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REVIEW ARTICLE

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Central aspects of systemic oestradiol negative- and positive-feedback on the reproductive neuroendocrine system

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Abstract

The central nervous system regulates fertility via the release of gonadotrophin-releasing hormone (GnRH). This control revolves around the hypothalamic-pituitary-gonadal axis, which operates under traditional homeostatic feedback by sex steroids from the gonads in males and most of the time in females. An exception is the late follicular phase in females, when homeostatic feedback is suspended and a positive-feedback response to oestradiol initiates the preovulatory surges of GnRH and luteinising hormone. Here, we briefly review the history of how mechanisms underlying central control of ovulation by circulating steroids have been studied, discuss the relative merit of different model systems and integrate some of the more recent findings in this area into an overall picture of how this phenomenon occurs.

KEYWORDS
feedback, GnRH, oestradiol

1 | INTRODUCTION

Gonadotrophin-releasing hormone (GnRH) neurones form the final common central output pathway controlling fertility in vertebrates. Their output is regulated primarily by homeostatic sex steroid feedback. However, during the preovulatory period of the mammalian female reproductive cycle in spontaneously ovulating species, the feedback action of oestradiol switches from negative- to positive-feedback. This initiates a surge of GnRH and subsequently luteinising hormone (LH) release and ultimately triggers ovulation. A central signal is required for ovulation in most mammals. In some species, including rabbits, ovulation is induced by copulation; this association made it possible to study the neural link to reproduction as early as the 18th Century. In 1797, Jon Haighton[1] recounted to the Royal Society his observation that, in rabbits, sex made "by sympathy the ovarian vesicles enlarge, project, and burst". Haighton rejected the hypothesis that semen directly stimulated the ovary to release an egg because he had severed the Fallopian tubes. He conjectured

sympathy, or cross-talk, between the vagina and ovaries via the nervous system occurred to induce ovulation. The study of the role of the brain in ovulation accelerated in the early 20th Century. In 1936, Marshall and Verney[2] induced ovulation when they passed electrical current through a rabbit's brain. A year later, Harris[3] refined their work when he induced ovulation by electrically stimulating a specific region of the brain, the hypothalamus.

A neural signal was also postulated to be necessary for ovulation in animals that do not require copulation to ovulate (ie, spontaneous ovulators). Humans, non-human primates, sheep, rodents and many other mammals ovulate spontaneously at the end of the follicular phase of the reproductive cycle (pro-oestrus in rodents). Studying spontaneous ovulation became possible as techniques, such as the vaginal smear, were developed to follow the cycle stage in live animals. In 1950, Everett and Sawyer[4] delayed spontaneous ovulation by anaesthetising rats with phenobarbital on the afternoon of pro-oestrus. In their control animals, ovulation occurred between 1.00 AM and 2.00 AM on the morning of oestrus (lights off at 7.00 PM), although anaesthesia delayed ovulation by 24 hours if administered during a critical period (3.00-5.00 PM before lights off) the previous day. It was hypothesised that a neural signal initiated spontaneous ovulation during this period. Eight years later, Critchlow[5] stimulated the hypothalamus directly to trigger "spontaneous" ovulation. In the 1950s, hypothalamic pathologies were first associated with both hypogonadism and precocious puberty in humans,[6] further supporting a central role in the regulation of fertility.

The study of the role of the brain in reproduction did not occur in isolation because a role was also emerging for the pituitary. In 1921 and 1922, Evans and Long[7-9] noted that injecting pituitary extract into a the peritoneal cavity of a rat enlarged its ovaries and disrupted its oestrous cycles. Similarly, surgical removal of the pituitary caused ovarian atrophy, and pituitary transplants beneath the hypothalamus (site of the sella turcica, home of the pituitary) restored oestrous cycles and spontaneous ovulation.[10,11] When the pituitary was transplanted to sites outside of the sella turcica, however, reproduction was not restored.[12] These studies supported two early hypotheses: first, the pituitary may be important for reproduction in spontaneously ovulating species and, second, communication with the hypothalamus is necessary for pituitary control of reproduction.

Support for the hypothalamic-pituitary control of ovulation and reproduction continued to expand through the 20th Century. A releasing factor in the hypothalamus had long been postulated to initiate pituitary hormone release to control reproduction. By 1971, Baba et al[13] had isolated and sequenced 11.4 mg of GnRH peptide from the hypothalami of 240 000 pigs. This GnRH is made and released by a small population (800-2500 neurones in mammals) scattered throughout the preoptic area and anterior hypothalamus.[14] Many of these neurones project to and secrete GnRH into the median eminence, from where it is carried down long portal vessels into the capillary beds of the anterior pituitary. There, GnRH binds to receptors on pituitary gonadotrophs to trigger the release of two hormones: follicle-stimulating hormone and LH. The release of these hormones stimulates follicular maturation and the production of sex steroids in the ovaries. Ovarian steroids provide feedback on the pituitary and hypothalamus to regulate hormone release. Collectively, hypothalamus, pituitary and ovaries control complex hormonal interactions to precisely coordinate the reproductive cycle. The focus of this review is on systemic feedback (a recent review of a potentially interesting role for neural steroids in this process is provided by Terasawa[15]).

2 | MODES OF OESTRADIOL FEEDBACK REGULATION OF THE HYPOTHALAMUS AND PITUITARY

In mammals, ovarian oestradiol was soon linked with ovulation induction[16] and studies showed that oestradiol differentially regulates pulsatile vs surge modes of GnRH release via negative- and positive-feedback, respectively. For the majority of the reproductive cycle, GnRH is released in a pulsatile manner and drives the pulsatile release of gonadotrophins.[17-20] Oestradiol is traditionally referred to as having negative-feedback actions on pulsatile hormone release. A closer examination of the actions of oestrogens suggests that this nomenclature is somewhat misleading. The term negative-feedback arises from the observation that mean LH levels are lower in oestrogen-treated than in ovariectomised (open-feedback loop) animals.[21-23] This is attributable primarily to a reduction in pulse amplitude because the frequencies of GnRH and LH release are often increased, or at least not suppressed, in higher oestrogen states produced by either steroid replacement in the physiological range or natural progression towards the late follicular phase.[22,24-28] For historical consistency, we refer to this action of oestradiol as negative-feedback, although we wish to clarify the term to mean the action of oestradiol to modulate the pulsatile pattern of GnRH/LH that characterises much of the female cycle.

In most mammals, there is a switch from pulsatile GnRH to a continuous surge of GnRH release at the end of the follicular phase that is induced by oestradiol positive-feedback. There is little evidence of episodic secretion during the surge, suggesting that it is a different mode of secretion or a continuous mode superimposed upon the episodic mode.[29-32] There remains some controversy over whether or not a GnRH surge exists in humans. It is certainly clear that, in old-world primates, a consistent GnRH pulse frequency can generate reproductive cyclicity at least over a few months.[33,34] This led to the postulate that GnRH is permissive for LH surge generation in these species, rather than deterministic. Other indirect measures of GnRH release have suggested that there is actually a decrease in GnRH during the LH surge in monkeys and women.[35-37] Oestradiol positive-feedback at the pituitary appears to be stronger in these species, as indicated by the ability of oestradiol to induce an LH surge in males and the ability of transplanted ovaries to produce cyclic hormonal changes reminiscent of the menstrual cycle in males.[38,39] This question is difficult to resolve without direct measurement of GnRH release itself. This is not currently possible in humans but, in rhesus monkeys, preovulatory, oestradiol-induced and progesterone-induced increases in GnRH release during the LH

surge have been observed,[30,40,41] suggesting that this phenomenon may also exist in humans.

3 | MODELS FOR STUDYING OESTRADIOL FEEDBACK

Because of the availability of a vast array of genetic and other technical tools, much of the work aiming to understand the neurobiology underlying these different modes of GnRH release has been carried out in rodent species, specifically laboratory mice. Three primary hormone replacement models have been used to induce negative- and positive-feedback in mice and were compared directly recently.[42] Early work in mice utilised paradigms consisting of ovariectomy (OVX) with low oestradiol replacement for approximately 1 week, followed by a rise in oestradiol on its own (E rise model) or in combination with a subsequent progesterone rise.[43] Another paradigm is to ovariectomise mice, and then provide a constant high physiological level of oestradiol (OVX+E).[44] This model takes advantage of a diurnal change in the feedback action of oestradiol in these species. Specifically, in rodents, ovulation is tightly coupled to time-of-day, and the GnRH/LH surges begin 1-2 hours before lights out in nocturnal species[4,32] and a similar time before lights on in diurnal species.[45] In mice, rats and hamsters, the OVX+E paradigm induces daily LH surges in the late afternoon and hence has been referred to as the daily surge model.[44,46,47] In OVX+E mice, LH release is suppressed in the morning (AM) and increased in the afternoon (PM) relative to ovariectomised mice that do not receive oestradiol (OVX). This pattern persists in brain slices, with GnRH firing rates and release suppressed during AM relative to PM in OVX+E mice.[44,48]

Of note, all of these models deviate from the natural oestrous cycle, and all have advantages and disadvantages. On the negative side, constant oestradiol, even at physiological levels, is not characteristic of the oestrous cycle. Furthermore, all of these OVX+E models operate on a different duration than the typical cycle, with the E rise model being longer and the daily surge being shorter. On the plus side, all of these paradigms permit the study of oestradiol feedback in genetic models that are not capable of generating a rise

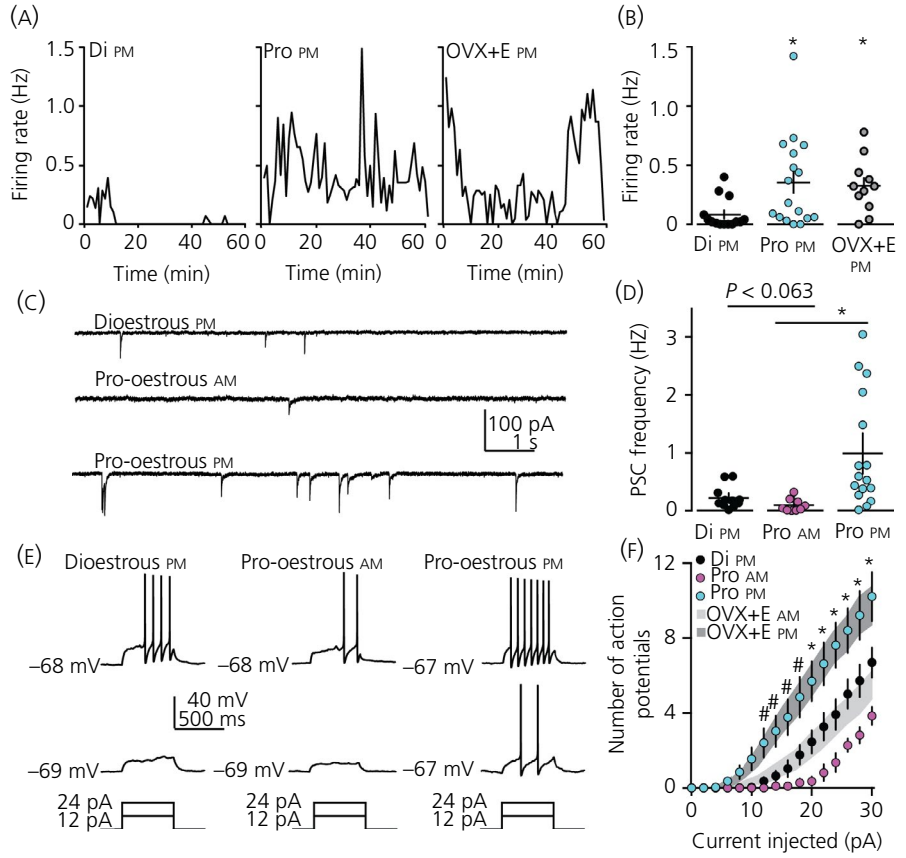

FIGURE 1 Comparison of daily surge model with the oestrous cycle. A, B, Representative firing patterns (A) and individual values and the mean ± SEM firing rate (B) of gonadotrophin-releasing hormone (GnRH) neurones from dieostrous (Di), pro-oestrous (Pro) or ovariectomised + oestradiol (OVX+E) mice recorded in the PM. C, D, Representative recordings (C) and individual values and the mean ± SEM frequency (D) of spontaneous GABAergic postsynaptic currents in GnRH neurones from dioestrous PM, pro-oestrous AM and pro-oestrous PM mice. E, Representative current-clamp recordings from dioestrous PM, pro-oestrous AM and pro-oestrous PM mice. F, Mean ± SEM number of action potentials in these groups; grey shaded areas show the range of the SEM for the same experiment in GnRH neurones from OVX+E AM and OVX+E PM mice. *$P < 0.05$. (A) and (B) are adapted with permission from Silveira et al[56] (C) to (F) are adapted with permission from Silveira et al[54,57]. PSC, postsynaptic current

in oestradiol on their own. The differences in these models also can make it possible to probe different aspects of positive-feedback. In the E rise model, the switch between negative- and positive-feedback relies on both an increase in oestradiol and on time of day. In the daily surge model, the switch between negative- and positive-feedback relies on time of day. An interesting biological question that remains to be answered is whether or not the underlying neurobiological mechanisms are the same in both of these models and how they compare to the natural cycle.

4 | DAILY SURGE VS THE CYCLE

The daily surge model has been used to characterise changes in multiple intrinsic and fast-synaptic properties during the switch from negative- to positive-feedback.[49-54] As this dataset has grown, it became increasingly important to compare at least some of the changes induced by this model to those that occur during the cycle. This was particularly important because the amplitude of the pro-oestrous surge was observed to be larger than the oestradiol-induced LH surge.[55,56] Accordingly, we examined three parts of the oestrous cycle. Dioestrous PM is a time of relatively low oestradiol that is characterised by pulsatile LH release. Pro-oestrous AM is a time when exposure to high oestradiol needed for surge induction has occurred, although the LH surge has not yet been triggered. Pro-oestrous PM is the time of oestradiol positive-feedback and the LH surge. GnRH neurone firing rate (dioestrous and pro-oestrous PM only), GABAergic fast synaptic transmission, GnRH neurone excitability and action potential properties were examined (Figure 1). The firing rates of GnRH neurones determined by extracellular recordings of GFP-identified GnRH neurones in brain slices prepared on the afternoon of dioestrus vs pro-oestrus were strikingly similar to those observed in the daily surge model from OVX+E AM vs OVX+E PM neurones, respectively.[56] Furthermore, the larger amplitude of the pro-oestrous LH surge was shown to be attributable at least in part to increased pituitary responsiveness to GnRH.[56] These observations suggest that the final output of the reproductive neuroendocrine system (GnRH release) is likely to be similar in the daily surge model and during the natural pro-oestrous surge.

Whole-cell recordings were used to examine synaptic and intrinsic properties of GnRH neurones during the cycle. The number of action potentials fired in response to fixed current injection is one way of characterising the integrated sum of the intrinsic properties of a neurone; this is often termed excitability. GnRH neurone excitability on dioestrous PM was strikingly similar to that in OVX AM, OVX PM and OVX+E AM in the daily surge model.[54,57] Similarly, the positive-feedback states (OVX+E PM and pro-oestrous PM) were comparable in excitability and greater than that observed during the negative-feedback/open-feedback loop conditions. We were initially surprised that OVX+E AM cells were not less excitable than cells from OVX mice because other properties, including potassium and calcium currents, are altered by oestradiol in the daily surge models in a manner that would typically reduce excitability. Computational modeling suggested an inverse relationship between the conductance and voltage-dependence of inactivation of a transient potassium current in GnRH neurones accounted for the similarity between OVX and negative-feedback states (OVX+E AM).[54]

Of interest in this regard, the excitability of GnRH neurones recorded on pro-oestrous AM was reduced compared to dioestrous PM. The same shifts in response to cycle stage were observed for GABAergic transmission to GnRH neurones, with transmission during the low oestradiol negative-feedback state of dioestrous PM being lower than during positive-feedback on pro-oestrous PM, although with GABA input during the high oestradiol negative-feedback of pro-oestrous AM being the lowest frequency. These results were again initially surprising. The ability of a high physiological and even pharmacological level of oestrogen to induce positive-feedback is consistent[43,58,59] but, in vivo, the negative-feedback actions of constant oestradiol on GnRH release appeared to be stronger than those of the rise in oestradiol during the cycle.[28,58] These observations had led us to postulate that a likely limitation of the daily surge model was that negative-feedback was stronger than would be typical during the cycle. Taken together, these newer data suggest that a possible limitation of the daily surge model is that negative-feedback in the model effectively recapitulates the lower oestradiol states of dioestrus, although it may fall short of the stronger negative-feedback that emerges on the morning of pro-oestrus.

The existence of a daily central signal for ovulation such as observed in the daily surge model was identified in the middle of the last century in studies demonstrating that barbiturate anaesthesia during a critical period on pro-oestrus blocked ovulation for 24 hours in rats.[4] Ovulation can occur on a daily basis during the breeding season in many fish and bird species.[60,61] Daily ovulation per se has not been observed in placental mammals, although the LH surge and ovulation occurs at a particular time of day in some mammals. This is especially observed, as noted above, in rodents. Interestingly, LH surges in women occur more often during late sleep/early wake hours,[62,63] and shiftwork, which can disrupt the circadian clock, is linked to menstrual cycle irregularities and an increased time to pregnancy.[64-66]

If a daily neural signal for ovulation can exist, why is it that mammals do not ovulate daily? This may be attributed in part to the time needed for a follicle to mature to the point that it can produce sufficient oestradiol to trigger positive-feedback. Of interest in this regard, *tau* mutant hamsters, in which the free-running period is approximately 20 hours vs just under 24 hours in the wild-type, exhibit oestrous cycles lasting five circadian days, or approximately 100 hours. This is similar in duration to the typical 4-day (96 hours) oestrous cycle in wild-type golden hamsters.[67] Daily LH surges are induced during subjective afternoon in OVX+E *tau* hamsters, and the period of consecutive LH surges was shorter than in wild-type hamsters.[68] These observations are consistent with the postulate that follicle maturation and subsequent oestradiol production are limiting and that the reproductive cycle does not result from a mere counting of circadian days. The provision of a constant high physiological oestradiol level, such as in the OVX+E daily surge model,

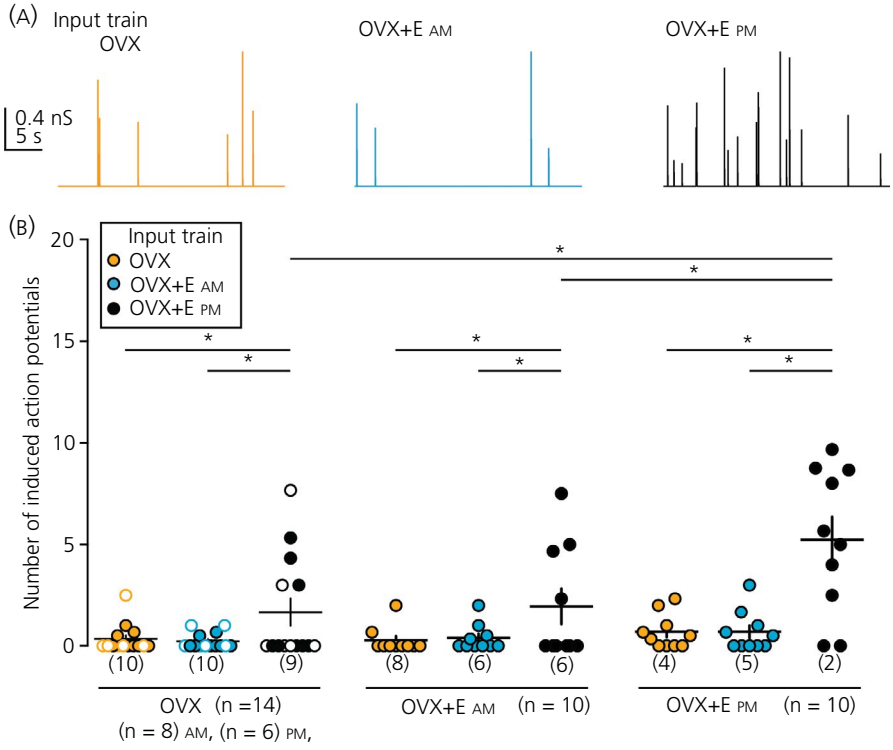

FIGURE 2 Both synaptic input and intrinsic properties contribute to increased gonadotrophin-releasing hormone (GnRH) neurone firing during positive-feedback. A, Representative conductance trains from ovariectomised (OVX) (orange), OVX + oestradiol (OVX+E) AM (blue) and OVX+E PM (black) conditions. B, Individual values and the mean ± SEM spikes induced during the three types of postsynaptic conductance trains in cells from all three animal models. In the OVX group, open circles denote cells recorded in the PM and closed circles denote cells recorded in the AM. Numbers in parentheses along the *x*-axis indicate the number of cells not firing any spikes. **P* < 0.05 two-way repeated measures ANOVA/Fisher's least significant test. Adapted with permission from Wang et al[71]

would circumvent this limitation, allowing a central signal to occur on a daily basis as observed.

5 | ARE SYNAPTIC AND/OR INTRINSIC CHANGES NEEDED TO PRODUCE INCREASED GNRH NEURONE OUTPUT DURING POSITIVE-FEEDBACK?

The daily surge model has produced data indicating that both synaptic and intrinsic properties of GnRH neurones are altered by oestradiol feedback mode.[50-54,69,70] Performing these studies typically required optimising recording conditions to isolate a single variable. Furthermore, most experiments were performed in voltage-clamp mode, which fixes the membrane potential to observe and quantify currents but, at the same time, precludes the membrane potential from responding to changes in intrinsic properties. To begin to address the question of whether intrinsic changes and/or synaptic changes are needed to generate an increased GnRH neurone firing during positive-feedback, we utilised dynamic clamp.[71] GABA is the primary fast synaptic input to GnRH neurones in adults and can be excitatory even in adulthood.[72,73] We mined our previous recordings of GABA transmission to GnRH neurones in the daily surge model[44] and selected traces that were representative of OVX (open loop), OVX+E AM (negative-feedback) and OVX+E PM (positive-feedback) conditions. Conductance trains mimicking these patterns were then applied in random order to GnRH neurones from these same animal models, effectively mixing or matching intrinsic properties of the recorded cell with the type of synaptic input (Figure 2). This approach revealed that both the synaptic inputs and intrinsic properties were important for the increased firing rate observed during positive-feedback.[72,73] Specifically, the GABA conductance train from positive-feedback induced more firing in all animal models, suggesting that an increased input frequency was important, and this positive-feedback train was most effective in cells recorded during positive-feedback, indicating that the intrinsic properties during positive-feedback poise the cell to be more responsive to excitatory synaptic input.

It is important to emphasise that additional factors not examined in the present study may contribute to surge generation. For example, oestradiol can alter excitatory fast glutamatergic transmission to GnRH neurones, and spines where glutamate afferents may synapse onto activated GnRH neurones are increased on pro-oestrus.[53,74,75] It is also important to point out that, in other animal models, no change in GABA postsynaptic current frequency has been reported during positive-feedback.[76] Arguing against a lack of a role for GABA in surge generation, specific knockout of oestrogen receptor alpha (ERα) from GABA neurones blocks positive-feedback,[77] although this could be attributable to reduced release of cotransmitters such as kisspeptin that would be activated by the action of oestradiol[78] because many kisspeptin neurones utilise GABA as a co-transmitter.[79,80]

6 | WHERE DOES OESTRADIOL ACT FOR NEGATIVE- AND POSITIVE-FEEDBACK?

A persistent question concerning oestradiol feedback involves where it occurs. This is because this feedback requires classical signalling via ERα,[81] which GnRH neurones typically do not express in

detectable levels.[82,83] Oestradiol feedback is thus likely transmitted to GnRH neurones by ERα-expressing afferents.[84] Kisspeptin is a neuromodulator that stimulates GnRH neurones.[85,86] These neurones project to GnRH neurones and are directly but differentially responsive to oestradiol.[87-89] Specifically, the mRNA for kisspeptin is increased by oestradiol in the kisspeptin neurones of the anteroventral periventricular (AVPV) nucleus, postulated to underlie positive-feedback, although decreased in kisspeptin neurones of the arcuate nucleus, postulated to underlie negative-feedback. To begin to determine the role of ERα in these cells, whole-body knockout of ERα from kisspeptin cells was performed using Cre-lox technology. These KERKO mice have disrupted cycles and do not exhibit oestradiol-induced LH surges.[90-92] This suggests that ERα in kisspeptin cells may be critical for both oestradiol negative- and positive-feedback. Relatively little was known about the properties of these kisspeptin neurones and how they respond to oestradiol. We thus began to characterise these properties in control and KERKO mice.

Anteroventral periventricular kisspeptin neurones were found to be more excitable during oestradiol positive-feedback on pro-oestrous PM than during negative-feedback on dioestrous PM[93] (Figure 3). This increased firing was attributable to oestradiol; adding progesterone did not produce a further elevation in firing rate. Burst firing by these neurones followed the same pattern, being increased during positive-feedback regardless of whether occurring during the cycle or induced by oestradiol. Both electrophysiological recordings measuring ionic currents and mRNA expression of these ion channel genes in pooled cells suggest several ionic conductances that can underlie burst firing are expressed by AVPV kisspeptin neurons, including hyperpolarisation-activated cation channels, T-type calcium channels and persistent sodium channels, and are also regulated by oestradiol.[93-96] Further support of a role for oestradiol comes from studies in KERKO mice. AVPV kisspeptin neurones were less excitable, fired fewer bursts and no longer changed firing rate in response to oestradiol.[97]

Oestradiol feedback also modulates synaptic transmission to AVPV kisspeptin neurones, increasing glutamate transmission and suppressing hyperpolarising GABAergic transmission to these cells, indicating that oestradiol tilts the balance toward excitatory inputs during positive-feedback.[98,99] Coupled with oestradiol up-regulation of intrinsic conductances underlying bursting firing, AVPV kisspeptin neurones are poised to increase output during positive-feedback to drive the GnRH/LH surge.

KERKO mice are a useful tool but lack both temporal and spatial regulation of ERα. Because Cre-lox will delete ERα as soon as *Kiss1* is expressed, there can be developmental changes in these cells or their networks.[100,101] Furthermore, the deletion of ERα from all kisspeptin cells makes it impossible to assess independently the role of AVPV and arcuate kisspeptin neurones. We thus used CRISPR/Cas9 to target *Esr1* in the AVPV of adult mice.[97] This approach successfully reduced ERα expression in AVPV kisspeptin neurones from approximately 75% in controls to approximately 25% in knockdown mice. These mice exhibited typical cycles but had markedly blunted

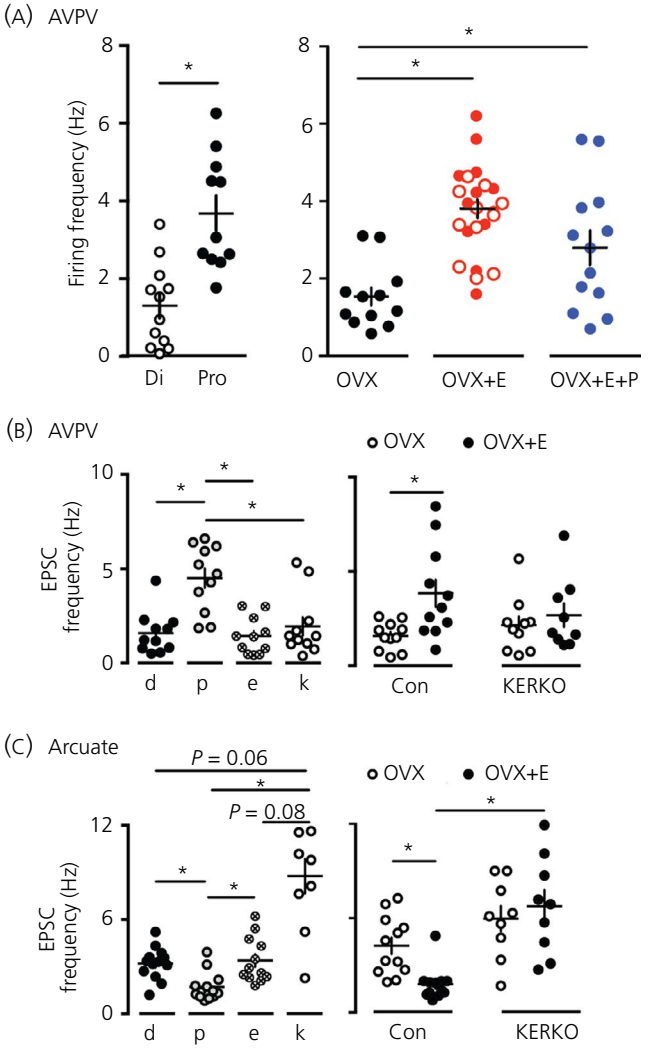

FIGURE 3 Oestradiol regulation of firing rate and excitatory postsynaptic current (EPSC) frequency in kisspeptin neurones of the hypothalamus. A, Anteroventral periventricular (AVPV) kisspeptin neurone firing rate is elevated during pro-oestrus (left) and by oestradiol (right). Open symbols indicate ovariectomised + oestradiol (OVX+E) mice injected with vehicle at the time of progestin injection; closed symbols indicate uninjected controls. B, C, Spontaneous glutamatergic EPSC frequency is regulated by cycle stage and oestradiol in both AVPV (B) and arcuate (C) kisspeptin neurones. Oestradiol regulation is lost in KERKO mice. Adapted with permission from Wang et al[93,98]. Con, control; Di, di-oestrus; K, KERKO; Pro, pro-oestrus; E, oestradiol; P, progesterone .

pro-oestrous and oestradiol-induced LH surges. Furthermore, their electrophysiological properties resembled those in KERKO mice. These studies suggest that ERα in AVPV kisspeptin neurones is required for the action of oestradiol on their intrinsic membrane excitability and that these effects are activational, rather than organisational.

Kisspeptin neurones in the hypothalamic arcuate nucleus (also called KNDy neurones as a result of their coexpression of kisspeptin, neurokinin B and dynorphin) are postulated to mediate oestradiol

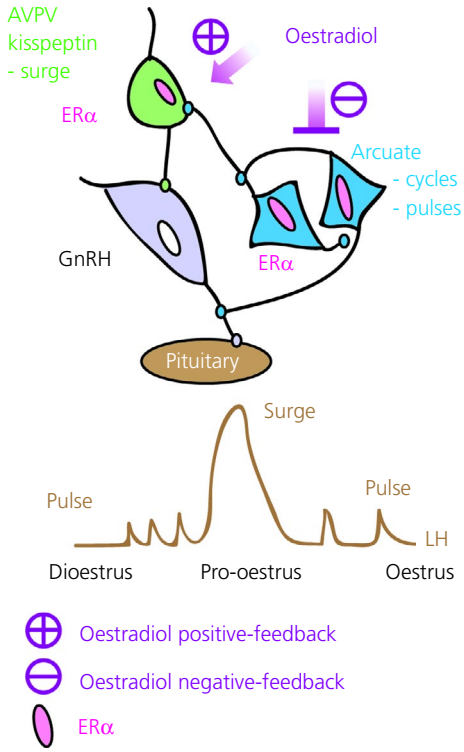

FIGURE 4 Schematic diagram of proposed feedback actions of oestradiol via anteroventral periventricular (AVPV) and arcuate kisspeptin neurones. Adapted with permission from Wang et al. [97] ER, oestrogen receptor; GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone

negative-feedback regulation of pulsatile GnRH/LH release , as well as to generate LH pulses.[87,102] Short-term extracellular recordings of these cells in OVX vs OVX+E mice during negative-feedback did not reveal any differences in firing pattern,[98] although an effect of steroids on a longer-term firing pattern of these cells, similar to that observed in males, cannot be excluded.[103] In KERKO mice, however, the firing rate of arcuate kisspeptin neurones in brain slices was markedly increased, as was LH pulse frequency in vivo.[98] Oestradiol also altered synaptic transmission to these cells, suppressing spontaneous glutamatergic transmission. Of note, the direction of regulation of glutamate transmission to these two kisspeptin populations is opposite.

Targeting the same CRISPR approach to the arcuate kisspeptin neurones produced a similar reduction in the percentage of neurones expressing ERα. By marked contrast to the mice in which the AVPV was targeted, mice with reduced ERα expression in the arcuate kisspeptin neurones had disrupted oestrous cycles, with an increasing tendency to remain in oestrus. This is similar to mice in which ERα was deleted from *Tac2*-expressing neurones via Cre-lox technology[92]; the overlap of ERα and *Tac2* expression in the brain is largely represented by the arcuate kisspeptin neurones. In the targeted CRISPR knockdown, arcuate kisspeptin neurones also exhibited an increased firing rate and increased levels of glutamatergic transmission. Taken together, these findings suggest that arcuate kisspeptin neurones mediate at least some aspects of negative-feedback via ERα. These observations are further consistent with a key role for these cells in generating pulsatile secretion because normal LH pulse frequency modulation is critical for producing cyclic changes in steroids.

7 | CONCLUSIONS AND FUTURE DIRECTIONS

Application of newer methodologies to the old question of how the action of oestradiol switches from negative- to positive-feedback has brought increased understanding and generated new questions (Figure 4). At the GnRH neurone, both fast-synaptic and intrinsic changes appear to contribute to initiating a robust GnRH surge, although the nature of these signals can be refined further. The postulated roles of AVPV kisspeptin neurones in positive-feedback and arcuate neurones in negative-feedback have been supported, although how these signals are generated in these cells and then conveyed to GnRH neurones largely remains a mystery. Mechanistic studies of population synchrony and the neurobiology of the interactions between kisspeptin neurones and GnRH neurones need to be pursued. Further investigation of the nature of the oestradiol-sensitive inputs to kisspeptin neurones may reveal additional interactions among these cells and/or new populations to study with respect to oestradiol feedback.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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