Cell and Tissue Research (2019) 375:179–191
https://doi.org/10.1007/s00441-018-2893-z

REVIEW

Neuropeptidergic modulation of GnRH neuronal activity and GnRH secretion controlling reproduction: insights from recent mouse studies

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Received: 1 April 2018 / Accepted: 6 July 2018 / Published online: 4 August 2018

Abstract

Gonadotropin-releasing hormone (GnRH) secretion from GnRH neurons and its modulation by neuropeptides are essential for mammalian reproduction. Here, I review the neuropeptides that have been shown to act directly and that may also act indirectly, on GnRH neurons, the reproduction-related processes with which the neuropeptides may be associated or the physiological information they may convey, as well as their cognate receptors, signaling pathways and roles in the modulation of GnRH neuronal firing, $[Ca^{2+}]_i$, GnRH secretion and reproduction. The review focuses on recent research in mice, which offer the most tractable experimental system for studying mammalian GnRH neurons.

Keywords GnRH neuron · Neuropeptide · Receptor · Signaling · Reproduction

Introduction

Gonadotropin-releasing hormone (GnRH; also known as GnRH1 or LHRH) neurons comprise a scattered group of ~ 600–800 cells in the mouse brain, with only ~ 70–200 of those cells being required for reproductive function, which form the final common pathway for the central control of reproduction (Wray et al. 1989; Herbison et al. 2008; see Constantin 2017, and Kaprara and Huhtaniemi 2017, for recent reviews on GnRH neurons and their role in the control of the hypothalamic–pituitary–gonadal axis in mice and humans). As shown in Fig. 1, they integrate steroidal, lactational, hunger, stress, satiety, circadian, odorant and pheromone signals. These signals are conveyed to a large extent by neuropeptides directly and/or indirectly, as well as by conventional neurotransmitters, gaseous transmitters, gliotransmitters and other factors (Boehm et al. 2005; Christian et al. 2005; Yoon et al. 2005; Pielecka et al. 2006; Pielecka and Moenter 2006; Christian and Moenter 2007, 2008a, b; Clasadonte et al. 2008, 2011; Chu et al. 2009; Leshan et al. 2009; Roa and Herbison 2012; Liu et al. 2014; Cimino et al. 2016; Hellier et al. 2018; Phumsatitpong and Moenter 2018). The cell bodies of GnRH neurons, which receive neuropeptidergic inputs from neurons in the hypothalamus and other brain areas (Turi et al. 2003; Yip et al. 2015), are distributed along a continuum in the medial and lateral preoptic area (POA) of the hypothalamus, the horizontal and vertical limbs of the diagonal band of Broca (DBB), the medial septal nucleus (MS) and to a lesser extent in several other brain areas (Schwanzel-Fukuda et al. 1987; Wray et al. 1989).

GnRH neurons synthesize and secrete GnRH (pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2) in a pulsatile manner (with a frequency of ~ 0.2–1 pulse/h, based on measurements of GnRH gene transcription and GnRH secretion in cultured hypothalamic slices containing GnRH neurons and of luteinizing hormone (LH) in gonad-intact, wild-type mice; Choe et al. 2013; Czieselsky et al. 2016) from axon terminals in the median eminence (ME) into the hypothalamo-hypophyseal circulation, as well as into the organum vasculosum of the lamina terminalis (OVLT). GnRH neuronal axon terminals, as well as dendrites, also receive neuropeptidergic inputs (d'Anglemont de Tassigny et al. 2008; Yip et al. 2015). GnRH secreted at the ME subsequently binds to GnRH receptors on pituitary gonadotrophs and stimulates the synthesis and pulsatile secretion of LH and follicle-stimulating hormone (FSH) into the general circulation. LH and FSH, which are required for the development and maintenance of the gonads and thus for fertility, bind to receptors on the gonads to

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00441-018-2893-z) contains supplementary material, which is available to authorized users.

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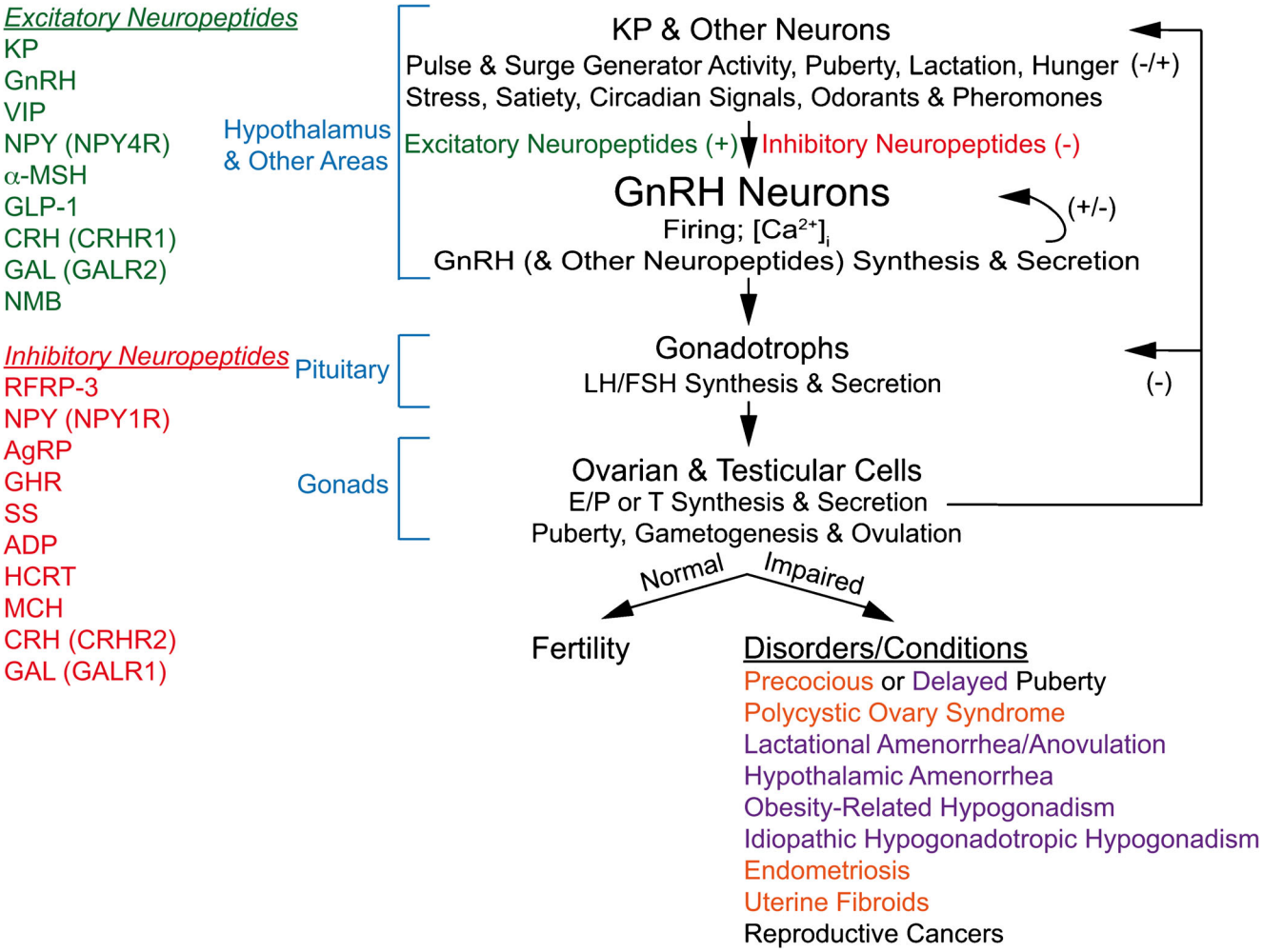

Fig. 1 Schematic diagram showing neuropeptide modulation of GnRH neuronal activity. Excitatory (*green*) and inhibitory (*red*) neuropeptides released from KP and other neurons in the hypothalamus and other brain areas (*blue*), which are required for pulsatile/surge GnRH secretion and puberty (and/or are associated with lactation, hunger, stress, satiety, circadian rhythms, odorants, or pheromones), modulate action potential firing, $[Ca^{2+}]_i$ and pulsatile/surge GnRH secretion in GnRH neurons. This results in modulated pulsatile/surge gonadotropin (LH/FSH) secretion from gonadotrophs in the pituitary (*blue*) and gonadal hormone (E and P in females; T in males) secretion from the gonads (*blue*), which is required for gonadal development and maintenance and thus fertility. In addition to performing a variety of important functions in reproductive and other tissues, E, P and T inhibit GnRH neurons (via KP neurons in the ARC) and gonadotrophs, except during proestrous in females when E and P excite GnRH neurons (via KP neurons in the AVPV). Impaired GnRH secretion may result in disorders/conditions (marked in orange or purple depending on whether they are associated with excessive or insufficient GnRH secretion, respectively) including pubertal disorders (precocious or delayed puberty), polycystic ovary syndrome, lactational amenorrhea/anovulation, hypothalamic amenorrhea, obesity-related hypogonadism, idiopathic hypogonadotropic hypogonadism, uterine fibroids and/or reproductive cancers (e.g., prostate, breast, endometrial and ovarian cancers). Also, GnRH and neuropeptides co-released with GnRH (e.g., galanin) from GnRH neurons may have autocrine effects on GnRH neuronal activity, which may be excitatory or inhibitory depending on the concentration and (although not shown in the figure) act on other neurons to modulate reproduction-related functions. Abbreviations are explained at their first occurrence in the main text

stimulate the synthesis and secretion of estradiol (E) and progesterone (P) in females and testosterone (T) in males.

E, P and T feed back onto the brain and the anterior pituitary to inhibit the reproductive axis. In females, E and P also trigger a surge of GnRH secretion in the afternoon on the day of proestrus that results in an LH surge and is required for ovulation (Fig. 1; Constantin 2017; Kaprara and Huhtaniemi 2017). E, P and T appear to act mainly indirectly on GnRH neurons (Smith 2008). E exerts its inhibitory and stimulatory effects on GnRH neurons by binding to estrogen receptor alpha (ERα), which is expressed in kisspeptin (KP) neurons (but not in GnRH neurons), where it regulates KP release onto GnRH neurons (as discussed below). E may also exert some of its inhibitory effects on GnRH neurons by binding to estrogen receptor beta, which is expressed in GnRH neurons but appears not to play a critical role (Cheong et al. 2014; Bálint et al. 2016). P exerts its

inhibitory and stimulatory effects on GnRH neurons via P receptors expressed in KP neurons (Stephens et al. 2015; Gal et al. 2016), whereas T exerts its inhibitory effects on GnRH neurons via E and ERs (through its conversion by aromatase to E) as well as via androgen receptors expressed in KP neurons (Walters et al. 2018).

In addition to the ME and OVLT, GnRH neurons project to other areas of the brain where neurons associated with various reproduction-related functions, including feeding, energy expenditure, glucose homeostasis, odor and pheromone processing, sexual/reproductive behavior and defensive behavior express GnRH receptors and whose activity may be modulated by GnRH released synaptically from GnRH neurons (Boehm et al. 2005; Yoon et al. 2005; Sotonyi et al. 2010; Wen et al. 2011; Schauer et al. 2015; Hellier et al. 2018).

Neuropeptides, along with various conventional neurotransmitters including γ-aminobutyric acid (GABA) and glutamate, act on GnRH neurons by binding to their cognate receptors, to regulate or modulate GnRH secretion and thus reproductive function. Receptor binding, which for almost all neuropeptides is coupled to activation of G proteins (G_q, G_s, or G_i in most cases) and their associated signaling pathways (see van den Pol 2012, for a discussion of general principles of neuropeptide modulation of brain circuits), is followed by plasma membrane depolarization or hyperpolarization, an increase or decrease in GnRH neuron action potential frequency and an increase or decrease in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), respectively, which in turn increases or decreases GnRH secretion, which may promote or inhibit reproductive function or the attainment of reproductive function (see, for example, Spergel et al. 1999; Xu et al. 2004; Han et al. 2005; Ducret et al. 2009; Constantin et al., 2010 and 2013; Kirilov et al. 2013). The direct or indirect effects of neuropeptides on GnRH neurons may result in normal fertility or pubertal disorders such as precocious or delayed puberty, or in disorders/conditions associated with infertility including polycystic ovary syndrome, lactational amenorrhea/anovulation, hypothalamic amenorrhea, obesity-related hypogonadism, idiopathic hypogonadotropic hypogonadism, endometriosis, uterine fibroids, or reproductive cancers associated with excessive or insufficient GnRH pulse frequency (Fig. 1; Schally et al. 2001; Harrison et al. 2004; León et al. 2014; DiVall et al. 2015; Celik et al. 2015; Herbison 2016). Conversely, neuropeptides or their antagonists may be used for physiological ovarian hyperstimulation for in vitro fertilization, or to treat reproductive disorders or reproductive cancers (Millar et al. 1987; Schally et al. 2001; Harrison et al. 2004; Celik et al. 2015; Gründker and Emons 2017). However, if one considers developing neuropeptides as therapeutics, it is important to keep in mind that many of them have stimulatory and inhibitory actions depending on the concentration, receptor subtype, hormonal milieu, species, etc. and they may affect only a subset of GnRH neurons.

This review focuses on the neuropeptides for which receptors have been demonstrated to be functionally expressed in GnRH neurons, their signaling pathways, their effects on GnRH neuron action potential firing, GnRH neuron $[Ca^{2+}]_i$ and GnRH secretion and whether they act directly on GnRH neurons. The latter is based on whether the effects are maintained in the presence of a cocktail of ionotropic GABA and glutamate receptor blockers to block fast synaptic transmission mediated by GABA and glutamate receptors, or in the presence of the cocktail plus the Na^+ channel blocker tetrodotoxin to block all action potential-dependent synaptic transmission.

Some neuropeptides (e.g., KP) have been viewed as regulators or powerful modulators of GnRH neuronal activity and/or reproductive function if they have powerful effects on GnRH neuronal activity and deletion of their receptors on GnRH neurons or presynaptic neurons results in large changes in GnRH neuronal activity, loss of reproductive function and/or failure to undergo normal pubertal development (i.e., failure to attain reproductive function). Other neuropeptides, in contrast, have been viewed as modulators rather than regulators or powerful modulators of GnRH neuronal activity and/or reproductive function if they have small or medium-sized effects on GnRH neuronal activity and deletion of their receptors on GnRH neurons or presynaptic neurons results in small or medium-sized changes in GnRH neuronal activity that may affect but do not severely impair reproductive function or pubertal development. Neuropeptides that directly modulate GnRH neuronal activity constitute a small fraction of all known neuropeptides (http://isyslab.info/NeuroPep/; http://www.neuropeptides.nl/tabel%20neuropeptides%20linked.htm) and are discussed below. Neuropeptides for which there is less evidence of direct modulation of GnRH neuronal activity are also discussed below. Due to space limitations, only recent research studies are cited (the author apologizes for not citing earlier research studies) and neuropeptides (including arginine-vasopressin, dynorphin, leptin and insulin) that appear to affect GnRH neurons only indirectly are neither listed nor discussed in this review.

Neuropeptide modulators of GnRH neuronal activity, GnRH secretion and reproduction that act directly on GnRH neurons

Neuropeptides associated with GnRH pulsatility, the preovulatory GnRH/LH surge, puberty, lactation, circadian rhythms, odorants and pheromones

Kisspeptin (KP)

KP (encoded by the *Kiss1* gene) and its signaling have been shown to be essential for reproduction and reproductive

maturation (puberty). KP, which is released from KP neurons in the arcuate nucleus (ARC) and anteroventral periventricular nucleus (AVPV) onto GnRH neurons, acts directly on GnRH neurons to increase firing (Han et al. 2005; Pielecka-Fortuna et al. 2008; Liu et al. 2011) by binding to the G_q-coupled G protein-coupled receptor 54 (GPR54), which activates phospholipase C beta (PLC-β) signaling pathways (including protein kinase C; PKC) and cellular Src tyrosine kinase (cSrc; Zhang et al. 2013a). This results in closure of G protein-coupled inwardly rectifying K^+ (GIRK) and slow afterhyperpolarization (sAHP) channels, opening of transient receptor potential canonical (TRPC) channels and plasma membrane depolarization, followed by Ca^{2+} entry through TRPC channels and voltage-gated Ca^{2+} channels (VGCCs) along with Ca^{2+} release from intracellular Ca^{2+} stores, which increases $[Ca^{2+}]_i$ in GnRH neuron cell bodies and axon terminals (Dumalska et al. 2008; Liu et al. 2008; Pielecka-Fortuna et al. 2008; Zhang et al., 2008, 2013a, and b; Constantin et al., 2009 and 2013; Zhang and Spergel 2012; Iremonger et al. 2017). This is followed by increases in GnRH, LH and FSH secretion in wild-type mice but not in *Gpr54* null mice, *Kiss1* null mice, or in mice in which only GnRH neurons lack GPR54 (Gottsch et al. 2004; Messager et al. 2005; d'Anglemont de Tassigny et al. 2007; Kirilov et al. 2013). ARC KP neuron $[Ca^{2+}]_i$ correlates with pulsatile secretion of LH and optogenetic, synchronous activation of KP neurons in the ARC induces pulsatile LH secretion in wild-type mice but not in *Gpr54* null mice, suggesting that synchronized KP release from KP neurons in the ARC is required for pulsatile GnRH/LH secretion (Han et al. 2015; Clarkson et al. 2017).

KP-GPR54 signaling from KP neurons in the AVPV, which integrate hormonal and circadian signals (Piet et al. 2015), is required for the secretory surge of GnRH/LH that initiates ovulation (Clarkson et al. 2008) as well as for normal puberty (Seminara et al. 2003; Han et al. 2005; Clarkson and Herbison 2006; Lapatto et al. 2007). ERα-dependent KP release from KP neurons in the AVPV drives the GnRH/LH surge (Herbison 2008), whereas ERα-dependent KP release from KP neurons in the ARC and AVPV mediates juvenile restraint and pubertal activation of GnRH/LH secretion, respectively (Mayer et al. 2010). The percentage of KP-responsive GnRH neurons and the amount of LH secreted in response to KP increases across pubertal development, which is likely due to increased release of KP (from AVPV KP neurons) onto GnRH neurons and a post-transcriptional change in GPR54 signaling in GnRH neurons (Han et al. 2005). KP neurons in the AVPV project to GnRH neuron cell bodies and dendrites in the POA and DBB, whereas KP neurons in the ARC project to GnRH nerve terminals in the ME, to stimulate GnRH/LH/FSH release (Clarkson and Herbison 2006; d'Anglemont de Tassigny et al. 2008; Kalló et al. 2012; Yip et al. 2015) and the percentage of GnRH neurons with appositions from KP projection fibers increases across pubertal development (Clarkson and Herbison 2006). KP also acts indirectly on GnRH neurons, by activating neuronal nitric oxide synthase (nNOS) in nNOS-expressing neurons in the POA, resulting in the synthesis of the gaseous transmitter nitric oxide (NO), which coordinates and is required for the proestrous GnRH/LH surge (Hanchate et al. 2012).

In addition to its role in modulating/regulating pulsatile and surge GnRH secretion and the onset of puberty, KP signaling to GnRH neurons may link lactational state, via prolactin (discussed below) and nutritional state and stress, via RFRP-3 and FGF21 (discussed below) as well as pituitary adenylate cyclase activating polypeptide (Ross et al. 2018), to fertility. KP may also mediate the effects of odorants and pheromones on GnRH secretion, which include increased GnRH secretion into the hypothalamo-hypophyseal portal circulation as well as in hypothalamic and other limbic regions involved in modulating mate preferences and facilitating sexual/reproductive behavior (Bronson and Stetson 1973; Boehm et al. 2005; Taziaux and Bakker 2015; Hellier et al. 2018).

Gonadotropin-releasing hormone (GnRH)

GnRH directly depolarizes ~50% of GnRH neurons in males and in females across the estrous cycle, which is accompanied by a decrease in $[Ca^{2+}]_i$; however, at proestrus in females, GnRH transiently hyperpolarizes a further 33% of GnRH neurons (12% directly and 21% indirectly), decreases $[Ca^{2+}]_i$ in 25% of GnRH neurons and increases $[Ca^{2+}]_i$ in 17% of GnRH neurons (Han et al. 2010). The differential effects of GnRH on GnRH neurons may depend in part on GnRH concentration-dependent coupling of the GnRH receptor (GnRHR) to G_s and G_i, as well as to G_q and may contribute to GnRH pulsatility and the proestrous GnRH/LH surge (Krsmanovic et al. 2003; Han et al. 2010). The effects of GnRH on GnRH neurons may also depend on those of other neuropeptides (e.g., galanin; Rajendren and Gibson 1999; Burger et al. 2018) and neurotransmitters (e.g., GABA: Vastagh et al. 2015; Zhu et al. 2015) that may be co-localized and co-released in GnRH neurons.

Vasoactive intestinal polypeptide (VIP)

VIP released from VIP neurons in the suprachiasmatic nucleus (SCN) may provide an excitatory signal from the circadian clock to GnRH neurons that helps time the proestrous GnRH/LH surge, which is dependent on the midcycle rise in circulating E and required for ovulation. Accordingly, *Vip* null mice and vasoactive intestinal polypeptide receptor 2 (*Vipr2*) null mice exhibit disrupted estrous cycles and/or deficits in ovulation (Dolatshad et al. 2006; Loh et al. 2014). Moreover, VIP axons appose 28% of GnRH neurons (Ward et al. 2009). VIP acts directly via VPAC1/VPAC2 on GnRH

neurons in males and females to increase their firing in 50–80% of GnRH neurons and $[Ca^{2+}]_i$ in 40% of GnRH neurons, possibly by activating a hyperpolarization-activated current (I_h) or reducing the amplitude of a Ca^{2+}-dependent K^+ current (I_{sAHP}) as in other neurons (Christian and Moenter 2008b; Piet et al. 2016). However, VIP responsiveness of GnRH neurons does not change across the estrous cycle and is independent of time of day (Piet et al. 2016), suggesting that VIP release, rather than GnRH neuron responsiveness to VIP, may change across the estrous cycle and depend on time of day. VIP may also act indirectly on GnRH neurons (Christian and Moenter 2008b).

Neuropeptides associated with hunger and/or stress

RFamide-related peptide-3 (RFRP-3)

RFRP-3, a mammalian ortholog of gonadotropin-inhibitory hormone that binds to the NPFF1 receptor to stimulate food intake and suppress the reproductive axis (León et al. 2014), inhibits 41% of GnRH neurons, excites 12% of GnRH neurons (perhaps indirectly) and has no effect on the remaining 47% of GnRH neurons, with most of the GnRH neurons inhibited by RFRP-3 being inhibited directly (Ducret et al. 2009). RFRP-3 fibers appose 26% of GnRH neurons and 19% of KP neurons (Rizwan et al. 2012). RFRP-3 modulates GnRH neuron firing via the G_i-associated GPR147, which appears to be coupled to a Ba^{2+}-sensitive inwardly rectifying K^+ channel and is expressed in 33% of GnRH neurons, as well as in 9–16% of KP neurons in the rostral periventricular area of the third ventricle (RP3V), which includes the AVPV and the adjacent median preoptic and periventricular preoptic nuclei (Wu et al. 2009a; Rizwan et al. 2012).

Neuropeptide Y (NPY)

NPY, an orexigenic neuropeptide that has been proposed to link energy state and reproduction (Crown et al. 2007), directly inhibits the firing of ~ 45% GnRH neurons via Y1 receptors but may also directly excite GnRH neurons via Y4 receptors, or indirectly inhibit firing by decreasing GABAergic input (Sullivan and Moenter 2004; Roa and Herbison 2012). NPY-containing axons arising from NPY neurons in the ARC, noradrenergic/adrenergic cell populations in the brainstem and additional unidentified sources, appose most (87%) GnRH neuron cell bodies and proximal dendrites (Turi et al. 2003; Ward et al. 2009).

Agouti-related peptide (AgRP)

Like those containing NPY, axons containing the orexigenic neuropeptide AgRP, which is synthesized and co-released with NPY from NPY neurons in the ARC, appose GnRH neurons, with the number of appositions being ~ 50% of that of NPY appositions onto GnRH neurons (Turi et al. 2003). AgRP is an inverse agonist of the melanocortin 3 and 4 receptors (MC3Rs and MC4Rs) and acts directly on GnRH neurons to stimulate (~ 25% of GnRH neurons) or inhibit (~ 10% of GnRH neurons) them. AgRP prevents the increase in firing in GnRH neurons evoked by the MC3R/MC4R agonist melanotan II (Israel et al. 2012; Roa and Herbison 2012). AgRP released from NPY/AgRP neurons in the ARC also appears to act indirectly on GnRH neurons, via KP neurons, to delay estrous cycles and decrease fertility (Padilla et al. 2017). These may be important mechanisms to inhibit the reproductive axis when energy reserves are low.

Ghrelin (GHR)

The orexigenic neuropeptide/hormone GHR (Comninos et al. 2014) decreases the firing rate and burst frequency of GnRH neurons in male mice and in metestrous but not proestrous female mice, by binding to the growth hormone secretagogue receptor (GHS-R) on GnRH neurons. This is followed by activation of a retrograde endocannabinoid signaling mechanism that decreases excitatory GABAergic release onto GnRH neurons (Farkas et al. 2013).

Somatostatin (SS)

Axons containing the orexigenic neuropeptide SS (Stengel et al. 2015) appose GnRH neurons, which appear to express SS receptor subtypes SSTR2, SSTR3 and SSTR4 (Todman et al. 2005; Vastagh et al. 2015). SS directly inhibits GnRH neurons (by producing an acute membrane hyperpolarization and a cessation of firing) via SSTR2 (Todman et al. 2005; Bhattarai et al. 2010).

Adiponectin (ADP)

ADP, a peripheral neuropeptide/hormone secreted by white adipose tissue and which plays an important role in energy homeostasis and appetite regulation (Kadowaki et al. 2008), hyperpolarizes, or decreases Ca^{2+} oscillations, in 20% of GnRH neurons via adiponectin receptor 2 (ADIPOR2) followed by activation of a protein kinase C zeta (PKCζ)/liver kinase B1 (LKB1)/5′ adenosine monophosphate-activated protein kinase (AMPK) signaling cascade (Klenke et al. 2014).

Hypocretin (HCRT)/orexin

The orexigenic neuropeptide HCRT/orexin inhibits GnRH neuron firing via the type I HCRT/orexin receptor (HCRTR1) in brain slices from female mice independent of E levels or time of day (Gaskins and Moenter 2012).

Melanin-concentrating hormone (MCH)

Axons containing the orexigenic neuropeptide MCH appose 86% of GnRH neurons (Ward et al. 2009). MCH inhibits GnRH neuron firing directly by binding to MCH receptor 1 (MCHR1) receptors followed by activation of Ba^{2+}-sensitive GIRK channels (Wu et al. 2009b).

Corticotropin-releasing hormone (CRH)

CRH, along with other factors, may mediate the inhibitory effect of stress on the reproductive axis (Jeong et al. 1999; Li et al. 2010). In diestrous female mice, CRH receptor type 1 (CRHR1) mRNA is expressed in ~25% of GnRH neurons and CRHR1/2 protein is expressed in ~30% of GnRH neurons (Jasoni et al. 2005). In ovariectomized (OVX) mice, CRH does not affect GnRH neuron firing. In OVX + E-treated mice, a low concentration (30 nM) of CRH, as well as the CRHR1-specific agonist stressin I, increases GnRH neuron firing (in ~40% of GnRH neurons), whereas a high concentration (100 nM) of CRH, as well as the CRHR2-specific agonist urocortin III, decreases GnRH neuron firing (in ~60% of GnRH neurons). This suggests that E is required for CRH to exert its effects on GnRH neurons, which are mediated by CRHR1 at low CRH concentrations and by CRHR2 at high CRH concentrations (Phumsatitpong and Moenter 2018).

Neuropeptides associated with satiety

α-Melanocyte-stimulating hormone (α-MSH)

The anorexigenic neuropeptide α-MSH, which is synthesized and released by pro-opiomelanocortin (POMC) neurons and the α-MSH analogue melanotan II, act directly via MC3Rs and MC4Rs on most (70%) GnRH neurons to increase their firing rate and induce expression of c-Fos (Israel et al. 2012; Roa and Herbison 2012). Also, most (87%) GnRH neurons are closely apposed by NPY fibers (Ward et al. 2009).

Glucagon-like peptide 1 (GLP-1)

Axons containing the anorexigenic neuropeptide GLP-1 innervate GnRH neurons and the GLP-1 analogue exendin-4 increases the firing rate of GnRH neurons, in male mice, by binding to GLP-1 receptor (GLP-1R) followed by activation of nitric oxide and suppression of endocannabinoid signaling pathways, which increases excitatory GABAergic synaptic input to GnRH neurons (Farkas et al. 2016).

Galanin (GAL)

The anorexigenic neuropeptide GAL is expressed in an E-dependent manner in KP neurons in the RP3V and ARC. GAL is likely co-released with KP from subsets of KP neuron axons onto GnRH neurons and GAL synaptic input to GnRH neurons is higher in adults than in juveniles (Rajendren and Li 2001; Porteous et al. 2011; Kalló et al. 2012). Both the GALR1 and GALR2 subtypes of GAL receptor appear to be expressed in GnRH neurons (Todman et al. 2005; Constantin and Wray 2016). GALR1 activation by GAL (or GAL 1–16) inhibits GnRH neuron Ca^{2+} oscillations, as well as KP-evoked Ca^{2+} responses and GnRH secretion, via G_i signaling and GIRK channels (Constantin and Wray 2016), whereas GALR2 activation by GAL directly depolarizes 55% of GnRH neurons and in some cases increases their firing rate (Todman et al. 2005).

Neuromedin B (NMB)

The anorexigenic neuropeptide NMB (Merali et al. 1999) directly depolarizes 56% of GnRH neurons via the bombesin receptor subtypes BB1, BB2 and BB3 (Todman et al. 2005).

Neuropeptides that may or may not act directly on GnRH neurons

Met-enkephalin (M-ENK)

The opioid peptide M-ENK is expressed in a subpopulation of KP neurons in the RP3V but not in KP neurons in the ARC (Porteous et al. 2011). M-ENK may be released along with KP onto GnRH neurons, which appear to express the delta opioid receptor for M-ENK (Todman et al. 2005), possibly resulting in decreased GnRH neuron firing. M-ENK may also act indirectly via GABAergic neurons to inhibit GnRH neuron firing (Sullivan and Moenter 2004).

Leu-enkephalin (L-ENK)

Neurons expressing the opioid peptide L-ENK appose GnRH neurons in the POA and ME in humans (Dudás and Merchenthaler 2003) but it is unknown whether L-ENK neurons appose GnRH neurons in mice or whether L-ENK, which, like M-ENK, is a delta opioid receptor agonist, affects GnRH neuronal activity.

Orphanin FQ (OFQ), a.k.a. nociceptin

OFQ, an endogenous ligand of the opioid receptor like (ORL)-1 receptor, inhibits GnRH release from rat hypothalamic slices (An et al. 2005) and [Arg(14), Lys(15)] OFQ,

an agonist of the ORL-1 receptor, inhibits LH pulse frequency in sheep (Foradori et al. 2007). However, whether OFQ acts directly on GnRH neurons is unknown.

Relaxin-3 (RLN3)

RLN3 increases plasma LH levels in a GnRH-dependent manner in rats and stimulates GnRH release from rat hypothalamic explants and immortalized GnRH neurons, which express the RLN3 receptors RXFP1 and RXFP3 (McGowan et al. 2008). However, whether RLN3 acts directly on native mouse GnRH neurons has not yet been shown.

Substance P (SP)

SP, which is encoded by the *Tac1* gene and binds to the SP receptor NK1R, a.k.a. TACR1, induces LH release in adult mice in a KP-dependent manner (Navarro et al. 2015). *Tac1* null mice exhibit delayed puberty onset and increased *GnRH* gene expression (Simavli et al. 2015; Maguire et al. 2017). SP axons appose most GnRH neurons, except in the anterior MS, where few SP axons appear to contact GnRH neurons (Hoffman 1985). However, whereas ~ 50% of ARC KP neurons and ~ 25% of AVPV KP neurons express TACR1 and ~ 50% of ARC KP neurons respond to an NK1R agonist, only ~ 25% of GnRH neurons express TACR1 (Navarro et al. 2015; Maguire et al. 2017). Taken together, the available evidence suggests that although SP may act directly on GnRH neurons, SP acts mainly indirectly via KP neurons and perhaps other neurons, to increase GnRH release.

Neurokinin B (NKB)

NKB, which is encoded by the *Tac2* gene and binds to the neurokinin 3 receptor (NK3R, a.k.a. TacR3), is co-expressed with KP in KP neurons in the ARC and likely co-released with KP from subsets of KP neuron afferents onto GnRH neurons in an E (via ERα)-dependent manner to regulate puberty onset (Kalló et al. 2012; Greenwald-Yarnell et al. 2016). Male *Tac2* and female *Tacr3* null mice exhibit normal sexual maturation and fertility, whereas female *Tac2* null mice exhibit delayed sexual maturation, suggesting that NKB is critical for sexual maturation in females and that NKB may regulate the timing of sexual maturation through other tachykinin receptors in the absence of TacR3 (True et al. 2015). A small subset (~ 10%) of GnRH neurons expresses NK3R (Navarro et al. 2015). The NK3R agonist senktide excites GnRH neurons indirectly via KP neurons in the ARC (Qiu et al. 2016) but also directly and/or indirectly evokes GnRH release from GnRH neuron axon terminals in the ME independently of KP (Gaskins et al. 2013).

Galanin-like peptide (GALP)

Like GAL, GALP, which has sequence homology to GAL, activates GALR2 but with higher affinity, increases c-Fos protein in GnRH neurons in the POA and stimulates GnRH-mediated LH secretion (Matsumoto et al. 2001). The effects of GALP on secretion are greater in males than in females and greater in pubertal males than in adult males (Castellano et al. 2006). Moreover, GALP-containing nerve terminals appose and make synaptic contacts with GnRH neurons in rats (Takenoya et al. 2006). Therefore, it seems likely that GALP would directly depolarize and possibly increase the firing of GnRH neurons; however, this has not yet been shown.

Neurotensin (NTS)

NTS axons appose ~ 30–50% of GnRH neurons and NTS receptor 2 is expressed in ~ 75% of GnRH neurons (Hoffman 1985; Dungan Lemko et al. 2010). However, it is unknown from which NTS neurons the axons arise and whether NTS directly affects GnRH neuronal activity.

Neuropeptide glutamic acid-isoleucine (NEI)

In rats, intracerebroventricular injection of NEI, a 14-amino acid peptide processed from prepro-MCH, increases serum LH levels and NEI fibers closely appose GnRH neurons in the POA/OVLT and are in close proximity to GnRH fibers in the ME (Attademo et al. 2004, 2006). Whether NEI directly affects GnRH neuronal activity is unknown.

Bradykinin (BK)

BK, which is expressed in the OVLT and ARC in the rat, stimulates GnRH secretion in male and proestrous female rat hypothalami in vitro and in immortalized GnRH neurons via the bradykinin B2 receptor and activation of a PKC signaling pathway and it appears to contribute to the steroid-induced GnRH/LH surge in the female ovariectomized rat (Shi et al. 1998). The bradykinin B2 receptor also appears to be expressed in mouse GnRH neurons (Todman et al. 2005). However, whether bradykinin acts directly on mouse GnRH neurons to stimulate GnRH neuronal activity or GnRH secretion has not been reported.

Endothelin (ET)

ET-B receptor immunoreactivity is observed in GnRH neuron fibers in the ME of rats (Yamamoto et al. 1997) and both ET-1 and ET-3 increase GnRH secretion in perifused hypothalamic cultures and immortalized GnRH neurons (Krsmanović et al. 1991; Moretto et al. 1993). Whether ET-1 or ET-3 affects

GnRH neuronal activity in the mouse has not yet been reported.

Angiotensin II (AT-II)

Exogenous (in OVX rats treated with E and P) and endogenous (in gonad-intact rats at proestrous only) AT-II stimulates GnRH/LH secretion but whether AT-II acts directly or indirectly on GnRH neurons is unknown (Steele et al. 1983, 1985, 1992).

Prolactin (PRL)

PRL stimulation of mammary gland development and lactogenesis results in amenorrhea/anovulation and hyperprolactinemia (mainly caused by a prolactinoma or the effects of drugs that interact with the dopamine system) is a major cause of infertility in both males and females (Donato Jr and Frazão 2016). A subpopulation of GnRH neurons expresses the PRL receptor. PRL phosphorylates 3′,5′-cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB) and induces phosphorylated Janus kinase/signal transducer and activator of transcription 5 (pSTAT5), which leads to changes in gene transcription in GnRH neurons and chronic PRL treatment suppresses LH secretion in females (Grattan et al. 2007; Brown et al. 2012). However, PRL does not appear to affect GnRH neuron firing (Brown et al. 2012), indicating that PRL acts on GnRH neurons mainly indirectly to suppress GnRH/LH secretion. Accordingly, chronic PRL treatment has been reported to induce pSTAT5 to a much greater extent in KP neurons than in GnRH neurons and to partially suppress KP mRNA and protein levels in KP neurons. Moreover, KP neuron activation (but not exogenous KP) fails to activate GnRH neurons during lactation (in contrast to diestrous), suggesting that inhibition of KP expression and consequently KP secretion, by PRL and other factors mediates the suppression of GnRH/LH secretion during lactation (Brown et al. 2014; Liu et al. 2014)

Fibroblast growth factor 21 (FGF21)

FGF21, a fasting-induced hepatokine, inhibits fertility by binding to its receptor, FGFR1 (a receptor tyrosine kinase) and co-receptor, β-klotho (KLB, a cell-surface protein with tandem glycosidase domains) and subsequently suppressing an SCN vasopressin (AVP) to the AVPV KP signaling pathway involved in the proestrous GnRH/LH surge (Owen et al. 2013). FGF21 may also inhibit fertility by increasing energy expenditure and the consequent caloric requirements, since (1) mice on a ketogenic diet remain fertile despite significant elevation in serum FGF21 levels, (2) absence of FGF21 in *Fgf21* null mice does not alter transient infertility induced by fasting, (3) FGF21 infused into the lateral ventricle does not suppress fertility and (4) a high fat diet restores fertility of female FGF21-overexpressing mice, which is associated with increased expression of *AVP* in the SCN and *Kiss1* in the AVPV (Singhal et al. 2016). However, mutations in *FGFR1* or *KLB* in humans result in idiopathic hypogonadotropic hypogonadism and lack of KLB in *Klb* null mice results in delayed puberty, altered estrous cyclicity and subfertility due to a hypothalamic defect associated with an inability of GnRH neurons to release GnRH in response to FGF21 (Xu et al. 2017). Thus, either an increase or decrease in FGF21/FGFR1/KLB signaling can result in infertility, consistent with the concept that a tightly regulated energy balance is required for optimal reproductive capacity and it is possible that functional hypogonadotropic hypogonadism, including hypothalamic amenorrhea and obesity-related amenorrhea, may also involve altered FGF21/FGFR1/KLB signaling (Xu et al. 2017). Immortalized GnRH neurons express FGFR1 and FGF21 can reach GnRH neurons via the ME and OVLT, suggesting that FGF21 may also act directly on GnRH neurons (Xu et al. 2017). Yet, whether native mouse GnRH neurons express FGFR1 and KLB and whether FGF21 affects GnRH neuronal firing or $[Ca^{2+}]_i$, remains to be determined.

A note on appositions, dendrites, axons, "dendrons" and action potential generation

Although most reports of appositions between presynaptic neurons and GnRH neurons are of appositions onto GnRH neuron cell bodies, it should be noted that GnRH neurons possess long dendritic processes, sometimes extending 1000 μm or more from the cell body. These processes are decorated with spine-like protrusions, including filopodia, which may serve as precursors for dendritic spines and like GnRH neuronal cell bodies and axon terminals may be apposed by presynaptic neurons that release neuropeptides. Mean dendritic spine density is 0.4–0.5 spines/μm, with dendritic spine density being highest in the first 50 μm of the dendrite (Campbell et al. 2005). Action potentials are initiated in the first 100–150 μm of the dendrite or in an axon-like process arising from a proximal dendrite, which together form a projection unit that functions simultaneously as a dendrite and an axon and is termed a "dendron" (Herde et al. 2013; Herde and Herbison 2015). Spine density in the cell body and proximal dendrites nearly doubles across puberty (from postnatal day 10 to postnatal day 60), reflecting increased excitatory input (Cottrell et al. 2006) and in females it increases by ~ 60% in GnRH neurons activated at the time of the GnRH/LH surge (Chan et al. 2011). Some GnRH neurons in the rostral POA within 100 μm of the OVLT reside and extend dendrites outside the blood–brain barrier, where they may directly sense molecules circulating in the bloodstream and also initiate action potentials (Herde et al. 2011; Herde and Herbison 2015).

Conclusion

The list of neuropeptides known to modulate or potentially modulate GnRH neuronal activity and GnRH secretion in mice is long and will likely grow as the effects on GnRH neurons of additional neuropeptides, including those of neuropeptides that are yet to be discovered, are investigated. While it is clear, based mostly on pharmacological and immunohistochemical studies, that some of the neuropeptides investigated thus far affect GnRH neurons directly and to which receptors they bind on GnRH neurons, further research is needed to elucidate their signaling mechanisms in GnRH neurons and to determine whether other known and yet to be discovered neuropeptides affect GnRH neurons directly or indirectly.

For most of the neuropeptides known to modulate GnRH neuronal activity, it also remains to be determined whether and under which physiological conditions, they are released endogenously onto GnRH neurons, the cells from which they are released and their reproduction-related roles (as well as those of their receptors). Studies utilizing optogenetics, in vivo electrophysiological recording, Ca^{2+} imaging or photometry (with genetically encoded Ca^{2+} indicators), retrograde transsynaptic viral tracing and/or mice with GnRH neuron-specific deletion (preferably inducible deletion to avoid developmental compensation) of selected neuropeptide receptors, some of which have already been performed (Constantin et al. 2013; Kirilov et al. 2013; Han et al. 2015; Yip et al. 2015; Clarkson et al. 2017), should be able to provide that information.

Acknowledgments This article is dedicated to the memory of Prof. Peter H. Seeburg (1944–2016).

Funding None.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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