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# Low Progesterone: Gateway Event to Menopausal Symptoms?

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## Abstract

An evolutionary-based explanation for menopausal hot flashes (VMS) is offered. Using mainly urinary assays for ovarian steroid, women in the early perimenopause were shown to experience VMS mainly in association with decreased progesterone metabolite excretion. Episodes of LH spikes were also prominent but the expected association with lowered estrogen excretion was absent. This hormonal scenario is most consistent with increased gonadotropin releasing hormone (GnRH) as a result of increased activity of the pulse generator. These events are consistent with the literature in terms of a GnRH-mediated alterations in the limbic system in lower mammalian species that exhibit the psychic manifestation of heat, a desire to mate and the optimal time for conception following the decline of progesterone from a previous non-conceptive luteal phase. The evolution of the menstrual cycle from the more ancient estrous cycle in which concealed ovulation replaces the demonstrated desire to mate (estrus) and the ability of a well-developed cerebral cortices in higher primates dampen most autonomic events. Higher brain functions in women modulate vestigial tendencies to stimulate the autonomic system until the ability of the ovary fails to produce sufficient progesterone. Declining progesterone allows the limbic system to be activated by the increased GnRH drive and menopausal symptoms can be the result.

***Keywords:*** *Progesterone; Menopausal Symptoms; Gonadotropin Releasing Hormone (GnRH)*

## Introduction

We have previously reported the causal endocrine pathway for vasomotor symptoms (VMS) [1] and presented a poster at the 2021 Virtual Endocrine Society Annual meeting on March 22, 2021 [2]. The first report describes the step-by-step process by which the hypothalamic-pituitary-ovarian (HPO) axis in mid-aged women collapses to result in the experience of VMS. Lowered progesterone (Po) is the first step in the cascade that permits the normal entrainment of luteinizing hormone (LH) secretion, via long-loop negative feedback, to dissipate. The latter report details the development and validation of an algorithm for detecting and identifying episodes of VMS. Both reports used the results from the Study of Women's Heath Across the Nation (SWAN) Daily Hormone Study (DHS) to identify the components of the complete causal pathway for VMS including its genesis and the final neuronal link originating in the GnRH complex of neurons (KNDy, see below) to the core body heat-control center. In the process of reporting this pathway and developing an algorithm, new information was revealed and expands what is currently recognized regarding the potential relatedness of apparently diverse menopausal symptoms. Three observations led logically to a new hypothesis regarding menopausal symptoms. First, the recognition that a single defect in ovarian

function can trigger a cerebral event that can have multiple neurological sequelae. Second, that while this event is associated with a downstream endocrine signature event, that signature event is not in the ultimate causal pathway to VMS. Third, the physiologic properties of several symptoms (sleep, mood, cognition, memory and core body temperature) are linked through a network of neuronal connections. Most importantly this hypothesis is based on the premise that the nature of the sequelae of single ovarian defects leads to a multitude of events that are specific to the individual trajectories of individual GnRH neurons and not the cause of the disruption of the pulse generator. The purpose of this perspective is to explain why it is important to explore, integrate and report on the role of radiating GnRH neurons into the limbic area on menopausal symptoms and the GnRH manifestations of physiologic changes that have potential to contribute to specific and functionally separate menopausal symptoms.

## Background

While it is generally accepted that in rodents, a cluster of neurons in the arcuate nucleus of the hypothalamus is the pulse generator for the neural decapeptide known as gonadotropin hormone releasing hormone or GnRH. This cluster of neurons control the secretion of luteinizing hormone (LH) from the anterior pituitary. Collectively, these neurons express three peptide neurotransmitters (kisspeptin, neurokinin B and dynorphin) and are referred to as the KNDy neurons [3]. The control of GnRH by this triad of neurotransmitters is referred to as the KNDy hypothesis and is applied to all characterized vertebrate species below the phylogenetic level of primates including humans. Thus, while gonadotropin GnRH is a major controlling factor in reproductive physiology in all but a few vertebrates, the precise control mechanisms involving KNDy are not described in humans. The key feature of this control mechanism is well-established in rodents and ungulate animal models is a short-loop feedback of GnRH/LH on the pulse generator to limit over stimulation of LH secretion and pituitary exhaustion of pituitary LH stores. Whether or not the KNDy hypothesis can be appropriately and equally applied to humans has not been established [4,5] and is a current topic of investigations. The presence or absence of a short-loop feedback loop, which would prevent hyper-stimulation by GnRH in humans, which is what we seem to observe with VMS, is critical to our understanding in drawing conclusions regarding the how KNDy contributes to VMS and other menopausal symptoms.

Recent observations in rodents [6,7] describe a direct neural connection between KNDy neurons and the core body temperature center in rodents indicating that the GnRH pulse generator, through KNDy, has the capacity to alter heat control in some vertebrates. Changes in circulating LH has long been associated with vasomotor symptoms (VMS) in mid-aged women and since LH is controlled by GnRH which, in turn, is controlled by the KNDy complex; it seems clear that VMS is also associated with the GnRH pulse generator but not necessarily with LH secretion. One key missing element has been the connection between the aging ovary and the GnRH pulse generator, and we have now established that as progesterone (Po) in mid-aged women. This and another report show that reduced Po secretion associates strongly with VMS as well as a pattern of LH secretion that implies an altered pattern in GnRH pulse generation [1].

The pattern of LH secretion that is associated with VMS in mid-aged women is an oscillatory pattern comprised of a day or two of excess LH production followed by a day or two extremely low LH excretion. This repeats eight to ten times in a twenty to thirty-day collection interval. Simultaneously, VMS is reported during both the peak (excess LH production) and the days for extremely low (nadir) LH production. This dissociation between the pattern of LH response to the GnRH pulse generator, supports two concepts. First, this dissociation clearly indicates the secretion of LH is not tightly connected to the expression of VMS, otherwise VMS would stop during the nadir of LH secretion/excretion. Secondly, if GnRH pulses are continuous while LH secretion stops, then the pituitary has experienced either fatigue, down-regulation or exhaustion and brings into question to the fail-safe operation of a short-loop feedback which would prevent such GnRH hyperstimulation. Since the phenomenon of oscillating LH production has not been reported in non-primate vertebrates, it is likely that this pattern of LH production, along with its association with VMS, may be a unique higher primate trait resulting from evolutionary adaptations such as concealed ovulation [8,9], a trait that is almost exclusively a primate trait in the expression of reproductive success.

The endocrine system is essentially an information transmitting network. Messages (hormones) are sent via the bloodstream its specific receiver (target cell) at some distance. Timing is key to the efficiency of this communication system and hormones are there for short-lived in order to insure that a single, timely message is received. Therefore, hormones are usually degraded or deactivated quickly and/or a feedback loop acts as a servo unit to stop a message once its message has been received. For LH, its primary role is to guarantee that adequate Po is produced to support a quality implantation site for the expected embryo. In the case of VMS, the principal feedback loop (long loop) for LH in women is Po from the corpora lutea. However, in lower vertebrates there is a short loop in LH that feeds back negatively on its stimulator, the GnRH pulse generator. High rates of LH secretion is then curtailed not only by the long loop from the ovary but also by its own high levels locally (short loop) in the arcuate nucleus near the pituitary. Some anatomical evidence exists for a short-short loop where GnRH feeds back on itself but this is not well-established at the functional level.

A short loop feedback for LH has not been established as an important mechanism in higher primates including humans. The uniqueness of the ovarian cycle in higher primates can be explained by the modification of the basic vertebrate estrus cycle, adapting it to the more complex primate menstrual cycle which, has the hallmark attribute of concealed ovulation. Regardless of the evolutionary explanation, the fact that a short loop for GnRH/LH has not been documented in humans suggests it generally plays a minor role in human reproductive physiology. It is possible this redundancy in the control of GnRH is non-essential in reproductive-age women and does not have physiologic significance in the menstrual cycle until the HPO axis begins to deteriorate and the long loop control of LH is diminished. This could be a natural result of evolutionary modifications of the estrus cycle in the process of developing the menstrual cycle and its signature characteristic of female-choice mate selection through concealed ovulation.

Concealed ovulation, as expressed in higher primates, requires at least four behavioral modifications, or adaptations, of the non-primate ovarian cycle to that of successful primate species. One was a loss of a mechanism for sexual receptivity to permit female mate selection. This loss of a behavioral manifestation of heat was critical for the highly social primate species to survive. An added trait that evolved with primates was a prolongation of the pre-ovulatory estrogen production rise to permit complex female social-mating strategies. A third, and another added trait, was the synchronization of spontaneous ovulation to follow perceptivity, parallel increasing attractiveness and then coincide with peak female attractiveness as programmed by a pre-ovulatory peak in estrogen production. All three of these evolutionary modifications of the female reproductive cycle involved modulation of KNDy functions because this complex of neural transmitters is the initiator and regulatory of all reproductive functions in virtually all well-characterized vertebrate species. These include first, the attenuation of GnRH pulse generation, second, an estrogen trigger to synchronize the LH surge to guarantee luteinization of the collapsed follicle and third, rewiring the behavioral circuitry in the neural pathway to attenuate lordotic reflexes, most likely through long GnRH neuron branches that extend into higher brain centers than control behavior and reflex muscle innervation. A large literature exists on GnRH neuron circuity and GnRH target cells, but that literature is too vast to review in this review and most of these neural connections are the subject of current investigations using non-primate species. In short, current data accommodate diverse theories that support that both central and somatic cells can be modified, modulated and/or remodeled by GnRH neuronal activities.

As non-primate ovarian, or estrous cycles were adapted to accommodate the primate menstrual cycle, more volition was invoked and, necessarily, some of the parasympathetic control of reproduction was relaxed, modified or omitted. This was necessary to accommodate a shift from pure sexual reproduction in non-primate species to the primate social-sexual expression of reproductive behavior. Previous reflex response to environmental cues to accomplish reproductive successes were replaced by considerations of social behaviors essential to the emerging colony or troop requirements involving sexual dimorphism and gender-specific social-sexual roles. These adaptations may have altered the role of GnRH in cognition, memory, and mood in higher brain centers as well as metabolism peripherally. While the function of these control centers shifted in their prominence, it is unlikely that the structural foundations are entirely erased. For example, clear structural evidence is described for GnRH short loop (neuron-neuron) feedback while functional confirmation of this safety mechanism is absent. Since it is well documented that many collateral extensions of the KNDy complex of neurons are present in multiple brain

centers and peripheral organs, it is mostly unclear what their specific functions are and if those functions change as reproductive status changes. We therefor posit that the role and effect of the GnRH pulse generator is modest when the higher primate menstrual cycle is in an operational mode. However, when the HPO axis deteriorates, reproductive capability ends and the HPO axis begins to deteriorate in higher primates that rudimentary systems may be awaken and unwanted physiologic changes ensue.

The role of the KNDy complex at the functional level is well established in terms of near-complete control of reproductive physiology. However, the development and structural characteristics of the kisspeptin neurons implies a much broader role in basic regulatory mechanism(s). Anterograde and retrograde tracings neuronal projections show that kisspeptin neurons from the arcuate nucleus and rostral periventricular areas of the third ventricle innervate a wide number of hypothalamic and limbic region nuclei [10]. The complexity of the network of neurons indicate that this neuroanatomical scaffolding may function to innervate and modulate a variety of limbic functions, such as sleep, memory mood, metabolic regulation and cognition, in concert with reproductive events [11]. Some of these relationships are established at puberty (see below) and it follows logically, since the GnRH pulse generator is controlled by long-loop feedback loops emanating from the ovary (i.e. estrogen, progesterone, etc.) which is controlled by the HPO axis, that a breakdown of the HPO axis may impact limbic control of basic physiologic functions.

It is not entirely surprising that over fifty years of research was required to arrive at the understanding that Po is linked to VMS though LH production patterns. In fact, LH which is key to understanding the causal pathway of VMS, has been a prime candidate as an important link and determining factor in VMS for all of those fifty years. However, we find now that LH is not directly in the causal pathway but points to a collateral event that is the distal component in the alteration of core body temperature. The difficulty in investigating LH-related phenomena stems for it pulsatile nature of secretion. Each pulse of LH is the result of a discrete GnRH pulse-signal to the pituitary to stimulate LH secretion and initiate new synthesis and accumulation of LH in storage granules within the pituitary. LH is released episodically in response to GnRH pulses and circulating LH concentration is always pulsatile with pulse frequency ranging from 30 to 240 minutes depending on the long-loop feedback effects of ovarian hormones. Several ovarian hormones act quickly to control LH with estradiol being the primary modulator having both positive and negative control functions. The negative control by estradiol is enhanced by the addition of progesterone. For these reasons, point-in-time circulating LH measurements have not been useful in monitoring day-to-day changes in LH secretion or even tracing changes in ovarian function in terms of aging. A stable LH baseline is not possible to document without multiple and/or longitudinal blood sampling. Overnight urinary analyses for accumulated LH resolves this issue and good progress is now being made on several fronts that involve LH action. The SWAN DHS focused on the breakdown of one long-loop feedback (estradiol plus progesterone) and how that open loop leads to extreme GnRH pulse generation, a subsequent cessation of the pituitary LH secretion and possibly evidence for the opening of an important short-loop feedback in associated with VMS. Any strategy that is planned to monitor human LH in the future will certainly need to include urinalysis [12].

GnRH is particularly sensitive to down-regulation, the phenomenon in which a signaling, or tropic, hormone loses its ability to act if presented in a constant, sustained fashion. In contrast, pulsative deliver of GnRH generally will not lead to down regulation and the tropic effect will be persistent. If constant GnRH is delivered to the pituitary, the pituitary will eventually stop responding to the GnRH signal and this would be a plausible explanation for the LH oscillation as a sequence of response, refractory down regulation, recovery and then a response upon recovery of LH stores. This is the observed pattern of LH in association with VMS. However, the fact that VMS continues unchanged during the nadirs of the LH oscillatory sequences indicates that GnRH pulses do, in fact, continue despite a failure to elicit LH secretion. This indicates that the pulsative mode of GnRH, pulsatile KNDy, also continues, but the pituitary fails to respond, most likely, due to a lack of LH stores. These observations reveal not only that the secretion of LH is not essential to cause VMS, but that the oscillations of LH that is observed is a cycle of depletion, repletion and depletion of LH stores which repeats until baseline Po rises enough to close the short loop feedback. More importantly, the LH oscillation provides a biomarker for the open long loop (estrogen + progesterone) and provides an avenue to explore the role of the KNDy in manifesting other symptoms such as poor sleep.

## The logic

It is generally accepted that KNDy neurons are under the control of ovarian hormone long-loop negative feedback control in all species. This is made apparent by the profound negative effect of exogenous estrogen in controlling fertility, ovarian function, VMS and essentially all reproductive function across phylogenies. McConnell[1] further posits that it is a failure of adequate Po, that acts in concert with estradiol to open an important long-loop negative feedback mechanism to allow the GnRH pulse generator to free run and send abnormal nerve pulses to the heat control center while simultaneously sending GnRH to the anterior pituitary to cause the release of LH. It is this simultaneous secretion of LH with VMS that permits tracking VMS through daily urine analyses of LH excretion profiles. At this time we understand two important attributes of the HPO breakdown in mid-aged women: first, it is clear that the initial event is a direct alteration of the GnRH pulse generator to bring it to a free running mode that is responsible for the simultaneous LH oscillation and VMS. Second, it is also clear that the free-running GnRH pulse generator continues after LH has stopped being secreted. Therefore, LH secretion is a result of the free running KNDy pulse generator via GnRH, but not required for VMS to occur. As a result LH excretion patterns are a a valuable indicator of how and when VMS occurs and when it may involve other control centers involved with symptoms. LH oscillations are therefore a biomarker for the free running of the GnRH pulse generator but not a specific biomarker for VMS. However, LH oscillations cannot occur without the concomitant free running of the GnRH (KNDy) pulse-generator. This suggests that collateral adverse effects of aberrant GnRH pulse frequency/amplitude can be identified by identifying, classifying and analyzing the specific signature pattern of LH secretion/excretion.

VMS is the first symptom to be characterized in terms of its causal pathway. In addition, it is clear that negative mood, which is often associated temporally with VMS, is not attributable to that same causal pathway[1]. Similarly, sleep is often associated with VMS but these is no evidence to connect sleep and VMS mechanistically. The same may be true for other symptoms that share specific attributes. LH and VMS are on the same initial causal pathway but bifurcate so that while they remain temporally related, the mechanism for VMS does not require alterations in VMS secretion patterns. The same may be true for other symptoms. Many symptoms may have the same initial cause, the Po gateway, but bifurcations in nerve transduction separate their expressions. In fact, in the bigger picture, all symptoms may have the same initial start: increased age, declining HPO integrity and reduced Po production.

Low Po is associated with alteration in the KNDy-generated GnRH pulse signals though collateral nerves to specific a higher brain centers that control, or are in synchrony with, well-define physiologic processes. This presents the potential for a specific causal pathway to dysregulate any number of physiologic functions as described above for one, VMS. If, however this alteration in pulse frequency is temporally related to a specific breakdown of the HPO axis and also temporally associated other peri-menopausal symptoms, then it is reasonable to consider a mechanistic overlap between VMS and the other perimenopausal symptoms. An example is presented here for changes in quality of sleep.

During late puberty, LH pulse frequency in girls is low while they are awake but increases during sleep. However, the addition of Po reduced pulse frequency during wakefulness, but not during sleep. The experience of VMS in adulthood is greater for women who also experienced a earlier menarche [13]. These observations show the early development of a Po-mediated modulation of the KNDy pulse generator in the human female that may imprint a predisposition to VMS for life. This sleep-wake alteration in LH pulse-amplitude remains to adulthood. In reproductive age women a sleep-induced slowing of pulse frequency and an increase in pulse amplitude is observed in the early follicular phase when Po circulating concentrations are low in coincidence with the recruitment of a dominant follicle. At the time of the sleep induce enhancement, the response of the pituitary to exogenous GnRH was not affected by sleep. These observations indicate that LH pulse modulation by progesterone is operating at the level of the KNDy pulse generator and is amplified by sleep in adult women. Thus in the development of normal menstrual cycles, nocturnal control of the KNDy pulse generator overrides the negative influence of Po while in adulthood, the lack of high levels of Po (early follicular phase) has a positive effect. Together, these results are consistent with the

Po gateway hypothesis. Simply stated this hypothesis posits that low levels of Po can directly modulate the GnRH pulse generator (KNDy) and lower Po circulating levels can act to enhance KNDy pulse amplitudes at the expense of KNDy pulse frequency. GnRH nerves emanate from the KNDY complex to multiple control centers in the brain, including the limbic system, that other symptoms such as cognition, mood and memory can be similarly affected.

While the developmental aspects of sleep modulating GnRH pulses is intriguing, this is so primarily because we find this connection before we find any others. What is perhaps even more fundamental is the intimate relation of Po, LH and ovulation. The vast majority of mammals share an estrous cycle and undoubtedly the estrus cycle evolved from that most common of reproductive characteristics. It was, and still is, the most popular, widely distributed and successful of mating strategies. It is based on spontaneous ovulation, which the primate menstrual cycle retains, but uses the fall of Po as the primary trigger to set the stage for the next opportunity for a fertile mating. This part of the estrous cycle was only partly maintained by primates. During the reproductive years the decline of Po to set the stage for ovulation is less important and almost stripped of any role. The decline of Po in humans appears to still have some mood-altering aspect in women, although this is a contentious issue. It plays a minor role in enhancing the ovulatory processes and some dismiss this altogether. After ovulation, however, Po plays a similar role in both estrous and menstrual cycles to insure the potential implantation site and act with estrogen to limit pituitary gonadotropin secretion.

There remains the possibility that all of the circuitry that was hard-wired in the estrous cycle to insure timely mating is not lost in the process of primates evolution. Original neural circuitries were buried under the new mechanisms to accommodate social sexual life which provide for mate selection by females. As long as the menstrual cycle is functioning properly the, before the pre-perimenopause break-down of the HPO, some of the older circuitry from the estrous cycle becomes partially reinstated in the decaying menstrual cycle. Instead of a smooth transition that includes mate choice, older, higher primate female individuals experience a hybrid model for preparing for ovulation and a timely mating. This then opens relic neural loops that were once important for triggering the psychological manifestations of heat, including alterations in body temperature, mood, appetite, memory, and cognition.

Several reports provide evidence that some menopausal symptoms are related or share an etiology [14,15]. While this is consistent with our current hypothesis, none of the claims of shared mechanisms have been substantiated at a functional level. In fact, we recently reported that causal pathway for VMS is through lowered Po, alterations in the KNDy pulse generator leading LH oscillations. In the same study, the above complete causal pathway does not associate with negative mood, indicating the exact causal pathway for VMS is not the same as that for negative mood. This conclusion is correct as far as it goes but is also consistent with both VMS and negative mood having the same genesis and initial neural links as VMS, but then contains bifurcation(s) that divert away from the causal pathway for VMS. This may be similar to links between poor sleep and other symptoms. Subtle differences in the modulation of the KNDy pulse generator may send subtle but profoundly different signature neural pulse patterns to diverse control centers throughout the brain.

In addition to the possible direct adverse effects of aberrant GnRH pulses having direct effects on other brain centers, there is the possibility an increased LH secretion caused by GnRH will disrupt normal function in peripheral organs that have extragonadal LH receptors. Examples of these possibilities are increased androgen production by the adrenal cortex, dysregulation of insulin by beta cells of the pancreas and changes in kidney function by altering aldosterone regulation. All three of these are reasonable possibilities because LH receptors have been established in all of these organs. A deeper investigation into the collateral neuronal signally between the KNDy complex, GnRH and the heat control center, other higher brain regions as well as peripheral organs with LH receptors all need to be included in this proposal to provide a comprehensive accounting of the role of the GnRH pulse generator in initiation and promoting of menopausal symptoms in general.

## Conclusion

A single defect in the normal events in human ovarian cyclicity may lead to activation of archaic limbic system effects. Specifically, the failure of the human ovary to supply enough progesterone in a cyclic manner to maintain higher brain functions to effectively dampen primitive neuronal pathways may result in one or more menopausal symptoms.

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