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Spinal associative plasticity in depth: evidence from animal model

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Spike-timing dependent plasticity (STDP) implies changes in the effectiveness of the synapse strength depending on exact timing of pre- and postsynaptic activation. STDP is thought to mediate forms of associative plasticity based on the Hebbian theory. Associative plasticity can be probed experimentally and non-invasively in humans by applying "paired associative stimulation" (PAS). The original PAS protocol described in humans (Stefan *et al.* 2000) consists of repetitive cortical and peripheral nerve stimuli delivered at specific interstimulus intervals (ISIs), able to elicit long-term potentiation (LTP)- and depression (LTD)-like plasticity in the primary motor cortex (M1). More recently, a number of modified PAS protocols have been designed and tested in humans such as protocols able to promote plasticity in the spinal cord (Suppa *et al.* 2017). Spinal PAS might be in theory applied to harness plasticity for motor recovery in patients with various neurological disorders. However, a number of issues, including the specific physiological basis of plasticity induced by various spinal PAS protocols, remain to be clarified. Understanding the precise neurophysiological basis of spinal associative plasticity is the necessary precondition of development of new non-invasive neurostimulation strategies in human neurological disorders.

The study of Mishra *et al.* (2017), recently published in *The Journal of Physiology*, is relevant since it provides new helpful insights into the physiological bases of spinal associative plasticity in animals. In the first set of experiments, the authors examined the exact timing and site of interaction between two stimuli, the first delivered over M1 and the second given over specific regions of the cervical spinal cord. The experiment was therefore designed to verify the collision between M1 and spinal stimuli within the spinal cord. M1 was stimulated by applying, epidurally, short trains of electric stimuli (3 biphasic pulses, each pulse of 0.2 ms with ISI of 3 ms). In contrast, a single electric stimulus was delivered epidurally over the cervical spinal cord by using two electrodes placed at various medio-lateral positions, such as the spinal midline, the dorsal root entry zone (DREZ), and finally, over the C5–C6 dorsal roots. Motor-evoked potentials (MEPs), evoked by cortical as well as spinal cord stimulation, were recorded by placing electrodes into the biceps muscle bilaterally. The main outcome measure in all the experiments was the area under the curve of MEPs (MEP AUC). The main finding of the first experiment was that MEP AUC increased when the spinal cord activation followed M1 activation at specific ISIs and particularly at 10 ms, suggesting exact timing of collision between the two stimuli. The most effective site for spinal cord stimulation was the DREZ, likely because of the proximity to large-diameter afferent fibres projecting to interneurons. Several control experiments further confirmed that the exact timing of interaction was 10 ms and that the most likely site of interaction between cortical and spinal stimuli was within the spinal cord.

In the second set of experiments, the authors repeatedly applied the M1 and spinal cord stimulation in order to elicit plasticity processes in the spinal cord. To this aim, the authors delivered M1 stimuli followed by spinal cord stimulation at 10 ms ISI. M1 stimulation was given at the threshold for evoking "cortical MEPs", whereas the spinal threshold was set below the threshold for evoking "spinal MEPs" (i.e. subthreshold). The modified PAS protocol designed by Mishra *et al.* (2017) consisted of paired (cortical and spinal) stimuli, delivered at 0.5 Hz, for 5 min (150 paired stimuli in total) or for 10 min (300 paired stimuli in total), in different experiments. MEPs were recorded and AUC measured before and after PAS every 10 min and for 60 min in total. As a measure of associative plasticity, the authors examined possible long-term changes in MEP AUCs after PAS. The main finding was that MEPs increased in amplitude following the shorter PAS (5 min PAS) as well as the longer PAS (10 min PAS). This finding suggests LTP-like plasticity processes occurring in the spinal cord. Detailed histograms in Fig. 7*Bb* showed prominent post-intervention changes at 0–10 min following the shorter PAS, whereas after the longer PAS, MEPs increased particularly at 30 min. In addition, differently from the shorter PAS, the longer PAS also increased MEPs at 40 min. Moreover, DREZ stimulation again elicited prominent changes in MEPs compared with midline spinal cord stimulation. Again, only PAS at 10 ms ISI was effective in driving associative plasticity in the spinal cord. Finally, M1, as well as spinal cord stimulation given alone, both left MEPs unchanged, further confirming that the observed plasticity required the associative, time-dependent collision between M1 and spinal cord stimuli.

We believe that the study of Mishra *et al.* is rather interesting and well focused on a relevant research issue. By applying a new spinal PAS protocol in animals, the authors provided new information on the physiological basis of associative plasticity in the spinal cord. The first strength of the study is the exact timing and site of interaction between cortical and spinal cord stimuli, in rats. The specific ISI of 10 ms between M1 and spinal cord activation fully agrees with the observation that, in rats, M1 stimulation evokes excitatory postsynaptic potentials (EPSPs) with a similar latency in C5–C6 anterior-horn α-motoneurons (Mishra *et al.* 2017). Concerning the exact site of interaction, the authors demonstrated that DREZ was the most effective site for spinal cord stimulation able to trigger LTP-like plasticity when activated 10 ms later than M1. This finding, coupled with further observations from several control experiments, suggests that spinal PAS operates through activation of large-diameter afferent fibres projecting indirectly to α-motoneurons through intermediate zone interneurons. The exact timing and site of interaction reported here by the authors are the basis for more advanced and effective spinal PAS protocols able to drive associative plasticity also in the human spinal cord.

The study of Mishra *et al.* is characterized by several possible limitations. First, the use of ketamine for general anaesthesia in rats might have interfered significantly with mechanisms of spinal plasticity.

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Ketamine acts as an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor and also inhibits the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor (Tyler *et al.* 2017), both required for synaptic plasticity. Hence, ketamine might have somehow affected the amount and duration of synaptic events in the spinal cord, thus changing the LTP-like plasticity processes here observed by the authors. Moreover, mechanisms of non-synaptic plasticity might have also contributed to the findings reported here. Non-synaptic plasticity includes long-term changes in intrinsic neruronal excitability owing to modification in voltage-gated channel activation. Non-synaptic plasticity affects synaptic integration, subthreshold propagation, spike generation and other fundamental neuronal mechanisms (Mozzachiodi & Byrne, 2010). Non-synaptic plasticity may crucially interact with synaptic plasticity in experimental settings similar to those reported here. We therefore believe that non-synaptic plasticity should not be fully excluded as a physiological process possibly contributing to the findings observed by Mishra *et al.* (2017). Another comment concerns the observation that none of the ISIs used during spinal PAS elicited LTD-like plasticity (as reflected by long-term inhibition of MEPs). It might suggest that plasticity processes other than those responsible for STDP contributed to the present findings. The authors indeed used the convergence model rather than STDP to explain their findings. Finally, the exact neuronal population activated in M1 by the three electric stimuli used here remains largely unclear and the timing of interaction between M1 and spinal cord activation cannot be easily translated to humans.

In conclusion the present work of Mishra *et al.* (2017) provides new helpful information on the physiology of spinal associative plasticity. These experiments overall are certainly useful to better understand the physiology of spinal cord plasticity and to design new non-pharmacological strategies based on non-invasive neurostimulation protocols for symptomatic improvement in patients with several post-traumatic or neuro-degenerative neurological disorders.

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