A role for GnRH in olfaction and cognition: Implications for veterinary medicine

Vincent Prévot, Anne Duittoz

Received: 24 April 2023 | Revised: 5 June 2023 | Accepted: 14 June 2023

DOI: 10.1111/rda.14411

Reproduction in Domestic Animals WILEY

REVIEW

A role for GnRH in olfaction and cognition: Implications for veterinary medicine

Vincent Prévot[1] | Anne Duittoz[2]

[1]Univ. Lille, Inserm, CHU Lille, Laboratory of Development and Plasticity of the Neuroendocrine Brain, Lille Neuroscience & Cognition, UMR_S1172, Lille, France

[2]Physiologie de la Reproduction et des Comportements (PRC) UMR7247 INRA, CNRS, Centre INRAE Val de Loire, IFCE, Université de Tours, Nouzilly, France

Correspondence
Vincent Prévot, Univ. Lille, Inserm, CHU Lille, Laboratory of Development and Plasticity of the Neuroendocrine Brain, Lille Neuroscience & Cognition, UMR_S1172, Lille, France.
Email: vincent.prevot@inserm.fr

Funding information
European Union Horizon 2020 research and innovation program, Grant/Award Number: 847941

Abstract

Pulsatile secretion of gonadotropin-releasing hormone (GnRH) is essential for the activation and maintenance of the function of the hypothalamic–pituitary-gonadal (HPG) axis, which controls the onset of puberty and fertility. Two provocative recent studies suggest that, in addition to control reproduction, the neurons in the brain that produce GnRH are also involved in the control postnatal brain maturation, odour discrimination and adult cognition. Long-acting GnRH antagonists and agonists are commonly used to control fertility and behaviour in veterinary medicine, primarily in males. This review puts into perspective the potential risks of these androgen deprivation therapies and immunization on olfactory and cognitive performances and well-aging in domestic animals, including pets. We will also discuss the results reporting beneficial effects of pharmacological interventions restoring physiological GnRH levels on olfactory and cognitive alterations in preclinical models of Alzheimer's disease, which shares many pathophysiological and behavioural hallmarks with canine cognitive dysfunction. These novel findings raise the intriguing possibility that pulsatile GnRH therapy holds therapeutic potential for the management of this behavioural syndrome affecting older dogs.

KEYWORDS
brain, hypothalamus, learning, neurodevelopmental diseases, reproduction, smell, well-aging

1 | INTRODUCTION

Gonadotropin-releasing hormone (GnRH) is synthesized and released by a handful of neurons (about 800 in rodents and about 2000 in primates), whose cell bodies are scattered in the ventral forebrain between the olfactory bulb and the hypothalamus (Casoni et al., 2016; Duittoz et al., 2021). These GnRH neurons, which ensure the survival of the species by controlling the ability of the individuals to reproduce, all project to the median eminence of the hypothalamus, where they open into the pituitary portal circulation connecting the neuroendocrine hypothalamus to the anterior pituitary gland (Boehm et al., 2015). Blood-borne GnRH travels to the pituitary to modulate the activity of gonadotropic cells producing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by acting onto its cognate receptor, GnRHR (McArdle & Roberson, 2015). LH and FSH are then released into the general circulation to promote the growth of the gonads, gametogenesis and the production of gonadal steroids, such as testosterone in males and oestrogens in females (Hunzicker-Dunn & Mayo, 2015; Smith & Walker, 2015). These gonadal steroids in turn provide positive or negative feedback loops onto the different stages of this hypothalamic–pituitary-gonadal (HPG) axis and thus allow the establishment of a permanent dialogue

between the brain, the hypophysis and the male testes or the female ovaries (Chachlaki, Garthwaite, & Prevot, 2017; Delli et al., 2021; Goodman, 2015; Goodman et al., 2022; Herbison, 2020).

In all mammals, GnRH is not released uniformly but in a specific pattern that is essential to its function, featuring a low-level basal secretion with superimposed pulsatile rhythms (Caraty et al., 1982; Frost et al., 2008; Sarkar & Minami, 1995). In mammals, each GnRH pulse in the portal circulation drives an LH pulse in the general circulation (Clarke & Cummins, 1982; Hoffman & Crowley Jr., 1982; Moenter, Brand, & Karsch, 1992; Moenter, Brand, Midgley, & Karsch, 1992) and their frequency appears to be tightly regulated across the estrous cycle by the fluctuating levels of gonadal steroids (Czieselsky et al., 2016; Moenter & Evans, 2022; Reame et al., 1984). In this manner, a permanent two-way dialogue is established between the brain, the pituitary and the gonads.

Intriguingly, studies in sheep have shown not only that GnRH from exogenous sources crosses the blood-brain barrier (Caraty & Skinner, 2008) but also that GnRH concentrations in the cerebrospinal fluid (CSF), thought to be derived mainly from the median eminence (Caraty & Skinner, 2008), are proportional to those in the portal blood vessels delivering the neurohormone to the anterior pituitary (Skinner et al., 1997).

In this review, we will provide a brief overview of the recent advances in our understanding of the development and the function of GnRH neurons throughout life focusing on the unexpected role of the timely activation of the HPG axis early after birth on brain development and the direct involvement of GnRH in olfactory and cognitive performance in adults. Knowing that long-term GnRH antagonists and agonists treatments, anti-GnRH immunization and castration are commonly used to control fertility and behaviour in veterinary medicine, we will also put into perspective the potential risks of these androgen deprivation therapies on olfactory and cognitive performances and well-aging in domestic animals.

2 | NATURAL HISTORY OF THE NEURONS PRODUCING GnRH

During embryonic development, in mammals, as in all known vertebrates, GnRH neurons are not born in the brain but originate in the nasal compartment where they originate both from the olfactory placode and the neural crest and migrate into the forebrain and hypothalamus along olfactory or terminal nerves (Casoni et al., 2016; Duittoz et al., 2021; Taroc et al., 2017). The complex developmental events leading to correct GnRH neuronal migration and secretion are tightly regulated by the specific spatiotemporal expression patterns of growth factors, adhesion molecules and diffusible guidance cues that are either attractive or repulsive (Giacobini, 2015). In addition to play a key role in the establishment of the scaffold along which GnRH neurons migrate into the brain (Hanchate et al., 2012; Imai et al., 2009; Marcos et al., 2017), these chemotrophic factors can also regulate the cell-autonomous migration, survival and function of GnRH neurons themselves (Vanacker et al., 2020), and their mutations in humans lead to dysfunctions in both olfaction and fertility (Cariboni et al., 2015; Hanchate et al., 2012; Kotan et al., 2021; Marcos et al., 2017). In domestic species, the development of GnRH neurons has been particularly well characterized in sheep. The nasal placode develops between the gestational age of 22 (G22) and G26 (total gestation: 145 days). The first GnRH immunoreactive cells appear at gestational age of G35 along the nasal septum in association with olfactory, vomeronasal nerves and the extracerebral part of the terminal nerves (Caldani et al., 1995). Between G40 and G60, GnRH neurons migrate into the brain, following the terminal nerves pathway towards the preoptic area and the anterior hypothalamus. The growth of axons towards the median eminence takes place between G60 and G70 (Caldani et al., 1995) concomitantly with the onset of LH beta subunit expression in pituitary (Messaoud-Toumi et al., 1993; Sheng et al., 1998).

At birth, GnRH neurons have reached their final destination within the forebrain, where they are diffusely distributed and are particularly abundant in the preoptic region in rodents and sheep and can be found in the tuberal region of the hypothalamus close to the median eminence in some species, particularly in primates. Regardless of their position, their axons target the pericapillary space of the median eminence in order to be able to release their neurohormone into the fenestrated vessels of the pituitary portal circulation for delivery to the anterior pituitary.

During postnatal development, GnRH neurons are subject to a sequence of complex maturational events affecting their biosynthetic capacity, neurosecretory pattern and morphology, which ultimately lead to sexual maturation and the initiation of puberty. This array of events, which may be linked, at least in part, to the integration of post-migratory GnRH neurons into the neural network responsible for relaying bodily information to these core neurons, has been divided in both sexes into four stages based on morphological and physiological parameters, as delineated earlier by Ojeda and colleagues (Ojeda et al., 1980): a neonatal period that comprises the first week of extra-uterine life (where the day of birth is designated postnatal day 0 or P0); an infantile period that extends from P8 to the age at weaning, characterized by a transient surge in GnRH production leading to gonadal activation occurring in humans and other mammals alike and termed minipuberty (Kuiri-Hanninen et al., 2014; Lanciotti et al., 2018; Prevot, 2015; Terasawa, 2022); a juvenile period during which the GnRH system is either progressively maturing in short-living species (Prevot, 2015) or quiescent in mammals with long life span (Boehm et al., 2015; Terasawa, 2022), respectively; and a peripubertal period that ends with the appearance of mature sperm in the vas deferens in males or with the occurrence of first ovulation in females, namely puberty (Boehm et al., 2015; Foster & Hileman, 2015; Prevot, 2015; Terasawa, 2022). In male lambs, during the first two weeks after birth LH plasma levels are low (<2 ng/mL/6 h) and LH pulse frequency is below 1 pulse/6 h. LH pulse frequency and pulse amplitude gradually increase from postnatal week 4 to week 8 (1 pulse/1 h and 6 ng/mL/6 h; Foster et al., 1978). Between weeks 8 and 16, the frequency of LH pulses decreases to 1–2 pulses/h, and testosterone levels increase suggesting the onset of puberty (Shropshire and Suffolk lambs).

In adults, GnRH is released in a pulsatile fashion into the pituitary portal circulation (Frost et al., 2008; Sarkar & Minami, 1995), and each pulse of GnRH elicits a pulse of LH in the general circulation (Caraty et al., 1982). In humans, one pulse of GnRH every 90 or 120 min is sufficient to promote ovulation and spermatogenesis, respectively, in patients with GnRH deficiency (Boehm et al., 2015). In females, pulse frequency appears to vary through the ovarian cycle. During the menstrual cycle in women, as shown by the use of 10-min sampling intervals, LH pulse frequency in the follicular phase is about 1 pulse every 60 min, whereas, during the luteal phase, it is 1 pulse every 180 min (Reame et al., 1984). These changes in pulse frequency are highly similar to the ones recently identified in mice with a similar sampling interval, with LH pulse frequency being the lowest in oestrus (Czieselsky et al., 2016).

During menopause or after gonadectomy, because of the deprivation of gonadal steroids and thus the absence of their negative feedback action on the hypothalamic GnRH neural network, GnRH/LH pulse frequency remains constantly high, for example at about one pulse per hour in women (Hall et al., 2000) and 3 pulses per hour in mice (Czieselsky et al., 2016).

3 | MINIPUBERTY IS A CRITICAL PERIOD FOR HPG AXIS DEVELOPMENT

In females, at the beginning of the infantile period, circulating FSH levels rise dramatically and reach peak values at 12 days of age in both rats (Dahl et al., 1988; Dohler & Wuttke, 1975; Kamberi et al., 1980; Kragt & Dahlgren, 1972) and mice (Prevot et al., 2003; Stiff et al., 1974) and at 1–3 month of age in baby girls (Kuiri-Hanninen et al., 2013; Kuiri-Hanninen, Kallio, et al., 2011). This infantile surge in FSH enhances the development of preantral follicles and rescues early antral follicles from apoptotic death (McGee & Hsueh, 2000). Blunting this infantile rise in FSH levels by GnRH antagonist treatment decreases ovarian weight and preantral follicle development in rats at P19, while FSH treatment reverses these effects (McGee et al., 1997). In addition, FSH-deficient mice are infertile due to the lack of maturation of secondary or preantral follicles into antral follicles (Kumar et al., 1997). Along the same lines, the absence of circulating FSH in *hpg* mice, which lack GnRH, is associated with a dramatic reduction in the number of follicles reaching the preantral stage and the complete absence of ovarian follicles attaining the antral stage (Halpin et al., 1986). Even if their fluctuation is less consistent during this period, LH levels are also elevated in both infantile rats and mice (Dohler & Wuttke, 1975; Ojeda & Ramirez, 1972; Prevot et al., 2003) and sporadic bursts of secretion have been reported to occur (Dohler & Wuttke, 1974, 1975). However, LH does not appear to play a major role in ovarian development at this early stage of sexual maturation since LH receptor knockout mice, in contrast to FSH knockout animals (Kumar et al., 1997), exhibit early antral follicles (Zhang et al., 2001). It is worth noting in this context that between 7 and 21 days of age, there is an overall increase in steroidogenic enzyme activity in the ovary, which leads, among other results, to a marked and continuous increase in the production of oestrogens, thought to be mainly due to increases in aromatase activity, and thus oestradiol synthesis by the immature ovary, under the influence of FSH (Fortune & Eppig, 1979; Francois et al., 2017; Funkenstein et al., 1980). Gonadal steroidogenesis is also seen to be activated during the postnatal gonadotropin surge in girls and is thought to play a role in normal female reproductive development (Kuiri-Hanninen et al., 2013; Figure 1).

How is minipuberty initiated? Two decades ago, it was shown that glial cells that functionally interact with GnRH neurons by releasing gliotransmitters such as prostaglandin E2 (PGE2; Clasadonte et al., 2011; Prevot & Sharif, 2022) are necessary for the normal initiation and progression of minipuberty in mice (Prevot et al., 2003). A 2021 study conducted in rats demonstrated that GnRH neurons themselves were actually playing a direct role in sculpting their own microenvironment by the active recruitment of glial progenitor cells during the infantile period (Pellegrino et al., 2021). These glial progenitors, which are attracted by GnRH neurons in the vicinity of their cell bodies, eventually differentiate into astrocytes and escort them into adulthood (Pellegrino et al., 2021). This event, which involves the release of PGD2 by the GnRH neurons and the activation of the DP1 PGD2 receptor in progenitor cells, is required for the maturation of the electrical activity of the GnRH neurons, probably by favouring the establishment of the excitatory glutamatergic inputs onto GnRH neuronal cell bodies, and minipubertal FSH release (Pellegrino et al., 2021). During postnatal development, astrocytes indeed control synapse formation and functional efficacy (Pfrieger & Barres, 1997; Ullian et al., 2001), shaping synaptic properties to fit ongoing developmental and functional needs, thus providing contextual guidance to the synapses (Mu et al., 2019; Papouin et al., 2017). Of note, this communication between GnRH neurons and glial cells is highly sensitive to endocrine disruption since postnatal exposure to low doses of the plasticizer bisphenol A (BPA), known to alter pulsatile GnRH release in infantile rats (Franssen et al., 2016), was seen to prevent the ability of GnRH neurons to attract newborn glial cells in their vicinity in female rat pups (Pellegrino et al., 2021). Blocking these maturational events leads to delayed puberty and alteration in the onset of estrous cyclicity (Pellegrino et al., 2021). Along the same line, sodium fluoroacetate (Kalmbach, 1945), which has been used extensively against mammalian "pest" species worldwide (e.g. coyotes and rodents), has been shown to blunt PGE_2-mediated gliotransmission in the GnRH system (Clasadonte et al., 2011). It is therefore not unreasonable to imagine that livestock grazing in areas polluted by fluoroacetate might experience reproductive problems.

How is minipuberty ended? FSH-induced oestrogen production during minipuberty is seen to activate a subset of oestrogen receptor alpha (ERα)-expressing nitric oxide (NO) synthetizing neurons in the surroundings of the GnRH neurons in infantile mice (Chachlaki, Malone, et al., 2017) and this event appears to be key to restricting the amplitude of minipuberty and to ending it (Chachlaki et al., 2022; Figure 1). NO is indeed a highly soluble, diffusible and membrane-permeable neurotransmitter, known to inhibit the electrical activity of GnRH neurons via the activation of the NO-sensitive guanylate

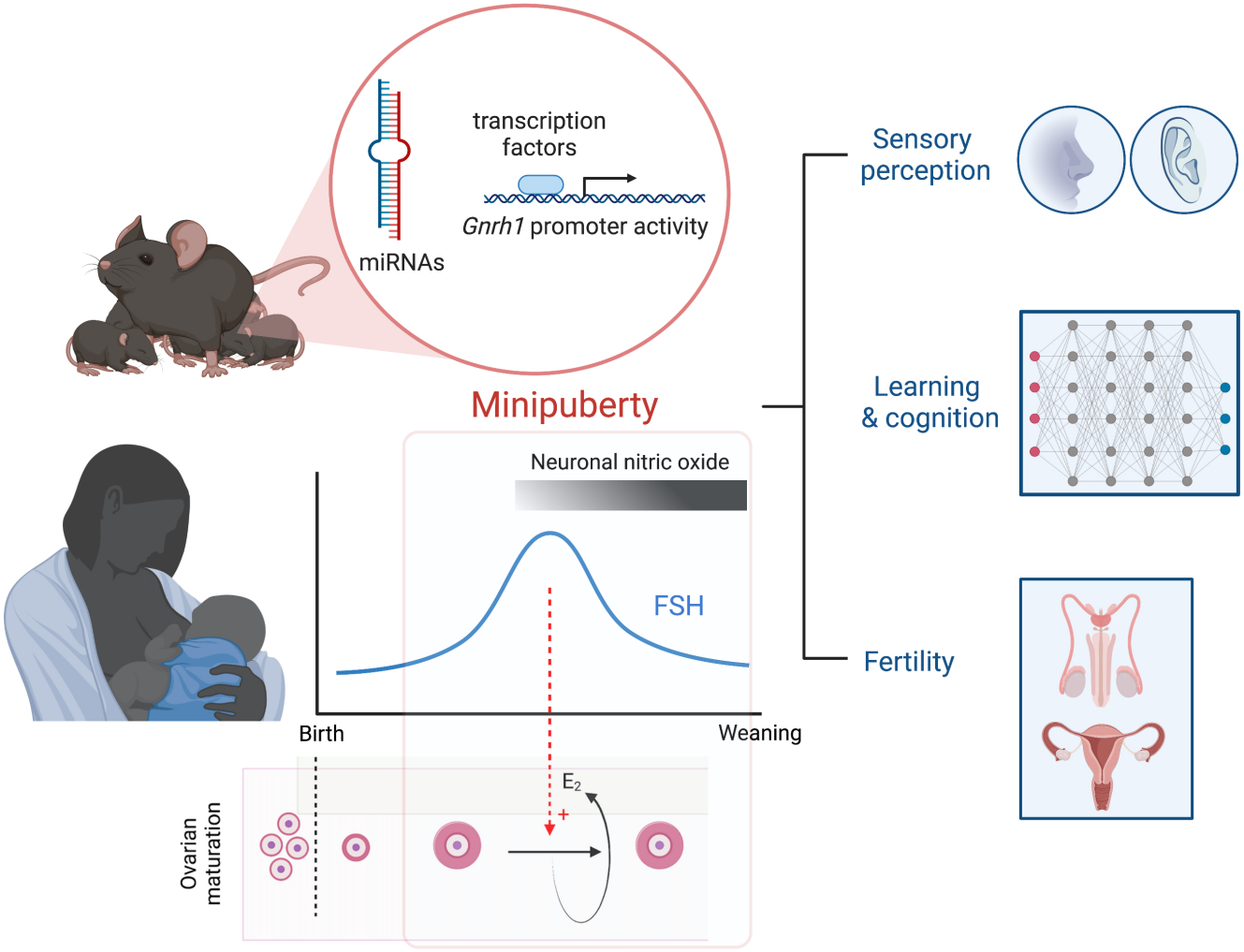

FIGURE 1 Minipuberty is a critical period for brain development. Preclinical studies have shown that during minipuberty, an infantile 'critical period' lasting just a few days in rodents and months in humans, a dramatic switch in the microRNA expression pattern of GnRH neurons inverts the balance between inductive and repressive signals, triggering increased hypothalamic GnRH expression and controlling the crucial transition from the early infantile phase, when its levels are low, to the GnRH-fuelled run-up to puberty. During minipuberty, activation of the GnRH neurons induces a dramatic rise in FSH levels, which promotes steroidogenesis at the gonads. This results in an increase in circulating gonadal steroids, which feedback onto the brain where they activate neurons expressing their receptors and, in particular, the hypothalamic neurons producing nitric oxide that control both the amplitude and termination of the minipubertal FSH surge. Failure of the infantile activation of nitric-oxide synthesizing neurons results in altered minipuberty and reproductive, sensory and cognitive comorbidities later in life that can be reversed by infantile exposure to inhaled nitric oxide. Created with BioRender.com.

cyclase and the production of cyclic guanosine monophosphate (cGMP), which induces membrane hyperpolarization via the activation potassium conductance in the GnRH neuron (Clasadonte et al., 2008). Mice knocked out for the neuronal nitric oxide synthetase (*Nos1*, also termed nNOS) show abnormally high levels of FSH associated with increased GnRH neuronal activity at minipuberty (Chachlaki et al., 2022). *Nos1* knockout (KO) mice also show delayed puberty onset and impaired adult estrous cyclicity. Intriguingly, selectively impairing Nos activity during the infantile period phenocopies the reproductive phenotype of *Nos1*KO mice and, in contrast, NO replenishment by inhaled NO or sildenafil, the inhibitor of phosphodiesterase 5 (enzyme hydrolysing cGMP into GMP [Chachlaki & Prevot, 2020]), during the infantile period not only rescues minipubertal FSH levels but also the reproductive phenotype in *Nos1* KO mice (Chachlaki et al., 2022). Combined, these results suggested that increased Nos1 activity during minipuberty is required for the hypothalamus-driven onset of gonadal steroid negative feedback and the repression of the HPG axis at the end of minipuberty and that the overall process is essential for the maturation of the HPG axis.

In males, circulating FSH levels in rats rise dramatically after the second week of life and appear to reach a maximum between 30 and 40 days of age, and then decrease when serum testosterone concentrations attain levels similar to those seen in adults (Chappel & Ramaley, 1985; Dohler & Wuttke, 1974, 1975; Ketelslegers et al., 1978; Nazian & Cameron, 1992; Negro-Vilar et al., 1973; Ojeda

& Ramirez, 1972). In mice, although an infantile surge of circulating FSH has been detected at the end of the infantile period at P23 in a recent study (Delli et al., 2023), others suggest that circulating FSH levels continue to rise until adulthood (Hazra et al., 2013; McGee & Narayan, 2013). Using ultrasensitive approaches to follow LH levels in the same mice at different time points of postnatal development using ultrasensitive approaches (Steyn et al., 2013) reveals that LH levels peak one week after weaning, that is, at 30 days of age in mice (Delli et al., 2023). In baby boys, as in girls, circulating gonadotropins peak at 1–3 month of age, and in contrast to girls LH levels predominate in boys (Andersson et al., 1998; Kuiri-Hanninen et al., 2014; Shinkawa et al., 1983). The key role of infantile/juvenile GnRH release in male sexual development has been shown using passive immunization (Bercu, 1982; Bercu et al., 1977; Vogel et al., 1983) or treatment with a GnRH antagonist (Kolho et al., 1988; van den Dungen et al., 1989), which result in delayed puberty, the permanent impairment of testicular function and defective adult sexual behaviour.

As in females, Nos1 neurons in the neighbourhood of the GnRH neurons in the preoptic region in male mice are activated concomitantly with the FSH surge (Delli et al., 2023). Knocking out Nos1 in males results in a marked delay in balano-preputial separation, an external marker of sexual maturation occurring after weaning, which is rescued by sildenafil treatment in the infantile period (Chachlaki et al., 2022). Unexpectedly, and in contrast to what is observed in females (Chachlaki et al., 2022), even though this activation of Nos1 neurons at P23 involves the action of oestrogens, it appears to be independent of gonadal steroids, as castration during the infantile period does not prevent it (Delli et al., 2023). In addition, male infantile Nos1 neurons do not express AR, but abundantly express ERα throughout postnatal development, similar to females, and the selective pharmacological blockade of ERα appears to blunt the age-dependent activation of Nos1 (Delli et al., 2023). This is in agreement with prior findings in the rhesus monkey showing that the postnatal functional maturation of the male HPG axis is testis- and male-gonadal-steroid-independent (Plant, 1980). Instead, it could be that, at least in males, an extragonadal source provides the estrogenic input necessary to promote the activation of Nos1 and subsequently, the GnRH system. In fact, in males, only about 20% of circulating oestrogens are produced by the testes, with the majority of estrogenic content coming from the conversion of testosterone by aromatase (Cyp19a1) in the brain or other peripheral tissues such as the adipose tissue, the bones or the skin (Cooke et al., 2017).

In both males and females, during minipuberty, GnRH neurons also undergo a switch in microRNA (miRNA) expression that in turn flips a switch in a multi-layered array of *Gnrh1* promoter activators and repressors, permitting the sustained increase of the neurohormone required for subsequent sexual maturation (Messina et al., 2016; Figure 1). Two miRNA species act as the linchpins of this process: the miR-200/429 family, which is not only upregulated during this critical period but selectively enhanced in GnRH neurons, and miR-155, which appears to act on other hypothalamic cell types as well, and mediates, for example, the effects of the concomitant release of NO upstream of GnRH neurons detailed in the previous paragraph. Interfering with the binding and function of these two key miRNA species blunts the infantile increase in GnRH expression, and the in vivo alteration of the miR-200/429-transcription factor micronetwork leads to the disruption of normal puberty onset as well as normal estrous cyclicity in adulthood. Suppressing the ability of GnRH neurons to synthesize mature miRNAs by knocking out *Dicer*, a gene encoding an RNAse-III endonuclease essential for miRNA biogenesis leads to the progressive loss of *Gnrh1* expression and GnRH production during postnatal development, yielding apubertal, hypogonadal and infertile male and female mice (Messina et al., 2016). Among the transcription factors targeted directly or indirectly by miR-155 and miR-200/429 are *Cebpb and Zeb1*, *respectively*, whose repression is required for normal *Gnrh1* expression from the second week of life by enabling, for example, the expression of activators such as *Otx2*, which is a target for Zeb1. Particularly intriguing is the fact that *Cebpb* encodes CAAT/enhancer binding protein β (C/EBPβ), a transcription factor that represses *Gnrh1* expression under the influence of NO (Belsham & Mellon, 2000). Thus, miR-155-induced repression of *Cebpb* expression at the time of minipuberty may be the key to avoiding the silencing of *Gnrh1* expression by the FSH-induced estrogenic activation of neuronal NO production near the GnRH neurons. Accordingly, mice in which *Dicer* is selectively knocked out in GnRH neurons exhibit a 10-fold higher expression of *Cebpb* transcript in GnRH neurons than control littermates, and pharmacological inhibition of Nos1 activity at minipuberty rescues *Gnrh1* mRNA levels in mutant mice (Messina et al., 2016).

Although rarely studied, the transient HPG axis activation during minipuberty is thought to be altered in patients with congenital hypogonadotropic hypogonadism (CHH; Boehm et al., 2015). In humans, the consequences of altered minipuberty are largely unknown beyond defects in testicular descent and penile growth (Kuiri-Hanninen et al., 2014; Lanciotti et al., 2018). However, findings published in 2022 show that rare heterozygous *NOS1* mutations cause CHH both in men and women (Chachlaki et al., 2022).

4 | MINIPUBERTY IS A CRITICAL PERIOD FOR BRAIN DEVELOPMENT

Recent striking evidence suggests that minipuberty, in addition to playing a role in the developmental process by which the capacity for sexual reproduction is achieved and maintained, could also affect brain development and the maintenance of sensory (e.g. olfaction and hearing) and cognitive performance throughout life (Chachlaki et al., 2022). The reasons for this provocative thought are twofold: by activating steroidogenic activity in the gonads and the release of oestrogens and testosterone, minipuberty could flip a switch in postnatal brain development by activating the neurons, including NO-producing neurons expressing the cognate gonadal-steroid receptors in the hypothalamus (Chachlaki, Malone, et al., 2017), but also in the whole brain (Chachlaki et al., 2022); by securing and stabilizing *Gnrh1* expression and GnRH production through specific

activation of miRNA-transcription-factor micro-networks in GnRH neurons (Messina et al., 2016), minipuberty could enable proper communication of hypothalamic GnRH neurons with neurons expressing the GnRHR in extrahypothalamic areas such as the hippocampus and cortex involved in sensory and cognitive processes (Manfredi-Lozano et al., 2022).

A landmark study published in 2022 has indeed shown that mice with exacerbated minipuberty due to the absence of *Nos1* expression develop in addition to their impaired fertility condition, olfactory, auditory and cognitive comorbidities, traits that are also found in probands with *NOS1* mutation (Chachlaki et al., 2022; Figure 1). The same study intriguingly shows that restoring NO levels or increasing the half-life of endogenous NO production in *Nos1* KO mice during the late infantile stage (between P10 and P23) using inhaled NO or sildenafil, respectively, rescues not only sexual maturation but also the ability of the animals to perceive social and non-social odours, as well as cognitive performances in adulthood (Chachlaki et al., 2022). Altogether, these findings in preclinical models suggest that NO may control the establishment and homeostasis of both reproductive and non-reproductive networks and the rise in FSH-induced oestrogen production during minipuberty may trigger the synchronous maturation of these varied Nos1-dependent networks. These results also resonate with what is known about the effects of preterm birth in humans. Preterm infants, who have an increased risk of developing impaired reproductive capacity (Swamy et al., 2008), intellectual disability, and hearing loss (D'Onofrio et al., 2013; Moster et al., 2008), also display abnormally high serum FSH levels during minipuberty (Kuiri-Hanninen, Kallio, et al., 2011; Kuiri-Hanninen, Seuri, et al., 2011), recapitulating some phenotypic aspects of Nos1-deficient patients with CHH and mice. Given the safe use of inhaled NO and sildenafil to promote lung maturation and vascularization in preterm infants, this line of treatment at minipuberty may be useful to improve brain development in infants, a hypothesis that is currently being investigated by the European miniNO consortium (https://minino-project.com). A similar therapeutic approach could be used in preterm canine neonates (Vannucchi et al., 2012, 2015) and to prevent neonatal mortality in pigs (Vanderhaeghe et al., 2011). It might be interesting to explore whether NO deficiency could also be a risk factor for neonatal mortality in precocial domestic species, including cattle (Mee et al., 2013), camelids (Kapustka & Budzynska, 2022; Nagy et al., 2023; Tibary et al., 2008; Whitehead, 2009), Equidae (Castagnetti et al., 2007) and deer (Qi et al., 2011).

5 | GnRH NEUROENDOCRINE NEURONS COMMUNICATE WITH GnRH-RECEPTOR-EXPRESSING NEURONS IN THE CEREBRAL CORTEX TO CONTROL SENSORY AND COGNITIVE PROCESSES

Advanced tissue-clearing approaches demonstrated that the GnRH neurons that have their cell bodies distributed from the olfactory bulb to the hypothalamus do not only send projections to the median eminence of the hypothalamus where they release their neurohormone into the pituitary portal blood but also send projections to extrahypothalamic areas in which lay neuronal populations expressing the GnRH receptor, including the hippocampus and the cortex, which are brain structures involved in learning and memory processes and social behaviours (Manfredi-Lozano et al., 2022; Figure 2). The use of viral approaches has intriguingly shown that these extrahypothalamic projections do not originate from a specific population of GnRH neurons but from the very hypophysiotropic GnRH neurons in the hypothalamus and that selectively and acutely inhibiting the neuronal activity of GnRHR-expressing neurons in the neocortex dramatically reduces both cognitive and olfactory performance (Manfredi-Lozano et al., 2022). Together, these findings highlight the possibility that normal cognitive and olfactory function depends on extrahypothalamic projections and the action of GnRH neuroendocrine neurons.

6 | RHYTHMIC GnRH RELEASE IS REQUIRED FOR OLFACTORY PERCEPTION AND COGNITION

A work published in 2013 showed that aging processes leading to cognitive decline and whole-body functional deterioration were associated with a neuroinflammatory-pathway-mediated decrease in hypothalamic *Gnrh1* expression (Zhang et al., 2013). In this study, infusion of either peripheral or central GnRH daily for 3 days rescued the survival of newborn cells in the hippocampus and the hypothalamus and ameliorated aging-related cognitive decline (Zhang et al., 2013). Studying age-related olfactory and cognitive decline in a mouse model of Down syndrome (Ts65Dn mice), a work published in 2022 revealed that the deterioration of sensory and learning performance in these mice, in contrast with the aforementioned study, did not involve neuroinflammation, but was reflected by an age-dependent decline in GnRH expression and production taking root at minipuberty (Manfredi-Lozano et al., 2022). Indeed, whereas GnRH production was comparable in trisomic and wild-type littermates at birth, the number of GnRH immunoreactive cell bodies was seen to decrease in young adults when cognitive alterations were first noted. This decrease in GnRH peptide production in adults was associated with the loss of GnRH-immunoreactive neuronal fibres in the hippocampus and the cortex and was accompanied by a striking imbalance in the expression of the miRNAs of the miR-200 family together with an upregulation of the *Gnrh1* promoter repressor *Zeb1* and the downregulation of the activator *Otx2* in the preoptic region where GnRH cell bodies reside in mice. Transcriptomic analysis in infantile GnRH neurons isolated at P12 using fluorescent-activated cell sorting demonstrated that the decrease in *Gnrh1* expression due to an imbalance in the transcription-factor-gene micro-network controlling its expression occurs as early as minipuberty in trisomic mice (Manfredi-Lozano et al., 2022). The loss of GnRH immunoreactivity in the brain of adult Ts65Dn mice was

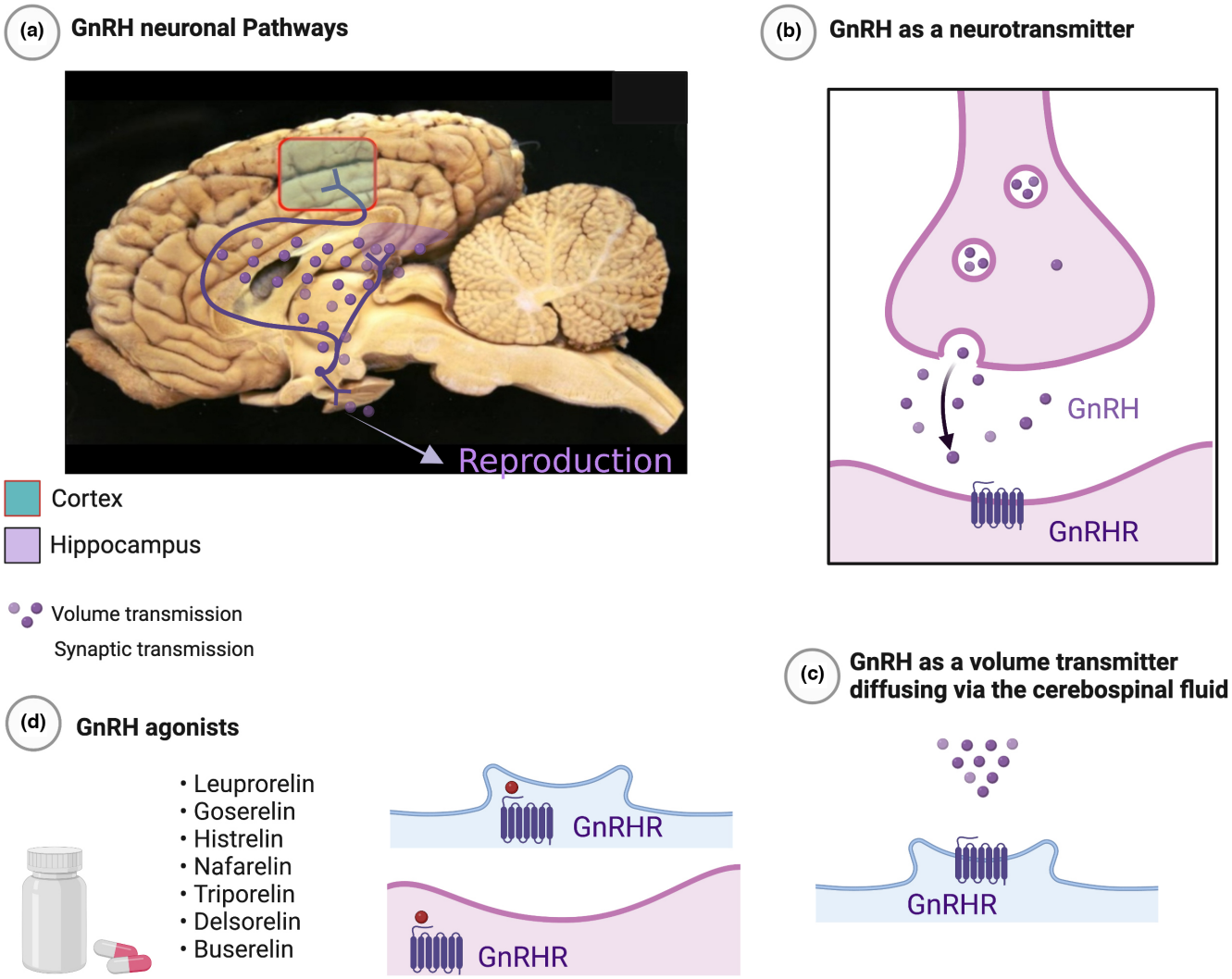

FIGURE 2 Transsynaptic and volume-transmission mediated delivery of GnRH to GnRHR-expressing neurons in extrahypothalamic brain regions. (a) Neuroendocrine GnRH neurons controlling reproduction also send neuronal processes to neocortical brain regions where GnRHR-expressing neurons are located and could therefore deliver GnRH synaptically to them (b). At the median eminence of the hypothalamus, each episode of GnRH release into the pituitary portal circulation corresponds to an episode of increase in GnRH concentrations in the cerebrospinal fluid, suggesting that CSF-borne GnRH could act remotely on GnRHR-expressing sites by volume transmission (c). (d) GnRH agonists from exogenous sources cross the blood–brain barrier and are therefore likely to inhibit GnRH signalling in GnRHR-expressing brain cell populations in addition to targeting pituitary gonadotrophs. Created with BioRender.com.

associated with an alteration in GnRH/LH pulsatile release both in males and females with normal LH pulse frequency but decreased LH pulse amplitude. Remarkably, altering GnRH pulsatile release in wild-type mice by a constant infusion of GnRH (Lutrelef®), which downregulates the GnRH receptor and blocks the reproductive axis (Belchetz et al., 1978), using an osmotic minipump for 15 days, not only blunted LH pulsatility but also resulted in deleterious consequences on both olfactory and cognitive performance in these mice (Manfredi-Lozano et al., 2022; Figure 3). By contrast, implantation with a subcutaneous programmable minipump delivering pulsatile GnRH for 15 days, rescued both olfactory discrimination and cognitive function and increased LH pulse amplitude to wild-type levels in Ts65Dn mice (Manfredi-Lozano et al., 2022; Figure 3). Of note, bilateral orchidectomy did not affect the rescue of olfaction or recognition memory by pulsatile GnRH, suggesting that the functional improvements observed were independent of the gonadotropic effects of GnRH, and could instead be due to the mobilization of cognitive reserves in male Ts65Dn mice (Manfredi-Lozano et al., 2022). In a pilot open-label study of 7 human patients with Down syndrome, pulsatile GnRH therapy using a LutrePulse pump, a safe treatment used for four decades in patients with CHH (Hoffman & Crowley Jr., 1982), for 6 months increased cognitive performances in these patients by 20–30% and restored functional connectivity in neuronal networks known to be altered in Down syndrome (Manfredi-Lozano et al., 2022), approaching control values using resting-state functional magnetic resonance imaging (Figueroa-Jimenez, Canete-Masse, et al., 2021; Figueroa-Jimenez, Carbo-Carrete, et al., 2021; Huang et al., 2015).

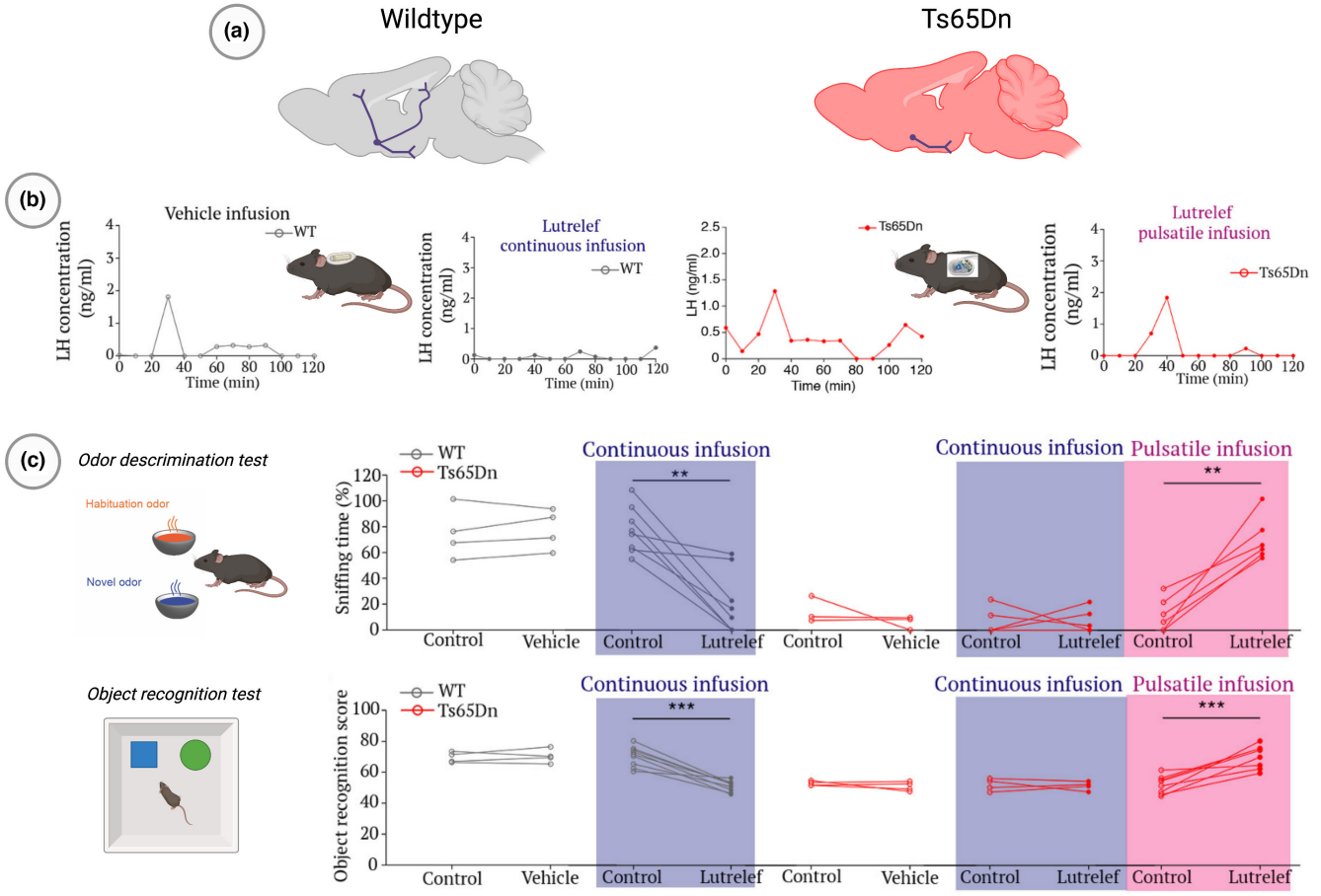

FIGURE 3 Pulsatile GnRH treatment rescues olfaction and cognition in a mouse model of Down syndrome, whereas continuous GnRH administration impairs these non-reproductive functions in wild-type mice. (a) Extrahypothalamic GnRH immunoreactivity is lost in the Ts65Dn mouse model of Down syndrome. (b) LH secretion profile in wild-type (WT) and Ts65Dn mice with or without implantation of an osmotic or programmable GnRH (Lutrelef®) minipump. (c) Effect of GnRH treatment on odour discrimination and object recognition tasks in adult mice. From Manfredi-Lozano et al. (2022) with permission.

In summary, whereas gonadotropin-induced gonadal function is not required for the cognitive or olfactory functions of GnRH, the GnRH pulsatile release required for pulsatile gonadotropin secretion appears to be equally essential for these non-reproductive GnRH-mediated brain functions (see for Review Manfredi-Lozano et al., 2022; Prevot et al., 2023). This raises the intriguing possibility that altered GnRH pulsatile release may be involved in age-related cognitive decline in the general population (Hoffmann, 2022). This could be especially true after menopause, that is, the end of any follicular growth, andropause or castration, when the pattern of GnRH secretion becomes permanently accelerated due to the absence of any negative feedback from gonadal steroids, which could, over time, result in functional alterations of the constantly active GnRH neurons. On the other hand, the findings discussed in this section also raise the provocative idea that well-aging could be programmed at minipuberty and that intervention during this critical window of postnatal development could improve cognitive and neurodegenerative disorders in specific conditions such as Huntington's disease (Braz et al., 2022), minipuberty-altering gene mutations (Chachlaki et al., 2022), but also possibly in cases of preterm birth (https://minino-project.com). Neonatal viral infection targeting GnRH neurons, which have access to the olfactory epithelium even after birth (Chachlaki et al., 2022; Sauvé et al., 2021), including infections by the SARS-CoV2 virus known to infect both humans (Sauvé et al., 2021) and animals (de Melo et al., 2021; Koeppel et al., 2022; Mastutik et al., 2022), could be one of the risk factors altering the course of minipuberty and thus predisposing the infected subjects to fertility, sensory and cognitive disorders later in life.

7 | CLINICAL IMPLICATIONS

7.1 | Potential adverse effects of long-term GnRH agonist/antagonist therapies

Like in men at risk of committing child sexual abuse (Landgren et al., 2020), long-lasting GnRH agonists and antagonists are being used in carnivores to induce a so-called hormonal gonadectomy to reduce sexual behaviour, libido and hypersexuality, in addition to trying to manage intermale dominance and excessive territorial

urine-making (Goericke-Pesch, 2017; Urfer & Kaeberlein, 2019). However, these treatments, in addition to desensitizing GnRHR at the pituitary gonadotrophs to suppress the reproductive axis are likely to also target GnRHR-expressing neurons in the brain and alter their function, which could lead to cognitive and sensory impairments (Figure 2). GnRH agonist/antagonist therapies, sometimes termed androgen deprivation therapy, that are also used in humans to treat prostate cancer were indeed reported to be associated with a decline in cognitive functions, visual–spatial abilities, executive functioning and worsening mood (Sharifi et al., 2005; Van Dam et al., 2016; Wu et al., 2013). Experiments in wildtype male mice show that continuous infusion of GnRH, in addition to suppressing LH pulsatility, has a deleterious effect on both olfactory and cognitive performance (Manfredi-Lozano et al., 2022), thus establishing a compelling causal link. The role of the neocortical GnRHR-expressing neurons in this process was demonstrated by selective and acute inhibition of the activity of these GnRHR-expressing neurons in the hippocampus and the cerebral cortex using the designer receptor exclusively activated by designer drugs (DREADDs) approach, resulting in a dramatic reduction in cognitive and olfactory performance (Manfredi-Lozano et al., 2022). However, the effects of continuous GnRH treatment on sensory perception and cognition could differ between species and sexes. Indeed, for example, in contrast to men and dogs, or even elephants in which the GnRH agonist leuprolide acetate blocks the musth and lowers testosterone (de Oliveira et al., 2004), continuous administration of GnRH agonists in bulls and red deer stags results in an increase in plasma testosterone concentration (Jimenez-Severiano et al., 2007; Lincoln, 1987; Melson et al., 1986; von Rechenberg et al., 1986) and potentially aggressive behaviour. This is seen despite the fact that, at least in bulls, GnRH agonist affects the pulsatile secretion of LH and T, and the GnRH-induced secretion of LH and FSH during treatment (Jimenez-Severiano et al., 2003; Melson et al., 1986), suggesting that chronic treatment with the agonist desensitizes the pituitary in bulls in the same way as in other species. Although the underlying mechanisms are not yet fully understood, it is believed that these male species differences in the response to continuous GnRH stimulation occur primarily in how the testes read basal LH secretion (Jimenez-Severiano et al., 2007); GnRH agonists appear to suppress LH pulsatility and maintain high basal LH levels (see for review [D'Occhio et al., 2000]). In contrast, in heifers, a GnRH agonist given for 3 weeks suppresses pulsatile LH secretion (but not FSH secretion) and blocks the development of follicles larger than 9 mm, LH surge and ovulation (Gong et al., 1995).

7.2 | Immunization against GnRH: A safer approach?

Active and passive immunization against GnRH has proven to be useful for practical on-farm applications aiming to shut down the reproductive system (Thompson, 2000). Because in contrast to most GnRH agonists and antagonists, neutralizing antibodies are unlikely to be transported into the central nervous system, immunization against GnRH appears to be a sound alternative to inhibiting reproductive functions without altering GnRH-driven sensory and cognitive processes in the brain. However, since the neutralizing antibodies may be able to reach the circumventricular organs of the brain lacking the classical endothelial blood–brain barrier (Prevot et al., 2021), such as the organum vasculosum laminae terminalis and the median eminence where are distributed GnRH neuron dendrites and neuroendocrine terminals (Barry et al., 1973; Herde et al., 2011), respectively, it would be interesting to investigate whether the GnRH neuronal system remains intact in the hypothalamus of animals in which immunization against GnRH has long-term effects.

7.3 | Potential use of pulsatile GnRH therapy to prevent gonadectomy-promoted cognitive decline, learning abilities and olfactory skills

In dogs and cats, desexing methods often involve surgical gonadectomy (Urfer & Kaeberlein, 2019). This method results in the elimination of sex steroids and thus the suppression of the negative feedback they exert onto the neuronal circuits controlling GnRH neuronal activity (Herbison, 2020). In all studied mammalian species, gonadectomy causes a permanent increase in GnRH/LH pulse frequency or amplitude. In women, this condition naturally occurs at menopause, that is the permanent loss of menses reflecting oocyte depletion and loss of gonadal steroids. Intriguingly, some studies show that GnRH/LH pulsatility decreases significantly in elderly menopaused women compared to young menopaused women (Hall et al., 2000). This suggests that long-term gonadal steroid deprival could eventually have detrimental effects on GnRH neuronal function and, because brain GnRH release plays a vital role in controlling mental and sensory abilities (Manfredi-Lozano et al., 2022), it may accelerate cognitive decline (Karlamangla et al., 2017; Santoro et al., 2021), as suggested by preclinical findings in mice (Anckaerts et al., 2019; Kara et al., 2021; Manfredi-Lozano et al., 2022), and may thus be a risk factor for dementia. In dogs, there is some evidence suggesting that gonadectomy increases the risk of cognitive dysfunction in both sexes (Azkona et al., 2009), and increases the speed of progression from mild to more severe cognitive impairment in male dogs (Hart, 2001). From the preclinical and clinical data obtained in mice and in men (Manfredi-Lozano et al., 2022), respectively, it could be expected that the implantation of a programmable minipump releasing one pulse every 2–3 h to mimic the GnRH/LH secretory pattern during the luteal phase in bitches (Concannon, 2012; Kooistra et al., 1999), or in males (Enright et al., 2010), protects cognitive functions in these pets by stimulating neocortical GnRHR expressing neurons at a physiological pace and hence compensate the potential exhaustion of GnRH neuronal function induced by long-term gonadectomy (Prevot et al., 2020).

Preclinical studies in mice demonstrated that alterations in GnRH neuronal function in addition to blunt learning abilities could also alter the ability of subjects to discriminate odours

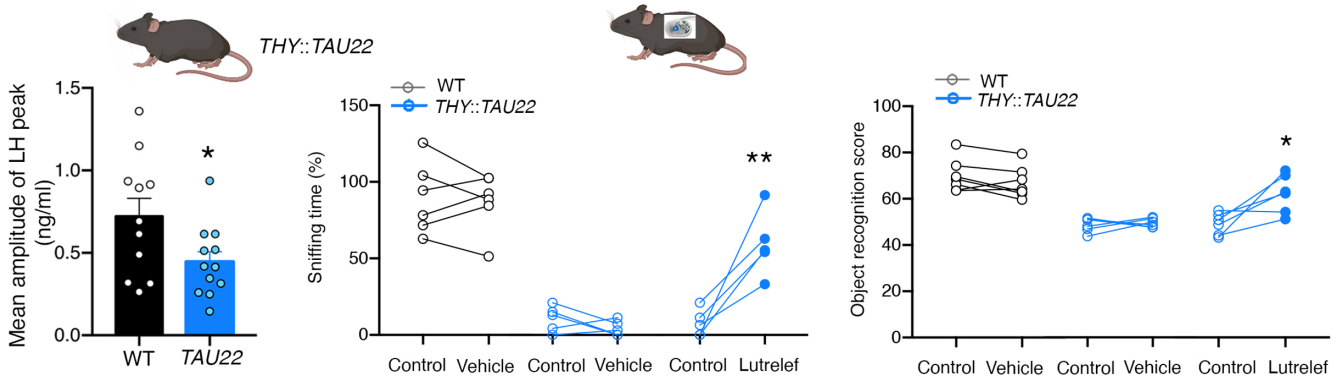

FIGURE 4 Pulsatile GnRH treatment rescues olfaction and cognition in a mouse model of Alzheimer's disease. LH pulsatility, olfaction and cognition are impaired in 12-month-old mice expressing the pathogenic TAU22 under the control of the neuronal *THY* promoter. Pulsatile GnRH (Lutrelf®) rescues odour discrimination and object recognition memory in these mice. From Manfredi-Lozano et al. (2022) with permission.

(Manfredi-Lozano et al., 2022). Scent-detecting dogs have been used to identify specific odours for a long time (Allen & Bennett, 2021; Moser et al., 2019; Simon et al., 2020). Despite the fact that the trainability of dogs may depend on sex, for example with respect to drug detection performance, males appear to perform better in drug detection training than females, neutered dogs of both sexes were shown to be less trainable than intact animals (Abdel Fattah & Abdel-Hamid, 2020). Decreased learning abilities in gonadectomized dogs is associated with and may be explained by the high anxiety levels in these animals (Flannigan & Dodman, 2001). Whether this could be due, at least in part, to an imbalance in the GnRH neuronal network is not known. However, a recent pilot study in human patients with Down syndrome (Manfredi-Lozano et al., 2022) who present with both altered learning capabilities and high anxiety shows that pulsatile GnRH therapy restoring the natural pattern of GnRH release improves cognitive performances by 20–30% and that this is accompanied by a decreased functional connectivity in the anxiety-related neuronal network linking the hippocampus to the amygdala to control values (Figueroa-Jimenez, Canete-Masse, et al., 2021; Figueroa-Jimenez, Carbo-Carrete, et al., 2021), as shown by resting-state functional magnetic resonance imaging (fMRI). It would be interesting to determine whether this ventral default mode network linking the hippocampus to the amygdala is also hyperactive in neutered dogs when compared to un-gonadectomized dogs using fMRI.

Overall, the realization that gonadectomy may accelerate age-acquired GnRH deficiency, leading to a decline in learning, memory and sensory performance, in a context where approximately half of the population of dogs used as pets in Western countries are subjected to desexing methods due to their beneficial effects on behaviour, but also on life-limiting diseases (Urfer & Kaeberlein, 2019), suggest that the combination of pulsatile GnRH therapy with gonadectomy might be ideal for improving behaviour and life span of pets while keeping their cognitive and olfactory performance intact (Prevot et al., 2020).

7.4 | Use of pulsatile GnRH therapy to mobilize the cognitive reserve and rescue olfaction in aging dogs

Sixty percent of older dogs, primarily those over 11 years of age, develop canine cognitive dysfunction (CDD), also known as canine cognitive dysfunction syndrome (Fast et al., 2013). CDD intriguingly shares many pathophysiological and behavioural hallmarks with human Alzheimer's disease, including progressive cognitive impairment, loss of normal sleep patterns, increased anxiety and aimless wandering, as well as amyloid-beta and possibly tau pathology in the brain (Prpar Mihevc & Majdic, 2019). Patients with Alzheimer's disease also show olfactory deficits, as in the case of other neurodegenerative diseases (Doty, 2012). In resonance with the previous section, gonadectomized dogs appear to be more likely to show signs of CDD than intact dogs (Azkona et al., 2009; Hart, 2001). This, together with the fact that the human literature suggests that men receiving androgen deprivation therapy, that is GnRH agonists, for prostate cancer, may be prone to accelerated cognitive decline and have a higher risk of developing dementia and Alzheimer's disease than controls (Cherrier & Higano, 2020; Sharifi et al., 2005), it could be hypothesized that altered brain GnRH signalling may play, at least in part, a role in this process. In line with this idea are RNA sequencing data showing that the genes involved in GnRH signalling are among the most down-regulated in discrete cortical areas of postmortem Alzheimer's disease patients (Manfredi-Lozano et al., 2022; Wang et al., 2016) and in the hippocampus of the *THY::TAU22* mouse Alzheimer's disease model (Chatterjee et al., 2018; Manfredi-Lozano et al., 2022), which progressively develop a hippocampal tau pathology in parallel with cognitive deficits (Schindowski et al., 2006; Van der Jeugd et al., 2013). Like Ts65Dn mice, the mouse model of Down syndrome, aged *THY::TAU22* mice show normal LH pulse frequency, but decreased LH amplitude (Figure 4), and pulsatile GnRH infusion is shown to rescue both odour discrimination (Figure 4) and object recognition memory (Figure 4) in these mice (Manfredi-Lozano et al., 2022). An alternative but not exclusive

hypothesis would involve FSH (Xiong et al., 2022), the circulating levels of which increase after gonadectomy and are seen to be elevated in human patients with cognitive disorders such as men with Down syndrome (Manfredi-Lozano et al., 2022). A 2022 study indeed suggests that FSH, by acting on neuronal FSH receptors in the cerebral cortex and the hippocampus may accelerate the onset of Alzheimer-like disease in alternative mouse models of the human disease by inducing the expression of *Cepbp* (Xiong et al., 2022), the very transcription factor known to repress the *Gnrh1* promoter in the hypothalamus (Belsham & Mellon, 2000; Messina et al., 2016), but also known to activate the expression of arginine endopeptidase, a delta-secretase that cleaves amyloid precursor protein, as well as tau, thought to favour the onset of Alzheimer-disease-like neuropathology (Zhang et al., 2014, 2015). Whereas treatment of ovariectomized Alzheimer's mice with FSH-neutralizing antibodies reverses Alzheimer-disease-like neuropathology (Xiong et al., 2022), pulsatile GnRH therapy is seen to reduce FSH levels in men with Down syndrome (Manfredi-Lozano et al., 2022), 75% of whom are known to develop dementia of the Alzheimer type at the age of 65 (Bull, 2020; Wiseman et al., 2015). Taken as a whole, these findings strongly suggest that cognitive deficits in dementia-like disorders could be caused by an alteration of GnRH production and its pulsatile release and that pulsatile GnRH therapy holds promise to improve both cognitive and sensory deficits in neurodegenerative disorders in mammals (Prevot et al., 2020), including dogs and other pets.

AUTHOR CONTRIBUTIONS

V.P. designed the structure of the Review and wrote it. A.D. discussed and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

V.P. discloses that he is the inventor of a patent covering the treatment of cognitive and sensory disorders, and dementia with pulsatile GnRH (Prevot et al., 2020). A.D. has no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Vincent Prévot https://orcid.org/0000-0001-7185-3615

REFERENCES

Abdel Fattah, A. F., & Abdel-Hamid, S. E. (2020). Influence of gender, neuter status, and training method on police dog narcotics olfaction performance, behavior and welfare. *Journal of Advanced Veterinary and Animal Research*, *7*, 655–662.

Allen, K., & Bennett, J. W. (2021). Tour of truffles: Aromas, aphrodisiacs, adaptogens, and more. *Mycobiology*, *49*, 201–212.

Anckaerts, C., van Gastel, J., Leysen, V., Hinz, R., Azmi, A., Simoens, P., Shah, D., Kara, F., Langbeen, A., Bols, P., Laloux, C., Prevot, V., Verhoye, M., Maudsley, S., & Van der Linden, A. (2019). Image-guided phenotyping of ovariectomized mice: Altered functional connectivity, cognition, myelination, and dopaminergic functionality. *Neurobiology of Aging*, *74*, 77–89.

Andersson, A. M., Toppari, J., Haavisto, A. M., Petersen, J. H., Simell, T., Simell, O., & Skakkebaek, N. E. (1998). Longitudinal reproductive hormone profiles in infants: Peak of inhibin B levels in infant boys exceeds levels in adult men. *The Journal of Clinical Endocrinology and Metabolism*, *83*, 675–681.

Azkona, G., Garcia-Belenguer, S., Chacon, G., Rosado, B., Leon, M., & Palacio, J. (2009). Prevalence and risk factors of behavioural changes associated with age-related cognitive impairment in geriatric dogs. *The Journal of Small Animal Practice*, *50*, 87–91.

Barry, J., Dubois, M. P., & Poulain, P. (1973). LRF producing cells of the mammalian hypothalamus. A fluorescent antibody study. *Zeitschrift für Zellforschung Und Mikroskopische Anatomie*, *146*, 351–366.

Belchetz, P. E., Plant, T. M., Nakai, Y., Keogh, E. J., & Knobil, E. (1978). Hypophysial responses to continuous and intermittent delivery of hypopthalamic gonadotropin-releasing hormone. *Science*, *202*, 631–633.

Belsham, D. D., & Mellon, P. L. (2000). Transcription factors Oct-1 and C/EBPbeta (CCAAT/enhancer-binding protein-beta) are involved in the glutamate/nitric oxide/cyclic-guanosine 5′-monophosphate-mediated repression of mediated repression of gonadotropin-releasing hormone gene expression. *Molecular Endocrinology*, *14*, 212–228.

Bercu, B. B. (1982). Neutralization of gonadotropin-releasing hormone in neonatal rats with permanent impairment of the hypothalamic-pituitary-testicular axis. *Biology of Reproduction*, *26*, 612–619.

Bercu, B. B., Jackson, I. M., Sawin, C. T., Safaii, H., & Reichlin, S. (1977). Permanent impairment of testicular development after transient immunological blockade of endogenous luteinizing hormone releasing hormone in the neonatal rat. *Endocrinology*, *101*, 1871–1879.

Boehm, U., Bouloux, P. M., Dattani, M. T., de Roux, N., Dode, C., Dunkel, L., Dwyer, A. A., Giacobini, P., Hardelin, J. P., Juul, A., Maghnie, M., Pitteloud, N., Prevot, V., Raivio, T., Tena-Sempere, M., Quinton, R., & Young, J. (2015). Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism–pathogenesis, diagnosis and treatment. *Nature Reviews. Endocrinology*, *11*, 547–564.

Braz, B. Y., Wennagel, D., Ratie, L., de Souza, D. A. R., Deloulme, J. C., Barbier, E. L., Buisson, A., Lante, F., & Humbert, S. (2022). Treating early postnatal circuit defect delays Huntington's disease onset and pathology in mice. *Science*, *377*, eabq5011.

Bull, M. J. (2020). Down syndrome. *The New England Journal of Medicine*, *382*, 2344–2352.

Caldani, M., Antoine, M., Batailler, M., & Duittoz, A. (1995). Ontogeny of GnRH systems. *Journal of Reproduction and Fertility Supplement*, *49*, 147–162.

Caraty, A., Orgeur, P., & Thiery, J. C. (1982). Demonstration of the pulsatile secretion of LH-RH into hypophysial portal blood of ewes using an original technic for multiple samples. *Comptes Rendus Des Séances de l'Académie Des Sciences. Série III*, *295*, 103–106.

Caraty, A., & Skinner, D. C. (2008). Gonadotropin-releasing hormone in third ventricular cerebrospinal fluid: Endogenous distribution and exogenous uptake. *Endocrinology*, *149*, 5227–5234.

Cariboni, A., Andre, V., Chauvet, S., Cassatella, D., Davidson, K., Caramello, A., Fantin, A., Bouloux, P., Mann, F., & Ruhrberg, C. (2015). Dysfunctional SEMA3E signaling underlies gonadotropin-releasing hormone neuron deficiency in Kallmann syndrome. *The Journal of Clinical Investigation*, *125*, 2413–2428.

Casoni, F., Malone, S. A., Belle, M., Luzzati, F., Collier, F., Allet, C., Hrabovszky, E., Rasika, S., Prevot, V., Chedotal, A., & Giacobini, P. (2016). Development of the neurons controlling fertility in humans: New insights from 3D imaging and transparent fetal brains. *Development*, *143*, 3969–3981.

Castagnetti, C., Mariella, J., Serrazanetti, G. P., Grandis, A., Merlo, B., Fabbri, M., & Mari, G. (2007). Evaluation of lung maturity

by amniotic fluid analysis in equine neonate. *Theriogenology*, *67*, 1455–1462.

Chachlaki, K., Garthwaite, J., & Prevot, V. (2017). The gentle art of saying NO: How nitric oxide gets things done in the hypothalamus. *Nature Reviews. Endocrinology*, *13*, 521–535.

Chachlaki, K., Malone, S. A., Qualls-Creekmore, E., Hrabovszky, E., Munzberg, H., Giacobini, P., Ango, F., & Prevot, V. (2017). Phenotyping of nNOS neurons in the postnatal and adult female mouse hypothalamus. *The Journal of Comparative Neurology*, *525*, 3177–3189.

Chachlaki, K., Messina, A., Delli, V., Leysen, V., Maurnyi, C., Huber, C., Ternier, G., Skrapits, K., Papadakis, G., Shruti, S., Kapanidou, M., Cheng, X., Acierno, J., Rademaker, J., Rasika, S., Quinton, R., Niedziela, M., L'Allemand, D., Pignatelli, D., … Prevot, V. (2022). NOS1 mutations cause hypogonadotrpic hypogonadism with sensory and cognitive deficits that can be reversed in infantile mice. *Science Translational Medicine*, *14*, eabh2369.

Chachlaki, K., & Prevot, V. (2020). Nitric oxide signalling in the brain and its control of bodily functions. *British Journal of Pharmacology*, *177*, 5437–5458.

Chappel, S. C., & Ramaley, J. A. (1985). Changes in the isoelectric focusing profile of pituitary follicle-stimulating hormone in the developing male rat. *Biology of Reproduction*, *32*, 567–573.

Chatterjee, S., Cassel, R., Schneider-Anthony, A., Merienne, K., Cosquer, B., Tzeplaeff, L., Halder Sinha, S., Kumar, M., Chaturbedy, P., Eswaramoorthy, M., Le Gras, S., Keime, C., Bousiges, O., Dutar, P., Petsophonsakul, P., Rampon, C., Cassel, J. C., Buee, L., Blum, D., … Boutillier, A. L. (2018). Reinstating plasticity and memory in a tauopathy mouse model with an acetyltransferase activator. *EMBO Molecular Medicine*, *10*, e8587.

Cherrier, M. M., & Higano, C. S. (2020). Impact of androgen deprivation therapy on mood, cognition, and risk for AD. *Urologic Oncology*, *38*, 53–61.

Clarke, I. J., & Cummins, J. T. (1982). The temporal relationship between gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH) secretion in ovariectomized ewes. *Endocrinology*, *111*, 1737–1739.

Clasadonte, J., Poulain, P., Beauvillain, J. C., & Prevot, V. (2008). Activation of neuronal nitric oxide release inhibits spontaneous firing in adult gonadotropin-releasing hormone neurons: A possible local synchronizing signal. *Endocrinology*, *149*, 587–596.

Clasadonte, J., Poulain, P., Hanchate, N. K., Corfas, G., Ojeda, S. R., & Prevot, V. (2011). Prostaglandin E2 release from astrocytes triggers gonadotropin-releasing hormone (GnRH) neuron firing via EP2 receptor activation. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 16104–16109.

Concannon, P. W. (2012). Research challenges in endocrine aspects of canine ovarian cycles. *Reproduction in Domestic Animals*, *47*(Suppl 6), 6–12.

Cooke, P. S., Nanjappa, M. K., Ko, C., Prins, G. S., & Hess, R. A. (2017). Estrogens in male physiology. *Physiological Reviews*, *97*, 995–1043.

Czieselsky, K., Prescott, M., Porteous, R., Campos, P., Clarkson, J., Steyn, F. J., Campbell, R. E., & Herbison, A. E. (2016). Pulse and surge profiles of luteinizing hormone secretion in the mouse. *Endocrinology*, *157*, 4794–4802.

Dahl, K. D., Jia, X. C., & Hsueh, J. W. (1988). Bioactive follicle-stimulating hormone levels in serum and urine of male and female rats from birth to prepubertal period. *Biology of Reproduction*, *39*, 32–38.

de Melo, G. D., Lazarini, F., Levallois, S., Hautefort, C., Michel, V., Larrous, F., Verillaud, B., Aparicio, C., Wagner, S., Gheusi, G., Kergoat, L., Kornobis, E., Donati, F., Cokelaer, T., Hervochon, R., Madec, Y., Roze, E., Salmon, D., Bourhy, H., … Lledo, P. M. (2021). COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. *Science Translational Medicine*, *13*, eabf8396.

de Oliveira, C. A., West, G. D., Houck, R., & Leblanc, M. (2004). Control of musth in an Asian elephant bull (*Elephas maximus*) using leuprolide acetate. *Journal of Zoo and Wildlife Medicine*, *35*, 70–76.

Delli, V., Dehame, J., Franssen, D., Rasika, S., Parent, A. S., Prevot, V., & Chachlaki, K. (2023). Male minipuberty involves the gonad-independent activation of preoptic nNOS neurons. *Free Radical Biology & Medicine*, *194*, 199–208.

Delli, V., Silva, M. S. B., Prevot, V., & Chachlaki, K. (2021). The KiNG of reproduction: Kisspeptin/ nNOS interactions shaping hypothalamic GnRH release. *Molecular and Cellular Endocrinology*, *532*, 111302.

D'Occhio, M. J., Fordyce, G., Whyte, T. R., Aspden, W. J., & Trigg, T. E. (2000). Reproductive responses of cattle to GnRH agonists. *Animal Reproduction Science*, *60-61*, 433–442.

Dohler, K. D., & Wuttke, W. (1974). Serum LH, FSH, prolactin and progesterone from birth to puberty in female and male rats. *Endocrinology*, *94*, 1003–1008.

Dohler, K. D., & Wuttke, W. (1975). Changes with age in levels of serum gonadotropins, prolactin and gonadal steroids in prepubertal male and female rats. *Endocrinology*, *97*, 898–907.

D'Onofrio, B. M., Class, Q. A., Rickert, M. E., Larsson, H., Langstrom, N., & Lichtenstein, P. (2013). Preterm birth and mortality and morbidity: A population-based quasi-experimental study. *JAMA Psychiatry*, *70*, 1231–1240.

Doty, R. L. (2012). Olfactory dysfunction in Parkinson disease. *Nature Reviews. Neurology*, *8*, 329–339.

Duittoz, A. H., Forni, P. E., Giacobini, P., Golan, M., Mollard, P., Negron, A. L., Radovick, S., & Wray, S. (2021). Development of the gonadotropin-releasing hormone system. *Journal of Neuroendocrinology*, *34*, e13087.

Enright, B. P., Leach, M. W., Pelletier, G., LaBrie, F., McIntyre, B. S., & Losco, P. E. (2010). Effects of an antagonist of neurokinin receptors 1, 2 and 3 on reproductive hormones in male beagle dogs. *Birth Defects Research. Part B, Developmental and Reproductive Toxicology*, *89*, 517–525.

Fast, R., Schutt, T., Toft, N., Moller, A., & Berendt, M. (2013). An observational study with long-term follow-up of canine cognitive dysfunction: Clinical characteristics, survival, and risk factors. *Journal of Veterinary Internal Medicine*, *27*, 822–829.

Figueroa-Jimenez, M. D., Canete-Masse, C., Carbo-Carrete, M., Zarabozo-Hurtado, D., Pero-Cebollero, M., Salazar-Estrada, J. G., & Guardia-Olmos, J. (2021). Resting-state default mode network connectivity in young individuals with down syndrome. *Brain and Behavior: A Cognitive Neuroscience Perspective*, *11*, e01905.

Figueroa-Jimenez, M. D., Carbo-Carrete, M., Canete-Masse, C., Zarabozo-Hurtado, D., Pero-Cebollero, M., Salazar-Estrada, J. G., & Guardia-Olmos, J. (2021). Complexity analysis of the default mode network using resting-state fMRI in down syndrome: Relationships highlighted by a neuropsychological assessment. *Brain Sciences*, *11*, 311.

Flannigan, G., & Dodman, N. H. (2001). Risk factors and behaviors associated with separation anxiety in dogs. *Journal of the American Veterinary Medical Association*, *219*, 460–466.

Fortune, J. E., & Eppig, J. J. (1979). Effects of gonadotropins on steroid secretion by infantile and juvenile mouse ovaries in vitro. *Endocrinology*, *105*, 760–768.

Foster, D. L., & Hileman, S. M. (2015). Puberty in the sheep. In T. M. Plant & J. Zeleznik (Eds.), *Knobil and Neill's physiology of reproduction* (pp. 1441–1486). Elsevier.

Foster, D. L., Mickelson, I. H., Ryan, K. D., Coon, G. A., Drongowski, R. A., & Holt, J. A. (1978). Ontogeny of pulsatile luteinizing hormone and testosterone secretion in male lambs. *Endocrinology*, *102*, 1137–1146.

Francois, C. M., Petit, F., Giton, F., Gougeon, A., Ravel, C., Magre, S., Cohen-Tannoudji, J., & Guigon, C. J. (2017). A novel action of follicle-stimulating hormone in the ovary promotes estradiol

production without inducing excessive follicular growth before puberty. *Scientific Reports*, *7*, 46222.

Franssen, D., Gerard, A., Hennuy, B., Donneau, A. F., Bourguignon, J. P., & Parent, A. S. (2016). Delayed neuroendocrine sexual maturation in female rats after a very low dose of bisphenol A through altered GABAergic neurotransmission and opposing effects of a high dose. *Endocrinology*, *157*, 1740–1750.

Frost, S. I., Keen, K. L., Levine, J. E., & Terasawa, E. (2008). Microdialysis methods for in vivo neuropeptide measurement in the stalk-median eminence in the rhesus monkey. *Journal of Neuroscience Methods*, *168*, 26–34.

Funkenstein, B., Nimrod, A., & Lindner, H. R. (1980). The development of steroidogenic capability and responsiveness to gonadotropins in cultured neonatal rat ovaries. *Endocrinology*, *106*, 98–106.

Giacobini, P. (2015). Shaping the reproductive system: Role of Semaphorins in gonadotropin-releasing hormone development and function. *Neuroendocrinology*, *102*, 200–215.

Goericke-Pesch, S. (2017). Long-term effects of GnRH agonists on fertility and behaviour. *Reproduction in Domestic Animals*, *52*(Suppl 2), 336–347.

Gong, J. G., Bramley, T. A., Gutierrez, C. G., Peters, A. R., & Webb, R. (1995). Effects of chronic treatment with a gonadotrophin-releasing hormone agonist on peripheral concentrations of FSH and LH, and ovarian function in heifers. *Journal of Reproduction and Fertility*, *105*, 263–270.

Goodman, R. L. (2015). Neuroendocrine control of gonadotropin secretion: Comaparative aspects. In T. M. Plant & J. Zeleznik (Eds.), *Knobil and Neill's physiology of reproduction*. Elsevier.

Goodman, R. L., Herbison, A. E., Lehman, M. N., & Navarro, V. M. (2022). Neuroendocrine control of gonadotropin-releasing hormone: Pulsatile and surge modes of secretion. *Journal of Neuroendocrinology*, *34*, e13094.

Hall, J. E., Lavoie, H. B., Marsh, E. E., & Martin, K. A. (2000). Decrease in gonadotropin-releasing hormone (GnRH) pulse frequency with aging in postmenopausal women. *The Journal of Clinical Endocrinology and Metabolism*, *85*, 1794–1800.

Halpin, D. M., Jones, A., Fink, G., & Charlton, H. M. (1986). Postnatal ovarian follicle development in hypogonadal (hpg) and normal mice and associated changes in the hypothalamic-pituitary ovarian axis. *Journal of Reproduction and Fertility*, *77*, 287–296.

Hanchate, N. K., Giacobini, P., Lhuillier, P., Parkash, J., Espy, C., Fouveaut, C., Leroy, C., Baron, S., Campagne, C., Vanacker, C., Collier, F., Cruaud, C., Meyer, V., Garcia-Pinero, A., Dewailly, D., Cortet-Rudelli, C., Gersak, K., Metz, C., Chabrier, G., … Dode, C. (2012). SEMA3A, a gene involved in axonal pathfinding, is mutated in patients with Kallmann syndrome. *PLoS Genetics*, *8*, e1002896.

Hart, B. L. (2001). Effect of gonadectomy on subsequent development of age-related cognitive impairment in dogs. *Journal of the American Veterinary Medical Association*, *219*, 51–56.

Hazra, R., Corcoran, L., Robson, M., McTavish, K. J., Upton, D., Handelsman, D. J., & Allan, C. M. (2013). Temporal role of Sertoli cell androgen receptor expression in spermatogenic development. *Molecular Endocrinology*, *27*, 12–24.

Herbison, A. E. (2020). A simple model of estrous cycle negative and positive feedback regulation of GnRH secretion. *Frontiers in Neuroendocrinology*, *57*, 100837.

Herde, M. K., Geist, K., Campbell, R. E., & Herbison, A. E. (2011). Gonadotropin-releasing hormone neurons extend complex highly branched dendritic trees outside the blood-brain barrier. *Endocrinology*, *152*, 3832–3841.

Hoffman, A. R., & Crowley, W. F., Jr. (1982). Induction of puberty in men by long-term pulsatile administration of low-dose gonadotropin-releasing hormone. *The New England Journal of Medicine*, *307*, 1237–1241.

Hoffmann, H. M. (2022). Boosting cognition with a hormone. *Science*, *377*, 1042–1043.

Huang, C. C., Hsieh, W. J., Lee, P. L., Peng, L. N., Liu, L. K., Lee, W. J., Huang, J. K., Chen, L. K., & Lin, C. P. (2015). Age-related changes in resting-state networks of a large sample size of healthy elderly. *CNS Neuroscience & Therapeutics*, *21*, 817–825.

Hunzicker-Dunn, M., & Mayo, K. (2015). Gonadotropinsignaling in the ovary. In T. M. Plant & J. Zeleznik (Eds.), *Knobil and Neill's physiology of reproduction* (pp. 895–946). Elsevier.

Imai, T., Yamazaki, T., Kobayakawa, R., Kobayakawa, K., Abe, T., Suzuki, M., & Sakano, H. (2009). Pre-target axon sorting establishes the neural map topography. *Science*, *325*, 585–590.

Jimenez-Severiano, H., D'Occhio, M. J., Lunstra, D. D., Mussard, M. L., Davis, T. L., Enright, W. J., & Kinder, J. E. (2007). Comparative response of rams and bulls to long-term treatment with gonadotropin-releasing hormone analogs. *Animal Reproduction Science*, *98*, 204–224.

Jimenez-Severiano, H., D'Occhio, M. J., Lunstra, D. D., Mussard, M. L., Koch, J. W., Ehnis, L. R., Enright, W. J., & Kinder, J. E. (2003). Effect of chronic treatment with the gonadotrophin-releasing hormone agonist azagly-nafarelin on basal concentrations of LH in prepubertal bulls. *Reproduction*, *125*, 225–232.

Kalmbach, E. R. (1945). "ten-eighty," a war-produced rodenticide. *Science*, *102*, 232–233.

Kamberi, I. A., de Vellis, J., Bacleon, E. S., & Inglish, D. (1980). Hormonal patterns of the hypothalamo-pituitary-gonadal axis in the rat during postnatal development and sexual maturation. *Endokrinologie*, *75*, 129–140.

Kapustka, J., & Budzynska, M. (2022). Reproductive losses and their causes in alpacas-A survey-based study. *Animals (Basel)*, *12*(21), 3030.

Kara, F., Belloy, M. E., Voncken, R., Sarwari, Z., Garima, Y., Anckaerts, C., Langbeen, A., Leysen, V., Shah, D., Jacobs, J., Hamaide, J., Bols, P., Van Audekerke, J., Daans, J., Guglielmetti, C., Kantarci, K., Prevot, V., Rossner, S., Ponsaerts, P., … Verhoye, M. (2021). Long-term ovarian hormone deprivation alters functional connectivity, brain neurochemical profile and white matter integrity in the Tg2576 amyloid mouse model of Alzheimer's disease. *Neurobiology of Aging*, *102*, 139–150.

Karlamangla, A. S., Lachman, M. E., Han, W., Huang, M., & Greendale, G. A. (2017). Evidence for cognitive aging in midlife women: Study of Women's health across the nation. *PLoS One*, *12*, e0169008.

Ketelslegers, J. M., Hetzel, W. D., Sherins, R. J., & Catt, K. J. (1978). Developmental changes in testicular gonadotropin receptors: Plasma gonadotropins and plasma testosterone in the rat. *Endocrinology*, *103*, 212–222.

Koeppel, K. N., Mendes, A., Strydom, A., Rotherham, L., Mulumba, M., & Venter, M. (2022). SARS-CoV-2 reverse zoonoses to pumas and lions, South Africa. *Viruses*, *14*(1), 120.

Kolho, K. L., Nikula, H., & Huhtaniemi, I. (1988). Sexual maturation of male rats treated postnatally with a gonadotrophin-releasing hormone antagonist. *The Journal of Endocrinology*, *116*, 241–246.

Kooistra, H. S., Okkens, A. C., Bevers, M. M., Popp-Snijders, C., van Haaften, B., Dieleman, S. J., & Schoemaker, J. (1999). Concurrent pulsatile secretion of luteinizing hormone and follicle-stimulating hormone during different phases of the estrous cycle and anestrus in beagle bitches. *Biology of Reproduction*, *60*, 65–71.

Kotan, L. D., Ternier, G., Cakir, A. D., Emeksiz, H. C., Turan, I., Delpouve, G., Kardelen, A. D., Ozcabi, B., Isik, E., Mengen, E., Cakir, E. D. P., Yuksel, A., Agladioglu, S. Y., Dilek, S. O., Evliyaoglu, O., Darendeliler, F., Gurbuz, F., Akkus, G., Yuksel, B., … Topaloglu, A. K. (2021). Loss-of-function mutations in SEMA3F and PLXNA3 encoding Semaphorin-3F and its receptor plexin-A3 respectively cause idiopathic hypogonadotropic hypogonadism. *Genetics in Medicine*, *23*(6), 1008–1016.

Kragt, C. L., & Dahlgren, J. (1972). Development of neural regulation of follicle stimulating hormone (FSH) secretion. *Neuroendocrinology*, *9*, 30–40.

Kuiri-Hanninen, T., Haanpaa, M., Turpeinen, U., Hamalainen, E., Seuri, R., Tyrvainen, E., Sankilampi, U., & Dunkel, L. (2013). Postnatal ovarian activation has effects in estrogen target tissues in infant girls. *The Journal of Clinical Endocrinology and Metabolism*, *98*, 4709–4716.

Kuiri-Hanninen, T., Kallio, S., Seuri, R., Tyrvainen, E., Liakka, A., Tapanainen, J., Sankilampi, U., & Dunkel, L. (2011). Postnatal developmental changes in the pituitary-ovarian axis in preterm and term infant girls. *The Journal of Clinical Endocrinology and Metabolism*, *96*, 3432–3439.

Kuiri-Hanninen, T., Sankilampi, U., & Dunkel, L. (2014). Activation of the hypothalamic-pituitary-gonadal axis in infancy: Minipuberty. *Hormone Research in Pædiatrics*, *82*, 73–80.

Kuiri-Hanninen, T., Seuri, R., Tyrvainen, E., Turpeinen, U., Hamalainen, E., Stenman, U. H., Dunkel, L., & Sankilampi, U. (2011). Increased activity of the hypothalamic-pituitary-testicular axis in infancy results in increased androgen action in premature boys. *The Journal of Clinical Endocrinology and Metabolism*, *96*, 98–105.

Kumar, T. R., Wang, Y., Lu, N., & Matzuk, M. M. (1997). Follicle stimulating hormone is required for ovarian follicle maturation but not male fertility. *Nature Genetics*, *15*, 201–204.

Lanciotti, L., Cofini, M., Leonardi, A., Penta, L., & Esposito, S. (2018). Up-to-date review about minipuberty and overview on hypothalamic-pituitary-gonadal Axis activation in fetal and neonatal life. *Frontiers in Endocrinology*, *9*, 410.

Landgren, V., Malki, K., Bottai, M., Arver, S., & Rahm, C. (2020). Effect of gonadotropin-releasing hormone antagonist on risk of committing child sexual abuse in men with pedophilic disorder: A randomized clinical trial. *JAMA Psychiatry*, *77*(9), 897–905.

Lincoln, G. A. (1987). Long-term stimulatory effects of a continuous infusion of LHRH agonist on testicular function in male red deer (*Cervus elaphus*). *Journal of Reproduction and Fertility*, *80*, 257–261.

Manfredi-Lozano, M., Leysen, V., Adamo, M., Paiva, I., Rovera, R., Pignat, J. M., Timzoura, F. E., Candlish, M., Eddarkaoui, S., Malone, S. A., Silva, M. S. B., Trova, S., Imbernon, M., Decoster, L., Cotellessa, L., Tena-Sempere, M., Claret, M., Paoloni-Giacobino, A., Plassard, D., … Prevot, V. (2022). GnRH replacement rescues cognition in down syndrome. *Science*, *377*, eabq4515.

Marcos, S., Monnier, C., Rovira, X., Fouveaut, C., Pitteloud, N., Ango, F., Dode, C., & Hardelin, J. P. (2017). Defective signaling through plexin-A1 compromises the development of the peripheral olfactory system and neuroendocrine reproductive axis in mice. *Human Molecular Genetics*, *26*, 2006–2017.

Mastutik, G., Rohman, A., I'Tishom, R., Ruiz-Arrondo, I., & de Blas, I. (2022). Experimental and natural infections of severe acute respiratory syndrome-related coronavirus 2 in pets and wild and farm animals. *Veterinary World*, *15*, 565–589.

McArdle, C. A., & Roberson, M. S. (2015). Gonadotropes and gonadotropin-releasing hormone signaling. In T. M. Plant & J. Zeleznik (Eds.), *Knobil and Neill's physiology of reproduction* (pp. 335–397). Elsevier.

McGee, E. A., & Hsueh, A. J. (2000). Initial and cyclic recruitment of ovarian follicles. *Endocrine Reviews*, *21*, 200–214.

McGee, E. A., Perlas, E., LaPolt, P. S., Tsafriri, A., & Hsueh, A. J. (1997). Follicle-stimulating hormone enhances the development of preantral follicles in juvenile rats. *Biology of Reproduction*, *57*, 990–998.

McGee, S. R., & Narayan, P. (2013). Precocious puberty and Leydig cell hyperplasia in male mice with a gain of function mutation in the LH receptor gene. *Endocrinology*, *154*, 3900–3913.

Mee, J. F., Sanchez-Miguel, C., & Doherty, M. (2013). An international delphi study of the causes of death and the criteria used to assign cause of death in bovine perinatal mortality. *Reproduction in Domestic Animals*, *48*, 651–659.

Melson, B. E., Brown, J. L., Schoenemann, H. M., Tarnavsky, G. K., & Reeves, J. J. (1986). Elevation of serum testosterone during chronic LHRH agonist treatment in the bull. *Journal of Animal Science*, *62*, 199–207.

Messaoud-Toumi, L. H., Taragnat, C., & Durand, P. (1993). Heterogeneity in the storage of gonadotropins in the ovine fetus and evidence for luteinizing hormone-follicle-stimulating hormone cells in the fetal pituitary. *Biology of Reproduction*, *48*, 1239–1245.

Messina, A., Langlet, F., Chachlaki, K., Roa, J., Rasika, S., Jouy, N., Gallet, S., Gaytan, F., Parkash, J., Tena-Sempere, M., Giacobini, P., & Prevot, V. (2016). A microRNA switch regulates the rise in hypothalamic GnRH production before puberty. *Nature Neuroscience*, *19*, 835–844.

Moenter, S. M., Brand, R. C., & Karsch, F. J. (1992). Dynamics of gonadotropin-releasing hormone (GnRH) secretion during the GnRH surge: Insights into the mechanism of GnRH surge induction. *Endocrinology*, *130*, 2978–2984.

Moenter, S. M., Brand, R. M., Midgley, A. R., & Karsch, F. J. (1992). Dynamics of gonadotropin-releasing hormone release during a pulse. *Endocrinology*, *130*, 503–510.

Moenter, S. M., & Evans, N. P. (2022). Gonadotropin-releasing hormone (GnRH) measurements in pituitary portal blood: A history. *Journal of Neuroendocrinology*, *34*, e13065.

Moser, A. Y., Bizo, L., & Brown, W. Y. (2019). Olfactory generalization in detector dogs. *Animals (Basel)*, *9*, 702.

Moster, D., Lie, R. T., & Markestad, T. (2008). Long-term medical and social consequences of preterm birth. *The New England Journal of Medicine*, *359*, 262–273.

Mu, Y., Bennett, D. V., Rubinov, M., Narayan, S., Yang, C. T., Tanimoto, M., Mensh, B. D., Looger, L. L., & Ahrens, M. B. (2019). Glia accumulate evidence that actions are futile and suppress unsuccessful behavior. *Cell*, *178*, 27–43.e19.

Nagy, P., Reiczigel, J., Barua, R., Das Gupta, A., & Juhasz, J. (2023). Pregnancy and parturition in dromedary camels III. Incidence, timing and factors affecting abortions and perinatal mortality under intensive management. *Theriogenology*, *197*, 322–333.

Nazian, S. J., & Cameron, D. F. (1992). Termination of the peripubertal FSH increase in male rats. *The American Journal of Physiology*, *262*, E179–E184.

Negro-Vilar, A., Krulich, L., & McCann, S. M. (1973). Changes in serum prolactin and gonadotropins during sexual development of the male rat. *Endocrinology*, *93*, 660–664.

Ojeda, S. R., Andrews, W. W., Advis, J. P., & White, S. S. (1980). Recent advances in the endocrinology of puberty. *Endocrine Reviews*, *1*, 228–257.

Ojeda, S. R., & Ramirez, V. D. (1972). Plasma level of LH and FSH in maturing rats: Response to hemigonadectomy. *Endocrinology*, *90*, 466–472.

Papouin, T., Dunphy, J. M., Tolman, M., Dineley, K. T., & Haydon, P. G. (2017). Septal cholinergic neuromodulation tunes the astrocyte-dependent gating of hippocampal NMDA receptors to wakefulness. *Neuron*, *94*, 840–854.e7.

Pellegrino, G., Martin, M., Allet, C., Lhomme, T., Geller, S., Franssen, D., Mansuy, V., Manfredi-Lozano, M., Coutteau-Robles, A., Delli, V., Rasika, S., Mazur, D., Loyens, A., Tena-Sempere, M., Siepmann, J., Pralong, F. P., Ciofi, P., Corfas, G., Parent, A. S., … Prevot, V. (2021). GnRH neurons recruit astrocytes in infancy to facilitate network integration and sexual maturation. *Nature Neuroscience*, *24*, 1660–1672.

Pfrieger, F. W., & Barres, B. A. (1997). Synaptic efficacy enhanced by glial cells in vitro. *Science*, *277*, 1684–1687.

Plant, T. M. (1980). The effects of neonatal orchidectomy on the developmental pattern of gonadotropin secretion in the male rhesus monkey (Macaca mulatta). *Endocrinology*, *106*, 1451–1454.

Prevot, V. (2015). Puberty in mice and rats. In T. M. Plant & J. Zeleznik (Eds.), *Knobil and Neill's physiology of reproduction* (pp. 1395–1439). Elsevier.

Prevot, V., Messina, A., Giacobini, P., Leysen, V., & Manfredi-Lozano, M. (2020). Pulsatile GnRH administration for treating cognitive disorders. In Inserm (ed) patent: WO/2020/221821, France.

Prevot, V., Nogueiras, R., & Schwaninger, M. (2021). Tanycytes in the infundibular nucleus and median eminence and their role in the blood-brain barrier. *Handbook of Clinical Neurology*, *180*, 253–273.

Prevot, V., Rio, C., Cho, G. J., Lomniczi, A., Heger, S., Neville, C. M., Rosenthal, N. A., Ojeda, S. R., & Corfas, G. (2003). Normal female sexual development requires neuregulin-erbB receptor signaling in hypothalamic astrocytes. *The Journal of Neuroscience*, *23*, 230–239.

Prevot, V., & Sharif, A. (2022). The polygamous GnRH neuron: Astrocytic and tanycytic communication with a neuroendocrine neuronal population. *Journal of Neuroendocrinology*, *34*, e13104.

Prevot, V., Tena-Sempere, M., & Pitteloud, N. (2023). New Horizons: Gonadotropin-releasing hormone and cognition. *The Journal of Clinical Endocrinology and Metabolism*. https://doi.org/10.1210/clinem/dgad319

Prpar Mihevc, S., & Majdic, G. (2019). Canine cognitive dysfunction and Alzheimer's disease - two facets of the same disease? *Frontiers in Neuroscience*, *13*, 604.

Qi, W. H., Li, J., Zhang, X. Y., Wang, Z. K., Li, X. X., Yang, C. Z., Fu, W. L., & Yue, B. S. (2011). The reproductive performance of female forest musk deer (*Moschus berezovskii*) in captivity. *Theriogenology*, *76*, 874–881.

Reame, N., Sauder, S. E., Kelch, R. P., & Marshall, J. C. (1984). Pulsatile gonadotropin secretion during the human menstrual cycle: Evidence for altered frequency of gonadotropin-releasing hormone secretion. *The Journal of Clinical Endocrinology and Metabolism*, *59*, 328–337.

Santoro, N., Roeca, C., Peters, B. A., & Neal-Perry, G. (2021). The menopause transition: Signs, symptoms, and management options. *The Journal of Clinical Endocrinology and Metabolism*, *106*, 1–15.

Sarkar, D. K., & Minami, S. (1995). Diurnal variation in luteinizing hormone-releasing hormone and beta-endorphin release in pituitary portal plasma during the rat estrous cycle. *Biology of Reproduction*, *53*, 38–45.

Sauvé, F., Nampoothiri, S., Fernandois, D., Coelho, C., Dam, J., Ternier, G., Costellessa, L., Iglesias, C., Müller-Fielitz, H., Dewisme, J., Cecon, E., Lebouvier, T., Perbet, R., Florent, V., Baroncini, M., Sharif, A., Ereno-Orbea, J., Mercado-Gomez, M., Palazon, A., … Prevot, V. (2021). SARS-CoV-2 infects human GnRH neurons and tanycytes, disrupting hypothalamic-pituitary hormonal axes. *Research Square*. https://doi.org/10.21203/rs.21203.rs-1050969/v1050961

Schindowski, K., Bretteville, A., Leroy, K., Begard, S., Brion, J. P., Hamdane, M., & Buee, L. (2006). Alzheimer's disease-like tau neuropathology leads to memory deficits and loss of functional synapses in a novel mutated tau transgenic mouse without any motor deficits. *The American Journal of Pathology*, *169*, 599–616.

Sharifi, N., Gulley, J. L., & Dahut, W. L. (2005). Androgen deprivation therapy for prostate cancer. *JAMA*, *294*, 238–244.

Sheng, C., McNeilly, A. S., & Brooks, A. N. (1998). Immunohistochemical distribution of oestrogen receptor and luteinizing hormone B subunit in the ovine pituitary gland during foetal development. *Journal of Neuroendocrinology*, *10*, 713–718.

Shinkawa, O., Furuhashi, N., Fukaya, T., Suzuki, M., Kono, H., & Tachibana, Y. (1983). Changes of serum gonadotropin levels and sex differences in premature and mature infant during neonatal life. *The Journal of Clinical Endocrinology and Metabolism*, *56*, 1327–1331.

Simon, A., Lazarowski, L., Singletary, M., Barrow, J., Van Arsdale, K., Angle, T., Waggoner, P., & Giles, K. (2020). A review of the types of training aids used for canine detection training. *Frontiers in Veterinary Science*, *7*, 313.

Skinner, D. C., Caraty, A., Malpaux, B., & Evans, N. P. (1997). Simultaneous measurement of gonadotropin-releasing hormone in the third ventricular cerebrospinal fluid and hypophyseal portal blood of the ewe. *Endocrinology*, *138*, 4699–4704.

Smith, L. B., & Walker, W. H. (2015). Hormone signaling in the testis. In T. M. Plant & J. Zeleznik (Eds.), *Knobil and Neill's physiology of reproduction* (pp. 637–690). Elsevier.

Steyn, F. J., Wan, Y., Clarkson, J., Veldhuis, J. D., Herbison, A. E., & Chen, C. (2013). Development of a methodology for and assessment of pulsatile luteinizing hormone secretion in juvenile and adult male mice. *Endocrinology*, *154*, 4939–4945.

Stiff, M. E., Bronson, F. H., & Stetson, M. H. (1974). Plasma gonadotropins in prenatal and prepubertal female mice: Disorganization of pubertal cycles in the absence of a male. *Endocrinology*, *94*, 492–496.

Swamy, G. K., Ostbye, T., & Skjaerven, R. (2008). Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. *JAMA*, *299*, 1429–1436.

Taroc, E. Z. M., Prasad, A., Lin, J. M., & Forni, P. E. (2017). The terminal nerve plays a prominent role in GnRH-1 neuronal migration independent from proper olfactory and vomeronasal connections to the olfactory bulbs. *Biology Open*, *6*, 1552–1568.

Terasawa, E. (2022). The mechanism underlying the pubertal increase in pulsatile GnRH release in primates. *Journal of Neuroendocrinology*, *34*, e13119.

Thompson, D. L. (2000). Immunization against GnRH in male species (comparative aspects). *Animal Reproduction Science*, *60-61*, 459–469.

Tibary, A., Rodriguez, J., & Sandoval, S. (2008). Reproductive emergencies in camelids. *Theriogenology*, *70*, 515–534.

Ullian, E. M., Sapperstein, S. K., Christopherson, K. S., & Barres, B. A. (2001). Control of synapse number by glia. *Science*, *291*, 657–661.

Urfer, S. R., & Kaeberlein, M. (2019). Desexing dogs: A review of the current literature. *Animals (Basel)*, *9*, 1086.

Van Dam, D., Wassersug, R. J., & Hamilton, L. D. (2016). Androgen deprivation therapy's impact on the mood of prostate cancer patients as perceived by patients and the partners of patients. *Psychooncology*, *25*, 848–856.

van den Dungen, H. M., Dijkstra, H., Hiehle, M. A., van Rees, G. P., & Schoemaker, J. (1989). Effects of LHRH antagonist administration to immature male rats on sexual development. *Physiology & Behavior*, *46*, 779–785.

Van der Jeugd, A., Vermaercke, B., Derisbourg, M., Lo, A. C., Hamdane, M., Blum, D., Buee, L., & D'Hooge, R. (2013). Progressive age-related cognitive decline in tau mice. *Journal of Alzheimer's Disease*, *37*, 777–788.

Vanacker, C., Trova, S., Shruti, S., Casoni, F., Messina, A., Croizier, S., Malone, S., Ternier, G., Hanchate, N. K., Rasika, S., Bouret, S. G., Ciofi, P., Giacobini, P., & Prevot, V. (2020). Neuropilin-1 expression in GnRH neurons regulates prepubertal weight gain and sexual attraction. *The EMBO Journal*, *39*, e104633.

Vanderhaeghe, C., Dewulf, J., Jourquin, J., De Kruif, A., & Maes, D. (2011). Incidence and prevention of early parturition in sows. *Reproduction in Domestic Animals*, *46*, 428–433.

Vannucchi, C. I., Kishi, D., Regazzi, F. M., Silva, L., Veiga, G., Angrimani, D., Lucio, C. F., & Nichi, M. (2015). The oxidative stress, antioxidant profile and acid-base status in preterm and term canine neonates. *Reproduction in Domestic Animals*, *50*, 240–246.

Vannucchi, C. I., Silva, L. C., Lucio, C. F., Regazzi, F. M., Veiga, G. A., & Angrimani, D. S. (2012). Prenatal and neonatal adaptations with a focus on the respiratory system. *Reproduction in Domestic Animals*, *47*(Suppl 6), 177–181.

Vogel, D. L., Gunsalus, G. L., Bercu, B. B., Musto, N. A., & Bardin, C. W. (1983). Sertoli cell maturation is impaired by neonatal passive immunization with antiserum to luteinizing hormone-releasing hormone. *Endocrinology*, *112*, 1115–1121.

von Rechenberg, W., Sandow, J., & Klatt, P. (1986). Effect of long-term infusion of an LH-releasing hormone agonist on testicular function in bulls. *The Journal of Endocrinology*, *109*, R9–R11.

Wang, M., Roussos, P., McKenzie, A., Zhou, X., Kajiwara, Y., Brennand, K. J., De Luca, G. C., Crary, J. F., Casaccia, P., Buxbaum, J. D., Ehrlich, M., Gandy, S., Goate, A., Katsel, P., Schadt, E., Haroutunian, V., & Zhang, B. (2016). Integrative network analysis of nineteen brain regions identifies molecular signatures and networks underlying

selective regional vulnerability to Alzheimer's disease. *Genome Medicine*, *8*, 104.

Whitehead, C. E. (2009). Management of neonatal llamas and alpacas. *The Veterinary Clinics of North America. Food Animal Practice*, *25*, 353–366.

Wiseman, F. K., Al-Janabi, T., Hardy, J., Karmiloff-Smith, A., Nizetic, D., Tybulewicz, V. L., Fisher, E. M., & Strydom, A. (2015). A genetic cause of Alzheimer disease: Mechanistic insights from down syndrome. *Nature Reviews. Neuroscience*, *16*, 564–574.

Wu, L. M., Diefenbach, M. A., Gordon, W. A., Cantor, J. B., & Cherrier, M. M. (2013). Cognitive problems in patients on androgen deprivation therapy: A qualitative pilot study. *Urologic Oncology*, *31*, 1533–1538.

Xiong, J., Kang, S. S., Wang, Z., Liu, X., Kuo, T. C., Korkmaz, F., Padilla, A., Miyashita, S., Chan, P., Zhang, Z., Katsel, P., Burgess, J., Gumerova, A., Ievleva, K., Sant, D., Yu, S. P., Muradova, V., Frolinger, T., Lizneva, D., … Ye, K. (2022). FSH blockade improves cognition in mice with Alzheimer's disease. *Nature*, *603*, 470–476.

Zhang, F. P., Poutanen, M., Wilbertz, J., & Huhtaniemi, I. (2001). Normal prenatal but arrested postnatal sexual development of luteinizing hormone receptor knockout (LuRKO) mice. *Molecular Endocrinology*, *15*, 172–183.

Zhang, G., Li, J., Purkayastha, S., Tang, Y., Zhang, H., Yin, Y., Li, B., Liu, G., & Cai, D. (2013). Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. *Nature*, *497*, 211–216.

Zhang, Z., Song, M., Liu, X., Kang, S. S., Kwon, I. S., Duong, D. M., Seyfried, N. T., Hu, W. T., Liu, Z., Wang, J. Z., Cheng, L., Sun, Y. E., Yu, S. P., Levey, A. I., & Ye, K. (2014). Cleavage of tau by asparagine endopeptidase mediates the neurofibrillary pathology in Alzheimer's disease. *Nature Medicine*, *20*, 1254–1262.

Zhang, Z., Song, M., Liu, X., Su Kang, S., Duong, D. M., Seyfried, N. T., Cao, X., Cheng, L., Sun, Y. E., Ping Yu, S., Jia, J., Levey, A. I., & Ye, K. (2015). Delta-secretase cleaves amyloid precursor protein and regulates the pathogenesis in Alzheimer's disease. *Nature Communications*, *6*, 8762.

How to cite this article: Prévot, V., & Duittoz, A. (2023). A role for GnRH in olfaction and cognition: Implications for veterinary medicine. *Reproduction in Domestic Animals*, *58(Suppl. 2)*, 109–124. https://doi.org/10.1111/rda.14411