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Thyroid hormone receptors and ligands, tissue distribution and sexual behavior

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1. Introduction

The thyroid hormones (THs) triiodothyronine (T_3) and tetraiodothyronine, or thyroxine (T_4), not only dramatically impact on development and differentiation, but also on the sexual and reproductive function. There is large body of literature, in fact, on the effects of THs on the reproductive function in both humans (Poppe and Velkeniers, 2004; Wajner et al., 2009) and animals (Hapon et al., 2010; Nelson et al., 2011).

For a long time the gonads were thought to be unresponsive to THs, but TH receptors (TR) were discovered in rat (Jannini et al., 1990; Palmero et al., 1988) and then in human testis (Jannini et al., 2000). In women, the association of menstrual disturbance with thyroid disease was described as early as 1840 by von Basedow, but the discovery of TRs in the ovary was carried out at the end of last century (Wakim et al., 1994b). Therefore, the link between thyroid and reproductive function was well established. Since then, research has shown that thyroid dysfunction is associated with an adverse effect on fertility, both in men (Wagner et al., 2009) and women (Dittrich et al., 2011). There is also evidence that THs can affect the sex steroid hormone axis (Bagamasbad and Denver, 2011), consequently sexual hormones and the pituitary gland can mediate the action of THs on the reproductive physiology.

While the effects of THs on fertility have been widely studied, little is known about their influence on sexual function. In the last few years, an increasing number of evidences have shown the influence of THs on male sexual function, particularly on ejaculation control as well on desire and erectile function (Carani et al., 2005; Corona et al., 2012b; Di Sante et al., 2016). The female sexual function and the relationship with thyroid function is still less studied. Furthermore, studies conducted on animals have shown the presence of TRs in the male (Carosa et al., 2010) and female genitalia (Rodriguez-Castelan et al., 2017). Moreover, knockout mice for TRs showed alterations in sexual behavior (Dellovade et al., 2000).

The purpose of this review is to summarize and discuss the available data on the influence of THs on male and female sexual function to understand the molecular mechanisms of the influence of the thyroid gland on sexual behavior and function.

2. Thyroid hormones and thyroid hormone receptors

TH action is mainly dependent on the binding of the cognate with specific receptors, the most important being at nuclear level (Mendoza and Hollenberg, 2017). Thyroid hormone receptors (TRs) belong to the steroid/thyroid receptors superfamily that evolved from a single ancestor gene (Carosa et al., 1998; Kostrouch et al., 1998). TR_α and TR_β are the product of two distinct genes that are further differentially spliced into $TR_{\alpha 1}$, $TR_{\alpha 2}$ (Jannini et al., 1992; Sap et al., 1986; Weinberger et al., 1986), and $TR_{\beta 1}$ and $TR_{\beta 2}$ (Lazar et al., 1988; Mitsuhashi et al., 1988). $TR_{\alpha 1}$ and $TR_{\beta 1}$ are widely expressed and act as thyroid hormone-dependent transcription factors, inducing or repressing gene expression in response to T_3. The differentially spliced product $TR_{\alpha 2}$ does not bind the hormone and exerts a dominant negative effect on the action of other TRs (Katz et al., 1995; Koenig et al., 1989). Although two different genes encode the two TR isoforms, they share a very high degree of structural homology and the more conserved part of protein is the DNA binding domain (Fig. 1). On the DNA, TRs recognize the sequence AGGTCA, to which they can bind as a monomer. In the thyroid responsive element (TRE) of the promoters of responsive genes this sequence is repeated with a space of 4 bp to permit the DNA bind of the heterodimer TR/retinoid X receptor (RXR). The presence of RXR increases the binding affinity (Lazar, 2003).

Thyroid hormones are hydrophobic and for a long time it was thought they entered the cytoplasm by passive diffusion. In recent years, it has become clear that this is not the case and several TH transport proteins have been identified (Friesema et al., 2003; Schweizer et al., 2014). To date, the most clinically relevant THs transporter is the monocarboxylate transporter 8 (MCT8), which is associated with a THs insensibility syndrome (Schwartz et al., 2005). It is now clear that TH transporters can modulate the real effect of THs because they regulate, at the tissue level, the availability of THs. Deeping on THs transporters is beyond the purpose of this review, but the future will show if their alterations may involve sexual function. Here we can highlight that MCT8 is expressed both in the testis and in the ovary (Friesema et al., 2003; Romano et al., 2017).

Inside cells, THs bind TRs to regulate target gene expression. The interaction of T_3 with the ligand domain induces a conformation change of the hormone-binding pocket. The change of conformation appears to be critical for the release of corepressor and the recruitment of coactivators on the regulated gene's promoters. In the classic view (Fig. 2), T_3 action is based on its positive effect on target genes. In the absence of T_3, the TRs recruit a multiprotein complex that includes nuclear corepressors, which in turn recruit histone deacetylase 3 (HDAC3) and other proteins to mediate transcriptional repression via histone deacetylation (Sun et al., 2013; You et al., 2013). The presence of T_3 leads to dismissal of

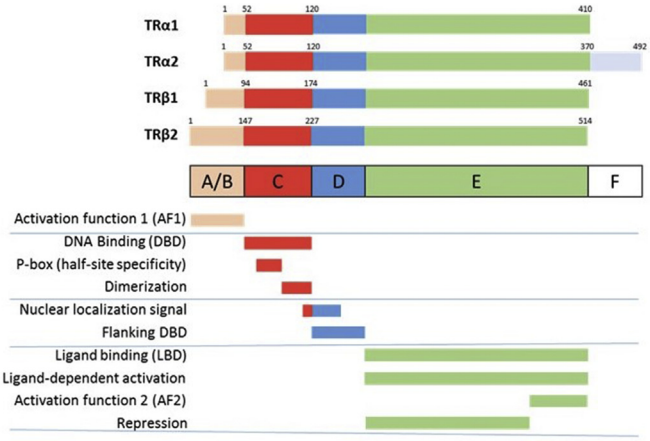

Fig. 1. Schematic representation of human TR isoforms and their domain functions.

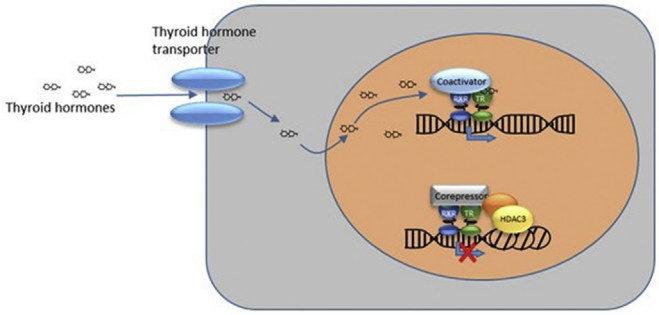

Fig. 2. Classical view of THs action. The interaction of T_3 with TH induces the release of corepressor and the recruitment of coactivators on the regulated gene's promoters. In the absence of T_3 the TRs recruit a multiprotein complex that includes nuclear co-repressors, which in turn recruit HDAC3 and other proteins to mediate transcriptional repression via histone deacetylation.

the corepressor complex and recruitment coregulators that induce histone acetylation and transcriptional activation. Some recent studies, based on chromatin affinity precipitation (ChAP)-seq and DNase hypersensitivity analysis showed extensive chromatin remodeling in the presence of T_3 stimulation in accord with the classical model of THs action (Ayers et al., 2014; Chatonnet et al., 2012; Grontved et al., 2015; Ramadoss et al., 2014). These studies have also established that RXR overlaps TR DNA binding, endorsing the fact that TRs act like heterodimers with retinoid X receptor (RXR) (Ramadoss et al., 2014). New studies demonstrated that the molecular mechanisms of T_3 actions are more complicated and the classical model does not explain the exact mechanism of action; in particular, the T_3 negative regulation remains a paradox, in the liver TRs down-regulate more genes in the presence of T_3 than they activate. Several hypotheses have been suggested to explain the molecular mechanism of T_3 negative gene regulation. One of these asserts the possibility that coregulators act as a repressor on promoters of negative regulated genes (Costa-e-Sousa & Hollenberg, 2012), but it is possible that numerous models will be required to explain the exact molecular mechanism of TRs action. To support the direct effects of THs on sexual function it is important to demonstrate that TRs are expressed in male and female genitalia.

3. Thyroid hormone receptors expression in sexual organs

3.1. Male

3.1.1. Thyroid hormone receptors in testis

T_3 regulates the maturation and growth of the testis, controlling Sertoli and, with much lower impact, Leydig cell proliferation and differentiation during testicular development in human and other mammalian species (Francavilla et al., 1991; Holsberger and Cooke, 2005; Jannini et al., 1999; Mendis-Handagama and Siril Ariyaratne, 2005). The first study describing the selective presence of specific TH nuclear binding sites in Sertoli cells of developing rat testis opened a new research avenue (Jannini et al., 1990), since these findings changed the classical view of the testis as a thyroid unresponsive organ (Barker and Klitgaard, 1952). Ontogenetic expression of TRs in human and in rat testis established that the fetal and prepubertal ages of Sertoli cells represent the period of maximal expression, but the binding capacity is not completely absent in the adult (Buzzard et al., 2000; Canale et al., 2001; Jannini et al, 1993, 1995, 1999, 2000; Tagami et al., 1990; Ulisse et al., 1992). In rats, TRs were present in different testicular cell types and their expression changes during testis maturation (Table 1). $TR_{\alpha1}$ expression was very high in Sertoli cells during their proliferative phase, until day 15 post-natal, then decreases and remains very low in adulthood (Jannini et al, 1994, 1999). $TR_{\alpha1}$ was also found in spermatogenic germ cells from intermediate spermatogonia to mid-cycle pachytene spermatocytes (Buzzard et al., 2000), as well in the interstitial compartment in immature testis, probably in the Leydig cells, but at very low levels (Buzzard et al., 2000). The same laboratoy found that the $TR_{\beta1}$ expression in immature Sertoli cells and spermatogenic germ cells was also very low in relation to $TR_{\alpha1}$ expression. This confirmed our findings, which previously showed that TR_{β} mRNA is below the threshold of detectability of both Northern and ribonuclease (RNase) protection analyses (Jannini et al., 1995). In fact, Palmero et al. (1995) demonstrated that $TR_{\beta1}$ is detectable only after 30 cycles of PCR amplification. According to our evidences using biochemical and molecular techniques of detection of TRs, studies on transgenic mice lacking either TR_{α} or TR_{β} have shown that the effect of T_3 on Sertoli cell proliferation is mediated through TR_{α} isoform (Holsberger et al., 2005). Furthermore, Fumel et al. (2015), using a TR_{α} dominant negative isoform selectively expressed in Sertoli and Leydig cells, confirmed the role of $TR_{\alpha1}$ in Sertoli cells during post-natal life and pointed out that T_3 does not regulate steroidogenic activity in a direct manner on Leydig cells, also fitting the spatio-temporal distribution of TRs previously demonstrated. Thyroid hormones modulates the activity of glucose transporters and aromatase in Sertoli cells to regulate the function of seminiferous epithelium (Carosa et al., 2005; Ulisse et al., 1994, 1998).

3.1.2. Thyroid hormone receptors in epididymis

The presence of $TR_{\alpha1}$ and β_1 isoforms was more recently demonstrated in epithelial cells derived from adult rat epididymis (De Paul et al., 2008) (Table 1). However, further studies are necessary to understand the role of TRs, if any, in epididymis function in light of the fact that TR proteins are localized in the cytosol of the cells, suggesting a possible active role for THs in the epithelial cells of epididymis acting through a non-genomic fashion (Bassett et al., 2003).

3.1.3. Thyroid hormone receptors in corpora cavernosa

All isoforms of TRs, i.e. α_1, α_2 and β_1 are expressed in rat and human penis (Table 1). In particular, $TR_{\alpha1}$ and $TR_{\alpha2}$ are present from perinatal to adult age, while the β_1 form is almost entirely absent in fetal cells while present in the adult. Immunohistochemistry experiments using an anti-$TR_{\alpha1}$ antibody demonstrated a widespread staining for this TR in both endothelial and muscular cells of the corpora cavernosa and corpus spongiosum of the human adult penis (Carosa et al., 2010).

3.2. Female

3.2.1. Thyroid hormone receptors in ovary

Thyroid function has been associated with female reproduction also in ancient medicine (Niazi et al., {Krassas, #9215)}, but only very recently to the female sexual function. Thyroid diseases have been associated with menstrual disturbance, miscarriages and infertility (Dittrich et al., 2011; Romano et al., 1991) (Table 2). Several studies have demonstrated the presence of TRs in all ovary cell types. $TR_{\alpha1}$ and β_1 are expressed in primordial, primary and secondary follicles (Aghajanova et al., 2009), and they are also present in follicular fluid and in granulosa cells (Aghajanova et al., 2009; Wakim et al., 1993, 1994b). Mature oocytes from women undergoing IVF express $TR_{\alpha1}$, $TR_{\alpha2}$, $TR_{\beta1}$, and $TR_{\beta2}$ mRNA, thus supporting the hypothesis that T_3 has a direct effect on the human oocyte (Stavreus Evers, 2012; Zhang et al., 1997). Furthermore, the corpus luteum of rats, cows and rabbits shows immunostaining for all isoforms of TRs (Aghajanova et al., 2011; Fedail et al., 2014;

Table 1
Thyroid hormone nuclear receptors (TRs) Expression in male genital tissues.

Tissue/Cell Type	Receptor isoform	Expression		References
		Fetal/Pre- pubertal	Adult	
Whole testis	$TR_{\alpha1}$	++	+	(Jannini et al., 1999) (Buzzard et al., 2000; Jannini et al., 2000)
	$TR_{\alpha2}$	++	++	(Buzzard et al., 2000; Jannini et al., 1999; Jannini et al., 2000)
	$TR_{\beta1}$	±	−	(Buzzard et al., 2000; Jannini et al., 2000)
Sertoli cells	$TR_{\alpha1}$	++	++	(Buzzard et al., 2000; Jannini et al., 2000)
	$TR_{\alpha2}$	?	?	
	$TR_{\beta1}$	?	±	(Palmero et al., 1995)
Leydig cells	$TR_{\alpha1}$	?	±	(Buzzard et al., 2000)
	$TR_{\alpha2}$	?	?	
	$TR_{\beta1}$	?	?	
Germ cells	$TR_{\alpha1}$	?	+	(Buzzard et al., 2000)
	$TR_{\alpha2}$	?	?	
	$TR_{\beta1}$	?	±	(Buzzard et al., 2000)
Epididymis	$TR_{\alpha1}$	?	+	(De Paul et al., 2008)
	$TR_{\alpha2}$	?	?	
	$TR_{\beta1}$	?	+	(De Paul et al., 2008)
Penis	$TR_{\alpha1}$	++	++	(Carosa et al., 2010)
	$TR_{\alpha2}$	++	++	(Carosa et al., 2010)
	$TR_{\beta1}$	−	++	(Carosa et al., 2010)

Table 2
Thyroid hormone nuclear receptors (TRs) expression in female genital tissues.

Tissue/Cell type		Receptor isoform	Expression	References
Ovary	Stroma	$TR_{\alpha1}$	++	(Rodriguez-Castelan et al., 2017) (Aghajanova et al., 2009; Wakim et al., 1994b)
	Epithelium	$TR_{\alpha2}$	++	(Rodriguez-Castelan et al., 2017)
	Primary follicle	$TR_{\beta1}$	++	(Aghajanova et al., 2009; Rodriguez-Castelan et al., 2017) (Wakim et al., 1994b)
	Corpus luteus	$TR_{\alpha1}$	++	(Rodriguez-Castelan et al., 2017) (Stavreus Evers, 2012) (Navas et al., 2014) (Stavreus Evers, 2012)
		$TR_{\alpha2}$	++	
		$TR_{\beta1}$	++	
Oviduct		$TR_{\alpha1}$	++	(Rodriguez-Castelan et al., 2017)
		$TR_{\alpha2}$	++	
		$TR_{\beta1}$	++	
Uterus	Endometrium	$TR_{\alpha1}$	++	(Rodriguez-Castelan et al., 2017) (Aghajanova et al., 2011) (Stavreus Evers, 2012)
		$TR_{\alpha2}$	+	(Aghajanova et al., 2011)
		$TR_{\beta1}$	++	(Rodriguez-Castelan et al., 2017) (Aghajanova et al., 2011) (Aghajanova et al., 2011) (Stavreus Evers, 2012)
	Myometrium	$TR_{\alpha1}$	+	(Rodriguez-Castelan et al., 2017) (Hulchiy et al., 2012)
		$TR_{\alpha2}$	+	(Rodriguez-Castelan et al., 2017)
		$TR_{\beta1}$	+	(Rodriguez-Castelan et al., 2017) (Hulchiy et al., 2012)
Vagina	Epithelium	$TR_{\alpha1}$	++	(Rodriguez-Castelan et al., 2017)
	Smooth muscle	$TR_{\alpha2}$	++	
	cells	$TR_{\beta1}$	+	
Clitoris	Smooth muscle	$TR_{\alpha1}$	++	(Rodriguez-Castelan et al., 2017)
	cells	$TR_{\alpha2}$	++	
	Corpus cavernosum	$TR_{\beta1}$	++	

Rodriguez-Castelan et al., 2017). Positive staining of ovarian stromal cells and in ovarian surface epithelium was also observed for both $TR_{\alpha1}$ and β_1 (Aghajanova et al., 2009; Wakim et al., 1994a).

3.2.2. Thyroid hormone receptors in oviduct

Papers that have studied the presence of TRs in oviduct are scarce. The presence of $TR_{\alpha1}$ was described in the epithelium and smooth musculature of ampulla and isthmus in rat (Navas et al., 2014) (Table 2). Recently, the expression of all TR isoforms was shown in the luminal and glandular epithelium and in smooth muscle cells of whole oviductal regions in rabbit (Rodriguez-Castelan et al., 2017).

3.2.3. Thyroid hormone receptors in uterus

Extensive studies were conducted in uterus during the normal menstrual cycle (Aghajanova et al., 2011) and during pregnancy (Stavreus Evers, 2012). The localization of $TR_{\alpha1}$ and $TR_{\beta1}$ has been found in the luminal epithelium, glandular epithelium and stroma of human endometrium throughout menstrual cycle (Aghajanova et al., 2011), however no staining was present for the α_2 isoform (Table 2). Despite the fact that the presence of binding sites for T_3 in the myometrium was shown in 1983 (Kirkland et al., 1983), only in recent years has $TR_{\alpha1}$ been described in the myometrium from macaques (Hulchiy et al., 2012), rats (Navas et al., 2014), and rabbits (Rodriguez-Castelan et al., 2017).

3.2.4. Thyroid hormone receptors in vagina

The presence of TRs in the vagina has been studied very recently (Rodriguez-Castelan et al., 2017) (Table 2). Both the vaginal epithelium and the smooth and striated musculatures of all portions of the vagina were positive for $TR_{\alpha1\text{-}2}$ and β_1. Notably, the positive immunostaining for all TR isoforms are found in smooth muscle cells of the corpus cavernosum of the clitoris and the epithelial cells of the Skens's gland, both involved in the female pleasure (Jannini et al., 2014). This finding is interesting because it reveals an additional connection between male and female

genitalia. Indeed, the presence of TRs in the erectile tissues of men and women could emphasize a similar involvement of T_3 action in the sexual function of both genders.

3.3. Brain

The brain may also be considered a sexual organ for regulating sexual desire and arousal (Ciocca et al., 2016). TH actions in the brain are extremely complex because they are fundamentals for brain development (Moog et al.). Indeed, hypothyroidism during fetal life is associated with cretinism, a severe form of mental retardation (Bernal, 2007). The expression of TRs in the brain has been extensively studied in mammalians: in mouse brain, TRs α and β isoforms are expressed in almost all parts of the brain with an overlapping distribution. Some differences between α and β isoform expression are observed in the hippocampus, amygdala and hypothalamus (Fig. 3) (Bernal, 2000).

In the human brain, TR mRNAs are detected at around 8 weeks of gestation (Iskaros et al., 2000). Concerning the receptor protein, there is only one study in which receptor concentrations were quantitated by ligand-binding assays (Bernal and Pekonen, 1984). The receptor protein concentration was found to be very low at 10 weeks of gestation, and increased by a factor of 10 up to the 16th week, coinciding with the period of neuroblast multiplication. During this time, the brain gains in weight and DNA content by about five-fold, so that the total brain T_3 receptor content increases 500 times. This coincides with the period of active neuroblast proliferation (Dobbing and Sands, 1970). In neural cell cultures, T_3 receptors have been detected in neurons, astrocytes and oligodendrocytes (Luo et al., 1986; Yusta et al., 1988).

4. Thyroid and sexual function in male

The association between thyroid diseases and sexual dysfunction in men has not been systematically studied until recently. Indeed, in the last 10 years, an increasing number of studies have correlated different aspects of sexual performance and thyroid functions. The first report that demonstrated a close correlation between specific sexual disorders in males with thyroid hypo- and hyperfunction was published in 2005 (Carani et al., 2005). In this study four major sexual alterations – HSDD (hypoactive sexual desire disorder), PE (premature ejaculation), DE (delayed ejaculation), and ED (erectile dysfunctions) – were associated with hyper- or hypothyroid status (Fig. 4). The main sexological complaint found in that study in hyperthyroid patients was PE, whereas in hypothyroid subjects, it was DE. Remarkably, both ejaculatory dysfunctions very frequently reverted upon

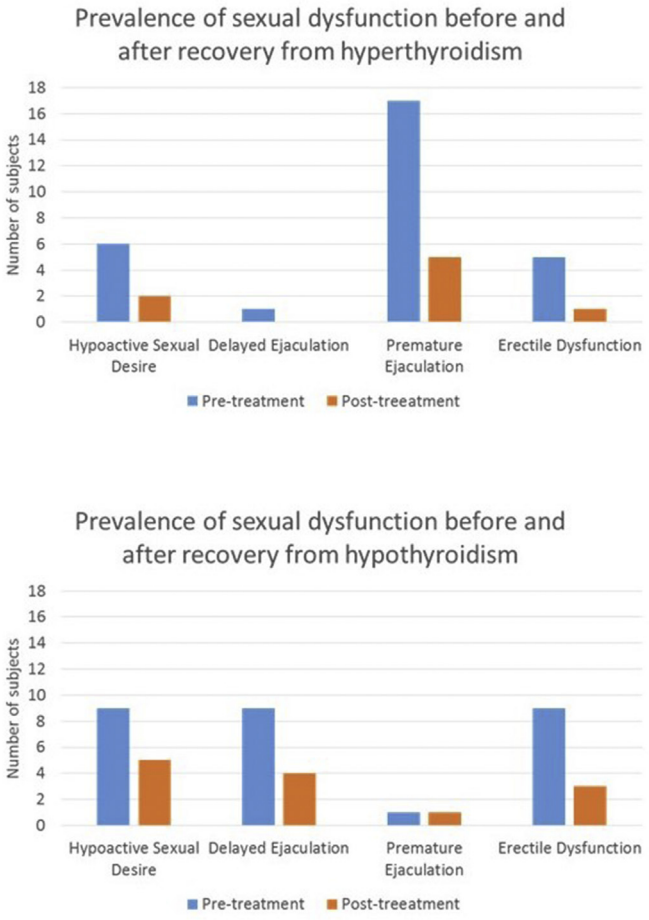

Fig. 4. Prevalence of sexual dysfunction in men with thyroid diseases. Modified from Carani et al. (2005).

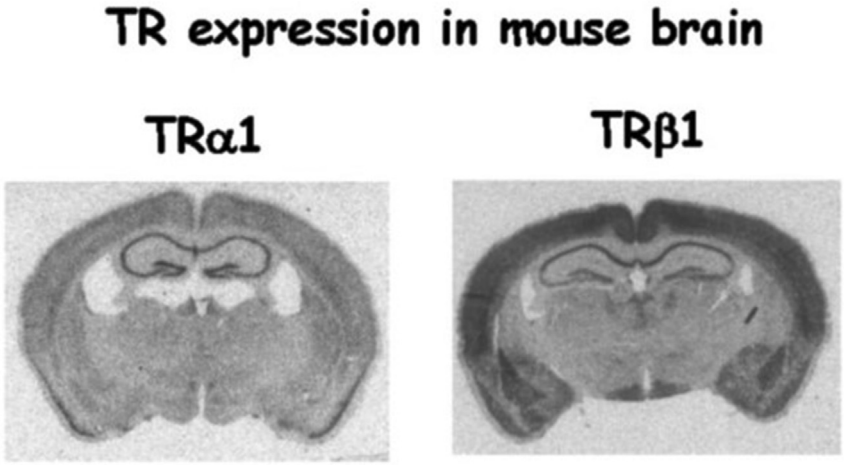

Fig. 3. TRs expression in mouse brain (Bernal, 2000). This image has been made freely available under a Creative Commons (CC-BY-NC-ND) license. A copy of the license can be viewed at http://creativecommons.org/licenses/by-nc-nd/2.0/.

achievement of euthyroidism in the absence of any other treatment for the sexual symptom. Although these can be considered secondary effects of treatment on mood, such a response on PE and DE was beyond all expectations, suggesting a direct involvement of thyroid hormones on the physiology of ejaculation. Now, it is known that TRs are located in the male genitals (Carosa et al., 2010), so it can be hypothesized a direct T_3 effect on erectile tissues and smooth muscle cells of the genital tract. Nevertheless, the molecular mechanisms involved in the T_3 action at this level remain unclear. Below we report all the evidences published to date about the influence of T_3 on the various aspects of male sexual function.

4.1. Thyroid and ejaculation

Several studies have confirmed the strong association between DE and PE with hypothyroidism and hyperthyroidism (Carani et al., 2005; Cihan et al., 2009a; Corona et al., 2011, 2012a, 2006b), respectively. This connection has been widely documented both in animal models and humans (Cahangirov et al., 2011; Cihan et al., 2009b). Cahangirov el al. (Cahangirov et al., 2011) demonstrated that hyperthyroidism in rats increases seminal vesicle contraction frequency and bulbospongiosus muscle contractile activity, which indicates that hyperthyroidism can affect ejaculatory emission and expulsion phases. In that study, after a 28-day washout period (to determine spontaneous recovery from hyperthyroidism) the aforementioned alterations were reversed, confirming the direct role of THs in the control of ejaculation. These results have been replicated in several clinical studies in human patients (Carani et al., 2005; Cihan et al., 2009a). In a series of 755 consecutive men seeking medical care for sexual dysfunction, including PE, the prevalence of suppressed thyroid-stimulating hormone (TSH), which is a marker of possible hyperthyroidism, was twofold higher in patients with PE than those reporting normal ejaculatory timing (Corona et al., 2004). A recent study in a Turkish population essentially confirms an association between the hyperthyroid state and PE, which was substantially ameliorated by therapy for the thyroid disease (Cihan et al., 2009a). However, and not surprisingly, Waldinger did not find any association between TSH levels and intravaginal ejaculation latency time (IELT) in a cohort of Dutch subjects (Waldinger et al., 2005) with lifelong PE, which logically suggests that the association with hyperthyroidism is restricted to the acquired type of PE. In light of all these reports, hyperthyroidism should be considered a novel and reversible etiological risk factor for PE, and TH disorders should be suspected, by simple physical examination, in the case of ejaculatory disorders (Jannini et al, 2011, 2015; McMahon et al., 2013; Sansone et al., 2015).

We found high prevalence of DE in hypothyroid patients, 64.3% (Carani et al., 2005) (Fig. 4). Furthermore, TSH levels were positively related to reported ejaculatory latencies (Corona et al., 2011). In patients with hypothyroidism, a resolution of DE was obtained in half of the subjects after thyroid hormone normalization (Carani et al., 2005) (Fig. 4). The view that thyroid hormones regulate the ejaculatory reflex is emerging and hypothyroidism should be ruled out in each patient with DE as recommended by International Society of Sexual Medicine (ISSM) guidelines (Corona et al., 2016). Hence, the view that thyroid hormones regulate the ejaculatory reflex is consistently emerging (Di Sante et al., 2016).

4.2. Thyroid and erectile dysfunction

Anecdotal reports suggest that ED is frequent (up to 70%) in men with hyperthyroidism (Meikle, 2004). Small studies in Italian and Greek patients with thyroid dysfunction found that both hypothyroidism and hyperthyroidism can be associated with ED and that the correction of the underlying thyroid conditions frequently restores erectile function (Fig. 4) (Carani et al., 2005) (Krassas et al., 2008). In Krassas et al.'s replication study (Krassas et al., 2008), 63% and 70% of the hypo- and hyperthyroid subjects, respectively, have some form of ED compared with 34% of the control group. While the prevalence of ED in hypothyroidism was similar in previous Carani et al.'s study (64% Carani et al., 2005), the reported number of hyperthyroid subjects with a pathological score of International Index of Erectile Function (IIEF) was lower (15%). In contrast, Veronelli et al. (2006) showed that 59% of men with thyroid problems had ED; interestingly, this result did not change when adjusted for age, suggesting that TH were more important than age in ED. A more recent study (Krysiak et al., 2017) documented that men with overt hypothyroidism obtained lower scores in all five domains of IIEF, while men with subclinical hypothyroidism only in erectile function domain. L-thyroxine treatment improved erectile function and normalized intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction in the formed group, as well as normalized erectile function in the latter. To date, no information on the prevalence of thyroid dysfunction in ED men is available either for the general population or for men seeking medical help for sexual problems. Further research is required to understand the nature of the link between thyroid disorders and ED; for now we can only emphasize that both α and β TRs have been described in rat and human corpora cavernosa endothelial and smooth muscle cells (Carosa et al., 2010; Owen et al., 2007). Studies in animal models of hyperthyroidism indicate an impairment of nitric oxide (NO)-dependent relaxation of corpora cavernosa (Hu et al., 2009; Ozdemirci et al., 2001). In rabbit corpora cavernosa strips, both acetylcholine- and electrical field stimulation-induced relaxation were impaired, whereas sensitivity to a NO donor, sodium nitroprusside, was unchanged (Ozdemirci et al., 2001). These data suggest an effect of thyroid hormones in penile NO formation, which has been demonstrated in a rat model (Hu et al., 2009). It is therefore possible that hyperthyroidism-associated ED could be due to a direct effect of TH on their cognate receptors.

4.3. Thyroid and hypoactive sexual desire

We found that low sexual desire may be related to hypothyroidism and can be normalized by TH therapy (Carani et al., 2005) (Fig. 4). The underlying pathogenic mechanisms have not been completely clarified. It is possible that a hypothyroidism-induced prolactin rise could mediate these negative effects on sexual desire. However, a direct role of THs on the central nervous system can also be hypothesized. THs are known to interfere with the functions of the reproductive axis in men (Bagamasbad and Denver, 2011; Krassas et al., 2010), which in turn might contribute to sexual dysfunction. Furthermore, hyperthyroidism-induced increase of sex hormone binding globulin (SHBG), which binds androgens with higher affinity than estrogens, might lead to a relative hyperestrogenism, which, per se, can alter sexual responses. In addition, the increase of prolactin that is often present in association with hyperthyroidism can be associated with a decrease in libido. All these findings demonstrate a non-controversial role of THs in human sexual dysfunction. (Maggi et al., 2013).

5. Thyroid and sexual function in female

While in male are relatively rare, thyroid hypo- and hyperfunctions are frequent in female. Thus, it is very surprisingly that the incidence of sexual dysfunction in women with hypo- or hyperthyroidism is still unknown. Thyroid disorders in women are, in fact, commonly associated with abnormalities of reproductive physiology such as menstrual irregularities and infertility (Krassas, 2000), but sexual function has been rarely studied. For instance, the

prevalence of menstrual disturbances in women with hypothyroidism has been estimated at 25–70%; ovulatory function and fertility are also affected (Bhasin et al., 2007). Both hyper- and hypothyroidism are associated with fatigue, myalgias, and mood disturbances such as irritability and depression, which can contribute to sexual dysfunction (Bhasin et al., 2007). Since the incidence of hypothyroidism also peaks at the age of menopause and perimenopausal symptoms could overlap with symptoms of hypothyroidism, screening for hypothyroidism in women at this age is generally recommended (Shifren and Gass, 2014). Indeed, persistent primary hypothyroidism is occasionally associated with hyperprolactinaemia, due to the stimulatory effect of the thyrotropin-releasing hormone (TRH) on the production of prolactin (Oppo et al., 2011). Thyroxine replacement therapy with a return to the euthyroid state restores menstrual and ovulatory function in most hypothyroid and hyperthyroid women, and also normalizes prolactin levels in those with coincident hyperprolactinaemia (Krassas, 2000). Few studies have investigated sexual function in women during thyroid diseases. In 2010, Atis et al. reported that women with hyperthyroidism and hypotyroidism have significantly lower female sexual function index (FSFI) domain scores compared with age-matched healthy women (Atis et al., 2010, 2011) (Table 3 and Fig. 5). According to the proposed FSFI full-scale cut-off level of 26.55 (Wiegel et al., 2005), 60% of women with hyperthyroidism in this study may have sexual dysfunction. One study conducted by Veronelli et al. revealed that diabetic, obese, and hypothyroidic women had a reduced score in the FSFI questionnaire when compared with healthy women (Veronelli et al., 2009). The same result was found by Oppo et al. (2011), who reported that abnormal thyroid function significantly impairs female sexual function, as assessed by the FSFI questionnaire, and that restoration of the euthyroid state is associated with a rapid improvement of most FSFI domain scores (Oppo et al., 2011). In addition, Oppo showed that restoration of biochemical euthyoidism was associated with normalization of the desire, satisfaction and pain domains, while arousal/lubrication and orgasm remained significantly different from healthy euthyroid controls, in spite of some improvement in orgasm.

Hyperthyroidism has been anecdotally connected in the mind of several endocrinologists with an increase in women's sexual desire. This is not the case in all studies reported, which mirrors findings of our report in males (Carani et al., 2005) and provides objective evidences that untreated thyrotoxicosis is associated with important female sexual dysfunction.

The finding that opposite endocrine conditions are associated with similar sexual dysfunctions may appear surprising, but the mechanisms involved in determination of sexual dysfunction in women are complex (Ghizzani et al., 2003; Graziottin, 2003; Jannini and Lenzi, 2003), and the role of altered thyroid status in female sexual functions is still unclarified. However, all these studies provide clear evidence that hyper- and hypothyroidism markedly impair sexual function in both women as in men (Oppo et al., 2011; Pasquali et al., 2013). Nevertheless, in women, in whom thyroid diseases are more frequent than in men, sexual function screening should be required (Balercia et al., 2007).

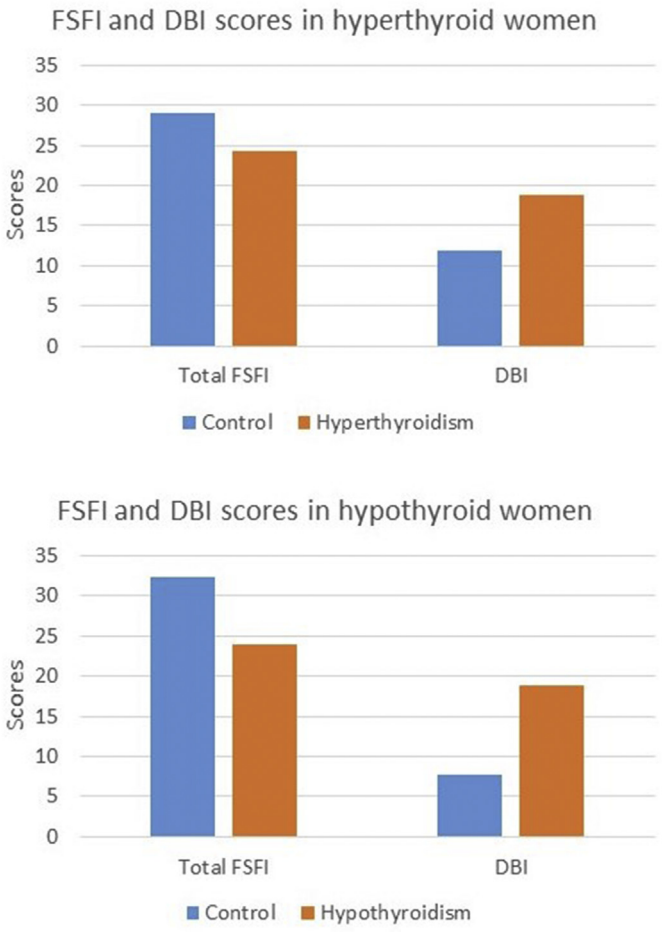

Fig. 5. Female Sexual Functions Index (FSFI) and Beck's Depression Inventory (DBI) questionnaire scores in women with thyroid diseases. Modified from (Atis et al., 2010); (Atis et al., 2011).

Emerging data suggests that, in women, sexual dysfunctions may be associated with thyroid autoimmunity, both in the presence of hypothyroidism and subclinical hypothyroidism (Krysiak et al., 2016; Pasquali et al., 2013).

Autoimmunity thyroiditis diseases are common in women. Actually, Hashimoto's thyroiditis is one of the most common human disorders, as well as the most frequent cause of hypothyroidism in developed countries (Caturegli et al., 2007). Several studies showed that women with autoimmune thyroiditis,

Table 3
FSFI (Female Sexual Functions Index) and BDI (Beck's Depression Inventory) questionnaire scores, modified from Atis et al., (2010), 2011.

	Control group	Hyper-thyroid	*P*	Control group	Hypo-thyroid	*P*
Total FSFI	29 ± 10.4	24.2 ± 9.9	*>0.02*	32.31 ± 3.5	23.92 ± 5.18	*>0.02*
Desire	4.3 ± 2.3	3.8 ± 2.1	*>0.05*	5.16 ± 0.74	4.01 ± 0.93	*>0.02*
Arousal	4.7 ± 2.2	3.4 ± 2.3	*>0.02*	5.37 ± 0.80	3.28 ± 1.30	*>0.02*
Lubrification	5.1 ± 1.6	4.3 ± 1.9	*>0.02*	5.40 ± 0.52	4.24 ± 0.82	*>0.02*
Orgasm	5.1 ± 1.5	4.0 ± 2.2	*>0.02*	5.46 ± 0.51	3.95 ± 1.23	*>0.02*
Satisfaction	4.9 ± 2.0	4.2 ± 1.9	*>0.02*	5.40 ± 0.54	4.06 ± 0.96	*>0.02*
Pain	5.0 ± 2.6	4.4 ± 2.3	*>0.02*	5.50 ± 0.56	4.37 ± 1.14	*>0.02*
BDI	11.9 ± 13.2	18.9 ± 15.4	*>0.02*	7.82 ± 5.20	12.8 ± 7.40	*>0.05*

compared with age-matched healthy controls, reported a significant increase in the prevalence of sexual dysfunction and displayed a significant decrease in sexual desire (Krysiak et al., 2016; Pasquali et al., 2013). In this respect, the availability of a shortened form of the FSFI questionnaire (Isidori et al., 2010) in all endocrine outpatient facilities would be useful to screen women with thyroid diseases. However, *mutatis mutandis*, it should be useful to screen all women complaining of sexual dysfunction for the presence of thyroid hypofunction and thyroid autoimmunity.

6. Thyroid and sexual behavior

Thyroid hormone regulates various developmental and pivotal physiological processes such as brain development. In effect, thyroid diseases are associated with altered mental processes in humans. Deficiency in TH activity during the perinatal period causes cretinism. Hypothyroidism in adults, although less dramatic, also induces cognitive dysfunction (concentration, memory psychomotor speed) and alterations in mood, with increased rates of depressive and anxiety symptoms (Bauer et al., 2008; Heinrich and Grahm, 2003; Sait Gonen et al., 2004). Certainly, mood alteration correlated to thyroid dysfunction may partly justify the alterations of sexual functions found in hyper- and hypothyroid patients, mainly with respect to sexual desire. Several studies conducted in animals have revealed that THs supported estrogen in the control of sexual behavior (Bagamasbad and Denver, 2011). Estrogen plays a critical role in reproductive development, physiology and sexual behavior, acting in the brain, in particular in the hypothalamus. The interplay between TH and estrogen actions on this brain region may provide a mechanism for assessing metabolic state, thus affecting reproductive physiology and behavior. For example, in birds and mammals, TH promotes the transition to anestrus. In some mammals, exposure to cold temperatures affects reproductive behavior, and increases plasma TH levels, suggesting the presence of cross-regulation between TH and estrogen (Vasudevan et al., 2002). Molecular data have implicated that TR, specifically $TR_{\alpha 1}$, inhibit estrogen-dependent gene expression in the hypothalamus (Vasudevan et al., 2002). Thyroid hormone administration inhibited lordosis behavior in estrogen-primed female mice (Morgan et al., 2000) and rats (Dellovade et al., 1996) (Fig. 6). Surprisingly, it has been shown that female mice knockout for $TR_{\alpha 1}$ (α1KO) showed poorer lordosis than wildtype (α1WT), while female knockout for TR_{β} (βKO) showed greater lordosis than wildtype females (βWT) (Dellovade et al., 2000) (Fig. 6). In agreement with those data, estrogen replacement plus TH treatment decreased lordosis behavior in ovariectomized (OVX) rats and mice, compared to estrogen replacement alone (Dellovade et al., 1996; Morgan et al., 2000). Similarly, thyroid-intact, OVX female rats that received estrogen replacement showed delayed onset of lordosis behavior compared to animals that were thyroidectomized, OVX + estrogen (Dellovade et al., 1996), suggesting that the actions of TH on sexual behavior are complex. Furthermore, the $TR_{\alpha 1}$ isoform subtly decreases the sexual behavior of gonadal-intact male mice (Vasudevan et al., 2013) (Fig. 6). Several studies on estrogens regulated gene promoters demonstrated that $TR_{\alpha 1}$ can decrease the transcriptional activation mediated by the estrogen receptor isoforms; this interaction may modulate sexual behavior in mice (Dellovade et al., 1996; Morgan et al., 2000 Dellovade et al., 2000).

The role of sexual hormones in arousal has been defined in humans. In the brain, estradiol synthesis increased in areas related to sexual arousal. Furthermore, it has been described that estrogen can sustain libido acting in the preoptic area and in the anterior hypothalamus (Schulster et al., 2016). Actually, in men the levels of aromatase are highest in those brain areas, where the estrogen receptors are expressed. However, the exact role of estrogens in male sexual function, including libido, is difficult to determine (Carani et al., 1997; Schulster et al., 2016). In male mice, a lack of estrogen receptors is associated with the reduction or abolition of sexual behavior (Ogawa et al, 1997, 2000).

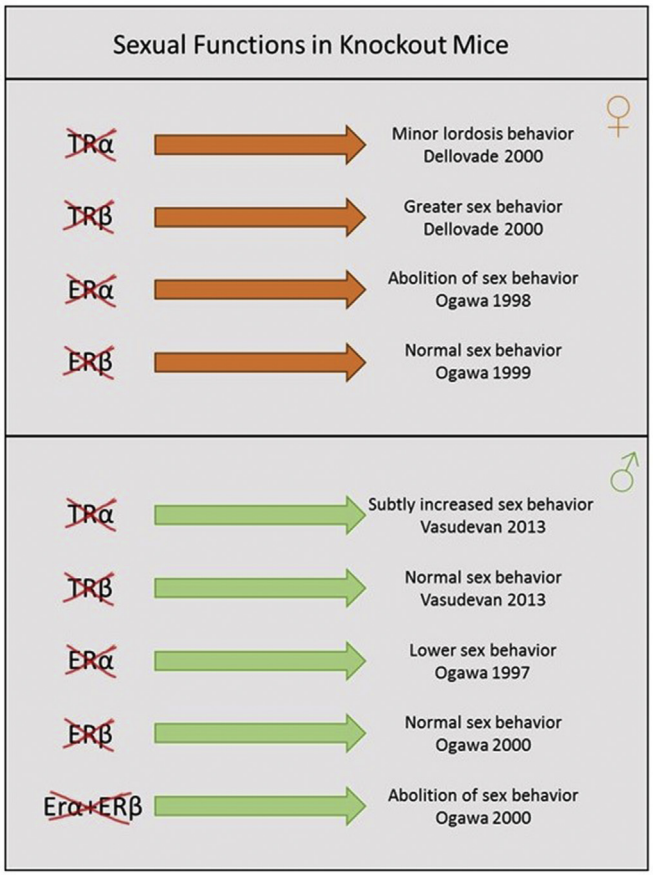

Fig. 6. Sexual behavior in female and male KO mice. Data are collected from: (Dellovade et al., 2000; Ogawa et al, 1997, 1998, 1999, 2000; Vasudevan et al., 2013).

The above-mentioned data showed that the alteration of thyroid function in men and women is associated with reduced sexual desire. Animal studies show us an interaction between THs and estrogen for sexual function regulation in the brain (Fig. 6). It is possible to hypothesize that the genesis of HSDD in men and women with thyroid diseases can be mediated by the action of THs on estrogen regulated genes in the hypothalamus (Schulster et al., 2016).

7. Thyroid and sexual orientation

Several experimental findings suggest that in human sexual orientation genes and hormones play a pivotal role (Jannini et al., 2010). A recent population-based study on > 5000 Danish homosexuals found a significantly higher frequency of Graves' disease when compared to general population, also when excluding men with HIV or AIDS (Frisch et al, 2014). This has been related to possible genetic/prenatal mechanisms linking the risk of Graves' disease with possible genes or genetic markers related to homosexuality carried on the X chromosome (Hu et al., 1995). Interestingly, the mothers of homosexual men are characterized by high frequency of extreme skewing of X-inactivation (Bocklandt et al., 2006), a similar high frequency that has been reported in females with the autoimmune thyroid disease (Brix et al., 2005). The possible relationship between thyroid and sexual orientation is

further suggested by the evidence that homosexuals display lower body mass index than heterosexual men, independently of diet or exercise (Blanchard and Bogaert, 1996; Deputy and Boehmer, 2010; Frisch and Zdravkovic, 2010). Moreover, homosexual adolescents more likely have mothers with thyroid dysfunction during pregnancy than heterosexuals (Sabuncuoglu, 2015). More recently, a genome-wide association study of male sexual orientation on a primarily European ancestry sample of >1000 homosexual men identified several single nucleotide polymorphisms on chromosome 13, in the region on genes expressed in the diencephalon previously reported as differing in size in men by sexual orientation (LeVay, 1991) and on chromosome 14 in the thyroid stimulating receptor locus (Sanders et al., 2017) further indicating a possible connection between thyroid, thyroid derangements and a subset of men having sex with men.All together, these findings suggest that the relationship between genes, thyroid function and male homosexuality would provide, if confirmed by more robust data, new interesting insights in the biology of male sexual orientation.

8. Conclusion

Many evidences show that alterations in thyroid function can affect both male and female sexual function. The presence of TRs in genitals provide the basis on which to hypothesize a direct effect of THs on sexual functions. However, the effect of THs is not only confined to genitals. In fact several data showed, as in the brain, THs may affect estrogens in the triggering of desire and libido. More studies are required to better delineate the real impact of thyroid in sexual function. Currently, it can be concluded that, despite the apparent, relative disinterestedness of the large majority of clinical endocrinologists dealing with thyroid diseases, demonstrated by a lack of use of psychometric tools designed to discover the presence of a sexual dysfunction (Corona et al., 2006a). THs strongly affect the human sexual function at various levels and that the thyroid gland must be considered, along with the genitals and the brain, a sexual organ.

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