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The Kisspeptin System as Putative Target for Endocrine Disruption of Puberty and Reproductive Health

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Abstract The activation of the reproductive axis at puberty and its proper function later on life are founded on a complex series of maturational events that include the sexual differentiation of the brain during early *critical* periods of development. Brain sex differentiation is driven (mostly) by endogenous sex steroids, which are also important regulators of the neuroendocrine networks governing puberty onset. Accordingly, both phenomena might be sensitive to the disrupting actions of exogenous compounds with sex steroid-like activity that may pose long lasting consequences in terms of reproductive health. Kisspeptins, the products of the *Kiss1* gene that act via the receptor, GPR54, are neuropeptides produced at discrete neuronal populations within the hypothalamus with key roles in brain sex differentiation, puberty onset and fertility. A subset of Kiss1 neurons has been recently shown to co-express neurokinin B (NKB), another neuropeptide with important reproductive roles. Compelling evidence has mounted recently that Kiss1 neurons are subjected to sexual dimorphism and physiologically sensitive to the *organizing* and *activational* effects of sex steroids, as documented in rodents, sheep and primates (including humans). These features provide the basis for the potential endocrine disruption of reproductive maturation and function by xeno-steroids targeting the Kiss1 system. Indeed, solid, as yet fragmentary, evidence obtained in rodents and sheep suggests that hypothalamic expression of *Kiss1* and/or kisspeptin fiber distribution are altered following inappropriate exposures to synthetic estrogenic and/or androgenic compounds during critical periods of development. Of note, administration of androgenic and estrogenic compounds during such critical periods has been shown to alter also the hypothalamic expression of NKB in rodents and sheep. As a whole, the data summarized in this chapter document the sensitivity of Kiss1 system to changes in sex

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steroid milieu during critical periods of sexual maturation, and strongly suggest that alterations of endogenous kisspeptin tone induced by inappropriate early exposures to environmental compounds with sex steroid activity might be mechanistically relevant for disruption of puberty onset and gonadotropin secretion later in life. The potential additional interactions of xeno-hormones with related neuropeptide systems (including NKB) and other environmental modulators (such as the nutritional state) of the Kiss1 system merits future investigation.

Introduction

During the last two decades, considerable attention has focused on the potential adverse effects for humans and wild-life species of a variety of natural and synthetic compounds, with ability to mimic or interfere the biological activities of endogenous hormones, thereby *disrupting* the development and/or function of different endocrine axes (Toppari et al. 1996). These are globally named endocrine disrupting compounds (EDCs), and include different man-made chemicals and by-products, as well as plant compounds, with either estrogenic, androgenic or anti-androgenic activity (Kelce and Gray 1999; Sikka and Naz 1999; Tena-Sempere et al. 2000). By far, the greatest concerns for the potential adverse effects of EDCs have concentrated on their deleterious impact on reproductive health. Indeed, different epidemiological studies have documented the recent worsening of several reproductive parameters, ranging from decreased sperm counts to increased incidence of testicular cancer and genital malformations, in different species, including (prominently) humans (Guillette 2006; Norgil Damgaard et al. 2002; Skakkebaek et al. 2006). Although multifaceted, this phenomenon is likely to involve environmental factors, including increasing exposures to different EDCs.

Among the potential reproductive end-points of endocrine disruption, the direct adverse effects of EDCs on the developing gonads and genitalia have been predominantly scrutinized, mostly because of the clinical manifestations (decreased sperm production; increased frequency of gonadal cancer and genital malformations) indicated above. More recently, however, experimental evidence has begun to accumulate suggesting that some suspected forms of endocrine disruption in humans and other species, such as changes in the tempo of puberty and some forms of infertility, may originate from primary defects not in the gonads and/or genitalia but rather in the development and/or function of the central (hypothalamic) systems controlling the reproductive axis (Bourguignon et al. 2010; Diamanti-Kandarakis et al. 2009; Gore 2008a). In this chapter, we will critically review the compelling, although as yet scarce, experimental data suggesting that the Kiss1 system might be a prominent target for disruption of reproductive health by inappropriate exposures to EDCs with sex-steroid like activity. As a means to provide a mechanistic basis for such a possibility, we will first summarize briefly our current knowledge on the essential roles of this hypothalamic system in the control of key aspects of reproductive maturation and function, and will

recapitulate the available experimental evidence supporting its physiological modulation by sex steroids along the lifespan.

Endocrine Disruption of Central Elements of the Reproductive Axis: Lessons from Physiology

Attainment of reproductive capacity at puberty, and its maintenance during adulthood, is the final consequence of a complex series of maturation events that involve proper functional organization at early stages of development of the central (hypothalamic) circuitries responsible for the control of the pulsatile secretion of gonadotropin-releasing hormone (GnRH), the major driving signal of pituitary gonadotropin synthesis and release (Fink 2000; Gore 2008a; Tena-Sempere and Huhtaniemi 2003). A first key component of this developmental phenomenon is the process of sexual differentiation of the reproductive brain; an event which is closely related with, but genuinely different from, other sex-determination phenomena, such a gonadal and genital differentiation (Gore 2008a). An important feature of brain sex differentiation is that it is sexually dimorphic and mainly driven by sex steroids. Thus, in rodents, where the molecular basis of this phenomenon have been deeply scrutinized, it is known that the process of brain sex differentiation takes place during a critical developmental period from late embryonic to early postnatal age (Tena-Sempere et al. 2000), when key neuronal networks at the hypothalamus become *organized* in a permanent manner differentially in males and females (Gore 2008a; Morris et al. 2004).

Rodent data have firmly demonstrated that the major molecular signal responsible for brain *masculinization* is estradiol, locally produced at high levels by aromatization of testis-derived testosterone (Gore 2008a; MacLusky and Naftolin 1981; Morris et al. 2004). In the female, low estrogen input due to quiescent ovaries and high levels of circulating α-fetoprotein is the major determinant of brain *feminization* (Gore 2008a). Importantly, such early differentiation phenomena translate into relevant sexually-dimorphic features, such as the timing of puberty (Ojeda et al. 2006, 2010), as well as different behaviors and neuroendocrine secretory patterns later on life (Gore 2008a; Morris et al. 2004). A hallmark of such neurohormonal sexual dimorphism is the cyclic secretory activity of the GnRH/gonadotropin system, which is based on the capacity of estrogens, selectively in the female, to induce the pre-ovulatory surge of gonadotropins from puberty onwards (Christian and Moenter 2010; Gore 2008a).

Recent experimental evidence suggests that, in addition to earlier (perinatal) periods, puberty itself may represent a second critical window for neuroendocrine development, during which changes in sex steroid input might induce permanent functional alterations of different neuro-hormonal axes later in life (Evuarherhe et al. 2009). Indeed, important developmental effects of estrogen on key hypothalamic networks governing puberty onset have been recently documented during (pre)pubertal maturation in mice (see Sect. "The Kiss1 System: Essential Regulator

of Brain Sex Differentiation and Puberty"). In addition to such potential organizing effects, it is well known that the pubertal transition is characterized by substantial acute changes in the sensitivity and responsiveness of reproductive hypothalamic networks to the regulatory effects of sex steroids (Ebling 2005). These changes importantly contribute, together with gonadal-independent variations of the central excitatory and inhibitory inputs to GnRH neurons (Ojeda et al. 2006, 2010), to define the timing of puberty.

Considering the above physiological features, it is plausible that xeno-hormones with sex steroid-like activities may impact at central levels to interfere with proper sexual differentiation and/or later maturation of the reproductive axis (Bourguignon et al. 2010; Diamanti-Kandarakis et al. 2009; Gore 2008a, b; Navarro and Tena-Sempere 2008). Yet, despite recent progress in this area, the mechanisms and targets for such a potential disruption of the reproductive neuroendocrine systems remain incompletely characterized. In this context, the use of experimental animal models, mimicking inappropriate early exposures to compounds with sex steroid activity, has provided valuable information (Tena-Sempere et al. 2000), and may prove helpful for further dissection of the central effects and mechanisms of action of specific EDCs. Indeed, these models may represent a good complement to robust *in vitro* and *ex vivo* approaches, commonly used for the evaluation of single EDC effects on key components of the reproductive brain, such as GnRH neurons themselves (Bourguignon et al. 2010; Gore 2008a). Indeed, neuroendocrine analyses in rodents subjected to protocols of neonatal exposure to estrogenic compounds, such as estradiol benzoate (EB) and diethylstilbestrol (DES), have revealed that disruption of sexual differentiation of the hypothalamus is linked to altered puberty onset and disturbed gonadotropin secretion, both at basal conditions and after gonadectomy (Pinilla et al. 1995; Tena-Sempere et al. 2000). Likewise, protocols of early postnatal exposure of female rats to estradiol and the estrogenic EDC, dichlorodiphenyltrichloroethane (DDT), have documented alterations in hypothalamic GnRH secretion by hypothalamic explants *ex vivo* and LH responses to GnRH *in vivo* in infantile/juvenile rats (Rasier et al. 2007). These studies, among others [for an extensive review see (Bourguignon et al. 2010; Diamanti-Kandarakis et al. 2009; Gore 2008a), and references therein], set the scene for specific mechanistic analyses on the impact and mode of action of 'actual' EDCs on the hypothalamic systems controlling reproduction, some of which have been recently initiated (Bourguignon et al. 2010; Gore 2008a). The potential involvement of the hypothalamic Kiss1 system in this phenomenon is proposed, on the basis of the available literature, in the following sections.

The Kiss1 System: Essential Regulator of Brain Sex Differentiation and Puberty

The so-called Kiss1 system has been recently recognized as an essential regulator of the reproductive axis, which is indispensable for its timely activation at puberty and its proper function (and hence, fertility) during adult life (Oakley et al. 2009;

Roa et al. 2008). Remarkably, the elements of this ligand-receptor system were sequentially identified between late 1990s and early 2000s in a field totally unrelated with reproduction. Thus, the *Kiss1* gene was originally catalogued as metastasis suppressor, as it was found to encode a number of structurally-related peptides, globally termed kisspeptins, with ability to suppress tumor spread (Oakley et al. 2009; Roa et al. 2008). Already in 2001, kisspeptins were shown to conduct their biological actions via the G protein-coupled receptor, GPR54 (Kotani et al. 2001; Muir et al. 2001; Ohtaki et al. 2001). However, recognition of the reproductive dimension of this system only came in late 2003, when inactivating mutations of GPR54 were found in patients suffering idiopathic forms of hypogonadotropic hypogonadism (de Roux et al. 2003; Seminara et al. 2003); findings that were replicated and extended in mice bearing null mutations of *GPR54* or *Kiss1* genes (d'Anglemont de Tassigny et al. 2007; Seminara et al. 2003). These seminal observations boosted an enormous interest in the area and initiated an ever growing number of studies aiming to characterize the physiological roles and mechanisms of action of kisspeptins and GPR54 in the control of different facets of reproductive function. As a whole, these studies have firmly substantiated the pivotal functions of kisspeptins in the control of the reproductive brain in different mammalian and non-mammalian species (d'Anglemont de Tassigny and Colledge 2010; Oakley et al. 2009; Popa et al. 2008; Roa et al. 2008). While the rapid expansion of this area makes it impossible to comprehensively condensate the state-of-the-art in this particular field within the limits of this chapter, we provide in this section some brief description on the brain distribution and major mechanisms of action of kisspeptins, together with a summary of their putative roles in sex differentiation and puberty onset, as a means to introduce and to ease the comprehension of later sections of this review.

Recent neuroanatomical studies, carried out mostly in laboratory rodents, but also in sheep and primates (including humans), have identified discernible populations of Kiss1 neurons, and some of their projections, at the hypothalamus (Herbison 2008; Popa et al. 2008; Roa et al. 2008). In the rat and mouse, where extensive mapping of these neuronal populations has been published, hypothalamic Kiss1 neurons appear to concentrate mostly at two areas: the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV) (Popa et al. 2008); the latter population appears to extend as a continuum along the rostral peri-ventricular area of the third ventricle (RP3V) (Herbison 2008). Prominent groups of Kiss1 neurons have been also detected in the ARC (or the equivalent infundibular area) in sheep and primates (Oakley et al. 2009; Roa et al. 2008); species where the presence and eventual physiological roles of a rostral population of Kiss1 neurons is still under some debate. Similarly, while direct synaptic contacts have been described between Kiss1 and GnRH neurons (Clarkson and Herbison 2006), the neuroanatomical features of the projections of Kiss1 neurons originating from the ARC and the AVPV need further clarification.

A wealth of experimental evidence, accumulated during the last 5 years, has demonstrated that the primary mechanism whereby kisspeptins participate in the

control of the reproductive axis involves its ability to operate upon, and stimulate, GnRH neurons, which have been shown to express GPR54 (d'Anglemont de Tassigny and Colledge 2010; Oakley et al. 2009; Popa et al. 2008; Roa et al. 2008). In fact, the potent stimulatory effects of kisspeptins on luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion are blocked by pre-treatment with a potent GnRH antagonist, while kisspeptin administration is able to activate (as reflected by c-fos induction) GnRH neurons. Moreover, kisspeptins have been reported to induce very potent depolarization responses in GnRH neurons, as well as the release of GnRH by hypothalamic preparations *ex vivo* and to the Cerebrospinal Fluid (CSF) *in vivo* (d'Anglemont de Tassigny and Colledge 2010; Oakley et al. 2009; Popa et al. 2008; Roa et al. 2008). Admittedly, whether these stimulatory effects take place preferentially at GnRH neuronal perikarya (in the preoptic area) and/or nerve terminals (in the median eminence) is yet to be defined. Regardless of the actual site(s) of action on GnRH neurons, the potent stimulatory effects of kisspeptins on GnRH secretion result in robust LH and FSH responses, as documented in different mammalian species, even at very low doses (Oakley et al. 2009; Roa et al. 2008).

Indirect evidence for the potential involvement of the populations of Kiss1 neurons in the process of brain sex differentiation came from comparative neuroanatomical studies in male and female rodents and primates. Thus, *Kiss1* mRNA expression has been shown sexually dimorphic at the AVPV in rats, with females having higher expression than males (Kauffman et al. 2007). A similar dimorphism appears to exist also in humans, where the populations of Kiss1 neurons at the infundibular and periventricular regions are more abundant in the female (Hrabovszky et al. 2010). Whether Kiss1 neurons at the ARC are also sexually dimorphic in number in rodents is presently under investigation; although initial reports documented that *Kiss1* mRNA levels were similar between sexes, recent immunohistochemical studies suggested that kisspeptin content at this hypothalamic site is probably higher in female rats also. As a whole, the above data evidence that the populations of Kiss1 neurons undergo a program of sexual differentiation, likely during early stages of development, which enables sex-specific configurations of Kiss1 networks later in life. Such a neuronal set-up appears to be functionally relevant for the expression of sexually-dimorphic neuroendocrine traits later in life, such as the positive feedback of estrogen and the pre-ovulatory surge of gonadotropins. The importance of kisspeptin signaling in this phenomenon is reinforced by the fact that pharmacological blockade of kisspeptin actions results in elimination of the pre-ovulatory peak of gonadotropins in cyclic female rats (Pineda et al. 2010).

Likewise, kisspeptins play an essential role in the regulation of timing of puberty, as evidenced by a combination of genetic, physiologic and pharmacological analyses in rodents and primates (Tena-Sempere 2010b). These analyses have documented that the hypothalamic Kiss1 system undergoes a complex and sophisticated activation program during puberty, which seems to involve four major components: (a) the elevation in the endogenous kisspeptin tone at the hypothalamus (Navarro et al. 2004; Shahab et al. 2005), (b) the increase in the sensitivity to the

stimulatory effects of kisspeptins in terms of GnRH/LH responses (Castellano et al. 2006; Han et al. 2005), (c) the enhancement of GPR54 expression and signaling efficiency (Han et al. 2005; Herbison et al. 2010), and (d) the elevation of the number of kisspeptin neurons and of their projections to GnRH neurons (Clarkson et al. 2009; Clarkson and Herbison 2006). The physiological relevance of the above maturational changes for the proper timing of puberty is stressed by the observation that selective blockade of kisspeptin actions during the pubertal transition significantly delays puberty onset in female rats (Pineda et al. 2010).

The Kiss1 System: Sensitivity to the *Activational* and *Organizing* Effects of Sex Steroids

Shortly after the disclosure of its reproductive dimension, sex steroids (mainly, estradiol and testosterone) were recognized as important regulators of hypothalamic *Kiss1* gene expression during adulthood. This important regulatory role was first evidenced by experiments of gonadectomy, with or without sex steroid replacement, in rodents, and has been later confirmed in different mammalian species, including primates (Oakley et al. 2009; Roa et al. 2008). A similar regulatory action is operative also in humans, as demonstrated by studies on the changes in hypothalamic *Kiss1* mRNA levels in postmenopausal women (Rance 2009). While detailed description of this phenomenon exceeds the limits of this review, it is important to stress two major features related with the activational regulation of hypothalamic *Kiss1* expression by sex steroids: (a) their effects are, at least in rodents, clearly nucleus-specific, since sex steroids suppress *Kiss1* mRNA levels at the ARC, but estrogen enhances *Kiss1* expression at the AVPV; and (b) given the above differential regulation, the ARC Kiss1 pathway has been involved in the negative feedback control of gonadotropin secretion, whereas Kiss1 neurons at the AVPV may mediate the positive feedback effects of estrogen, which are responsible for the pre-ovulatory surge of gonadotropins (Oakley et al. 2009; Roa et al. 2008).

In addition to the above activational effects, compelling evidence has mounted recently that the developmental changes of the Kiss1 system, summarized in the previous section, are shaped to a large extent by the organizing and regulatory actions of sex steroids acting during critical periods of perinatal or postnatal development. This contention has been documented for the process of brain sex differentiation in rodents. Indeed, studies in rats and mice have substantiated that changes in sex steroid inputs to the developing brain during early critical periods of maturation alter the normal process of sexual differentiation of Kiss1 neuronal populations. Thus, neonatal exposure to high doses of androgen in female rats suppressed the expression of *Kiss1* mRNA at the AVPV in adulthood, when neonatally androgenized females displayed *Kiss1* mRNA levels similar to those of adult males, but much lower than in cyclic females (Kauffman et al. 2007). Conversely, neonatal orchidectomy in rats, which eliminated androgen secretion

(and hence, actions) during the critical period of brain sex differentiation, resulted in the feminization of *Kiss1*/kisspeptin expression at the AVPV, which was much higher than in control adult males (Homma et al. 2009). The functional relevance of the above changes is stressed by the observation that neonatally androgenized females were devoid of positive feedback actions of estrogen in adulthood (Kauffman et al. 2007), while neonatal orchidectomy resulted in the acquisition of positive feedback and surge-like LH responses to ovulatory doses of estradiol (Homma et al. 2009).

In addition to androgens, estrogen has been also documented as an important organizing signal for the hypothalamic Kiss1 system, acting during critical windows of development. Thus, neonatal estrogenization of female rats decreased the number of Kiss1 neurons at the AVPV and disrupted the positive feedback effects of estradiol (in terms of LH secretion) in adulthood (Homma et al. 2009). Similarly, neonatal exposures to synthetic estrogens, known to disturb proper activation and function of the gonadotropic axis (Tena-Sempere et al. 2000), persistently suppressed the hypothalamic expression of *Kiss1* gene at the expected time of puberty and adulthood in male and female rats (Navarro et al. 2004, 2009). In good agreement, studies in α-fetoprotein (AFP) knock-out mice, which are developmentally exposed to excessive estrogenic input due to the lack of this scavenger protein of circulating estrogens, have demonstrated that in the female such an excessive exposure to estrogen results in lower numbers of Kiss1 neurons and perturbs the ability of estradiol to induce pre-ovulatory-like LH surges and to activate Kiss1 neurons at the AVPV in adulthood (Gonzalez-Martinez et al. 2008). Admittedly, however, mechanistic interpretation of the above results is potentially confounded by the fact that this KO model does not allow proper discrimination between early organizing versus later activational actions of sex steroids.

Besides its organizing effects during early (perinatal) development, estrogen appears to be important also for shaping the expansion of the AVPV population of Kiss1 neurons in the female mouse during the pubertal transition, as documented by the effects of ovariectomy during the late infantile period (Clarkson et al. 2009). Likewise, in aromatase null (ArKO) mice, where transformation of androgen into estrogen is blocked, the pubertal increase of Kiss1 neurons at the AVPV was prevented (Clarkson et al. 2009), and kisspeptin-IR at this site was substantially reduced at adulthood (Bakker et al. 2010). As a whole, these data would imply that some sort of positive feedback of estrogen on the hypothalamic Kiss1 system may exist before puberty. It remains to be defined which level of estrogenic input is required for the (proper) pubertal activation of the Kiss1 system. Similarly, whether inappropriate exposures to sex steroid-acting compounds during the pubertal transition have long-lasting consequences in terms of configuration, and eventual function, of the populations of Kiss1 neurons at the hypothalamus awaits further investigation.

The Kiss1 System as Target of Endocrine Disruption: Experimental Evidence

As reviewed in previous sections, a large body of experimental data has accumulated in recent years to demonstrate that Kiss1 neurons at specific hypothalamic nuclei are putative components of the mechanisms of brain sex differentiation, and highly sensitive to the organizing actions of endogenous, and eventually exogenous, sex steroids. This phenomenon, which is of substantial physiological relevance, may pose also potential pathophysiological implications, as it provides the neurohormonal substrate for the perturbation of the development and function of the gonadotropic axis by the impact of EDCs on the developing Kiss1 system, acting at early, critical periods of maturation (Tena-Sempere 2010a). Admittedly, however, the available evidence is still fragmentary and mostly derived from analyses of standard models of perinatal estrogenization or androgenization in rodents, rather than '*real-life*' protocols of exposure to EDCs. Notwithstanding, considering the recommendation to enhance basic, mechanistic studies and to apply the precautionary principle in the field of endocrine disruption research (Diamanti-Kandarakis et al. 2009), a succinct critical review of the available evidence is provided below, as a means to pave the way for further analyses in this area.

In the rat, protocols of neonatal exposure to the synthetic estrogen, estradiol benzoate (EB), have been shown to induce a persistent decrease in hypothalamic expression of *Kiss1* gene at the time preceding puberty in male and female rats (Navarro et al. 2009). This phenomenon, which was also observed in adult animals submitted to neonatal exposure to EB (Navarro et al. 2004), was dose-dependent, with detectable effects in terms of suppressed *Kiss1* mRNA levels at a range of doses (1–10 μg; on d-1 postpartum) that is considered moderate as compared to standard protocols of neonatal estrogenization in rodents. Of note, hypothalamic *Kiss1* responses to gonadectomy (i.e., increase in its mRNA levels) were also blunted in neonatally estrogenized rats, suggesting that disturbed responses to negative gonadal feedback following early exposures to estrogenic compounds might involve also altered expression and/or function of the Kiss1 system (Navarro et al. 2009). In good agreement, neonatal exposures to EB resulted in significantly decreased kisspeptin fiber density in the ARC and AVPV in female rats at adulthood; effects that were partially mimicked by neonatal treatments of females with the selective ligand of estrogen receptor (ER)α, PPT, that decreased kisspeptin fibers at the ARC, and the phytoestrogen, genistein, which suppressed kisspeptin fiber density at AVPV in adulthood (Bateman and Patisaul 2008). Indeed, a recent study has demonstrated that neonatal exposure to a high dose of genistein, as it is the case also for EB, disturbs the normal pattern of postnatal expansion of kisspeptin fiber density at the AVPV (and the ARC) in female rats; neonatally treated rats having persistently lower numbers of kisspeptin fibers than controls along the pubertal transition (Losa et al. 2011).

In the same vein, neonatal exposure to the xeno-estrogen, bisphenol A (BPA), in rats significantly reduced hypothalamic *Kiss1* mRNA levels at puberty (Navarro

et al. 2009), as well as kisspeptin immunoreactivity at the ARC (as estimated in terms of fiber density) in adult female rats (Patisaul et al. 2009). Admittedly, however, the effects of BPA were detected at rather high doses and were not observed in males, which appeared less sensitive to the potential disrupting effects of this EDC (Patisaul et al. 2009). Also of note, recent, as yet preliminary, evidence obtained in mouse off-spring from mothers exposed orally to BPA suggest that, in some conditions, this xeno-estrogen might induce also up-regulatory actions on kisspeptin content at the hypothalamus. Indeed, such protocol of exposure to BPA has been reported to enhance kisspeptin expression of kisspeptin at the ARC and AVPV, especially in male mice; a response that partially obliterated the sexual dimorphism (females >> males) that is usually observed, in terms kisspeptin content, at the hypothalamus of adult rodents (Panzica et al. 2009).

In any event, it is important to stress that the impact of potential EDCs on the hypothalamic Kiss1 system has not been only documented in rodents but also in sheep. Thus, recent data demonstrated that in utero exposure of sheep to a complex cocktail of EDCs contained in sewage sludge, used as agricultural fertilizer in pastures and thus an optimal model for investigation of 'real-life' mixtures of ED, induced a significant decrease in *Kiss1* mRNA levels at the rostral, mid and caudal regions of the hypothalamus of exposed fetuses (Bellingham et al. 2009). Remarkably, no effect was observed when exposures were conducted during adulthood, thus emphasizing the notion that the Kiss1 system may be especially vulnerable to the disrupting actions of compounds with sex steroid activities when exposures take place during critical periods of maturation (Bellingham et al. 2009). As additional note, it is to be stressed that the above protocols of fetal sewage sludge exposures resulted also in reduced numbers of kisspeptin immunopositive cells at the pituitary (Bellingham et al. 2009). In this sense, expression and (activational) sex steroid regulation of Kiss1 and GPR54 mRNAs/proteins have been previously demonstrated in the rat pituitary (Richard et al. 2008). This observation raises the appealing possibility of additional sites, other than the hypothalamus, for the disrupting neuroendocrine effects of EDCs on the Kiss1 system. Admittedly, however, the physiological relevance of kisspeptin actions and regulation directly at the pituitary level is yet to be fully unfolded (Roa et al. 2008).

All in all, the data summarize above provide strong, as yet circumstantial, evidence for the possibility that inappropriate exposures to sex-steroid acting compounds during early critical windows of brain sex differentiation might have a *disorganizing* impact on the maturation of the hypothalamic Kiss1 system, with durable consequences that may manifest later in life (i.e., during puberty and adulthood). In keeping with such possibility, functional studies conducted in some of the above models have conclusively shown that the decreased pubertal expression of *Kiss1* gene following neonatal exposures to estrogenic compounds is associated to defective gonadotropin secretion (both in basal and post-gonadectomy conditions), which can be rescued by administration of exogenous kisspeptin (Navarro et al. 2009). Similarly, some of the above protocols of neonatal exposure to chemicals with estrogenic actions linked to decreased kisspeptin fiber density at certain hypothalamic nuclei in adult female rats caused also reduced GnRH

neuronal activation (Bateman and Patisaul 2008). Admittedly, however, defective activation of GnRH neurons has not been detected following neonatal exposures to other estrogenic compounds, such as BPA (Adewale et al. 2009). In any event, these functional data strongly suggest that by targeting the developing hypothalamic Kiss1 system, and thereby by presumably causing a decrease in the endogenous kisspeptin tone, compounds with sex steroid-like activities might interfere with normal maturation and later function of the reproductive axis. While the evidence supporting this possibility is compelling, it must be emphasized, as general call of caution, that most of the work conducted so far in this area has addressed putative mechanisms of disruption rather than the consequences of '*real-life*' exposures to complex mixtures of ED, presumably at low doses (Tena-Sempere 2010a).

Other Central (Related) Targets for Endocrine Disruption: A Case for NKB?

Although abundant physiologic evidence and growing pharmacological data support the contention that the hypothalamic Kiss1 system might be a potential target for endocrine disruption, there are strong experimental indications that EDCs may have an impact also upon other key elements of the reproductive brain, whereby they may contribute to alter basic neuroendocrine networks responsible for the proper maturation and function of the reproductive axis (Bourguignon et al. 2010; Diamanti-Kandarakis et al. 2009; Gore 2008a). While thorough recapitulation of such evidence is beyond the scope and aims of this review, it is important to stress that a wealth of data has documented the potential impact of different EDCs, such as dichlorodiphenyltrichloroethane (DDT), vinclozolin and certain polychlorinated biphenils (PCBs), as well as complex mixtures of EDCs (present in sewage sludge) on the development, neurosecretory function and even viability/apoptosis of the GnRH system in different species (Bellingham et al. 2010; Bourguignon et al. 2010; Dickerson et al. 2009; Rasier et al. 2007; Wadas et al. 2010), as assessed by a combination of *in vitro*, *in vivo* and *ex vivo* approaches. Of note, the effects of EDCs, such as DDT, on GnRH secretory function appears to be multifaceted, and involve the modulation of glutamate stimulation of GnRH neurons via multiple pathways (Bourguignon et al. 2010). In addition to GnRH neurons themselves, fragmentary evidence has suggested the impact of early exposures to putative EDCs on other hypothalamic pathways and signals, such as galanin, in sheep fetuses exposed to sewage sludge (Bellingham et al. 2010), and ocytocin, in female rats exposed neonatally to BPA (Adewale et al. 2011). As a whole, the above data illustrate the potential complexity of the neuroendocrine effects of EDCs, which may impact at different levels/elements of the reproductive brain. Elucidation of the complete set of targets for such compounds appears critical to provide an integral mechanistic insight into their mode of action and potential adverse effects upon the reproductive axis.

Very recently, NKB has emerged as co-transmitter and putative auto-regulator of the population of Kiss1 neurons located at the ARC/infundibular region in different species, including rodents, sheep and humans (Lehman et al. 2010). The functional relevance of NKB in reproductive control has gained momentum with the observation that humans with inactivating mutations in the genes encoding NKB (*TAC3*) or its receptor (*TACR3*) suffer hypogonadotropic hypogonadism (Topaloglu et al. 2009); hence, a phenotype similar to that of GPR54 null patients. In keeping with such a *positive* role in the control of the reproductive axis, very recent experimental data have documented the stimulatory effects of agonists of NKB on LH secretion in female rats, sheep and monkeys (Billings et al. 2010; Navarro et al. 2011; Ramaswamy et al. 2010); yet, lack of stimulatory effects or even inhibitory actions of NKB on gonadotropin secretion have been also reported in some species and physiological conditions. The demonstration that Kiss1 neurons at the ARC co-express and are targets of NKB (Lehman et al. 2010), together with its putative effects on the GnRH pulse generator (Wakabayashi et al. 2010), has led to the contention that NKB participates in the fine tuning of kisspeptin output at the hypothalamus, thereby playing a role in the regulation of pulsatile GnRH secretion. Given the close relationship with the Kiss1 system, the question arises as whether NKB might be an additional target for endocrine disruption of the reproductive brain.

Admittedly, the above issue has not been directly addressed since, to our knowledge, the impact of early exposures to EDCs on the developmental expression of NKB has not been reported to date. Yet, the physiological knowledge available strongly supports such a possibility. First, hypothalamic expression of NKB (mRNA/protein) at the ARC is under the regulation of sex steroids in adulthood, as documented in models of gonadectomy, with a clear parallelism between Kiss1 and NKB expression. Thus, in female rats, estrogen suppressed *NKB* (as well as *Kiss1*) mRNA expression, therefore suggesting a role in negative feedback control (Navarro et al. 2010). Even more interestingly from the perspective of endocrine disruption, NKB expression in the ARC appears to be sensitive to the organizing effects of sex steroids, as documented in the sheep and rodents. Thus, in the sheep, the expression of NKB is sexually dimorphic (with females having double the number of NKB neurons than males) and was markedly suppressed in the female by prenatal exposure to testosterone (Cheng et al. 2010). Similarly, in the rat, NKB neurons at the ARC are responsive to sex steroids at different developmental stages (including puberty), with an androgen-dependent sexual dimorphism in the postnatal ontogeny of NKB peptide expression, that increased earlier in females along pre-pubertal maturation (Ciofi et al. 2007). Similarly, our preliminary evidence suggests the neonatal estrogenization suppresses both kisspeptin and NKB immunoreactivity at the ARC in adulthood more prominently in females, and that LH responses to the NKB agonist, senktide, are sexually dimorphic in the rat, with stimulatory responses being detected only in adult females, but not in adult male rats (*our unpublished data*). In this context, the possibility that developmental exposures to sex steroid-acting compounds may have a durable impact on the organization of the hypothalamic NKB system is

plausible and merits specific investigation. Noteworthy, protocols of prenatal androgenization in the female sheep have been reported to suppress NKB expression, but not kisspeptin immunoreactivity, at the ARC (Cheng et al. 2010). Therefore, it is possible that, depending on the species, type of compound and developmental window of exposure, sex steroids compounds might variably affect the maturation and/or expression of Kiss1 and NKB systems, as putative mechanism for alteration of the reproductive brain.

Open Questions and Future Directions

As reviewed in previous sections, accumulating (although still limited) experimental evidence points out that the hypothalamic Kiss1 system may be a target for endocrine disrupting compounds with activity as estrogens or anti-androgens, acting at critical windows of development. While the physiological features of this system, as exquisitely responsive to sex steroids at different developmental stages and fundamental for proper puberty onset and fertility, make this possibility highly plausible, it must be stressed that most of the work conducted so far in this area has addressed putative mechanisms of disruption (i.e., if this phenomenon is biologically possible) rather than the consequences of 'real-life' exposures (i.e., whether this phenomenon is actually taking place). In other words, while it is tenable that EDCs may target the developing Kiss1 system, the pathophysiological relevance of such phenomenon in terms of reproductive health warrants additional experimental work, involving exposures to complex cocktails of EDC with similar or dissimilar modes of action, ideally at low doses, in line with very recent studies initiated in the sheep (Bellingham et al. 2009). Admittedly, most of the studies on the neuro-endocrine effects of EDCs have focused on their impact on different aspects of GnRH neuronal development and secretory function (Bourguignon et al. 2010; Diamanti-Kandarakis et al. 2009; Gore 2008a). In any event, identification of the potential impact of such compounds upon Kiss1 neurons may allow to revisit and to provide a mechanistic insight for previously documented neuroendocrine effects of some EDCs, which were reported prior to the recognition of the prominent reproductive roles of the Kiss1 system. For instance, it was described that neonatal exposures to genistein and BPA alter sexual differentiation of AVPV in rats (Patisaul et al. 2006); considering the prominent population of Kiss1 neurons at this site and its striking sexual dimorphism, it is worthy to explore whether alterations in the maturation of Kiss1 system are involved in this phenomenon. Similarly, specific mechanistic studies targeting the Kiss1 system need to be implemented as to provide the basis for some of the suspected clinical phenotypes of reproductive endocrine disruption. For instance, recent preliminary evidence suggests that early (gestational) exposures to BPA can up-regulate kisspeptin content at the hypothalamus in adult mice (Panzica et al. 2009); specific studies monitoring earlier changes (i.e., during the pubertal transition) might help to define whether and how a similar phenomenon might contribute to the trend of

advancement of the age of puberty in girls, especially if internationally adopted, as detected in different studies in Europe and USA (Bourguignon et al. 2010).

Another interesting question, from a mechanistic perspective, arising from the data summarized in previous sections is the molecular basis for the observed organizing changes detected in Kiss1 neurons following inappropriate exposures to sex steroid-acting compounds. In principle, different mechanisms, including differential epigenetic regulation as well as regulation of cell viability/apoptosis, might contribute to the sexual dimorphism of Kiss1 neuronal populations detected in physiological conditions, and its alteration following estrogenic or androgenic exposures during early development. While this issue had been only superficially addressed, a recent report has evaluated the contribution of BAX-mediated cell death in the development of Kiss1 neurons at the ARC and AVPV, and its potential implication in the sexual dimorphism of these populations, which is especially prominent at the AVPV. Studies in BAX KO mice revealed that females had a larger Kiss1 population at the AVPV, irrespective of the presence of BAX. However, BAX-mediated apoptosis appears critical to shape Kiss1 neuronal population at the ARC (Semaan et al. 2010). In this context, it would be interesting to evaluate whether such BAX-dependent mechanism might be sensitive to the effects of sex steroids, especially at early windows of development.

Other potential source of mechanistic variability may come from the recently-recognized phenomenon that both estrogen-responsive-element (ERE)-dependent and – independent mechanisms are involved in the activational regulation of *Kiss1* gene expression by estrogen. Thus, while all Kiss1 neurons have been shown to abundantly express ERα, recent studies have demonstrated that the stimulatory actions of estradiol on *Kiss1* mRNA levels at the AVPV are conducted through a classical ERE pathway whereas its inhibitory effects on *Kiss1* expression at the ARC do not appear to require such a classical pathway, suggesting alternative regulatory mechanisms (either ERE-independent genomic actions or non-nuclear receptor mediated events) (Gottsch et al. 2009). Admittedly, the potential contribution of such differential signaling to the developmental actions of endogenous (and eventual exogenous) sex steroids has not been evaluated yet. However, such divergent regulatory pathways may help to explain the different sensitivity of Kiss1 neurons to the organizing effects of sex steroids in different hypothalamic nuclei (Kauffman et al. 2007).

Finally, besides xeno-hormones, different environmental cues have been proven to impact the expression and/or function of hypothalamic Kiss1. Among those, the nutritional state of the organism is known to influence pubertal timing and fertility at least partially through the modulation of Kiss1 (Castellano et al. 2009). Intriguingly, EDC have been recently proposed as potential modifiers of body weight as well, and endocrine disruption has been hypothesized as potential contributor to the increased prevalence of obesity and metabolic syndrome in human populations (Diamanti-Kandarakis et al. 2009). Whether early exposures to EDC might have a combined impact on body weight and reproductive maturation and function remains to be solved. Of note, our preliminary studies suggest that postnatal overfeeding in rats causes a persistent increase in body weight and acceleration

of puberty that is linked to enhanced expression of Kiss1/kisspeptin at the hypothalamus, whereas the opposite trends (delayed puberty; decreased Kiss1/kisspeptin levels at the hypothalamus) are detected in female rats subjected to postnatal underfeeding (Castellano et al. 2010). In this context, it will be interesting to determine whether neonatally over- or under-weighed animals are more prone to disruption (either in terms of precocious activation or inhibition) of normal development of hypothalamic Kiss1 system by exposures to compounds with sex steroid-like activity. Similarly, the influence of early exposures to EDC in the generation of reproductive diseases, such as polycystic ovarian syndrome (PCOS), linked to severe metabolic complications warrants specific investigation (Diamanti-Kandarakis et al. 2009).

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References

Adewale HB, Jefferson WN, Newbold RR, Patisaul HB (2009) Neonatal bisphenol-a exposure alters rat reproductive development and ovarian morphology without impairing activation of gonadotropin-releasing hormone neurons. Biol Reprod 81(4):690–699

Adewale HB, Todd KL, Mickens JA, Patisaul HB (2011) The impact of neonatal bisphenol-A exposure on sexually dimorphic hypothalamic nuclei in the female rat. Neurotoxicology 32(1):38–49

Bakker J, Pierman S, Gonzalez-Martinez D (2010) Effects of aromatase mutation (ArKO) on the sexual differentiation of kisspeptin neuronal numbers and their activation by same versus opposite sex urinary pheromones. Horm Behav 57(4–5):390–395

Bateman HL, Patisaul HB (2008) Disrupted female reproductive physiology following neonatal exposure to phytoestrogens or estrogen specific ligands is associated with decreased GnRH activation and kisspeptin fiber density in the hypothalamus. Neurotoxicology 29(6):988–997

Bellingham M, Fowler PA, Amezaga MR, Rhind SM, Cotinot C, Mandon-Pepin B, Sharpe RM, Evans NP (2009) Exposure to a complex cocktail of environmental endocrine-disrupting compounds disturbs the kisspeptin/GPR54 system in ovine hypothalamus and pituitary gland. Environ Health Perspect 117(10):1556–1562

Bellingham M, Fowler PA, Amezaga MR, Whitelaw CM, Rhind SM, Cotinot C, Mandon-Pepin B, Sharpe RM, Evans NP (2010) Foetal hypothalamic and pituitary expression of gonadotrophin-releasing hormone and galanin systems is disturbed by exposure to sewage sludge chemicals via maternal ingestion. J Neuroendocrinol 22(6):527–533

Billings HJ, Connors JM, Altman SN, Hileman SM, Holaskova I, Lehman MN, McManus CJ, Nestor CC, Jacobs BH, Goodman RL (2010) Neurokinin B acts via the neurokinin-3 receptor in the retrochiasmatic area to stimulate luteinizing hormone secretion in sheep. Endocrinology 151(8):3836–3846

Bourguignon JP, Rasier G, Lebrethon MC, Gerard A, Naveau E, Parent AS (2010) Neuroendocrine disruption of pubertal timing and interactions between homeostasis of reproduction and energy balance. Mol Cell Endocrinol 324(1–2):110–120

Castellano JM, Navarro VM, Fernandez-Fernandez R, Castano JP, Malagon MM, Aguilar E, Dieguez C, Magni P, Pinilla L, Tena-Sempere M (2006) Ontogeny and mechanisms of action for the stimulatory effect of kisspeptin on gonadotropin-releasing hormone system of the rat. Mol Cell Endocrinol 257–258:75–83

Castellano JM, Roa J, Luque RM, Dieguez C, Aguilar E, Pinilla L, Tena-Sempere M (2009) KiSS-1/kisspeptins and the metabolic control of reproduction: Physiologic roles and putative physiopathological implications. Peptides 30(1):139–145

Castellano JM, Bentsen AH, Sanchez-Garrido MA, Ruiz-Pino F, Romero M, Pineda R, Garcia-Galiano D, Aguilar E, Pinilla L, Dieguez C, Mikkelsen J, Tena-Sempere M (2010) Early metabolic programming of puberty onset: impact of changes in perinatal feeding on the timing of puberty and the development of hypothalamic kisspeptin system. The Endocrine Society San Diego, USA, pp P2–272

Cheng G, Coolen LM, Padmanabhan V, Goodman RL, Lehman MN (2010) The kisspeptin/neurokinin B/dynorphin (KNDy) cell population of the arcuate nucleus: sex differences and effects of prenatal testosterone in sheep. Endocrinology 151(1):301–311

Christian CA, Moenter SM (2010) The neurobiology of preovulatory and estradiol-induced gonadotropin-releasing hormone surges. Endocr Rev 31(4):544–577

Ciofi P, Lapirot OC, Tramu G (2007) An androgen-dependent sexual dimorphism visible at puberty in the rat hypothalamus. Neuroscience 146(2):630–642

Clarkson J, Herbison AE (2006) Postnatal development of kisspeptin neurons in mouse hypothalamus; sexual dimorphism and projections to gonadotropin-releasing hormone neurons. Endocrinology 147(12):5817–5825

Clarkson J, Boon WC, Simpson ER, Herbison AE (2009) Postnatal development of an estradiol-kisspeptin positive feedback mechanism implicated in puberty onset. Endocrinology 150(7):3214–3220

de d'Anglemont Tassigny X, Colledge WH (2010) The role of kisspeptin signaling in reproduction. Physiology (Bethesda) 25(4):207–217

de d'Anglemont Tassigny X, Fagg LA, Dixon JP, Day K, Leitch HG, Hendrick AG, Zahn D, Franceschini I, Caraty A, Carlton MB, Aparicio SA, Colledge WH (2007) Hypogonadotropic hypogonadism in mice lacking a functional Kiss1 gene. Proc Natl Acad Sci USA 104(25):10714–10719

de Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E (2003) Hypogonadotropic hypogonadism due to loss of function of the Kiss1-derived peptide receptor GPR54. Proc Natl Acad Sci USA 100(19):10972–10976

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC (2009) Endocrine-disrupting chemicals: an endocrine society scientific statement. Endocr Rev 30(4):293–342

Dickerson SM, Guevara E, Woller MJ, Gore AC (2009) Cell death mechanisms in GT1-7 GnRH cells exposed to polychlorinated biphenyls PCB74, PCB118, and PCB153. Toxicol Appl Pharmacol 237(2):237–245

Ebling FJ (2005) The neuroendocrine timing of puberty. Reproduction 129(6):675–683

Evuarherhe O, Leggett JD, Waite EJ, Kershaw YM, Atkinson HC, Lightman SL (2009) Organizational role for pubertal androgens on adult hypothalamic-pituitary-adrenal sensitivity to testosterone in the male rat. J Physiol 587(Pt 12):2977–2985

Fink G (2000) Neuroendocrine regulation of pituitary function: general principles. In: Conn PM, Freeman ME (eds) Neuroendocrinology in physiology and medicine. Humana Press, New Jersey, pp 107–134

Gonzalez-Martinez D, De Mees C, Douhard Q, Szpirer C, Bakker J (2008) Absence of gonadotropin-releasing hormone 1 and Kiss1 activation in alpha-fetoprotein knockout mice: prenatal

estrogens defeminize the potential to show preovulatory luteinizing hormone surges. Endocrinology 149(5):2333–2340
Gore AC (2008a) Developmental programming and endocrine disruptor effects on reproductive neuroendocrine systems. Front Neuroendocrinol 29(3):358–374
Gore AC (2008b) Neuroendocrine systems as targets for environmental endocrine-disrupting chemicals. Fertil Steril 89(2 Suppl):e101–e102
Gottsch ML, Navarro VM, Zhao Z, Glidewell-Kenney C, Weiss J, Jameson JL, Clifton DK, Levine JE, Steiner RA (2009) Regulation of Kiss1 and dynorphin gene expression in the murine brain by classical and nonclassical estrogen receptor pathways. J Neurosci 29(29):9390–9395
Guillette LJ Jr (2006) Endocrine disrupting contaminants – beyond the dogma. Environ Health Perspect 114(Suppl 1):9–12
Han SK, Gottsch ML, Lee KJ, Popa SM, Smith JT, Jakawich SK, Clifton DK, Steiner RA, Herbison AE (2005) Activation of gonadotropin-releasing hormone neurons by kisspeptin as a neuroendocrine switch for the onset of puberty. J Neurosci 25(49):11349–11356
Herbison AE (2008) Estrogen positive feedback to gonadotropin-releasing hormone (GnRH) neurons in the rodent: The case for the rostral periventricular area of the third ventricle (RP3V). Brain Res Rev 57:277–287
Herbison AE, de Tassigny X, Doran J, Colledge WH (2010) Distribution and postnatal development of Gpr54 gene expression in mouse brain and gonadotropin-releasing hormone neurons. Endocrinology 151(1):312–321
Homma T, Sakakibara M, Yamada S, Kinoshita M, Iwata K, Tomikawa J, Kanazawa T, Matsui H, Takatsu Y, Ohtaki T, Matsumoto H, Uenoyama Y, Maeda K, Tsukamura H (2009) Significance of neonatal testicular sex steroids to defeminize anteroventral periventricular kisspeptin neurons and the GnRH/LH surge system in male rats. Biol Reprod 81(6):1216–1225
Hrabovszky E, Ciofi P, Vida B, Horvath MC, Keller E, Caraty A, Bloom SR, Ghatei MA, Dhillo WS, Liposits Z, Kallo I (2010) The kisspeptin system of the human hypothalamus: sexual dimorphism and relationship with gonadotropin-releasing hormone and neurokinin B neurons. Eur J Neurosci 31(11):1984–1998
Kauffman AS, Gottsch ML, Roa J, Byquist AC, Crown A, Clifton DK, Hoffman GE, Steiner RA, Tena-Sempere M (2007) Sexual differentiation of Kiss1 gene expression in the brain of the rat. Endocrinology 148(4):1774–1783
Kelce WR, Gray LE (1999) Environmental antiandrogens as endocrine disruptors. In: Naz RK (ed) Endocrine disruptors. Effects on male and female reproductive systems. CRC Press, Boca Raton, pp 247–277
Kotani M, Detheux M, Vandenbogaerde A, Communi D, Vanderwinden JM, Le Poul E, Brezillon S, Tyldesley R, Suarez-Huerta N, Vandeput F, Blanpain C, Schiffmann SN, Vassart G, Parmentier M (2001) The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. J Biol Chem 276(37):34631–34636
Lehman MN, Coolen LM, Goodman RL (2010) Minireview: kisspeptin/neurokinin B/dynorphin (KNDy) cells of the arcuate nucleus: a central node in the control of gonadotropin-releasing hormone secretion. Endocrinology 151(8):3479–3489
Losa SM, Todd KL, Sullivan AW, Cao J, Mickens JA, Patisaul HB (2011) Neonatal exposure to genistein adversely impacts the ontogeny of hypothalamic kisspeptin signaling pathways and ovarian development in the peripubertal female rat. Reprod Toxicol 31(3):280–289
MacLusky NJ, Naftolin F (1981) Sexual differentiation of the central nervous system. Science 211(4488):1294–1302
Morris JA, Jordan CL, Breedlove SM (2004) Sexual differentiation of the vertebrate nervous system. Nat Neurosci 7(10):1034–1039
Muir AI, Chamberlain L, Elshourbagy NA, Michalovich D, Moore DJ, Calamari A, Szekeres PG, Sarau HM, Chambers JK, Murdock P, Steplewski K, Shabon U, Miller JE, Middleton SE, Darker JG, Larminie CG, Wilson S, Bergsma DJ, Emson P, Faull R, Philpott KL, Harrison DC (2001) AXOR12, a novel human G protein-coupled receptor, activated by the peptide KiSS-1. J Biol Chem 276(31):28969–28975

Navarro VM, Tena-Sempere M (2008) The KiSS-1/GPR54 system: putative target for endocrine disruption of reproduction at hypothalamic-pituitary unit? Int J Androl 31(2):224–232

Navarro VM, Castellano JM, Fernandez-Fernandez R, Barreiro ML, Roa J, Sanchez-Criado JE, Aguilar E, Dieguez C, Pinilla L, Tena-Sempere M (2004) Developmental and hormonally regulated messenger ribonucleic acid expression of KiSS-1 and its putative receptor, GPR54, in rat hypothalamus and potent luteinizing hormone-releasing activity of KiSS-1 peptide. Endocrinology 145(10):4565–4574

Navarro VM, Sanchez-Garrido MA, Castellano JM, Roa J, Garcia-Galiano D, Pineda R, Aguilar E, Pinilla L, Tena-Sempere M (2009) Persistent impairment of hypothalamic KiSS-1 system after exposures to estrogenic compounds at critical periods of brain sex differentiation. Endocrinology 150(5):2359–2367

Navarro VM, Castellano JM, McConkey SM, Pineda R, Ruiz-Pino F, Pinilla L, Clifton DK, Tena-Sempere M, Steiner RA (2011) Interactions between Kisspeptin and Neurokinin B in the control of GnRH secretion in the female rat. Am J Physiol Endocrinol Metab 300(1):202–210

Norgil Damgaard I, Main KM, Toppari J, Skakkebaek NE (2002) Impact of exposure to endocrine disrupters in utero and in childhood on adult reproduction. Best Pract Res Clin Endocrinol Metab 16(2):289–309

Oakley AE, Clifton DK, Steiner RA (2009) Kisspeptin signaling in the brain. Endocr Rev 30(6):713–743

Ohtaki T, Shintani Y, Honda S, Matsumoto H, Hori A, Kanehashi K, Terao Y, Kumano S, Takatsu Y, Masuda Y, Ishibashi Y, Watanabe T, Asada M, Yamada T, Suenaga M, Kitada C, Usuki S, Kurokawa T, Onda H, Nishimura O, Fujino M (2001) Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. Nature 411(6837):613–617

Ojeda SR, Lomniczi A, Mastronardi C, Heger S, Roth C, Parent AS, Matagne V, Mungenast AE (2006) Minireview: the neuroendocrine regulation of puberty: is the time ripe for a systems biology approach? Endocrinology 147(3):1166–1174

Ojeda SR, Dubay C, Lomniczi A, Kaidar G, Matagne V, Sandau US, Dissen GA (2010) Gene networks and the neuroendocrine regulation of puberty. Mol Cell Endocrinol 324(1–2):3–11

Panzica GC, Mura E, Miceli D, Martini MA, Gotti S, Viglietti-Panzica C (2009) Effects of xenoestrogens on the differentiation of behaviorally relevant neural circuits in higher vertebrates. Ann N Y Acad Sci 1163:271–278

Patisaul HB, Fortino AE, Polston EK (2006) Neonatal genistein or bisphenol-A exposure alters sexual differentiation of the AVPV. Neurotoxicol Teratol 28(1):111–118

Patisaul HB, Todd KL, Mickens JA, Adewale HB (2009) Impact of neonatal exposure to the ERalpha agonist PPT, bisphenol-A or phytoestrogens on hypothalamic kisspeptin fiber density in male and female rats. Neurotoxicology 30(3):350–357

Pineda R, Garcia-Galiano D, Roseweir A, Romero M, Sanchez-Garrido MA, Ruiz-Pino F, Morgan K, Pinilla L, Millar RP, Tena-Sempere M (2010) Critical roles of kisspeptins in female puberty and preovulatory gonadotropin surges as revealed by a novel antagonist. Endocrinology 151(2):722–730

Pinilla L, Tena-Sempere M, Gonzalez D, Aguilar E (1995) Mechanisms of altered LH secretion in neonatally oestrogenized male rats. J Endocrinol 147(1):43–50

Popa SM, Clifton DK, Steiner RA (2008) The role of Kisspeptins and GPR54 in the neuroendocrine regulation of reproduction. Annu Rev Physiol 70:213–238

Ramaswamy S, Seminara SB, Ali B, Ciofi P, Amin NA, Plant TM (2010) Neurokinin B stimulates GnRH release in the male monkey (*Macaca mulatta*) and is colocalized with Kisspeptin in the arcuate nucleus. Endocrinology 151(9):4494–4503

Rance NE (2009) Menopause and the human hypothalamus: evidence for the role of kisspeptin/neurokinin B neurons in the regulation of estrogen negative feedback. Peptides 30(1):111–122

Rasier G, Parent AS, Gerard A, Lebrethon MC, Bourguignon JP (2007) Early maturation of gonadotropin-releasing hormone secretion and sexual precocity after exposure of infant female rats to estradiol or dichlorodiphenyltrichloroethane. Biol Reprod 77(4):734–742

Richard N, Galmiche G, Corvaisier S, Caraty A, Kottler ML (2008) KiSS-1 and GPR54 genes are co-expressed in rat gonadotrophs and differentially regulated in vivo by oestradiol and gonadotrophin-releasing hormone. J Neuroendocrinol 20(3):381–393

Roa J, Aguilar E, Dieguez C, Pinilla L, Tena-Sempere M (2008) New frontiers in kisspeptin/GPR54 physiology as fundamental gatekeepers of reproductive function. Front Neuroendocrinol 29(1):48–69

Semaan SJ, Murray EK, Poling MC, Dhamija S, Forger NG, Kauffman AS (2010) BAX-dependent and BAX-independent regulation of Kiss1 neuron development in mice. Endocrinology 151(12):5807–5817

Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JS Jr, Shagoury JK, Bo-Abbas Y, Kuohung W, Schwinof KM, Hendrick AG, Zahn D, Dixon J, Kaiser UB, Slaugenhaupt SA, Gusella JF, O'Rahilly S, Carlton MB, Crowley WF Jr, Aparicio SA, Colledge WH (2003) The GPR54 gene as a regulator of puberty. N Engl J Med 349(17):1614–1627

Shahab M, Mastronardi C, Seminara SB, Crowley WF, Ojeda SR, Plant TM (2005) Increased hypothalamic GPR54 signaling: a potential mechanism for initiation of puberty in primates. Proc Natl Acad Sci USA 102(6):2129–2134

Sikka SC, Naz RK (1999) Endocrine disruptors and male infertility. In: Naz RK (ed) Endocrine disruptors. Effects on male and female reproductive systems. CRC Press, Boca Raton, pp 225–246

Skakkebaek NE, Jorgensen N, Main KM, Rajpert-De Meyts E, Leffers H, Andersson AM, Juul A, Carlsen E, Mortensen GK, Jensen TK, Toppari J (2006) Is human fecundity declining? Int J Androl 29(1):2–11

Tena-Sempere M (2010a) Kisspeptin/GPR54 system as potential target for endocrine disruption of reproductive development and function. Int J Androl 33(2):360–368

Tena-Sempere M (2010b) Roles of Kisspeptins in the control of hypothalamic-gonadotropic function: Focus on sexual differentiation and puberty onset. Endocr Dev 17:52–62

Tena-Sempere M, Huhtaniemi I (2003) Gonadotropins and gonadotropin receptors. In: Fauser BCJM (ed) Reproductive medicine – Molecular, cellular and genetic fundamentals. Parthenon Publishing, New York, pp 225–244

Tena-Sempere M, Pinilla L, Gonzalez LC, Aguilar E (2000) Reproductive disruption by exposure to exogenous estrogenic compounds during sex differentiation: lessons from the neonatally estrogenized male rat. Curr Top Steroid Res 3:23–37

Topaloglu AK, Reimann F, Guclu M, Yalin AS, Kotan LD, Porter KM, Serin A, Mungan NO, Cook JR, Ozbek MN, Imamoglu S, Akalin NS, Yuksel B, O'Rahilly S, Semple RK (2009) TAC3 and TACR3 mutations in familial hypogonadotropic hypogonadism reveal a key role for Neurokinin B in the central control of reproduction. Nat Genet 41(3):354–358

Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ Jr, Jegou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Muller J, Rajpert-De Meyts E, Scheike T, Sharpe R, Sumpter J, Skakkebaek NE (1996) Male reproductive health and environmental xenoestrogens. Environ Health Perspect 104(Suppl 4):741–803

Wadas BC, Hartshorn CA, Aurand ER, Palmer JS, Roselli CE, Noel ML, Gore AC, Veeramachaneni DN, Tobet SA (2010) Prenatal exposure to vinclozolin disrupts selective aspects of the gonadotrophin-releasing hormone neuronal system of the rabbit. J Neuroendocrinol 22(6):518–526

Wakabayashi Y, Nakada T, Murata K, Ohkura S, Mogi K, Navarro VM, Clifton DK, Mori Y, Tsukamura H, Maeda K, Steiner RA, Okamura H (2010) Neurokinin B and dynorphin A in kisspeptin neurons of the arcuate nucleus participate in generation of periodic oscillation of neural activity driving pulsatile gonadotropin-releasing hormone secretion in the goat. J Neurosci 30(8):3124–3132

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