 1975; Willer, 1977; Willer et al., 1984; Boureau et al., 1978a,b; Rossi and Decchi, 1994; Rossi et al., 1996). Percutaneous microneurographic studies have confirmed that the RIII reflex does not appear unless small-diameter, myelinated A-delta fibers are activated (Wiesenfeld-Hallin et al., 1984).

However, facilitation of the RIII reflex through C-fiber activation has been demonstrated in humans, suggesting that C-fiber afferents also contribute to the nociceptive flexor reflex (Gronroos and Pertovaara, 1993; Andersen et al., 1994; Schomburg et al., 2000; Plaghki et al., 1998).

Furthermore, Willer et al. (Willer et al., 1980; Willer and Albe-Fessard, 1983) demonstrated that, using particular stimulation paradigms (temporal summation, spatial summation, repeated low intensity stimulus), A-alpha-beta fibers may be shown to be involved in evoking the RIII reflex.

Similar to this mechanism in humans, activation of A-beta, A-delta and C-fibers has been shown to evoke hind-limb flexor reflexes also in animal models, including cats (Le Bars et al., 1976; Leahy and Durkovic, 1991; Schomburg et al., 2000), rabbits (Clarke et al., 1989, 2003), rats (Schouenborg and Dickenson, 1985; Woolf and Wall, 1986a,b; Strimbu-Gozariu et al., 1993; Guirimand et al., 1995), and horses (Spadavecchia et al., 2002, 2003, 2004).

Ellrich and Treede (1998) reported that the RII component in humans could correspond to a reflex in the cat evoked by a low-threshold mechanoreceptive input from the sole of the foot in tibialis anterior motor neurons (Lehay and Durkovic, 1991; Degtyarenko et al., 1996).

With regard to the nociceptive component, the flexor reflex pattern recorded from the femoris biceps muscle in response to electrical stimulation of the ipsilateral sural nerve is composed of separate fast and slow reflexes, which are mediated by myelinated A-fibers and unmyelinated C-fibers, respectively (Schomburg et al., 2000; Falinower et al., 1994). In mice, it has recently been shown that concomitant activation of A-delta and C-fibers by electrical stimuli elicited a biphasic withdrawal reflex movement that is composed of short- and long-latency movements of the ipsilateral hind paw, and mediated by A-delta fibers and C-fibers, respectively (Kimura et al., 2004, 2005). Thus, there are some differences and some similarities in the flexion reflex pattern recorded from the lower limb in humans and from the hind paw in animals.

It should be considered that different afferent fibers, called flexor reflex afferents (FRAs), may evoke a flexion reflex in both humans and animals (Lundberg, 1979; Lundberg et al., 1987; Schomburg, 1990; Guieu and Serratrice, 1992). Included in this group of afferents are cutaneous low-threshold

mechanoreceptors, cutaneous nociceptive afferents, group II, III and IV muscle afferents, and joint afferents. This term was introduced early on to indicate that all these afferents can induce a similar predominant effect (flexor motoneuron excitation and extensor motoneuron inhibition ipsilaterally). These afferents develop a widespread multisensorial convergence onto common interneurons in the spinal cord (Schomburg, 1990; Andersen et al., 2000), and spatial and temporal interactions between signals contribute to producing the FR (Lundberg, 1979; Schomburg, 1990). Experimental data in both humans (RII and RIII reflexes) and animals (both early and late nociceptive reflexes) have confirmed that the LLFR may be facilitated or inhibited by different afferent fibers indicating a spinal convergence of different nociceptive and non-nociceptive cutaneous, muscle and joint afferents (Shahani, 1970; Lundberg et al., 1978, 1987; Willer et al., 1980; Lundberg, 1979; Willer and Albe-Fessard, 1983; Jankowska, 1992, 2001; Andersen et al., 1994, 1995b, 2000; Plaghki et al., 1998; Ellrich and Treede, 1998; Schomburg et al., 1999).

In this regard, whereas Sherrington (1910) mainly described the flexion reflex as a mechanism for withdrawing a limb from noxious stimuli, it is now apparent that painful stimuli may evoke the flexion reflex, but are not necessary for segmental activation of FRAs. From this perspective, the LLFR elicited by painful stimulation is only a part of the flexion reflex circuitry, which is an interneuronal network receiving all the FRAs (see below).

3.3. Spinal control

The anatomical substrate mediating the LLFR in humans seems to be entirely located at spinal level and to be composed of a complex network of interneurons (Shahani and Young, 1971; Jankowska, 1992, 2001; Burke, 1999). Iles (1977) assumed that these reflexes were transcortical in origin; however, the observation of both LLFR components in patients suffering from complete or incomplete transection of the spinal cord (Shahani and Young, 1971) strongly suggests that the reflex generator for both components is of spinal derivation. The LLFR parameters depend on the state of the segmental common interneuron activity. These spinal interneurons integrate both descending motor commands and the multisensorial feedback and project the output to motoneurons (Lundberg, 1979; Schomburg, 1990). The interneuronal network of FRAs comprises the entire population of interneurons that may produce a flexion response, but flexion is only one aspect of the FRA system (Rossi et al., 1996; Decchi et al., 1997). The convergence on the same spinal interneural network allows the integration of all available information, which ensures fast regulation and the production of the appropriate withdrawal reflex under the current motor program (Baldissera et al., 1981; Jankowska, 1992, 2001; Burke, 1999).

3.3.1. Spinal neurons and interneurons

The neurons defined wide dynamic range (WDR) neurons seem to be particularly important in mediating the FR and have been shown to be involved in its generation in animals (Nishioka et al., 1995; Schouenborg and Dickenson, 1985; Schouenborg and Kalliomäki, 1990; You et al., 2003; Li and Chen, 2004). These multireceptive neurons, located in lamina V of the dorsal horn of the spinal cord, are activated by a variety of noxious and innocuous stimuli (Craig, 2003). For this reason, these neurons play a key role in pain processes and constitute a strategic site where various types of excitatory and inhibitory influences converge. However, their role in the generation of the RIII or RII in humans should be further investigated.

Recent evidence, in both animals and humans, has shown that each muscle or group of muscles mediating the FR has a separate cutaneous receptive field (Schouenborg and Kalliomäki, 1990; Schouenborg et al., 1992, 1994; Schouenborg, 2002; Andersen et al., 1999, 2001; Clarke and Harris, 2004) corresponding to the skin area that is withdrawn from the stimulus by contraction of that same muscle (Schouenborg et al., 1994). Early on, Grimby (1963) observed foot dorsiflexion as a result of stimulation of the medial and distal sole of the foot, ankle extension after stimulation of the plantar surface of the heel, foot inversion following stimulation of the medial side of the sole, and eversion after stimulation of the lateral side of the sole.

More recently, in humans, it has been shown that proximal muscles have large receptive fields while more distal muscles have smaller receptive fields covering only a part of the foot (Sonnenborg et al., 2001). Stimulation of the dorsal side of the foot evokes inversion as the dominant ankle movement along with plantar flexion (functional extension) by activation of gastrocnemius and soleus muscles, whereas stimulation of the plantar side of the foot evokes dorsal flexion and eversion as the dominant ankle movement by activation of the tibialis anterior muscle (Andersen et al., 1999). These findings indicate the presence of a spinal modular organization of interneurons mediating the FR in both humans and animals (Schouenborg, 2002). The presence of a modular organization contrasts with the older FRAs concept which presupposed a much more diffusely organized reflex network causing simultaneous activation of flexor muscles and inhibition of extensor muscles having large receptive fields. It should be considered that the organization in modules of the interneuronal network has a clear functional significance. The withdrawal pattern of the motor response depends closely on the pattern of concurrent afferent input and on the actual motor context: a spinal network encodes the stimulation site information into the motoneuron recruitment that activates the muscles in such a way that the exposed skin area is optimally withdrawn from the potentially dangerous stimulation (Schouenborg et al., 1994). Thus, the stimulation of particular limb areas will activate only those modules best positioned to withdraw the limb from the painful source (Clarke and Harris, 2004). Moreover, the modular organization, mediated by several cutaneous and proprioceptive inputs of the FRAs system, may be a particularly efficacious neural substrate model to provide feedback during normal locomotion and posture (Sonnenborg et al., 2001; Andersen et al., 2003; Spaich et al., 2004).

Furthermore, in animals, it has been observed that the FR efficacy is ‘‘imprinted’’ on the receptive fields of the FR

network, suggesting that a ''learning'' mechanism is involved in the functional modification of this network during development (Schouenborg, 2002). This is further confirmed by the presence of cerebellar modules with the same receptive field organization as the FR (Garwicz, 2002; Garwicz et al., 2002). Thus, there is functional adaptation of the FR during development (see Section 4). It appears likely that an experience-dependent weighting of somatosensory input according to loading/unloading of receptors reflects a general principle for sensorimotor transformation (Schouenborg, 2002).

It has been shown that this fine modular organization of the FR is widely reorganized in animals with spinal sensitization (Clarke and Harris, 2001; Harris and Clarke, 2003), as well as in humans with spinal cord injury (Andersen et al., 2004; Spaich et al., 2005).

3.4. Supraspinal control

3.4.1. Control by several brain structures

The FRAs interneuronal network forms a multisensorial feedback mechanism, channelling information from a great variety of converging segmental and descending systems. After the early experiments of Sherrington (1910) and Eccles and Lundberg (1959) in animals (e.g., decerebrate state), the presence of a powerful descending control on FR pathways was demonstrated, and it was revealed that manipulation of the ''state'' of the central nervous system (CNS) can reveal important information about the organization of the spinal circuitry.

It is well known that several supraspinal structures, such as the cerebral cortex, cerebellum, basal ganglia and brainstem, are involved in the modulation of the FR in animals (Schomburg, 1990). The FR is inhibited by the dorsal reticulospinal tract and facilitated by corticospinal and rubrospinal pathways (Lundberg and Voorhoeve, 1962; Schwindt, 1981; Fleshman et al., 1988). This descending modulation seems to act tonically and phasically on the FR circuitry.

An LLFR elicited in spinal cord-injured humans results in a more intense and longer-lasting response (Dimitrijevic and Nathan, 1968), suggesting that a tonic inhibitory modulation by several supraspinal pathways is present in normal subjects. Generally, a reflex component with longer latency and much greater amplitude following the RIII has been demonstrated in patients with spasticity (Shahani and Young, 1971, 1980). This late component can be differentiated from the genuine RIII reflex (Parise et al., 1997). In spasticity, decreased amplitude of all LLFR components as well as prolonged latencies and duration have also been found (Dimitrijevic and Nathan, 1970, 1971; Meinck et al., 1985b; Shahani and Young, 1971, 1974). However, the alterations observed mainly concerned the RIII reflex and the presence of this late component following the RIII reflex (Dimitrijevic and Nathan, 1971; Meinck et al., 1985b; Shahani and Young, 1971, 1974, 1980; Bussel et al., 1989; Hornby et al., 2004). Very recently, Deutsch et al. (2005) found impairment of the intralimb coordination of the LLFR response in patient with chronic, complete spinal cord injury, possibly reflecting a functional reorganization of the flexion pathways of the spinal cord.

Furthermore, Shahani and Young (1980) and Parise et al. (1997) considered the flexor spasms observed in spastic patients to be due to abnormal excitability of the LLFR secondary to the lack of inhibitory descending influences.

The treatment of spasticity with baclofen (Delwaide, 1985; Davidoff, 1980; Muller et al., 1987; Shahani and Young, 1974, 1980; Milanov, 1992a; Parise et al., 1997), benzodiazepine (Meinck et al., 1985b; Milanov, 1992b), progabide (Mondrup and Pedersen, 1984), tizanidine (Chen et al., 1987; Milanov and Georgiev, 1994), and transcutaneous electrical nerve stimulation (TENS) (Gregoric, 1998) has been shown to normalize the parameters of the LLFR and to reduce the spasticity, indicating the presence of strong tonic supraspinal influences on the neuronal spinal circuit mediating the LLFR and suggesting that the interneurons mediating the LLFR may be involved in the physiopathology of spasticity.

Other disorders of the CNS, including extrapyramidal and cerebellar diseases, have been associated with abnormal LLFR excitability, suggesting that these structures modulate the LLFR.

In fact, the first component of the LLFR has been described to be increased in patients with Parkinson's disease (Shahani and Young, 1971; Delwaide et al., 1990). The role of the cerebellum in limb withdrawal reflexes has been extensively studied in animals (Bloedell and Bracha, 1995). More recently, Kolb et al. (2000) and Timmann et al. (1996) demonstrated that specific parts of the cerebellar nuclei are involved in the control of conditioned and unconditioned limb withdrawal reflexes in both cat and man. Recently, Maschke et al. (2002), using positron emission tomography, investigated cerebellar areas involved in LLFR control in healthy humans. They found LLFR-related areas in vermal lobules III–VI with the local maximum in vermal lobule V. Their findings suggested that activation may be caused by cerebellar modulation of the efferent reflex pathway. Similar findings have been obtained more recently by other authors (Dimitrova et al., 2004).

Taken together, these data indicate that the descending control on the LLFR may be extremely complex and dynamic. Furthermore, the LLFR, selecting between its different reflex modules, may be modulated by supraspinal influences. In line with this assertion, Andersen et al. (2004) have shown that in spinal injured patients the reflex receptive field (RRF) of the ankle flexor and the ankle extensor muscles covers the entire sole of the foot, indicating an expansion of RRFs following spinal cord injury. Thus, a lack of descending inhibitory control and/or increased sensitivity of the spinal reflex loop may result in a lack of the specific modular organization of the LLFR, reinforcing the suggestion that these RRFs can be dynamically controlled by the brain.

3.4.2. Cognitive state and the flexion reflex

Several findings suggest that activity generated by alteration of the psychological/mental state can modulate the LLFR.

Thus, hypnosis, sleep, stress and attention can all modify LLFR excitability (see below).

In a study by Bathien and Hugelin (1969), it was observed that attention induced an inhibition of RIII of the LLFR, which suggested an increase in the descending inhibition. Willer et al. (1979a) found similar results in subjects who were performing a calculation test (whose attention, again, was diverted away from the stimulus). Stress induced by warning the subject that a very painful shock is coming may also result in inhibition of the RIII (Willer, 1980; Willer and Albe-Fessard, 1980; Willer and Bussel, 1980). This mechanism is probably mediated by descending inhibition through endogenous opioids, given that naloxone reversed the effect (Willer and Albe-Fessard, 1980).

There is some experimental evidence in humans that anxiety, too, can modify RIII reflex excitability. Willer (1975) found that subjects naive to RIII recordings behaved in very different ways depending on whether they were anxious (increased threshold) or strongly attentive to the stimuli (lowered threshold). However, very recently French et al. (2005) showed that individual differences in anxiety do not significantly affect the nociceptive LLFR threshold level. Thus, this aspect should be further investigated.

An interesting recent study showed affective modulation of the RIII reflex and pain ratings (Rhudy et al., 2005). The authors investigated the effect of emotion on the RIII reflex and on pain perception in 28 participants, who were required to look at pictures of different emotional valence (unpleasant, neutral, pleasant). They found an increase in RIII reflex size and pain perception when the subjects viewed unpleasant pictures and an inhibition of the reflex and of pain when they looked at pleasant pictures.

3.4.3. Diffuse noxious inhibitory controls

It has been shown that in normal humans the RIII component of the LLFR is strongly inhibited through a spinal-supraspinal feedback loop that is part of a system of diffuse noxious inhibitory controls (DNICs) used in studies of pain modulation (Le Bars et al., 1979a,b; Le Bars and Willer, 1989; Willer et al., 1984, 1989a; De Broucker et al., 1990; Villanueva and Le Bars, 1995; Bouhassira et al., 2003; Serrao et al., 2004; Mohri et al., 2005) (Fig. 3). DNIC may be defined as the inhibition of nociceptive neurons in the spinal and trigeminal dorsal horns produced by a noxious stimulus applied in any part of the body distant from the neuron's excitatory receptive field (Villanueva and Le Bars, 1995). There is a clear relationship between the intensity of the conditioning stimulus and the strength of the resultant DNIC (Le Bars et al., 1992; Villanueva and Le Bars, 1995). Inhibition of the RIII reflex is followed by an after-effect, which can last for several minutes. Moreover, inhibition of the RIII reflex is blocked by low doses of morphine (Le Bars et al., 1992). Anatomical and electrophysiological studies, performed in both animals and humans, indicate that DNIC derives from a complex spino-bulbo-spinal loop, specifically activated by A-delta and C peripheral fibers (Villanueva and Le Bars, 1995; Willer et al., 1999).

De Broucker et al. (1990) studied the effect of heterotopic painful stimulation activating DNICs in patients with thalamic lesion and in patients with Wallenberg's syndrome. They found that the DNICs circuitry involved the brainstem and that the crossed components of the spinoreticular pathways were involved in this system. They suggested that the DNICs signal transmitted nociceptive information in the ventrolateral quadrant and the dorsolateral funiculus, which contains ascending and descending inhibitory pathways modulating spinal transmission, as demonstrated in rats (Villanueva et al., 1986a,b).

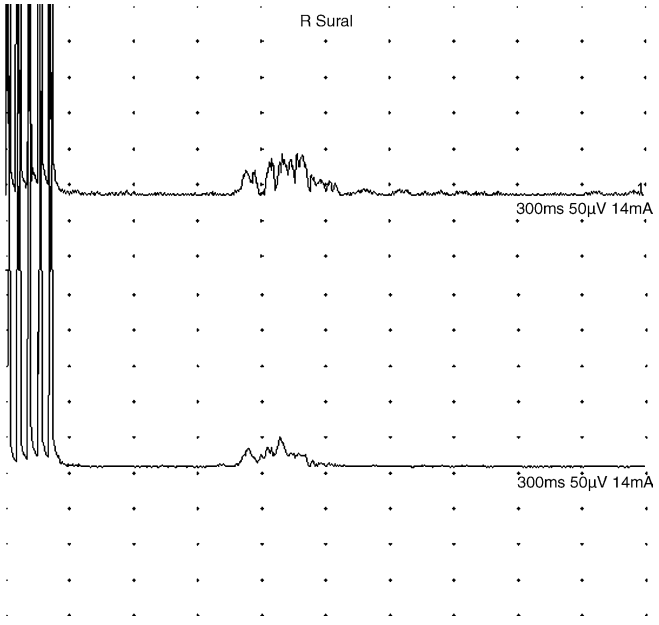

Fig. 3. RIII reflex before (upper trace) and during (lower trace) the cold pressor test activating DNICs in a representative subject. Activation of the DNICs induces a clear reduction of the RIII reflex size.

Thus, the brainstem, specifically the medullary reticular formation, is the key neuronal link of the loop subserving DNICs (Roby-Brami et al., 1987; Willer et al., 1999). The inhibitory bulbospinal pathways are serotonergic (Dickenson et al., 1981; Chitour et al., 1982; Sandrini et al., 1993a, 2000a,b; Willer et al., 1999) and inhibit all the activities of the convergent WDR neurons at trigeminal and spinal levels, but additional non-serotonergic mechanisms are also involved (Dickenson et al., 1981; Willer et al., 1999). Thus, the WDR neurons are the site where the DNICs exert their inhibitory modulation. As these neurons are activated in unpredictable but permanent ways by all non-noxious and noxious stimuli, it has been postulated that the resulting ''basic somesthetic activity'', when transmitted to higher centers, could constitute a ''noise'' from which these centers would have difficulty extracting a clear pain signal. In this regard, the DNICs could provide the filter that would allow such an extraction to be achieved.

3.5. Locomotion

As previously mentioned, in addition to nociceptive function, the FRA circuitry is suspected to be involved in control of posture and locomotion (Lundberg, 1969, 1979; Grillner, 1985; Grillner et al., 1995).

This link between nocifensive, postural and locomotor functions is attributable to the fact that the interneuronal network mediating the FRA pathways is modulated by the transmission of descending motor commands to the target motoneurons (Baldissera et al., 1981; Jankowska and Hammar, 2002).

In animal models, investigation of spinal locomotor centers has shown that interneurons of the FRA system (Lundberg, 1979) contribute to the generation of the locomotor rhythms at spinal level (Grillner, 1985; Grillner et al., 1995). The FRA system behaves like a lower motor center (Lundberg, 1979) that is placed in the immediate vicinity of the ''final common path'' (Sherrington, 1904) of the spinal motoneurons. Alternatively, the interneurons of these FRA pathways may not be a part of the rhythm generator, but interposed between the generator and the motoneurons (Schomburg et al., 1998).

In animal studies, Lundberg (Lundberg, 1979; Lundberg et al., 1987) pointed out that the FRAs are mainly activated by non-noxious events. Thus, FRAs, in addition to their classic nocifensive function, are very likely activated during the normal course of movements by the movements themselves, giving them a proprioceptive as well as a protective function. However, it should be considered that in humans it is plausible that the interneurons involved in the LLFR are only a part of the FRA interneuronal system. Thus, interneuronal pathways involved in locomotion and posture may only partially share the circuitry involved in withdrawing a limb from a noxious source.

In humans, the nociceptive component of the LLFR, which is usually elicited at rest in sitting or supine position, seems to behave like a nociceptive reflex at rest and like a non-nociceptive reflex during voluntary muscle contraction (Rossi and Decchi, 1994; Rossi et al., 1996). Rossi and Decchi (1994), studying the nociceptive mediated A-delta fiber component of the LLFR, showed that posture, balance, limb load, and pre-contraction level of the muscles all affect the size of the reflex in free standing position. Furthermore, Rossi et al. (1996) found that the conduction velocity of the afferents responsible for tibialis anterior (TA) response at rest was within the range of A-delta pain afferents (mean 27.4 m/s), whereas during voluntary contraction it was within the A-beta fiber range (mean 45.1 m/s). They hypothesized that descending command made the discharge of low-threshold, fast-conducting fibers sufficient for reflex activation of TA motoneurons.

Kugelberg et al. (1960) and Shahani and Young (1971) had already found conduction velocities of 35–40 m/s (i.e., in the non-nociceptive A-beta fiber range) in the fibers responsible for nociceptive responses. As this estimation was based on reflex responses of voluntarily activated muscles, it presumably reflected the non-nociceptive component of the reflex during contraction.

Thus, sustained muscle contraction would eliminate the need for discharge of the pain volley, and the activation of low-threshold cutaneous afferents would be sufficient to induce segmental flexor muscle activation (Meinck et al., 1985a,b). From this perspective, the FRAs provide feedback information during movements via segmental pathways that are subjected to the control of the supraspinal pathways, such as the brainstem (Jankowska and Lundberg, 1981) and cortico-spinal descending pathways (Capaday et al., 1999; Schubert et al., 1997), in a state-dependent and phase-dependent manner (Burke, 1999).

In early experiments on several animal species, it was shown that spinal networks are capable of generating locomotor-like activity. Graham Brown (1911), in his ''half-center'' hypothesis, proposed that the generation of the alternating activity could involve two interneuronal centers showing mutual reciprocal inhibition. In the 1960–1970s, Lundberg, Jankowska and colleagues described segmental pathways activated by FRAs that were organized on the basis of reciprocal inhibitory interactions; transmission in one prevented simultaneous transmission in the other. In animal preparations, it was shown that a train stimulation of the FRAs could evoke brief periods of alternating activity in flexor and extensor nerves (Lundberg, 1969, 1979; Jankowska and Lundberg, 1981; Jankowska, 1992). It was supposed that these bursts were correlates of locomotor activities and that the pathways of these FRAs responses contained the rhythm generator of spinal locomotion (Lundberg, 1979). These FRAs pathways were activated by i.v. injection of monoaminooxidase inhibitors, L-dopa and noradrenergic agonists, inducing spontaneous locomotor activity in acute and chronic spinal cats (Jankowska et al., 1967a,b; Lundberg, 1979; Forssberg and Grillner, 1973; Grillner and Zangger, 1979; Forssberg et al., 1980; Barbeau et al., 1987).

However, the existence of spinal circuitry for locomotion (the so-called central pattern generator, CPG) in humans and primates is still debated (Eidelberg et al., 1981; Vilensky et al., 1992; Vilensky and O'Connor, 1998; Bussel et al., 1988, 1996; Stewart et al., 1991; Dietz et al., 1994, 2002; Dietz, 1995, 2003; Calancie et al., 1994; Wernig and Muller, 1992; Wernig et al., 1995). Stepping is observed in anencephalic infants (Forssberg, 1985), which suggests that a spinal mechanism coordinates these movements. Furthermore, a rich vein of direct and indirect experimental evidence for a spinal pattern generator of locomotion in humans has been found in patients with spinal cord lesions (Bussel et al., 1989; Calancie et al., 1994; Dietz, 1995; Harkema et al., 1997; Zehr and Stein, 1999). In line with the results of animal experiments, it is very likely that there is a spinal stepping generator in humans. In the past decade, several research groups have demonstrated that stepping-like leg muscle activation patterns can be induced in patients with spinal cord injuries when leg movements are imposed on a moving treadmill (Wernig and Muller, 1992; Barbeau and Rossignol, 1994; Dietz, 1995).

Roby-Brami and Bussel (1987) stimulated the sural and the tibial nerves in 16 patients with complete spinal cord injury. They found early as well as late (following RIII) components of the LLFR in the EMG. The later components had a lower threshold and also occurred independently of the early components. In another study, the same authors found that the H reflex of the ipsilateral anterior tibialis muscle was facilitated and the H reflex of the contralateral anterior tibialis muscle was inhibited after stimulation of FRAs in patients with spinal cord injury (Roby-Brami and Bussel, 1992). From these results they concluded that the late LLFR (following the RIII) in patients with spinal cord injury is identical to the late FR in

acute spinal cats after DOPA, as described by Anden, Lundberg, Jankowska and co-workers (Anden et al., 1963; Jankowska et al., 1967a,b). Furthermore, as in animals, noradrenergic agonists given orally (Stewart et al., 1991) or intrathecally (Dietz et al., 1994; Dietz, 1995) have been shown to reduce spasticity in human subjects with a clinically complete spinal cord injury and to ameliorate the locomotion of subjects with an incomplete spinal cord section (Stewart et al., 1991; Granat et al., 1991; Norman et al., 1998), probably acting in different ways at spinal and supraspinal level. Other investigators (Nicol et al., 1995), in an experiment involving repetitive electrical stimulation of the common peroneal nerve in a patient with spinal cord injury, suggested the presence of a spinal rhythm that induced excitation and inhibition of the LLFR. They found that if the interval between two stimuli was 2 s, only the second stimulus produced an LLFR response, whereas if the interval was up to 3 s, both stimuli gave a reflex response. This investigation, as well as those of other authors (Calancie et al., 1994; Knikou et al., 2005; Deutsch et al., 2005), who found rhythmically alternating flexion–extension movements after FRAs stimulation in patients with spinal cord injury, prove that the human spinal cord, in cooperation with the peripheral nervous system, is able to produce rhythmic movements. Thus, this rhythmicity can be influenced by stimulation of the FRAs and the spinal rhythm modulates the excitability of the LLFR.

There exists experimental evidence, in both humans and animals, of differentiation of the FRAs system during the execution of cyclic movements, such as pedaling (Brown and Kukulka, 1993; Andersen et al., 1995a) and walking (McCrea, 2001; Duysens et al., 1990a,b, 1992; Andersen et al., 2003; Spaich et al., 2004), and the modifications range from changes in reflex gain to complete reorganization of spinal interneuronal pathways, with new reflexes emerging during locomotion (McCrea, 2001). Furthermore, the reflex- and CPG-derived excitation and inhibition of motoneurons cooperate in producing a stable locomotor pattern under widely varying conditions (Grillner, 1985; McCrea, 2001).

It is interesting to consider that the FRA system is probably involved in all movements. The FRAs concept was developed to address the functional organization of spinal FRA interneurons, not to explain a specific motor behavior. Lundberg's FRA hypothesis predicts that higher centers evoke movements through activation of subsets of both excitatory and inhibitory spinal interneurons contacting motoneurons. In fact, the extensive convergence of afferent and descending systems on interneurons in FRA pathways practically ensures their continuous involvement in all movements. The complex FRA circuitry in the spinal cord allows a distributed processing system without the need for multiple descending pathways: if appropriately connected to key interneurons, fewer descending pathways could control the actions of entire spinal reflex pathways.

3.5.1. State-dependent and phase-dependent modulation of the flexion reflex

Electrical stimulation of the cutaneous nerve during human locomotion produces reflexes that are task-dependent (e.g., phasic locomotor versus tonic maintained activity) (Lisin et al., 1973; Kanda and Sato, 1983; Duysens et al., 1993), intensity-dependent (e.g., noxious versus non-noxious stimulation) (Belanger and Patla, 1984; Crenna and Frigo, 1984; Duysens et al., 1990a,b; Andersen et al., 2003; Spaich et al., 2004; Mileva et al., 2004), and phase-dependent (swing versus stance) (Yang and Stein, 1990; Duysens et al., 1990a,b, 1992; De Serres et al., 1995; Zehr et al., 1997, 1998; Zehr and Stein, 1999; Andersen et al., 2003; Spaich et al., 2004; Mileva et al., 2004).

It thus seems clear that FRs are subject to state-dependent modulation (Burke, 1999; Bara-Jimenez et al., 2000) and show a phasic flexibility that allows them to respond appropriately and instantaneously to dynamically changing states in the various phases of locomotion in humans (Schubert et al., 1997). This state-dependent control of the FRA pathways depends largely on interactions at ''pre-motoneuronal'' level, occurring before the inputs reach the target motoneurons. Such interactions involve excitatory and/or inhibitory postsynaptic inputs that converge on pre-motoneuronal interneurons in the spinal cord, or presynaptic modulation of transmission at synaptic terminations somewhere in the pathway, most likely on primary afferent terminals (Burke, 1999). Thus, generally, the LLFR should be considered as including various afferents, spinal circuits and supraspinal modulatory pathways. None or only part of the LLFR circuitry may be utilized in the context of locomotion and posture.

It has been shown, during fictive locomotion in spinal cats, that stimulation of the FRAs, including the group II and III afferents, enhances ongoing flexion or resets the step cycle to flexion (Schomburg et al., 1998). Depending on the gait phases, either a suppression or a facilitation of the FR may occur. This has functional significance, since the continued ability of all group afferents to evoke FRs during locomotion could be counterproductive: the evoking of a FR with every step could disrupt the gait cycle (Perreault et al., 1995). During the swing phase, an unforeseen obstacle may activate sensitive skin receptors on the dorsum of the foot eliciting a flexor response superimposed on the pre-programmed flexion. The correcting movement will be rapid and will depend upon the point in the step cycle at which it occurs (Forssberg et al., 1977). On the contrary, during the stance phase of gait, inhibition of the FR and facilitation of the extensor responses may be useful in order to maintain balance (Forssberg et al., 1975; Forssberg, 1979; Duysens and Pearson, 1976; Duysens and Loeb, 1980). Forssberg et al. (1975) and Miller et al. (1977) used the term ''phase-dependent reflex reversal'' to indicate, broadly, that the largest responses occurred in flexors during swing and in extensors during stance.

In humans (as in animals), a phase-dependent reflex reversal has been shown during locomotion after stimulation of low- and high-threshold cutaneous afferents (Duysens et al., 1990a,b, 1992; Zehr et al., 1998; Schomburg et al., 1998; Zehr and Stein, 1999; Bastiaanse et al., 2000; Spaich et al., 2004).

A facilitatory response in the tibialis anterior muscle (foot dorsiflexion) and biceps femoris (flexion at knee) is more evident after a high-intensity stimulation of the tibial and

sural nerves evoking an LLFR response. The largest response was shown in the middle of the swing phase (Duysens et al., 1990a,b, 1992; Zehr et al., 1998), and a facilitatory response was shown in the gastrocnemius medialis (plantar flexion) in late stance and early swing (Duysens et al., 1990a,b, 1992; Zehr et al., 1998). During this latter response a suppression of the tibialis anterior activity was demonstrated (Duysens et al., 1992). At the knee joint, only the vastus lateralis has been shown to be clearly modulated during the gait cycle (Crenna and Frigo, 1984; Zehr et al., 1998). Vastus lateralis facilitation during the swing phase in addition to the stance phase was also reported by Zehr et al. (1998) and regarded as a safety mechanism since it increases knee stiffness and reduces the possibility of limb collapse, thus having a balance stabilizing function.

Zehr et al. (1998) found subtle differences between high- and medium-intensity stimulation, probably due to different response strategies. They found that during high-intensity stimulation, inhibitory and excitatory responses were evoked, which allowed accommodation at the proximal segments, such as the knee, and hip flexion with some foot dorsiflexion, and no excitatory responses on the gastrocnemius. Thus, during the swing phase, the foot withdraws from the encountered obstacle. However, with medium-intensity stimulation, the reflex function tends to stabilize gait during stance and to play only a minor role during swing.

Very recently, Spaich et al. (2004) investigated the modulation and topography of the LLFR elicited by painful electrical stimulation of the sole of the foot in humans, during gait. They found a site-dependent modulation of reflex topography in the distal muscles during the gait cycle. They found a large response in the tibialis anterior, evoked at the arch of the foot, and a small response at the heel during heel-contact versus heel-off and swing phase; they also found a large response in the soleus elicited at the arch of the foot during the swing, after heel-contact and during the foot-flat phase of the gait cycle. On the contrary, the EMG responses in the flexors and extensors of the knee and extensors of the contralateral leg were generally not dependent on the stimulation site. On kinematic evaluation of three joints, these responses showed site-dependency, especially during the swing phase in which maximal flexion was obtained by stimulation at the arch of the foot.

Thus, during locomotion, modulation of the reflex probably ensures an appropriate withdrawal but preservation of balance seems to be the most important factor and to involve all the spinal reflexes (Rietdyk and Patla, 1998). During locomotion, the LLFR pattern is highly dependent on the current motor task, indicating that proprioceptive input and the spinal motor system functionally modulate the LLFR (Crenna and Frigo, 1984; Andersen et al., 1995a; Zehr and Stein, 1999), even resulting in reflex reversal (e.g., extension rather than flexion) if necessary (Duysens et al., 1990a,b).

Finally, the site-dependency of the withdrawal reflex (Spaich et al., 2004), primarily in distal muscles, links the modular organization of the LLFR to the functional task during gait.

3.6. Posture

Cutaneomuscular reflexes, including the LLFR during stance, have been studied in relation to both non-painful (Burke et al., 1991; Duysens et al., 1993; Komiyama et al., 2000) and painful (Rossi and Decchi, 1994; Decchi et al., 1997; McIlroy et al., 1999; Bent et al., 2001) stimulation. In humans, changes in body position are known to modify the excitability of the LLFR (Paquet et al., 1996; Knikou and Rymer, 2003).

In general, during standing, unlike sitting or supine conditions, the balance between the reflexes in distal muscles, such as the soleus and tibialis anterior, is shifted toward the plantar flexors (Andersen et al., 1999). A possible explanation for these smaller tibialis anterior reflexes and larger soleus reflexes in standing compared with relaxed conditions may be the load on the limb. In short, when the limb supports the body, tibialis anterior reflexes are suppressed compared with a condition in which the body load is supported by the contralateral leg (Rossi and Decchi, 1994). Smaller tibialis anterior versus soleus reflexes during standing have been shown for tibial nerve stimulation, which was associated with larger ipsilateral vastus lateralis reflexes and contralateral soleus reflexes in order to maintain balance (Paquet et al., 1996).

Rossi and Decchi (1994) showed a reduction of the area of the LLFR evoked in the ipsilateral tibialis anterior muscle after a painful electrical stimulation of the foot in the standing position. Similarly, Paquet et al. (1996) found that the LLFR area was significantly smaller in the tibialis anterior in supported stance than in sitting, indicating that LLFR excitability in the tibialis anterior was reduced in standing. The authors showed that decreased LLFR excitability was accompanied by enhanced extensor muscle excitability on both sides.

McIlroy et al. (1999) and Bent et al. (2001) studied the relation between the preparatory balance adjustments, occurring prior to voluntary movement, and the LLFR during standing in humans. They found that, during standing, subjects included, as part of the limb flexion reaction to noxious stimulation, a rapid preparatory and modifiable balance response. This resulted in a significant delay of limb withdrawal and had the effect of stabilizing the individual prior to the instability created by the unloading of the withdrawing limb.

Thus, these data led to the suggestion that the hierarchy of control is prioritized, attributing primary importance to the maintenance of balance, even though this prolongs exposure to the noxious stimulus.

Andersen et al. (2003) determined the spatial topography of LLFR organization during standing. They assessed the LLFR receptive fields in humans during standing with even support on both legs and found that in the standing posture, in contrast to the sitting relaxed condition, the ankle extensor played a dominant role in the withdrawal pattern. The RRF for the soleus muscle covered most of the proximal sole of the foot, unlike that for sitting posture which mainly covered the medial, proximal part of the sole (Andersen et al., 1999, 2003). Furthermore, the larger RRF and the stronger reflexes found in the soleus muscle compared with the tibialis anterior showed

that unloading of the limb by ankle extension was the dominant reaction. Compared with a condition in which there is no load on the limb, these stronger soleus muscle reflexes most likely reflect a change in reflex gain based on other proprioceptive inputs and different descending motor commands (Schomburg, 1990). For the more proximal muscles, including the knee flexors, stronger reflexes than during relaxed conditions (in accordance with RRF for the biceps femoris), mainly evoked at the distal part of the sole (Andersen et al., 2001), were observed as well. With regard to the knee extensor muscles, Andersen et al. (2003) found only small reflex responses in the vastus lateralis because it was pre-contracted to maintain the upright posture.

4. Development of the flexion reflex

In contrast to the old Sherringtonian concept of the flexion reflex, recent studies investigating its modular organization (Schouenborg et al., 1994; Weng and Schouenborg, 1998; Levinsson et al., 1999; Sonnenborg et al., 2000, 2001; Andersen et al., 1999, 2001, 2003; Schouenborg, 2002, 2003) have clearly demonstrated that the LLFR is characterized by a series of skin reflexes, each showing, in both animals and humans, a precise relationship with receptive field, dorsal horn neurons and muscles. Thus, each withdrawal reflex strongly depends on the area effectively evoking the reflex and should be regarded as a functional module (Grillner, 2004).

Interestingly, this experimental evidence has opened up the question of the development of the LLFR and, more generally, of the development of sensorimotor integration at spinal level.

In rats, studied during the first postnatal weeks, it has been shown that the FR circuitry is imprinted through extensive postnatal adjustments that allow erroneous connections to be eliminated and adequate connections to be selected in proportion to the withdrawal reflex efficiency (Holmberg and Schouenborg, 1996a,b). Furthermore, this reflex transformation, displaying a strong degree of plasticity, can adapt to experimental modifications through tendon transfer or peripheral innervation (Holmberg and Schouenborg, 1996b; Holmberg et al., 1997).

Waldenström et al. (2003), studying neonatal rats, showed that during development tactile stimulation provides the necessary information for the modular organization of the nociceptive withdrawal reflex. Thus, tactile input alone is sufficient to imprint the reflex circuits, independently of the nociceptive input. This is particularly interesting given that the LLFR is mainly evoked by nociceptive stimulation and has been widely used as tool for investigating nociception in both animals and humans. There is growing evidence that the development of pain circuitry depends on non-noxious sensory activity in the healthy newborn (Fitzgerald, 2005).

Thus, nociceptive input becomes important only later, during the development of the CNS. From this perspective, tactile input somehow seems to form a sensory template, which is also used by the nociceptive fiber input from a given skin area to generate the appropriate reflex response (Grillner, 2004).

Petersson et al. (2003) supposed that the FR module could be self-organizing and detect withdrawal efficiency on the basis of the tactile feedback. Because it has been shown that, during early development, the movement repertoire is dominated by spontaneous muscle twitches occurring during sleep (Gardner et al., 1975; Blumberg and Lucas, 1994, 1996; Karlsson and Blumberg, 2002), the authors hypothesized that tactile feedback could be linked to the spontaneous activity in reflex interneurons that induces muscle twitches. The authors (Petersson et al., 2003) tested their hypotheses using a computer simulation and demonstrated that an unsupervised correlation-based learning mechanism, using spontaneous muscle twitches, can account for the functional adaptation of the withdrawal reflex system. Furthermore, they showed that tactile feedback resulting from the spontaneous muscle twitches could modify the sensorimotor transformation in a predictable manner.

Thus, the spontaneous electrical activity of the spinal interneurons and the subsequent muscle twitches seem to be the primum movens for the development of the FR, through a response to tactile input from a given skin area with a feedback learning mechanism. This concept is further reinforced by previous findings that spontaneous muscle twitches may be generated intrinsically by spontaneous neuronal activity in the spinal cord independently of supraspinal control (Fitzgerald and Koltzenburg, 1986; Waldeström et al., 2003). Following this line of evidence, Fitzgerald (1987) showed that the first movements of the humans fetus are apparently random and spontaneous and that their onset coincides with the growth of dorsal root afferents into the spinal cord. She hypothesized that such movements are the result of reflex responses to sensory stimulation.

The learning process thus arises from single muscle twitches that can be produced by synchronous activation of the reflex-encoder interneurons in the deep dorsal horn, which exhibit a Ca2+-dependent plateau potential (Petersson et al., 2003).

The importance of these recent findings is that this model may be a common mechanism for the organization of spinal reflexes or, in general, for sensorimotor experience-tactile adaptation in the development of the CNS in animals as well as in humans (Grillner, 2004).

It is reasonable to think that during the maturation of the CNS, this modular organization may be fine-tuned by descending controls, allowing a fuller movement repertoire (Hart and Giszter, 2004). This is further supported by the fact that a spinal transaction at birth interferes with FR adaptation (Levinsson et al., 1999). Furthermore, the deep dorsal horn neurons, organized in receptive field modules and musculotopically mapped, show neural plasticity and, as recently demonstrated in healthy humans and spinal cord-injured patients (Schmit et al., 2003; Andersen et al., 2004, 2005), may be reorganized in several spinal and supraspinal lesions.

After birth, the LLFR undergoes further modifications. In children, especially in the early years of life when motor and behavioral adaptation takes place through exteroceptive experiences, the LLFR has been seen to undergo plastic modifications during the ontogenesis of the nervous system (Vecchierini-Blineau and Guihneuc, 1982).

Vecchierini-Blineau and Guihneuc (1982) studied the LLFR in the tibialis anterior and short head of biceps muscles after electrical stimulation of the cutaneous area around the toes in awake or sleeping children from 3 days to 3 years of age. They found the presence of both the RII and the RIII components of the LLFR from birth and significant variations in the thresholds. In awake children, they found that the threshold for the tibialis anterior was much lower than for the short head of the biceps from birth to 1 year of age. After 20 months of age, the reflex thresholds tended to be similar to those of adults, that of the tibialis anterior being higher than that of the short head of the biceps. In sleeping children, they found a marked depression of the RII component in all phases of sleep, a depression of the RIII in both muscles during non-REM sleep, and its abolition in older children during REM sleep.

5. Variations in humans

Numerous studies have investigated variations of the LLFR in humans (Table 1), and revealed a complex mechanism of spinal and supraspinal interaction with the LLFR circuitry. However, whereas little attention has been paid to the RII component of the LLFR, considerable importance has been attached to the nociceptive LLFR (RIII reflex or nociceptive flexion reflex, NFR) and to its role as a tool for pain evaluation. Psychological and emotional states, as well as physiological functions, such as the menstrual cycle, cardiac activity, circadian variations, and so on, can all alter noxious evoked spinal activity and influence the processing of pain in both animals and humans. From this perspective, many studies of variations of the RIII reflex in physiological conditions in humans have sought to further understanding of the physiological pain processing mechanisms.

5.1. Mental and psychological states: hypnosis, sleep, stress and attention

5.1.1. Hypnosis

The therapeutic application of hypnosis to relieve acute, subacute and chronic pain is becoming a widely accepted procedure (Hilgard and Hilgard, 1975; Orne and Dinges, 1984; Moret et al., 1991; Patterson and Jensen, 2003; Cyna et al., 2004). The cortex, limbic system, reticular formation, descending inhibitory pathways and spinal cord have all been supposed to be involved in hypnosis (DeBenedittis and Sironi, 1988; Faymonville et al., 2000; Rainville and Price, 2003; Feldman, 2004). Recent neuroimaging studies have shown that the mid-cingulate cortex plays a crucial role in the antinociceptive effect of hypnosis (Faymonville et al., 2003). Several neurophysiological techniques, including cortical evoked potentials and EEG, have yielded contrasting data and shown non-specific patterns (Halliday and Mason, 1964; Spiegel et al., 1985, 1989; Arendt-Nielsen et al., 1990; Meier et al., 1993).

The RIII reflex during hypnosis has been investigated in several human studies (Kiernan et al., 1995; Zachariae et al., 1998; Danziger et al., 1998a; Sandrini et al., 2000a). It has been demonstrated that whereas both poorly and highly hypnosis-susceptible subjects can show reduced RIII reflex size during hypnotic foot analgesia, the largest reduction compared with neutral hypnosis was found only in the highly susceptible subjects (Zachariae et al., 1998).

Table 1
RIII reflex changes during several physiological conditions in healthy subjects

Physiological conditions	RIII reflex		Authors
	Threshold	Size	
Hypnosis	Increased	Reduced	Hernandez-Peon et al. (1960), Hagbarth and Finer (1963), Kiernan et al. (1995), Zachariae et al. (1998), Danziger et al. (1998a), Sandrini et al. (2000a)
Sleep	Increased (mainly in NREM)		Baldissera et al. (1966), Sandrini et al. (2001)
Stress	Increased/unvaried*	Reduced/unvaried*	Bathien (1971), Willer (1975), Akil et al. (1976), Willer (1980), Willer et al. (1981), Willer and Ernst (1986), Terkelsen et al. (2004)*
Distraction/attention	Increased/unvaried*	Reduced/unvaried*	Bathien and Hugelin (1969), Willer et al. (1979b), Dowman (2001)*
Age	Increased with age		Vecchierini-Blineau and Guihneuc (1982), Sandrini et al. (1989)
Gender	Reduced temporal summation threshold		France and Suchowiecki (1999), Serrao et al. (2004)
Menstrual cycle	Reduced during luteal phase		Tassorelli et al. (2002)
Circadian variation	Reduced in early morning, increased at midnight		Sandrini et al. (1986a)
Physical activity	Increased		Guieu et al. (1992a)
Cardiac activity	Increased during systole, decreased during diastole	Reduced during systole, reduced during diastole	Edwards et al. (2001, 2002)
Gastric and rectal distension	Increased	Reduced	Bouhassira et al. (1994, 1998)

Study of the effect of hypnosis on the LLFR was pioneered by Hernandez-Peon et al. (1960) and by Hagbarth and Finer (1963), who found a reduction of the RIII reflex during hypnotic analgesia.

Kiernan et al. (1995) investigated in detail the effect of hypnosis on both LLFR components (RII and RIII reflexes) and found only the late reflex component (RIII reflex) to be markedly abolished. They suggested that hypnotic analgesia inhibited the nociceptive afferents at spinal level. The fact that a reduction of the RIII without a generalized decrease in alpha motoneuron excitability (assessed by H-reflex study) was observed suggested that hypnotic sensory analgesia was mediated, at least in part, by descending antinociceptive mechanisms in the spinal cord.

However, other studies have shown that the RIII reflex may be either inhibited or facilitated, although an increase in the pain perception threshold was found (Danziger et al., 1998a).

Danziger et al. (1998a) approached the problem of hypnotic analgesia from a different angle. They measured RII (11 pts) and RIII (18 pts) reflexes and late somatosensory potentials in selected subjects reporting a high level of hypnotic analgesia. They found that the RIII reflex was either inhibited or facilitated during effective hypnotic analgesia, depending on the individual subject, whereas, at the same time, the late somatosensory potentials were reduced in all the subjects. No modification of the RII reflex was observed. Furthermore, in 7 out of 18 patients they found that the increased pain threshold was associated not with a depression of the RIII reflex but with a facilitation of it. They concluded that the RIII reflex response and pain sensation may be controlled separately and that different modulation strategies could be operative during effective hypnotic analgesia in a subject-dependent manner.

Sandrini et al. (2000a) explored the effects of hypnosis on the RIII reflex and on both pain perception and DNICs during the cold pressor test (CPT). They found that hypnosis increased pain tolerance and reduced both pain perception and the RIII component of the LLFR during the CPT. Moreover, it was observed that DNICs were less activated during hypnosis than without hypnosis, suggesting that both DNICs and hypnosis use the same descending inhibitory pathways, most probably the reticulospinal pathways, for the control of pain (Sandrini et al., 2000a).

5.1.2. Sleep

Noxious stimuli and painful disorders interfere with sleep, but sleep disturbances also contribute to the experience of pain. Thus, there is a reciprocal relationship between sleep quality and pain (Moldofsky, 2001). A close relationship between sleep disturbances and chronic pain syndromes, including fibromyalgia, headache and others, has been observed (Moldofsky, 2001, 2002; Dodick et al., 2003; Rains and Penzien, 2003; Straube and Forderreuther, 2004).

Animal studies have shown that the monosynaptic and polysynaptic spinal reflexes, including the FR, are more stable during synchronized sleep than during wakefulness. Instead, during desynchronized sleep, both are either greatly depressed or abolished for long periods, and the threshold for evoking reflexes is increased (Baldissera et al., 1966). In humans, reflexes with a double component, such as the FR, evoked during sleep, have been found to show an increased latency and duration of the second component, and absence of the first component (Shahani, 1968).

Sandrini et al. (2001) examined in detail the effects of the different sleep stages on the nociceptive component of the lower limb FR. They found that the RIII reflex threshold was significantly increased during stage 2 NREM sleep, and remained raised during stages 3 and 4. During REM sleep, a further increase in the reflex threshold was observed. Moreover, the same authors (Sandrini et al., 2001) found a prolongation of the RIII latency during stage 4 NREM sleep, and a further latency increase during REM sleep. In addition, they found maximum amplitude and duration increases during REM sleep.

As the opiate receptor/endorphin system and descending supraspinal serotonergic pathways both play an important role in the modulation of sleep (Puizillout et al., 1979; Wilson and Dorodz, 1984; Jouvet, 1984), both may be responsible for the RIII reflex changes occurring during sleep. However, Sandrini et al. (2001) hypothesized that because plasma endorphin levels did not correlate with RIII reflex circadian variations (Sandrini et al., 1986a), the opioid system may play an only minimal role in the modulation of the RIII reflex during sleep. On the contrary, the reduction of the brainstem serotonergic excitatory influences on the spinal cord may explain the increase in the nociceptive reflex threshold during sleep. This effect may occur directly at the level of the RIII circuitry or indirectly through a hyperpolarization of the spinal motoneurons (McGinty et al., 1973). To explain the prolonged latency observed, the authors hypothesized a reduction of the reflex excitability; the prolonged duration, on the other hand, was hypothesized to reflect temporal and spatial summation phenomena producing changes in the interneuron excitability, possibly secondary to the effects of different supraspinal influences during sleep.

Interestingly, it has recently been shown that sleep is particularly important in spinal self-organization and maturation of the FR. Petersson et al. (2003) used a computer simulation to show that an unsupervised correlation-based learning mechanism, using spontaneous muscle twitches, can account for the functional adaptation of the withdrawal reflex system (see Section 4).

5.1.3. Stress

It is known that stress is an important trigger activating endogenous analgesia substrates (Akil et al., 1976; Rosecrans and Chance, 1976). Stress-induced analgesia has been demonstrated in a wide variety of animals and in human studies, and can be elicited by a wide range of stressors (Matsuda et al., 1996; Ashkinazi and Vershinina, 1999; Terkelsen et al., 2004).

It has been shown that stress can produce variations in the vegetative responses such heart rate and respiration frequency as well as a facilitation of monosynaptic reflexes associated with a powerful inhibition of nociceptive reflexes in humans

(Bathien, 1971; Willer, 1975). Akil et al. (1976) were the first to show experimentally that stress induces the release of endogenous opioid peptides and causes inhibition of nociceptive reflexes. Similarly, Willer (1980) demonstrated that stress, induced by warning the subject that a very painful shock is coming, resulted in inhibition of the RIII reflex. This mechanism was probably mediated by endogenous opioids because naloxone reversed the effect (Willer and Albe-Fessard, 1980; Willer et al., 1982a). To confirm previous reports of this kind, Willer et al. (1981) and Willer and Ernst (1986) demonstrated that anxiety or stress produced by anticipation of an intense and inescapable noxious foot shock produced progressive pain inhibition and tachycardia and inhibited the RIII reflex.

The stress-induced activation of the reticular formation, which has been observed to induce somato-vegetative variations in humans (Routtenberg, 1969; Lindsley, 1970; Willer, 1980), may be implicated in the inhibition of the RIII. This is in accordance with the results of experiments on animals which showed that electrical stimulation of the mesencephalic reticular formation resulted in stereotyped arousal including increased heart rate and respiration and inhibition of nociceptive flexion reflexes (Dell et al., 1954; Hugelin, 1961, 1972). Moreover, the periacqueductal gray (PAG) has been implicated in the inhibition of reflex responses to nociceptive stimulation evoked by highly stressful situations (Millan et al., 1987; Fields, 2000). Microinjections of a few micrograms of morphine in the PAG raise the threshold for withdrawal reflexes in animals (Carstens et al., 1990; Urban and Smith, 1994). Furthermore, it has been shown that stress analgesia could be blocked by lesions of the PAG and of the nucleus raphe magnus (Kelly and Franklin, 1984). Thus, one mechanism of morphine analgesia is to activate the systems that are activated by stress. This is particularly true in animal experiments, frequently involving a considerable degree of stress, in which morphine presumably potentiates the natural antinociceptive effect of stress.

However, other analgesia mechanisms, including adrenergic, serotonergic and dopaminergic mechanisms, in addition to the endogenous opioid descending systems described in relation to nociceptive reflexes, may be active in response to stress (Pertovaara et al., 1991; Milne and Gamble, 1990; Altier and Stewart, 1999; Fields, 2000; Jedema and Grace, 2003).

In contrast to the above results, it should be mentioned that Terkelsen et al. in a very recent study (Terkelsen et al., 2004), exposing healthy subjects to a stressful, paced auditory serial subtraction paradigm and measuring the RIII reflex after a sural nerve stimulation, demonstrated that mental stress inhibited pain perception and heart rate variability but not the nociceptive reflex.

5.1.4. Attention/distraction

Several studies have shown that attention to a painful stimulation increases reported pain, while distraction decreases pain (Levine et al., 1982; Miron et al., 1989; Arntz and de Jong, 1993).

Recent imaging studies have shown that the reduction of pain perception whilst attention is diverted away from noxious stimuli is modulated mainly by certain brain structures, including the anterior cingulate cortex, orbitofrontal regions, PAG and posterior thalamus (Davis et al., 1997; Bantick et al., 2002; Frankenstein et al., 2001; Valet et al., 2004). On the basis of these results, it has been suggested that the cingulo-frontal cortex may exert top-down influences on the PAG and posterior thalamus to gate pain modulation during distraction (Valet et al., 2004).

Although a vast majority of studies have consistently demonstrated increased acute pain perception when attention is directed toward pain, some studies have given contrasting data. Keogh et al. (2000) observed in males – but not in females – an inhibition of pain during the directing of attention toward the pain. However, these authors used the cold pressor test, and their study is thus hardly comparable with acute pain studies. Furthermore, they considered tolerance to pain, a parameter that may not be a direct indicator not of pain perception, but rather of the capacity to endure ongoing pain. Moreover, Suls and Fletcher (1985) found that attention diverted away from the noxious stimulus was an effective means of reducing acute pain, whereas for pain of more than 2 weeks' duration, the directing of attention toward the stimulus gave more pain relief.

Early on, Bathien and Hugelin (1969) studied a sample of normal subjects during the execution of tests that demanded their attention and observed an inhibition of the RIII reflex, which suggested an increase in the descending inhibition. Willer et al. (1979b) was the first to study in detail the effects of attention and distraction on both the RIII reflex and the perception of pain in healthy subjects performing a calculation test; again, the subjects' attention was diverted away from the stimulus. They found a reduction of the perception of pain and an increase of the RIII threshold with a reduction of its amplitude. Willer et al. (1979b) suggested that serotonergic descending inhibition through the reticulospinal tract could be responsible for this effect.

In contrast to the above results, more recently, Dowman (2001) studied the effects of attentional set on subjective magnitude ratings, spinal reflexes, and somatosensory evoked potentials elicited by innocuous and painful sural nerve stimulation in 24 subjects. They found that attentional set had no effect on the spinal nociceptive withdrawal reflex.

Methodological differences between these studies, including stimulation parameters, environmental and subjective influences, and application times, may explain these contrasting results.

5.2. Effects of anthropometric characteristics and physiological activities

5.2.1. Relationship with age

The effect of aging on pain is a much debated topic (Gibson and Helme, 2001; Helme and Gibson, 2001; Edwards et al., 2003). The experience of persistent pain may become more prevalent and disabling with advancing age (Harkins, 1996; Helme and Gibson, 2001; Helme, 2001; Zarit et al., 2004). Only

few studies have investigated changes in the LLFR at different ages (Vecchierini-Blineau and Guihneuc, 1982; Sandrini et al., 1989). Vecchierini-Blineau and Guihneuc studied lower limb polysynaptic reflexes in children during the first 3 years of life and observed prolonged RII and RIII reflex latencies in comparison with those of adults. These variations are probably related to maturation of the nervous system. Sandrini et al. (1989) studied both the RII and the RIII component of the LLFR in relation to age in a sample of 71 healthy subjects with an age range of 7–40 years. They found that the RIII threshold was significantly reduced in school-age children when compared with normal adult values, whereas the RII threshold showed only a tendency toward lower values. Moreover, a direct correlation of RIII threshold with age was observed.

The authors suggested that a lowered threshold of the RIII component could be due to reduced inhibitory descending control on spinal neurons, a suggestion strongly supported by recent experimental evidence of a reduction of pain-modulatory capacity in the elderly (Edwards et al., 2003).

5.2.2. Gender differences

Gender differences in the perception and modulation of pain have been extensively described (Berkley, 1997). This differential reporting of pain may be a result of biological, social, cultural, and psychological differences (Levine and De Simone, 1991; Filligim et al., 1996; Berkley, 1997).

Several psychophysical and neurophysiological studies on temporal summation of pain, using thermal, electrical and mechanical stimuli (Price, 1972; Sarlani and Greespan, 2002; Staud et al., 2003; Serrao et al., 2004) have shown a greater temporal summation in women, suggesting an upregulation of central processing of nociceptive inputs in females compared to males.

These findings are seen as indirect support for the hypothesis that endogenous analgesic mechanisms are functionally hypoactive in women, leading to an increased predisposition to chronic painful conditions (Bush et al., 1993; White and Harth, 2001).

Interestingly, Frot et al. (2004) showed that, despite their lower pain ratings, men reported more pain-related anxiety than women.

In line with these findings, some studies have shown a clear gender difference of the RIII reflex threshold (France and Suchowiecki, 1999; Serrao et al., 2004).

France and Suchowiecki (1999) studied the effect of DNICs using repeated assessment of RIII reflex activity before, during and after exposure to forearm ischemia. They found that women exhibited significantly lower RIII thresholds than men, and reported significantly greater pain in response to both forearm ischemia and the repeated electrocutaneous stimulation required to elicit the RIII. However, they did not find a significant difference between the sexes in the degree of attenuation of RIII secondary to activation of DNICs.

A recent study (Serrao et al., 2004) reports greater temporal summation of the RIII reflex in women, suggesting an upregulation of central processing of nociceptive inputs in females compared to males. Furthermore, the authors studied the effect of DNICs on the RIII reflex elicited by both single and repeated (temporal summation) electrical stimulation. Unlike France and Suchowiecki (1999), they observed that the degree of attenuation of the RIII reflex after a single or repeated stimulation was greater in men than in women. This finding lends indirect support to the hypothesis that endogenous analgesic mechanisms, including DNICs or other aminergic nuclei, are functionally hypoactive in women.

5.2.3. Menstrual cycle

Cyclical fluctuation of gonadal steroids may provide a partial explanation for the increased pain perception observed in women and for common episodic pain syndromes like migraine which recur with menstrual periodicity (Silberstein and Merriam, 1993).

Only a few studies have investigated the changes in pain perception across the menstrual cycle by means of painful electrical stimulation. Veith et al. (1984) found no differences in pain threshold across the menstrual cycle, whereas Giamberardino et al. (1997) found a higher threshold in the luteal phase than in the preovulatory and premenstrual phases.

More recently, Tassorelli et al. (2002) evaluated the RIII in healthy women during the follicular and luteal phases of their menstrual cycle. They observed that during the luteal phase, the threshold of the RIII and the psychophysical threshold for pain were both significantly reduced compared with the follicular phase, which suggested that women are probably more sensitive to painful stimulation during the luteal phase (mid- to late-luteal phase) than during the follicular phase.

The demonstrations that female sex hormones can modulate neuronal excitability possibly via effects on ion channels (Majewska, 1992; Wong et al., 1996; Moss et al., 1997) provide further confirmation that estrogens and progesterone play a pivotal role in pain modulation. From this perspective, the RIII reflex and pain perception changes may be induced by gonadal hormones mainly acting on opioid or serotonergic systems (Ginzler, 1980; Basbaum and Fields, 1984; Taylor et al., 1984). This is also supported by the observation that both descending opiate and serotonergic pathways strongly inhibit the RIII reflex in humans (Willer, 1985; Sandrini et al., 1986a,b,c, 1993a,b).

5.2.4. Circadian variations

Studies investigating the daily rhythmicity of pain and nociceptive reflexes in both humans and animals are few and contrasting. Studies on animals have shown the occurrence of greater pain sensitivity during both the dark phase (Pickard, 1987; Martinez-Gomez et al., 1994; Christina et al., 2004) and the light phase of the light–dark cycle (Rosenfeld and Rice, 1979). Circadian changes in pain thresholds have also been reported in humans (Procacci et al., 1974; Rogers and Vilkin, 1978; Strian et al., 1989).

Sandrini et al. (1986a) showed that both the RII and RIII components of the LLFR exhibited circadian rhythmicity. They found the lowest values in the early morning for both RII and RIII reflexes and the highest values at midnight. As the authors

did not find any significant correlation between the RIII threshold and the beta-endorphin levels, they suggested that endogenous opioids play a minimal role in circadian modulation of the nociceptive component of the LLFR. The authors hypothesized that daily fluctuations of serotonergic inhibitory descending control of the spinal nociceptive reflex could explain the periodicity in the modulation of the RIII threshold, a hypothesis based on experimental evidence of similar circadian variations in the caudal nucleus raphe magnus and in the nucleus reticularis paragigantocellularis involved in these pathways (Pujol et al., 1981).

5.2.5. Physical activity

There is some psychophysical evidence of a beneficial effect of exercise on the perception of pain (Pertovaara et al., 1984; Olausson et al., 1986; Kemppainem et al., 1990). Moreover, the literature contains several reports of the positive effect of physical activity on chronic pain syndromes (Ferrari, 2002; Ambrose et al., 2003; Warnock and Clayton, 2003; Rainville et al., 2004).

Guieu et al. (1992a) used the RIII reflex to test objectively whether physical effort increased the nociceptive threshold in high-level athletes versus control subjects. They found that physical activity enhanced the leg RIII threshold. Since physical activity has been shown to activate the stress mechanism (Willer, 1983), they argued that intense concentration and stress-induced analgesia may explain these results. During physical activity both hypoalgesia and reduction of the RIII threshold may be due to the release of chemical substances including endorphins (Colt et al., 1981) and adrenal corticotrophin hormone (Kemppainem et al., 1990).

5.2.6. Cardiac activity

Edwards et al. (2001, 2002) found that the RIII reflex was modulated across the cardiac cycle in normotensive subjects. They recorded the RIII reflex from the hamstring muscles during systole, when baroreceptors are maximally activated, and during diastole when baroreceptor inputs are minimal, at several intervals after the R-wave (from 5 to 100 ms). They found the smallest RIII reflex at 300 ms and the largest at 600 ms, revealing a striking association between nociceptive responses and natural variations in baroreceptor activity across the cardiac cycle in normotensive subjects. They suggested that arterial baroreceptor stimulation during systole could, via central baroreflex pathways, activate brainstem structures, such as the locus coeruleus, periacqueductal gray, nucleus raphe magnus and rostral ventral medulla, responsible for descending supraspinal pain pathways and result in antinociception.

5.2.7. Gastric and rectal distension

There are some studies that have documented the influence of gastric and rectal distension on the RIII reflex in humans, offering further scope for studying the spinal projections from viscera afferents and their correlations with the nociceptive pathways, which are not completely understood in man (Bouhassira et al., 1994, 1998). Moreover, viscerosomatic convergence of nociceptive information is a process that is often observed in animals during the recording of neuronal activity in many regions of the CNS and is considered to be the mechanism underlying referred pain (Cervero, 1995; Ness and Gebhart, 1990).

Bouhassira et al. (1994, 1998) studied the effects of non-painful and painful gastric and rectal visceral stimulation on the RIII reflex in humans. In the first experiment (Bouhassira et al., 1994), they tested the effects of five levels of gastric distension, obtained by means of a balloon placed in the proximal part of the stomach and connected to an electronic barostat. They found that the 600, 800, and 1000 mL levels inhibited the RIII reflex by 25%, 35%, and 55%, respectively, and the magnitude of this inhibition correlated significantly with both the degree of distension and the intensity of visceral perception.

In the second experiment (Bouhassira et al., 1998), they showed different effects of rectal distension on the RIII reflex depending on the mode of distension (rapid or slow ramp). They found that rapid distension induced both facilitatory and inhibitory effects on the RIII reflex.

Instead, slow-ramp rectal distensions produced only inhibitory effects on the RIII reflex. To explain these results, the authors hypothesized a convergence of visceral and RIII reflex afferents at the same levels of the spinal cord inducing an early RIII facilitation in the lower limb and a supraspinal inhibitory control, possibly through a DNIC-like mechanism, and producing the inhibition of the RIII reflex.

Furthermore, the authors suggested that the opposite effects of rapid- and slow-ramp distensions on the RIII reflex could be due to the selective activation of different populations of rectal mechanoreceptors.

6. Neurotransmitters and pharmacological modulation

As the excitability of the spinal neuronal substrate responsible for the LLFR depends largely on descending supraspinal commands, as well as on several peripheral afferent inputs, various neurotransmitters within the brain and spinal cord are presumably involved in the LLFR pathways. There is experimental evidence, in both humans and animals, that neurotransmitters such as serotonin (5-HT), dopamine, norepinephrine, GABA and glutamate, released by afferent fibers, descending terminations or local interneurons in the dorsal horn, can all modulate the LLFR in an inhibitory or excitatory way. These neurotransmitters interact with a complex mechanism and cooperate with other substances, such as substance P, vasoactive intestinal peptide (VIP), peptide Y, and galanin, to exert their effects.

Likewise, several drugs, including antidepressant agents, opioid agonists, and antiepileptic drugs, by reducing or increasing some neurotransmitters or directly changing the membrane excitability, have been shown to modify drastically the excitability of the LLFR pathways (Table 2).

Most studies have been conducted on the nociceptive component of the LLFR (RIII reflex, NFR), whereas little attention has been paid to the ‘‘tactile’’ component (RII reflex). Thus, in these studies, the RIII reflex has been used as tool to investigate the chemical and pharmacological modulation of

Table 2
Effect of the various pharmacological substances on RIII reflex excitability in humans

Substances	RIII excitability	Authors
Opiatergic drugs		
Agonists	Inhibition (reversed by naloxone)	Willer and Bussel (1980)
Morphine		Willer (1985)
Fentanyl		Willer et al. (1985)
FK 33–824		Willer et al. (1986b)
Antagonists		Chabal et al. (1989)
GB 52	Unvaried	Kwasucki (1990), Le Bars et al. (1992), Bossard et al. (2002)
Serotoninergic drugs		
Agonists		Willer et al. (1982b)
Indalpine	Inhibition	Sandrini et al. (1986b,c)
Tegaserod	Reduced inhibition induced by rectal distension	Coffin et al. (2003)
Amytriptiline	Inhibition	Sandrini et al. (1993b)
Dothiepin	Reduced inhibition induced by DNICs	
Antagonists		
Ritanserin	Inhibition	
Adrenergic drugs		
Agonists	Inhibition	Remy-Neris et al. (1999), Barbeau and Norman (2003)
Dopaminergic drugs		
Agonists		Paradiso et al. (2002)
Apomorphine	Inhibition	
GABAergic drugs		
Agonists		Muller et al. (1987)
Baclofen		Mertens et al. (1995), Parise et al. (1997), Dachy and Dan (2002, 2004)
Glutamatergic drugs		
Antagonists		Arendt-Nielsen et al. (1994, 1995)
Ketamine	Reduced temporal summation	Petersen-Felix et al. (1995), Poulsen et al. (1995), Guirimand et al. (2000), Bossard et al. (2002)
Others		
Capsaicin	Increased	Gronroos and Pertovaara (1993)
NSAIDs	Inhibition	Willer and Bathien (1977), Willer and Harrewyn (1987), Willer et al. (1989b), Piletta et al. (1990, 1991), Guieu et al. (1992b), Sandrini et al. (1992a, 2002)
Nefopam hydrochloride	Inhibition	Guirimand et al. (1999)
Flupirtine	Inhibition	Timmann et al. (1995)
Tizanidine	Inhibition	Delwaide and Pennisi (1994)

pain processing and, more particularly, nociceptive neurotransmission at spinal level.

6.1. Opioids—morphine, naloxone and others

It is known that endogenous opioids such as enkephalins and dynorphins play a crucial role in pain control at both spinal and supraspinal level (Basbaum and Fields, 1984; Faull and Villiger, 1987; Stevens and Seybold, 1995; Coggeshall and Carlton, 1997). A rich vein of studies have demonstrated that the FR is strongly influenced by the opiates and opioids in animals (Catley et al., 1984; Woolf and Wall, 1986a; Clarke and Ford, 1987; Hori and Watanabe, 1987; Gamble and Milne, 1990; Hao et al., 1990; Wiesenfeld-Hallin et al., 1991; Xu and Wiesenfeld-Hallin, 1991; Carstens and Ansley, 1993; Luo et al., 1994; Schomburg and Steffens, 1995; Tokuyama et al., 1998; Advokat and Duke, 1999; Hu et al., 1999; Clarke and Ward, 2000; Gozariu et al., 2000; Schomburg et al., 2001; Jenkins et al., 2004).

In humans, pharmacological studies have demonstrated a direct and powerful effect of morphine on the LLFR (Willer and Bussel, 1980; Willer, 1985; Willer et al., 1985; Kwasucki, 1990; Le Bars et al., 1992; Bossard et al., 2002). In particular, morphine i.v., given at different doses, induces a potent inhibition of the RIII and a parallel increase in the subjective pain threshold (Willer, 1985; Willer et al., 1985). This effect is dose-dependent and completely reversed by naloxone; it can also be observed in paraplegic patients with transection of the thoracic spinal cord, which clearly indicates that it is due to a direct action of morphine at spinal level (Willer and Bussel, 1980). A marked naloxone-reversible inhibition of the RIII is also induced by FK 33–824 (1.0 mg, i.v.), a synthetic

methionine enkephalin (Roby et al., 1983), and by dermorphin (0.16 mg/kg/day i.v.), a potent opiate-like peptide (Sandrini et al., 1986c), in both normal subjects and paraplegic patients, showing that these drugs, too, have a direct spinal effect.

Furthermore, Chabal et al. (1989) studied the effect of fentanyl (25 mg), an opioid analgesic that mimics the action of natural endorphins, on the RIII and on pain perception in patients with chronic pain. They observed that in five out of eight subjects the RIII reflex was completely abolished within 15 min. In these patients a decrease in reported pain paralleled the decrease of the reflex. According to the authors, these results could be explained by an effect of fentanyl modulating nociception at spinal cord level. Finally, an inhibitory effect of a single dose of intravenous morphine (0.1 mg/kg) on the FR has also been observed in neonates (Franck et al., 2000).

Thus, in humans, the opioid drugs seem to reduce RIII excitability by acting directly on the spinal transmission of nociceptive signals, and interact with different spinal opiate receptor populations in inducing analgesia.

This may occur predominantly at presynaptic sites (i.e., reduction of transmitters released from C-fiber afferents), although a postsynaptic inhibition of spinal dorsal horn nociceptive neurons may occur as well (i.e., hyperpolarization due to an increase of potassium currents) (Basbaum and Fields, 1984).

Interestingly, Willer et al. (1979c) and Sandrini et al. (1999) showed that in normal (''pain-free'') conditions, naloxone administration, in doses able, specifically, to antagonize μ receptors, did not modify the threshold of the RIII, which suggests that endogenous opioid systems are not tonically active in humans (Willer et al., 1979c; Sandrini et al., 1999). Similar evidence was produced by a study in which the enkephalinase inhibitor (GB 52) was unable to modulate either the RIII or pain sensation, suggesting that the nociceptive inputs at spinal level are not tonically modulated by the enkephalinergic descending system (Willer et al., 1986b).

Nonetheless, the existence of descending inhibitory opiatergic pathways remains debated and the mode of their action on the spinal nociceptive transmission may be more complex (Basbaum and Fields, 1984). Several observations indicate that the opiatergic system may influence LLFR excitability and pain perception through other supraspinal pathways or through other neurotransmitters. In fact, Le Bars et al. (1992) demonstrated that low doses of morphine hydrochloride (0.05 mg/kg, i.v.) can completely block, in a naloxone-reversible manner, the inhibitory effects of DNICs triggered by heterotopic nociceptive events. Moreover, in rats, it has been shown that low doses of morphine may induce the release of excitatory neuropeptides such as substance P and VIP, thereby facilitating instead of depressing the flexor reflex and spinal nociceptive transmission and suggesting that there may exist a similar mechanism in humans (Wiesenfeld-Hallin et al., 1991).

In addition, interruption of these descending pathways resulting in a receptor supersensitivity could explain the high sensitivity of paraplegic patients to the administration of morphine or morphine-like substances (Willer and Bussel, 1980; Sandrini et al., 1986c).

Finally, it has been suggested that several conditions, such as stress, sleep, hypercapnia, the menstrual cycle, physical activity and acupuncture, may exert their antinociceptive function and reduce RIII excitability by descending inhibition through the endogenous opioid system (Willer and Albe-Fessard, 1980; Willer et al., 1981; Colt et al., 1981; Willer, 1983; Wilson and Dorodz, 1984; Basbaum and Fields, 1984; Gamble and Milne, 1990; Guieu et al., 1992a).

6.2. Monoamines—aminergic drugs

Monoamines (noradrenaline, dopamine and serotonin) play a crucial role in suppressing the transmission of the pain impulse and all have been demonstrated to have a marked influence on the LLFR.

It should be considered that monoamines are released in the spinal cord mainly by the descending modulatory pathways. Downward modulation occurs mainly through the release, by the PAG, rostral ventral medulla, and locus coeruleus, of the neurotransmitters serotonin and norepinephrine, which have axons that traverse the dorsal lateral funiculus to modulate pain directly through connections to secondary afferent neurons in the dorsal horn or to interneurons in laminae I and II (Miletic et al., 1984). Likewise, the DNIC system, another descending system that operates through a spino-bulbo-spinal serotonergic pathway, mediates RIII and pain, diffusely acting on the spinal WDR neurons (Le Bars et al., 1979a,b; Le Bars and Willer, 1989; Willer et al., 1984).

However, interaction and cooperation of monoamines with other neurotransmitters, such as enkephalins, and substance P, may also produce modification of the RIII and of pain processing.

6.2.1. Serotonin—5HT receptor agonists and antagonists

It has been shown that the descending pain modulatory system, which includes serotoninergic pathways, exerts powerful inhibitory effects on the nociceptive messages at spinal level (Besson and Chaouch, 1987; Duggan and Morton, 1988).

The nucleus raphe magnus (NRM) is the major site of the descending brainstem serotoninergic pathways (Fields and Basbaum, 1978). It has been demonstrated that the NRM can modulate the FR in animals (Pearson et al., 1974; Jorum and Shyu, 1987). Indeed, Jorum and Shyu (1987) showed that low-intensity (20–50 μA) stimulation of the NRM in animals resulted in an inhibition of the FR, as shown by its increased latency and decreased amplitude.

The DNICs, another serotoninergic descending system, have also been shown to strongly inhibit or abolish the hind-limb FR in animals and the LLFR in humans (see Section 3.4) (Le Bars et al., 1979a,b; Le Bars and Willer, 1989; Villanueva et al., 1984, 1986a,b; Dickenson et al., 1981; Chitour et al., 1982; Willer et al., 1984, 1999; Roby-Brami et al., 1987; De Broucker et al., 1990; Villanueva and Le Bars, 1995; Sandrini et al., 1993a, 2000a; Bouhassira et al., 2003; Serrao et al., 2004; Mohri et al., 2005).

Numerous experimental studies have explored the direct action of serotonin on the spinal neurons involved in pain transmission, using the hind-paw FR or the tail-flick reflex as tools of investigation. From these studies, it has emerged that serotonin exerts its action though a complex mechanism and intricate chemical interactions. The activation of 5-HT receptors at spinal cord level can produce multiple physiological events, and activation of different subtype receptors can induce inhibitory or excitatory responses (Alhaider and Wilcox, 1993). Furthermore, serotonin neurons can modulate the spinal transmission of nociceptive inputs directly, by activating opiatergic or GABAergic neurons, or by interacting with norepinephrine and other neurotransmitters (Ogren and Holm, 1980; Alhaider et al., 1991; Zhang et al., 1995; Kang et al., 1998; Kukushkin and Igon'kina, 2003).

This complex action may explain the heterogeneous results produced by pharmacological studies on the hind-limb FR in rats. In the different experimental paradigms used, which have involved intrathecal administration of serotonin, the use of intact or spinalized rats, and different 5-HT receptor agonists and antagonists, both inhibitions and facilitations of the FR have been observed (Maj et al., 1976; Carstens and Campbell, 1988; Murphy et al., 1992; Zhang et al., 1995; Borszcz et al., 1996; Jenkins et al., 2000; Machacek et al., 2001; Kukushkin and Igon'kina, 2003; Honda et al., 2003).

Several studies on serotonergic and anti-serotonergic drugs have been performed in humans, too.

Willer et al. (1982b) reported that administration of indalpine, a drug that blocks serotonin (5-HT) uptake, induced a significant increase in the RIII threshold, which was partially naloxone reversible. The fact that this effect did not occur in patients with a complete transection of the thoracic spinal cord led to the suggestion that it was exerted via the descending serotonergic pathways. Sandrini et al. (1986b) showed that ritanserin, a drug that selectively antagonizes 5-HT2 receptors, inhibited the RIII reflex in normal subjects, and that this effect was not reversed by naloxone. Given the low density of 5-HT2 receptors at spinal level, it was suggested that this effect was mediated mainly by descending pathways. These findings have been also seen in animal experiments (Barber et al., 1989; Wallis et al., 1993).

Furthermore, Sandrini et al. (1986c) also demonstrated a marked inhibition of the RIII reflex in humans by amitriptyline, a drug producing analgesia mainly by blocking serotonin uptake. This effect was not naloxone reversible.

More recently, Coffin et al. (2003) showed that in healthy subjects, tegaserod, a 5-HT4 receptor partial agonist, interacting with the spinal processing of sensory visceral information, reduced the inhibition of the RIII reflex induced by rectal distension.

Serotonergic modulation by DNICs has been investigated in pharmacological studies in humans. Sandrini et al. (1993b) showed that dothiepin (an antidepressant interacting with serotonin receptors) induced an increase of the RIII threshold and of the subjective pain threshold after a 14-day treatment. The effects of dothiepin on DNICs were investigated using the cold-pressor test (CPT) as conditioning stimulation. After dothiepin, a reduced inhibition of the RIII during the CPT and a significant facilitation immediately after it were observed, while subjective pain perception was normally inhibited (Sandrini et al., 1993b).

In short, in both animals and humans there is a potent inhibitory effect by descending serotoninergic pathways. However, as demonstrated in animals, a more complex action of serotonin in modulating the flexion reflex may also be supposed in humans.

6.2.2. Epinephrines—alpha2-adrenoceptor agonists and antagonists

The effects of adrenaline (A), noradrenaline (NA), and adrenergic agonists and antagonists on the FR have been widely studied in animal models. Wiesenfeld-Hallin (1987) showed that low doses of NA depressed and high doses facilitated the flexor reflex in decerebrate and spinalized rats. The author suggested that the primary effect of NA was inhibitory in the dorsal horn (where the neurons mediating these effects are sensitive to NA), and excitatory in the ventral horn.

In more detail, it has been observed that the alpha2-adrenoceptor antagonist potentiates, and the alpha2-agonist depresses all the spinal reflexes, including the FR, in several animal species (Jagiello-Wojtowicz, 1981; Miller and Proudfit, 1990; Onttonen et al., 2000; Clarke et al., 2001). Moreover, a tonic adrenergic inhibition of the FR in rabbits subjected to different levels of surgical preparation has been observed (Ogilvie et al., 1999). Thus, in intact rats the predominant effect is inhibition of the FR by supraspinal descending norepinephrine through alpha2 receptors. However, an increase instead of a decrease of the flexor reflex size evoked by alpha adrenoceptor agonists was observed (Kehne et al., 1985; Rawlow and Gorka, 1986). Kehne et al. (1985) showed a shift in the effects of clonidine from alpha2-adrenergic mediation of FR inhibition in intact rats to alpha1-adrenergic mediation of excitation in spinalized rats. The explanation given was that spinal transection unmasked clonidine's alpha1-adrenergic stimulatory effect.

To summarize, the supraspinal adrenergic pathways have a powerful suppressive effect on the FR at spinal level in intact animals. This is in accordance with the demonstration that the majority of NE-containing fibers and terminations in the spinal cord arise from supraspinal sources (Jones, 1991) and the NA coeruleospinal system, in particular, appears to play a significant role in spinal nociceptive processing (Jones, 1991). These supraspinal noradrenergic fibers terminate and release NA in the superficial dorsal horn. The released A or NA might take part in the modulation of nociceptive transmission by acting directly on the spinal adrenergic receptors or inhibiting the glutamate and substance P release from primary afferent terminals or increasing the release of inhibitory neurotransmitters from lamina II (substantia gelatinosa) neurons.

Zakrzewska and Koziel (1977) studied, in humans, before and after ethylbenzatropine administration, the effect on the monosynaptic H reflex of calf muscles of stimulation of the nerve afferents producing the polysynaptic LLFR of the short head of the biceps femoris muscle. They found that after one

single intramuscular dose of ethylbenzatropine, the facilitating effect of the H reflex by FRAs disappeared. The authors explained these results as due to an inhibitory action of NA in certain chains of spinal interneurons.

Moreover, it should be considered that epinephrines have been shown to play an important role in the initiation and modulation of the locomotor activities, acting at CPG level and changing the FRA circuitry excitability at spinal level (Jankowska et al., 1967a,b; Forssberg and Grillner, 1973; Barbeau and Rossignol, 1991). In fact, it has been demonstrated that L-dopa, which is a precursor of NA, and other noradrenergic agonists, can induce coordinated locomotion in spinalized cats and change the excitability of the FR (Grillner, 1981). It has been suggested that the L-dopa modulation of the excitability of the FRAs circuitry in spinalized and decerebrated cats (Jankowska et al., 1967a,b; Anden and Engel, 1974) may be exerted by releasing NA from noradrenergic reticulospinal axon terminations (Lundberg, 1982).

However, only few studies have observed the effect of the noradrenergic agonists on LLFR excitability in humans (Remy-Neris et al., 1999; Barbeau and Norman, 2003). Remy-Neris et al. (1999), first, and Barbeau and Norman (2003), later, studied the effect of intrathecal injection of clonidine in spinal injured patients. They showed a consistent, dose-dependent, decrease of the flexion reflex amplitude and threshold concerning both RIII reflex and late reflex (following RIII) components. These effects were accompanied by a powerful antispastic effect and an improvement of gait in some patients.

Barbeau and Norman (2003) observed that this drug did not change the excitability of the monosynaptic H reflex, which suggested that no change in motoneuron excitability occurred and that the decrease of the LLFR was probably due to clonidine acting on interneurons at pre-motoneuronal level.

6.2.3. Dopamine—apomorphine and others

It has been shown that dopaminergic descending supraspinal processes can mediate the antinociceptive action on neurons in the superficial laminae (I–II) of the spinal dorsal horn (Jensen and Smith, 1983; Jensen et al., 1984) and are able, irrespective of their nociceptive or non-nociceptive origin, to strongly depress FRAs pathways with an effect comparable to that of the opioids (Schomburg and Steffens, 1998). In animals, the mixed D1/D2 agonist pergolide produced a dose-related decrease in the magnitude of the flexor reflex (Shannon et al., 1991).

Moreover, both 5-HT and NA descending fiber systems may exert tonic inhibitory effects on spinal dopamine nociceptive processes (Jensen and Smith, 1982).

In humans, Paradiso et al. (2002) studied the effect of apomorphine on the LLFR in patients with periodic limb movements (PLMs) and clearly showed that dopaminergic mechanisms are involved in spinal FR excitability control in humans, too. Observing that both PLMs and the LLFR were completely abolished 30 min after subcutaneous injection of apomorphine, they suggested the existence of a common mechanism for PLMs and LLFR (Paradiso et al., 2002).

6.3. GABA—benzodiazepines and baclofen

GABA and glycine are the main inhibitory neurotransmitters in the dorsal horn of the adult spinal cord (Todd and Sullivan, 1990; Todd and Spike, 1993). In animals, GABA-A and GABA-B receptor agonists have been shown to reduce the magnitude of the flexion reflex (Schwarz et al., 1995). In humans, the effect of the activation of both receptor types on LLFR excitability has been studied using the benzodiazepines and baclofen (Willer and Ernst, 1986; Milanov, 1992a,b; Mertens et al., 1995; Parise et al., 1997; Yablon and Stokic, 2004).

The benzodiazepines act primarily through GABA-A receptors, linking to specific binding sites in the macromolecular protein complex (Braestrup and Nielsen, 1983). Benzodiazepines appear to potentiate the inhibitory action of GABA. Willer and Ernst (1986) investigated the modulation induced by a benzodiazepine (diazepam) on the RIII in humans. The analgesic effects of a repeated stress induced by anticipation of pain (noxious footshock) were studied on both the threshold of the RIII and the corresponding pain sensation after a 4-day treatment with diazepam versus placebo. The study showed that diazepam treatment, given at an anxiolytic dosage, was able to reduce both the analgesia and the depression of the RIII reflex produced by the stressful situation. Furthermore, diazepam was able to reduce both the hyperalgesia and the facilitation of the RIII produced by subsequent naloxone administration. The effects observed probably resulted from a decreased reactivity to the stressor in some central and peripheral nervous structures. A peripheral mechanism might be proposed since numerous benzodiazepine binding sites have been described in both central and peripheral structures (Braestrup and Nielsen, 1983); moreover, benzodiazepines reduce the corticosteroid and brain catecholamine responses during stress (Keim and Sigg, 1977). Centrally, there may occur a regulatory effect of some endogenous benzodiazepine-like system on opiate receptors implicated in the opioid form of stress-induced analgesia.

Several studies have investigated the effect of intrathecal baclofen infusion on the LLFR in spastic or dystonic children and adult patients (Muller et al., 1987; Mertens et al., 1995; Parise et al., 1997; Dachy and Dan, 2002, 2004). These studies have yielded similar results and it has been demonstrated that both the RIII reflex and the late responses (following the RIII), which typically occur in spastic patients (see Section 3.4), were inhibited (and their reflex thresholds significantly increased) or abolished by baclofen treatment. It has thus been proposed that the LLFR technique be used as a tool for quantifying the benefit of antispastic treatment and as an ancillary indicator for determining the minimal effective dose of intrathecal baclofen (Parise et al., 1997).

6.4. Glutamate—NMDA receptor agonists and antagonists

Glutamate is the primary nociceptive neurotransmitter at spinal synapses and activates glutamate receptors of several types, such as alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, *N*-methyl-D-aspartate

(NMDA) receptors and metabotropic glutamate receptors. Thus, the role of glutamate in pain transmission at spinal level is crucial (Dickenson, 1990, 1995). A growing body of evidence has demonstrated that glutamates strongly influence flexion reflex excitability, and the FR has been widely used to explore the role of glutamate receptors, especially the NMDA receptors, in the development of the plastic events leading to pathological pain conditions in both humans and animals (Xu et al., 1995; Anderson and Winterson, 1995; Guirimand et al., 2000; Bossard et al., 2002; Li et al., 2003; Harris et al., 2004). In the spinalized rat, plasticity in the flexion reflex has been induced by stimulation of C-fibers (Woolf and McMahon, 1985), which appear to be NMDA receptor-dependent (Woolf and Thompson, 1991; Anderson and Winterson, 1995; Durkovic and Prokowich, 1998).

It has been shown that in the spinal cord, the release of glutamate from peripheral nerves causes activation of the NMDA receptors in persistent pain states which, in concert with other systems, generates spinal sensitization. Central sensitization of pain pathways, that is, the enhanced responsiveness of central pain transmission neurons, is a distinct, long-lasting form of neuronal plasticity, involving the activation of intracellular signaling cascades leading to a facilitatory excitatory synaptic response. This sensitization, considered a key phenomenon in many, if not all, types of chronic pain (Woolf, 1996; Baranauskas and Nistri, 1998), is well demonstrated by studies on the wind up of the LLFR in animals and on temporal summation in humans (Woolf and McMahon, 1985; Woolf and Thompson, 1991; Anderson and Winterson, 1995; Durkovic and Prokowich, 1998; Arendt-Nielsen et al., 1994, 1995; Serrao et al., 2004). These two similar phenomena have been considered experimental manifestations of sensitization which can lead to allodynia, hyperalgesia and chronic pain conditions (Price, 1972; Schouenborg and Sjolund, 1983; Price et al., 1994; Petersen-Felix et al., 1995; Arendt-Nielsen et al., 1995; Poulsen et al., 1995; Guirimand et al., 2000; Bossard et al., 2002).

In humans, the effects of small systemic doses of ketamine, an NMDA receptor antagonist, on the temporal summation (i.e., wind up) of both the RIII and sensations of pain was investigated by Guirimand and co-workers (2000). First, the recruitment (stimulus/response) curve for the RIII was built using stimuli up to the pain tolerance threshold. The RIII threshold and its recruitment curve were not significantly altered after the injection of ketamine (0.15 mg/kg i.v.) or placebo. By contrast, the significant increase (i.e., wind up) in both the reflex responses and the sensations of pain observed during the higher frequency stimulation were significantly reduced after the administration of ketamine, but not placebo. The wind-up phenomenon (i.e., the progressive increase of the responses induced by repetitive nociceptive stimuli) might represent an elementary form of the central sensitization involved in various painful syndromes, and it depends on the activation of NMDA receptors, because it was selectively reduced after the administration of ketamine.

Interestingly, a co-localization of opioid receptors and NMDA receptors has been shown within a single neuron both in the brain and spinal cord dorsal horn (Mao, 1999). In accordance with this finding, experimental studies in animals have suggested that a combination of morphine and NMDA receptor antagonists may have additive or synergistic analgesic effects. Bossard and co-workers (2002) investigated the nature of the interaction between these two classes of analgesic agents, analysing the effects of morphine (0.1 mg/kg), ketamine (0.1 mg/kg followed by 4 mg/kg/min) and their combination on the RIII. The effects of the drugs were tested on: (1) the stimulus-response curves of the reflex up to the tolerance threshold; and (2) the progressive increase of the reflex and painful sensations (i.e., the wind-up phenomenon). The stimulus-response curve of the RIII was significantly reduced after injection of a combination of ketamine and morphine, but was not modified when placebo or each of the active drugs was administered alone. The wind up of the RIII and painful sensation was not significantly altered after the injection of placebo, ketamine, morphine or a combination of these drugs. The study demonstrated a synergistic interaction between morphine and ketamine, which tends to confirm that there is interesting scope for using this type of combination in the clinical setting. The differential effects observed on the recruitment curve and wind up indicate, however, that the mechanisms of the interaction between opiates and NMDA receptor antagonists are not univocal but depend on the modality of activation of the nociceptive afferents.

6.5. Neuropeptides

A growing body of evidence in animal experiments indicates that numerous other neurotransmitters are involved in the modulation of the FR and pain transmission at spinal level. However, in humans, similar mechanisms can only be supposed.

In particular, substance P has been shown to be an important mediator of the spinal flexion reflex in intact rats. Many studies that used the FR as a pain evaluation tool indicate that endogenous substance P has a role in the increased excitability of spinal interneurons and support the hypothesis that substance P released in the spinal cord contributes to the hyperalgesia that accompanies peripheral inflammation (Woolf and Wiesenfeld-Hallin, 1986; Xu et al., 1990, 1992; Wiesenfeld-Hallin et al., 1990; Parsons et al., 1996; Inoue et al., 1998).

Other substances, including neurokinin A, bradykinin, VIP, cholecystokinin, calcitonin gene-related peptide (CGRP) have all been found to facilitate the nociceptive flexion reflex enhancing nociceptive neurotransmission at the level of the spinal cord (Xu et al., 1990, 1995; Jia and Seybold, 1997; Lucas et al., 1998; Linden et al., 1999).

On the contrary, other neuropetides, such as galanin, neuropeptide Y, and growth hormone releasing factor, have been shown to have an inhibitory effect on the FR circuitry and an antinociceptive function (Wiesenfeld-Hallin et al., 1989; Xu et al., 1994, 1997, 1998a,b; Xu and Wiesenfeld-Hallin, 1996; Luo and Wiesenfeld-Hallin, 1993). In particular, endogenous and exogenous galanin was found to reduce central sensitization following the wind up of the flexion reflex (Xu et al., 1990,

1998b; Kerr et al., 2001; Grass et al., 2003). However, the role of galanin is still debated and existing data are contrasting (Kerr et al., 2001).

6.6. Capsaicin

Capsaicin, the main pungent ingredient in ''hot'' peppers, evokes a sensation of burning pain by selectively activating C-polymodal nociceptors. In animals, capsaicin, at low concentrations, selectively desensitizes nerve fibers to repeated stimuli in adult neurons (Szallasi et al., 1994; Szallasi and Blumberg, 1996, 1999).

The effect on the LLFR of selective activation of nociceptive primary afferent fibers by capsaicin was studied in healthy human subjects (Gronroos and Pertovaara, 1993). Capsaicin applied to the distal innervation area of the sural or saphenous nerve produced a significant decrease of the threshold for the RIII induced by electrical stimulation of the proximal sural nerve trunk, and this threshold decrease was rapidly attenuated by a cool compress, concomitantly with attenuation of the capsaicin-induced spontaneous pain. The non-nociceptive H reflex was not modified by capsaicin. Thus, the facilitation was selective for the nociceptive reflex and depended, at least partly, on the ongoing afferent barrage in C-fibers.

6.7. Non-steroidal anti-inflammatory drugs

Different studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs), including acetaminophen (paracetamol), nimesulide, indomethacin, ketoprofen, and acetylsalicylic acid, induce an inhibition of the nociceptive reflex, expressed in terms of reduced area of the reflex response and/or increased threshold of the response, through a central mechanism (Willer and Bathien, 1977; Willer and Harrewyn, 1987; Willer et al., 1987, 1989b; Piletta et al., 1990, 1991; Guieu et al., 1992b; Sandrini et al., 1992a, 2002). This central effect involves supraspinal structures which, activated and/or inhibited by the drug, exert a depressive effect on the nociceptive reflex activity at spinal level. At least three supraspinal structures (hypothalamus, PAG, thalamus) have been identified as possible sites responsible for the central analgesic effect of aspirin-like drugs in animal studies; it has been suggested that these three structures interact with each other, at least during the effect of NSAIDs on the RIII (Willer et al., 1989b).

6.8. Others

Nefopam hydrochloride, an analgesic with a profile distinct from that of opioids or of anti-inflammatory drugs, has been shown to induce a powerful depression of the RIII, increasing the threshold of the reflex and decreasing the slope of the recruitment curve. This effect is probably produced through central (spinal and/or supraspinal) mechanisms (Guirimand et al., 1999).

Flupirtine, an analgesic and muscle relaxant drug, has been shown to reduce the size of both the RII and the RIII components of the LLFR in humans (Timmann et al., 1995). As the analgesic effect has been demonstrated to occur at both spinal and supraspinal level, a direct or indirect action on the spinal cord with possible NMDA-receptor spinal transmission has been hypothesized (Timmann et al., 1995).

It has been shown that tizanidine reduces the flexor reflex in the tibialis after 30 min and suppresses it completely after 60 min. Several mechanisms, including presynaptic and postsynaptic inhibition probably involving glutamatergic transmission, have been hypothesized (Delwaide and Pennisi, 1994).

7. Non-pharmacological analgesic techniques

The nociceptive flexion reflex (RIII, NFR) has been used as an experimental model of pain to examine the antinociceptive effect of several non-pharmacological forms of analgesic intervention. In healthy subjects, with few exceptions, the most common non-pharmacological procedures for pain management have been shown to be associated with an inhibition of the RIII reflex. These data suggest an involvement of spinal inhibitory mechanisms in different analgesic strategies.

7.1. Acupuncture

Acupuncture is known to alleviate several forms of clinical and experimentally induced pain, but only a few studies have examined the effects of acupuncture on the RIII reflex.

In normal volunteers, electro-acupuncture has been found to produce a specific inhibition of the RIII (Boureau et al., 1977, 1978a,b). In fact, the heterosegmental electrical stimulation of the Hoku point resulted in a 115% increase in the RIII threshold, whereas that of a control point as well as the absence of electrical stimulation did not produce any effect. These results have been taken as indirect evidence that spinal presynaptic inhibition of nerve fibers, similar to those involved in analgesia, by opioids and central stimulation, may account for acupuncture analgesia (Boureau et al., 1977, 1978a,b).

The inhibitory effects of acupuncture on the RIII have been replicated in a study including patients with several forms of headache (Amelin et al., 1998). In this clinical population, acupuncture produced divergent effects on the RIII and unmodified subjective pain reports, whereas amitriptyline increased both RIII and subjective pain threshold.

7.2. Transcutaneous electrical nerve stimulation

The modulatory effects of transcutaneous electrical nerve stimulation (TENS) on the RIII have been investigated in several studies using different methodologies and giving contrasting results. In healthy subjects, TENS has shown inhibitory, neutral and even excitatory influences on the RIII reflex.

Prolonged application of conventional TENS (i.e., low-intensity, high-frequency electrical stimuli activating large-diameter cutaneous afferents) at sciatic or lumbo-sacral level, has been found to induce an inhibition of the RIII evoked in

biceps femori and more distal limb muscles, whereas placebo TENS application (low-frequency, low-intensity electrical stimuli) induced no significant change in the RIII threshold and amplitude (Facchinetti et al., 1984; Chan and Tsang, 1987). The RIII inhibition had a gradual onset, a progressive course and a gradual offset, outlasting the TENS application. This inhibitory action was found to peak at the end of TENS application in a study that computerized area and amplitude values of the RIII (Chan and Tsang, 1987), and 30 min after the end of stimulation in a study that considered RIII latency (Facchinetti et al., 1984). TENS application induced a significant increase in plasma β-lipotropin and β-endorphin levels preceding the RIII changes but no change in ACTH or cortisol plasma levels (Facchinetti et al., 1984). The magnitude of the plasma opioid level changes was significantly correlated with the changes observed in the RIII threshold. These data suggest that activation of the endogenous opioid system may explain the ''post-stimulation analgesia'', whereas more localized synaptic inhibitory mechanisms may be operational during stimulation.

The inhibitory effect of TENS at lumbar level was reproduced in a subsequent study on a small group of healthy volunteers and found to be independent of any possible inhibition acting on the motoneuron pool (Sandrini et al., 1992b).

More recently, Danziger and colleagues (1998b) compared the effects of two types of short-lasting (2 min) TENS upon the RIII, when applied homotopically (sural nerve) and heterotopically (first interosseous space of the controlateral hand). They reported an inhibition of the RIII with low-intensity/high-frequency (100 Hz) non-noxious TENS applied homotopically but not heterotopically. By contrast, low-frequency (3 Hz) noxious stimulation, activating small nociceptive fibers, resulted in a biphasic facilitatory–inhibitory effect when applied segmentally and in inhibition followed by after-effects when applied heterotopically. Although the 2-min application of TENS is not an accurate replication of typical clinical application of this modality, this study highlighted the importance of different stimulation parameters and sites of stimulation in conditioning the RIII.

The results produced by all the above studies remain questionable, however, because of various methodological drawbacks, such as absence of control groups and small numbers of subjects studied. When a rigorous methodological protocol was applied, the segmental application of TENS (homotopical sural nerve) for 15 min at different frequencies (5, 100, 200 Hz) did not (with the parameters and application time employed in these studies) produce any significant change in pain perception or in the RIII and H reflexes (Cramp et al., 2000; Walsh et al., 2000).

These discrepancies have been confirmed in the few studies that have investigated the effects of TENS in clinical populations suffering from chronic painful conditions (Garcia-Larrea et al., 1989a,b, 1990; Cheing and Hui-Chan, 1999). In the first of these studies only two of the five patients receiving TENS showed inhibition of the RIII (Garcia-Larrea et al., 1989a,b), whereas in a later study by the same group (Garcia-Larrea and Mauguiere, 1990) it is not clear how many of the six patients receiving TENS showed inhibition of the RIII reflex. These studies did not include control or placebo groups and TENS parameters were not standardized. More recently, it has been reported that a single 60-min session of TENS at lumbosacral level produced a significant reduction in the perception of chronic pain, but no effect on the perception of acute electrically induced pain or the corresponding RIII area (Cheing and Hui-Chan, 1999).

The conflicting results obtained with regard to the effects of TENS on the RIII indicate that difficulties may result in differential activation of pain modulation mechanisms (i.e., involvement of segmental presynaptic and postsynaptic inhibitory processes, activation of DNICs – see previous sections – and the temporal summation of nociceptive responses in dorsal horn convergent neurons) and thus different net effects (Danziger et al., 1998b). Further work is necessary to examine the relative influence of each of these factors on the RIII and their clinical significance.

7.3. Other therapies, including neurosurgical procedures

Interferential therapy (*IFT*) is a popular non-pharmacological modality for the treatment of pain that consists of the application of two slightly different medium-frequency currents that ''interfere'' with the tissues to produce a ''low'' beat frequency. A single 15-min session of IFT at different stimulation frequencies had no effect on the subjective pain report, H reflex or RIII (Cramp et al., 2000). In the same study no differences were observed between IFT and TENS, nor was any frequency-specific effect observed.

Piezo-electric currents (PECs), when applied for 2-min at 3 Hz, either segmentally or heterotopically, have been shown to produce a potent inhibitory effect on the RIII, greater than that induced by noxious TENS (Danziger et al., 1998b).

These effects were associated with long-lasting, local, neurogenic inflammation-type changes to the skin, which were well tolerated by all the subjects, possibly due to a continuous activation of nociceptors and supraspinal inhibitory mechanisms.

The RIII has been studied in patients with chronic pain undergoing functional *neuro-surgical analgesic procedures* (Garcia-Larrea et al., 1989a,b). Dorsal column stimulation was associated with inhibition of the RIII, which was correlated with pain relief. These inhibitory effects showed a certain interindividual variability, ranging from complete suppression of the RIII to no effect, with an isolated report of paradoxical facilitation (Garcia-Larrea et al., 1989a). Significant RIII depression has been found to be associated with good clinical efficacy of spinal cord stimulation in the short and medium term (Garcia-Larrea et al., 1989a, 2000). Interestingly, in uncooperative patients the RIII measurement was found to be helpful in selecting the most appropriate parameters (intensity, frequency) of neurostimulation.

Associated RIII and somatosensory evoked potential recording has been found to be useful in evaluating the anatomo-physiological effects of posterior selective rhizotomy in the dorsal root entry zone (Garcia-Larrea et al., 1989b). In

fact, the abolition or strong attenuation of the RIII with no attenuation of the evoked potentials is a neurophysiological marker indicating that surgical rhizotomy is restricted to the dorsal root entry zone with preservation of the lemniscal pathways. These findings indicate that the routine recording of the RIII may be a useful tool for the objective evaluation of analgesic procedures (Garcia-Larrea et al., 2000).

Motor cortex stimulation (MCS) is increasingly being used as a technique for refractory pain control but its use is largely empirical. It has recently been demonstrated that MCS was able to inhibit the RIII in a manner similar to that described for spinal cord stimulation (Garcia-Larrea et al., 1999). Thus, the analgesic effect of MCS seems to include an inhibitory action on the nociceptive afferent transmission in the dorsal horn, a suggestion supported by the results of a recent study (Senapati et al., 2005).

These findings combined with somatosensory evoked potential and functional neuroimaging data have provided the neurobiological basis for the use of MCS in pain therapy.

8. Pain conditions and other diseases

The RIII has been used in clinical studies designed to clarify the functioning of the antinociceptive system and the way it is controlled by some neurotransmitters as well as the mechanism of action of some analgesics. Furthermore, the RIII has been used to study the pathophysiology of clinical syndromes characterized by chronic pain or by altered pain perception. Changes in the RIII have also been investigated in non-painful disorders (obesity, arterial hypertension, and other diseases) as electrophysiological markers of nociceptive system dysfunction to further knowledge of the pathophysiological mechanisms of associated conditions.

From these studies it emerges that the RIII may be a practical pain-measuring tool useful for diagnostic purposes and for the exploration of aspects of human nociceptive reactions in both experimental and pathological situations.

8.1. Congenital indifference to pain

Although the terms ‘‘congenital indifference to pain’’ and ‘‘congenital insensitivity to pain’’ have often been used interchangeably, in recent years they have acquired different meanings. The presence of peripheral neuropathy has become a criterion for diagnosing congenital insensitivity to pain and for distinguishing it from congenital indifference to pain (Nagasako et al., 2003). The latter has been defined by Thrush (1973) as having the following characteristics: congenital absence of pain sensation involving the whole body surface, preservation of other sensory modalities, and presence of tendon reflexes. Neuropathological examination of verified cases has failed to demonstrate any abnormality, suggesting a possible functional dysfunction of descending antinociceptive pathways as the pathogenetic mechanism of the disorder. Patients with congenital insensitivity to pain have greatly increased RIII reflex thresholds, about 350% higher than normal subjects (Dehen et al., 1978; Willer, 1990). In these patients the intravenous administration of naloxone at low doses (1.2 mg, ineffective in normal subjects) caused a large (more than 67%) and rapid, but transitory, decrease of the RIII threshold that was reproducible on further testing after an interval of 8 days. In contrast, an equal quantity of saline did not induce any modification, whereas the administration of 0.1 mg fentanyl citrate, a powerful morphinomimetic agent, brought about a rapid but transitory elevation (37%) of the reflex threshold. These results indicate that abnormal central processing of pain sensation, consisting of tonic hyperactivity of a morphine-like pain-inhibiting nociceptive system, may underlie the state of analgesia that characterizes this condition in which pain nerve fibers are histologically undamaged.

8.2. Painful thalamic syndrome, thalamic analgesia and Wallenberg’s syndrome

In thalamic syndromes the RIII threshold and subjective pain threshold have been found to be increased on the pain side compared to the unaffected side, where they were normal (Willer et al., 1986a). Treatment with indalpine caused an increase similar to that observed in normal subjects on the non-painful side, whereas on the pain side a further increase in the reflex threshold, but not in the subjective pain threshold, was observed. All the indalpine-induced changes were reversed by naloxone. These data might suggest that thalamic pain is due to the involvement of projections to the somatosensory and integrative cortical areas.

In three patients with typical vascular thalamic lesions producing controlateral analgesia, and three patients with caudal medullary lesions (Wallenberg’s syndrome) (De Broucker et al., 1990), the effect of ‘‘heterotopic noxious conditioning stimulation’’ (HNCS) was tested to assess the possible involvement of supraspinal structures in mediating the suppression of painful sensation and RIII reflex observed in healthy subjects and termed DNICs (Willer et al., 1984; see Section 3.4). In patients with thalamic lesions, as in normal subjects, HNCS applied to the analgesic hand produced a profound inhibition of the RIII reflex that was otherwise normal. In Wallenberg’s syndrome (as in anterolateral cordotomies) the RIII was attenuated in the limb controlateral to the lesion (De Broucker et al., 1990). The reasons for this remain unclear.

These data indicate that attentional processes, and spinothalamic and lemniscal pathways are not involved in the triggering of DNICs in humans. On the contrary, as in animals, the brainstem and the spinoreticular tract for the ascending part are key neuronal links in the loop subserving DNICs in humans.

8.3. Spinal cord lesions (tetraplegia, paraplegia and Brown–Sequard syndrome)

Patients affected by spinal cord lesions have served as a unique clinical model for evaluating the functional/anatomical substrate of descending inhibitory pathways modulating the spinal transmission of nociceptive information. In tetraplegic patients suffering from a clinically complete spinal cord

transection at C5–C6–C7 level, the RIII was normally elicited (Roby-Brami et al., 1987). In the same patients the application of HNCS below the level of transection did not produce any depressive effect on the RIII. In a single case of hemispinal section at T6 level, producing a clinically ''impure'' Brown–Sequard syndrome, the RIII was normally elicited in the analgesic limb (Bouhassira et al., 1993). The application of HNCS was ineffective in triggering DNICs when applied below and controlaterally to the lesion, whereas the RIII reflex elicited below and homolaterally to the lesion was completely insensitive to any of the conditioning stimuli. These results have suggested that in humans the ascending part of the spino-bulbo-spinal loop subserving DNICs is completely crossed at spinal level, traveling through the ventro-lateral funiculi, whereas the descending part is confined to the white matter of ipsilateral dorso-lateral funiculi. Thus it appears that there is a general similarity in the organization of DNIC circuits in humans and in animals (see Section 3.4).

After unilateral cervico-thoracic anterolateral cordotomy FR responses controlateral to the cordotomy presented two post-operative changes: (a) a dissociation between the RIII and subjective pain, representing a possible specific electrophysiological marker of spino-thalamic fiber lesions; (b) a reversible attenuation of RIII responses indicating the existence of facilitatory inputs traveling in the anterolateral/ventral cord (Garcia-Larrea et al., 1993).

Paraplegic patients with traumatic lesions of the spinal cord at dorsal level have been investigated with the aim of clarifying the mechanisms of morphine analgesia (Willer and Bussel, 1980; Roby et al., 1981). In these patients, as well as in normal subjects, the intravenous administration of morphine (0.3 mg/kg) selectively and specifically depressed the RIII reflex, whereas monosynaptic responses mediated by large-diameter fibers (e.g., H reflex) were unaffected. These data have reinforced the hypothesis that the spinal level is one of the main sites of morphine-induced analgesia.

In a recent paper the progressive increase of flexion responses with repeated nociceptive stimuli (i.e., wind up of the FR) was investigated in 12 individuals with complete chronic spinal cord injury to evaluate the excitability of the flexor motoneuron pool and its role in the pathophysiology of flexion spasms (Hornby et al., 2003). A wind up of flexion responses of the lower limb was consistently observed in all patients and lasted for a time interval $\leq$3 s. Such long-lasting increases in FR responses are indicative that cellular mechanisms such as plateau potentials in spinal motoneurons and/or interneurons might mediate spinal cord hyperexcitability in the absence of descending modulatory input.

8.4. Headaches

The RIII reflex has been tested in several primary headache syndromes (Sandrini et al., 1986d, 1991, 1993a,b, 2000b). As the RIII reflex has proved to be strongly modulated by antinociceptive descending pathways, it may be usefully applied in migraine and other primary headaches as a tool to investigate the CNS pain modulatory pathways and their role in the pathophysiology of primary headaches. It is, in fact, known that these descending modulatory systems act on both trigeminal and spinal neurons (Fields and Basbaum, 1978).

Furthermore, until recently, nociceptive reflexes exploring pain in the trigeminal district have been poorly specific (Cruccu et al., 2004). In addition, it should be considered that in the cranio-facial region, pain-induced motor response recruitment is more variable and needs to be integrated with more complex motor activities resulting from visual, acoustic, vestibular, and other stimuli, making these methods less standardized and sensitive than RIII to changes in gain of nociceptive transmission.

8.4.1. Migraine, chronic tension-type headache, and other chronic daily headaches

No significant difference in the RIII reflex threshold and pain sensation threshold was found in migraine patients, during a pain-free period, when compared to control subjects (Sandrini et al., 1986d). The RIII reflex in chronic daily headaches has been evaluated in several studies designed to clarify the functioning of the antinociceptive status at spinal level.

A significant reduction of pain threshold/reflex threshold ratio (T_p/T_r), related to a significant reduction of subjective pain threshold with normal T_r, has been indicated as a distinctive feature of chronic tension-type headache (CTTH) (Sandrini et al., 1991). On the contrary, patients with chronic migraine, defined as ''migraine with interparoxysmal headaches'', presented a significant reduction of the RIII threshold but normal T_p/T_r ratio (Sandrini et al., 1986d, 1991). A significant correlation between T_p/T_r ratio and Hamilton rating scales for Anxiety was found in both groups. Patients suffering from chronic migraine exhibited an inverse relationship between headache severity evaluated by means of the total pain index and RIII threshold values (Sandrini et al., 1986d). Amitriptyline and other serotonergic drugs (ritanserin, fluoxetine) caused a significant increase in the reflex threshold in the chronic daily headache group as a whole; this increase was correlated with the total pain index but was independent of the improvement in the depression scales, suggesting that the analgesic effect of these drugs is distinct from its antidepressant actions (Sandrini et al., 1986d; Nappi and Sandrini, 1992; Sandrini et al., 1993). Together, these data indicate the existence of an impairment of psychological and neural mechanisms of pain in chronic headaches. Amplification of subjective nociceptive perception seems to be a typical feature of CTTH biotype, whereas a reduced inhibition of pain might characterize the chronic migraineurs. These findings have not been completely replicated in other studies. Boureau et al. (1991) found no difference in RIII threshold between patients with chronic pain (nine with headaches and nine with myofascial syndromes) and controls, but these patients were on treatment, including antidepressants, which may explain the absence of reflex changes. More recent research assessing the RIII in CTTH patients revealed a significantly lower reflex threshold than in the control group (Langemark et al., 1993). A high degree of correlation was found between the RIII threshold and tolerated stimulus strength, and the slopes of the stimulus intensity/visual

analog scale pain rating response curves were steeper in patients with CTTH than in control subjects (Langemark et al., 1993). The RIII and pain threshold did not correlate with the cerebrospinal fluid met-enkephalin-immunoreactivity, a marker of the enkephalinergic antinociceptive system at spinal/trigeminal level (Langemark et al., 1995). These results suggest that CTTH patients have a widespread generalized pain hypersensitivity and that CTTH may represent a disorder of a central endogenous nociceptive system in which there is a dysfunction of the descending inhibitory system.

8.4.2. *Cluster headache and other trigeminal-autonomic cephalagias*

As for the other primary headaches, the threshold of the RIII in cluster headache (CH) has been evaluated with the aim of obtaining, for the formulation of pathophysiological considerations, indirect objective information about the function of pain control systems.

It has been shown that the RIII threshold is asymmetrically reduced during the active phase of CH (Sandrini et al., 2000b). In this study, the RIII reflex threshold and the threshold of pain sensation, in patients with episodic CH, were found to be significantly reduced, in parallel, on the symptomatic side only during the active phase. In these patients an inverse correlation was found between the severity of CH, measured as the ratio between number of cluster periods and years of illness duration, and the pain threshold, indicating a possible role for secondary central sensitization in pain pathways. These data are in agreement with previous observations from explorations of pain mechanisms using other neurophysiological methods (i.e., corneal reflex, pain pressure threshold) and support the notion that, during the active phase of CH, there is a lateralized upregulation of nociceptive transmission extending to extracephalic parts of the body, indicating an impairment of the descending pain modulatory pathways (prevalence of facilitatory versus inhibitory influences) that parallels the periodicity of the disorder.

In a subsequent study the same group confirmed and extended these findings demonstrating an impairment of circadian rhythmicity of the RIII threshold in CH (Nappi et al., 2002). In patients with episodic CH, persistence of a significant 24-h rhythm during both the active and remission phase was observed, but a shift of the phase was observed during clinical activity when compared with the remission period. A lack of circadian RIII threshold rhythmicity was found in the patients with chronic CH. These data suggest that, in CH, an impairment of the pain control system is associated with a periodic failure of the mechanisms involved in the organization of biological rhythms. These findings are in line with recent studies supporting a primary pathogenetic role of hypothalamic pacemaker regions of the brain which may play a facilitatory role, releasing or entraining the trigemino-vascular pain system.

Chronic paroxysmal hemicrania (CPH) is a rare form of trigeminal-autonomic cephalagia (TAC) characterized by unilaterality of pain, multiple and relatively short-lasting attacks, ipsilateral autonomic symptoms and signs, and absolute indomethacin response. Due to the low prevalence of this disorder only one study, of five patients, has been carried out to assess pain response by means of the RIII (Antonaci et al., 1994). In CPH patients on indomethacin the RIII threshold was reduced on the symptomatic side when compared to controls but no major asymmetry between symptomatic and non-symptomatic side was found. The RIII threshold was not modified by daily intake of indomethacin in spite of the complete clinical responsiveness to this drug. These data seem to indicate a peculiar pattern of response of the nociceptive system in CPH when compared to CH, but due to the limited number of patients no hypothesis can even be attempted.

8.5. *Fibromyalgia and other chronic painful disorders*

Evidence has been provided that in patients suffering from fibromyalgia (FM), not using centrally acting analgesics, there is an upregulation of the RIII and its supraspinal regulation, consisting of a reduced RIII threshold evoked by non-painful areas (Desmeules et al., 2003; Banic et al., 2004) and activation of DNIC activity by non-nociceptive, mechanical stimuli (Guieu et al., 1994a; Desmeules et al., 2003). This decrease in the RIII threshold, indicating a state of hypersensitivity of spinal neurons to peripheral stimulation, was associated with a parallel decrease in subjective pain threshold (Desmeules et al., 2003; Banic et al., 2004) and unrelated to the clinical variables of the disease (Desmeules et al., 2003).

These electrophysiological findings, when pooled with the available literature data, are indicative of a CNS sensitization of pain pathways and a possible alteration of the central modulatory inhibitory pathways in patients with FM. Regardless of the causal mechanism, these neurobiological changes can explain exaggerated pain following low-intensity or nociceptive inputs from undamaged tissues (Banic et al., 2004). In diagnostic terms, despite the large interindividual variability of the RIII reflex threshold, a cutoff value of <27.6 mA for the RIII gave a sensitivity of 73% and a specificity of 80% for detecting central allodynia in FM (Desmeules et al., 2003). Critical questions, such as the gender effect on the neurophysiological abnormalities, the extent to which central sensitization precedes or is the consequence of the manifestations of disease, the specificity of the RIII decrease in FM, and its clinical usefulness, remain to be answered.

Examination of the RIII reflex in patients with other chronic painful disorders has yielded conflicting data.

In 27 patients with chronic pain after whiplash injury, RIII responses to single and repeated electrical stimulation were significantly lower than in healthy control subjects, whereas the differences in subjective pain thresholds between the two groups were not significant (Banic et al., 2004). This indicates that electrophysiological measurements may be more sensitive and reliable than pain threshold measurements for detecting hypersensitivity of spinal cord neurons in patients. The presence of spinal cord hypersensitivity in two different painful syndromes such as FM and whiplash syndrome (WS) suggests that it may be an electrophysiological marker of other

chronic musculoskeletal pain states. In accordance with this assumption, the RIII has been found to be hyperexcitable and unmodified by pain relief maneuvers in a small group of patients suffering from patello-femoral dysfunction (Leroux et al., 1995). On the contrary, in a study of 53 patients with various chronic pain syndromes other than FM (Boureau et al., 1991), most on analgesic treatment, no differences in RIII and pain threshold were found between controls and patients, and no correlation between experimental pain measures and clinical pain was observed.

However, chronic pain patients reported a higher threshold for unpleasantness and judged the suprathreshold stimuli significantly less intense and less unpleasant than the control group. In line with these findings, Peters et al. (1992), in 12 patients suffering from chronic low back pain, found a significantly higher pain threshold not paralleled by a higher RIII threshold. Naloxone was ineffective in modifying the RIII and pain thresholds in both patient and control groups. These results support the notion that chronic pain patients may have a reduced sensitivity to acute pain related to the person's subjective report of pain and does not result from a DNICs effect but from a defective perceptual/attentional interpretation of the pain experience (Peters et al., 1992). However, these conclusions may be influenced by the relatively small number of patients suffering from these heterogeneous disorders and, most importantly, by the concomitant intake of centrally acting analgesics.

Although the RIII reflex has been used to assess the efficacy of analgesic pharmacological and non-pharmacological procedures (Willer et al., 1985; Garcia-Larrea et al., 1989a, 1999; Sandrini et al., 2000b), there has been little exploration of neuropathic pain patients. The threshold of the RIII nociceptive reflex and the concomitant pain sensation were similar in patients with chronic neuropathic pain presenting with or without spontaneous ongoing pain (Bouhassira et al., 2002), suggesting that this type of clinical pain is not able, and/or not intense enough, to trigger DNICs or to induce significant changes in the RIII.

Very recently, Coffin et al. (2004) investigated the effects of rectal distension on the RIII reflex in 14 patients suffering from irritable bowel syndrome (IBS) and 10 healthy volunteers. In the IBS patients, slow-ramp distension induced a facilitation instead of an inhibition of the RIII: in the same way, the inhibitions induced by rapid distensions in healthy subjects were significantly reduced. These data suggest that a hyperexcitability of spinal nociceptive processes may be implicated in the pathogenesis of the chronic visceral hypersensitivity observed in patients with IBS.

In summary, studies of the RIII in chronic pain patients have given heterogeneous results. A divergence between painful sensation and the RIII has been reported in some studies (Boureau et al., 1991; Garcia-Larrea et al., 1993; Leroux et al., 1995; Andersen et al., 1996; Banic et al., 2004), challenging the role of the RIII as an objective tool of pain assessment. However, these data may merely be an indication that in pathological conditions this simple relationship is not present (Garcia-Larrea et al., 1993). The variability of RIII measurements may be explained by considering the development of chronic pain as a heterogeneous phenomenon resulting from different, dynamic pathogenetic processes. In the recently released EFNS guidelines on neuropathic pain assessment (Cruccu et al., 2004), the RIII was considered ''the nociceptive reflex that is most used and appears to be the most reliable in assessing treatment efficacy'' (grade B recommendation).

That said, the RIII has been found to be consistently hyperexcitable in painful conditions such as FM, IBS, WS and some forms of chronic headaches, in which, in the absence of evident tissue damage, a hyperexcitability of spinal or higher brain center neurons, also called central sensitization, is supposed to play an important role in the development and maintenance of chronic spontaneous pain and centrally mediated allodynia.

8.6. Acute painful states

It is well known that heterotopic experimental pain stimuli inhibit the perception of pain and the RIII response to a test stimulus, through specific neurophysiological mechanisms involving endogenous modulation of the spinal transmission of nociceptive signals (see Section 3.4.3). A number of studies have shown that clinical pain (e.g., sciatica, post-operative pain after meniscal surgery) might also be effective in specifically activating DNICs by reducing the RIII amplitude or raising the RIII threshold (Willer et al., 1985, 1987; Willer and Harrewyn, 1987; Guieu et al., 1993a). However, no evidence of RIII modulation by pain from oral surgery was found (Peters et al., 1992), suggesting that different forms of acute pain are not equally effective in activating DNICs. This hypothesis was recently substantiated by Bouhassira et al. (2003), who investigated the pain-inhibiting effects induced by allodynia in patients with traumatic peripheral nerve injuries. Static mechano-allodynia (mediated by fine nociceptive fibers) induced inhibitions of both the RIII reflex and the concomitant painful sensation, similar to those induced by experimental pain stimuli, and these were probably due to an increased activation of DNICs. On the contrary, dynamic allodynia (mediated by myelinated fibers) reduced the pain sensation, but did not inhibit the RIII responses, suggesting that in this case the counter-irritation effect may take place at supraspinal level. These findings indicate that the mechanisms of the pain-inhibiting-pain phenomenon are not determined by the intensity or etiology of the clinical pain, but by its pathophysiological mechanisms.

8.7. Obesity and hypertension

Obese women have shown decreased RIII thresholds which are inversely correlated with overweight state (Pradalier et al., 1980, 1981). It was postulated that this interrelationship between pain and obesity may be related to a disorder of the endogenous opioid system, but subsequent human and animal investigations aimed at elucidating the nature of the opioid-feeding-pain relationship led to a wide variety of findings, some of them apparently contradictory (Ramzan et al., 1993; Johnson, 1995). Thus, no definitive conclusion has been reached.

Over the last two decades research has provided evidence for a relationship between hypertension and hypoalgesia (France, 1999). This relationship has been found even in normotensive subjects at risk of hypertension (offspring of parents with hypertension), who exhibit a specific increase of the RIII threshold compared to the offspring of normotensive subjects (Page and France, 1997; France and Suchowiecki, 2001; France et al., 2002a). These data indicate that pain hyposensitivity may be related to physiological processes associated with the development of the hypertension rather than with high blood pressure per se. These findings have been explained by hypothesizing an enhanced activation of descending pain inhibitory pathways, possibly involving a baroreflex mechanism (France, 1999). Nevertheless, the elevated RIII thresholds in men and women at risk of hypertension were not related to defective DNIC-like activity (France and Suchowiecki, 2001; France et al., 2002a), to abnormal temporal summation of pain, or to dysregulation of attentional manipulation of pain (France et al., 2002a), or of the endogenous opioid system (France et al., 2005). These findings have never been reproduced by other groups and the mechanisms underlying decreased RIII activity in patients at risk of hypertension remain to be elucidated.

8.8. Others

There are isolated reports of abnormally increased RIII reflex thresholds in patients suffering from Parkinson's disease (Guieu et al., 1992c) and temporal lobe epilepsy (Guieu et al., 1992d). The administration of naloxone reversed the observed findings in two patients with Parkinson's disease but was ineffective in the epileptic group, indicating a differential involvement of the opioid system in the pathophysiology of the observed hypoalgesia. Nociceptive flexion reflex thresholds in patients with generalized epilepsy did not differ from those of control subjects (Guieu et al., 1992c).

The influence of psychiatric factors on the RIII has been investigated in several studies. The RIII threshold and the subjective pain threshold of patients with schizophrenia receiving no treatment did not significantly differ from those of control subjects (Guieu et al., 1994b). This indicates that the clinical observation of pain insensitivity in patients with psychotic illness may be related to the pharmacological treatment or may be the result of denial rather than insensitivity to pain. On the contrary, in patients with pronounced neurotic symptoms, the RIII threshold and subjective pain sensitivity have been found to be decreased (Kwasucki, 1994).

Catastrophizing, meaning the tendency to ruminate on, magnify, or feel helpless in the face of pain, has been found to be positively correlated with subjective pain thresholds but had no influence on RIII threshold levels (France et al., 2002b). Thus, cognitive and emotional factors associated with catastrophizing are a potential source of divergence between the RIII reflex and the subjective pain experience.

The RIII threshold has been found to be significantly higher in a small number of patients with hypothyroidism than in controls (Guieu et al., 1993b). No correlation was found with the TSH level and in the course of substitution treatment the RIII gradually returned to normal. The mechanisms of the observed hypoalgesia in patients with thyroid hormone deficiency are not clear. The potential role of concomitant weight gain or psychiatric status has not been specifically investigated.

9. Conclusions

The LLFR is a useful tool for exploring the mechanisms both of pain and of motor functions at spinal and supraspinal level. It is easily recorded and widely used in research laboratories in Europe and the USA. It can be recorded with most commercial EMG devices, although, in several laboratories, special equipment is used for quantitative analysis (Sandrini et al., 1993a,b).

Although many aspects of the LLFR have been extensively studied, several others, including the RII component and the use of the RIII reflex in clinical evaluation of neuropathic pain, have not been fully evaluated and merit further exploration.

Furthermore, more recent evidence on the temporal summation of the RIII reflex and its modulation by antinociceptive pathways suggest that this promises to become, in the near future, an active and fascinating field, reinforcing the usefulness of the RIII reflex in the clinical and pharmacological study of pain in humans.

In addition, as the LLFR is a multisegmental and easily recorded reflex, its modulation during movement should be further investigated in order to shed more light on the adaptive behaviors of the spinal cord during gait and lower limb movements.

In this context, the study of the LLFR has proved to be a useful tool for clinical and pharmacological pain assessment and a looks set to play an increasingly central role in the exploration of pain and motor functions at spinal and supraspinal level.

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