hypothesis

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Effect of gonadotropin inhibitory hormone (GnIH) secretion on post-ejaculatory refractory period: A hypothesis

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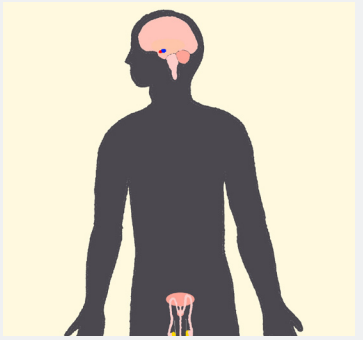

Illustration by Laura Isouthco

ABSTRACT The exact underlying mechanism regulating the human post-ejaculatory refractory period is not yet known. The main finding of previous research has been an occurrence of surge-like increases in plasma prolactin and oxytocin levels immediately after orgasm. However, recent advances in neuroendocrinology have resulted in the identification of a new peptide, the gonadotropin inhibitory hormone (GnIH), which is considered to inhibit the hypothalamic-pituitary-gonadal axis and sexual functions. This paper hypothesizes that GnIH causes refractoriness of the post-ejaculatory refractory period, and on the basis of studies on hormonal fluctuations at the time of orgasm, we hypothesize that in addition to its pulsatile pattern of secretion, GnIH might also exhibit a surge-like pattern of secretion.

INTRODUCTION The neuroendocrinological effects on sexual arousal and orgasm in humans are poorly understood. As a recent review states, our knowledge of the post-ejaculatory refractory period mechanism is limited[1]. Krüger et al.[2] analyzed plasma concentrations of adrenaline, noradrenaline, cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, growth hormone (GH), ß-endorphin, and testosterone before, during, and after masturbation-induced orgasm and showed that only plasma concentration of prolactin increased significantly in both men and women. Thereafter, Exton et al.[3] showed that this increase in plasma prolactin during sexual stimulation is orgasm-dependent and does not increase without orgasm. Prolactin concentration has been shown to increase during orgasm and remain elevated for 60 minutes[2,4,5]. However, in those men who exhibit multiple orgasms and a short refractory period, the orgasm-induced prolactin surge appears to be absent[6]. Therefore, it has been proposed that the orgasm-induced surge of prolactin controls sexual drive and refractoriness through the central nervous system (CNS)[7]. Nevertheless, the mechanism of prolactin regulation following orgasm remains unknown.

Interestingly, it seems that the high post-ejaculatory levels of plasma prolactin are identical to levels of this hormone detected in lactating females[8,9]. There are similar patterns of hormonal release exhibited by lactating females and those experiencing the post-ejaculatory refractory period. In a series of studies, McIntash and Barfield[10-12] investigated the role of brain serotonin, dopamine and norepinephrine in the control of copulation and the post-ejaculatory refractory period in rats. They showed that noradrenaline and dopamine pathways decrease the duration of the post-ejaculatory refractory period, whereas the duration is lengthened by the serotonergic pathways. Additionally, in lactating female rats, suckling has been found to increase the activity of serotonin-containing neurons[13] that facilitate prolactin release during lactation[14], whereas norepinephrine[15] and dopamine[16,17] are inhibited by suckling. Therefore, we hypothesize that the underlying mechanisms for inhibition of reproductive functions during lactation and during the post-ejaculatory refractory period are similar.

Recently, a new RFamide-related peptide (RFRP) has been discovered[18] which is considered to have inhibitory effects on reproductive functions. This peptide is a homolog of gonadotropin inhibitory hormone (GnIH)[19], an RFamide duodecapeptide in the hypothalamus of quails *(Coturnix japonica)*, which inhibits LH release from the anterior pituitary[18]. The inhibitory effects of GnIH on gonadotropin release have also been identified in mammals, such as hamsters *(Mesocricetus auratus)*, rats *(Rattus norvegicus)*, and mice *(Mus musculus)*[20], and have also been confirmed in male and female rats[21,22], sheep[23,24], and humans[25]. Studies of the inhibitory effects of this RFRP on the hypothalamus, pituitary, and gonads of mammals are reviewed elsewhere[26].

HYPOTHESIS This paper hypothesizes that after orgasm, a GnIH surge occurs which increases plasma prolactin levels and inhibits the hypothalamic-pituitary-gonadal axis, which leads to the occurrence of a refractory period after ejaculation in males.

Supporting Argument Krüger et al.[27] analyzed the effects of acute pharmacological manipulations of plasma prolactin levels on sexual arousal, orgasm, and the refractory period. They observed that increasing prolactin concentrations by protirelin administration could not alter sexual parameters such as the refractory period. Therefore, they concluded that post-orgasmic increases of prolactin do not provide direct negative feedback to the CNS. Hinuma et al.[28] examined the effects of hRFRP-1 on pituitary-hormone secretions in rats and showed that plasma prolactin levels begin to increase 10 minutes after administration and then decline, reaching baseline levels at 60 minutes. RFRPs did not alter plasma levels of other pituitary hormones (GH, FSH, LH, thyroid-stimulating hormone, and adrenocorticotropic hormone). Also, this study showed that the effect of RFRPs on plasma prolactin levels is dose-dependent, which suggests a surge-like pattern. The relationship between RFRP release and plasma levels of prolactin has been confirmed, as it has been shown that during lactation, while prolactin levels are higher, GnIH expression increases in lactating rats[29]. These results are consistent with the reported increasing patterns of prolactin after orgasm[2,4,5].

In many mammals such as sheep[30], rhesus macaques[31], and humans[25], GnIH neuron terminals have been identified in proximity to gonadotropin-releasing hormone (GnRH) neuron bodies, and more than 85 percent of GnRH neurons in hamsters also have GnIH receptors (GPR147)[32]. Because GnIH hyperpolarized[33] and decreased electrical activity of GnRH neurons in mice[34], it is possible that GnIH surge through the inactivation of GnRH neurons, inhibits the hypothalamic-pituitary-gonadal axis.

In addition, GnIH axons project to the median eminence in humans[25], rhesus macaques[25], and hamsters[32], which might directly regulate pituitary function through the hypophysial portal system. GnIH has also been identified in the hypophyseal portal system and GPR147 is found to be expressed in the pituitary gonadotropes of sheep[36]. Therefore, it is plausible that after orgasm, GnIH releases into hypothalamic-hypophyseal portal veins with a direct effect on the pituitary and induced refractoriness.

Another probable neuronal pathway in which GnIH surge can cause the post-ejaculatory refractory period is through the inhibition of dopaminergic neurons. Dopamine expressing neurons that are located in the arcuate and paraventricular nuclei of the hypothalamus inhibit prolactin secretion from the pituitary[37]. Because of the expression of GPR147 mRNA in dopaminergic neurons[35] and increased prolactin secretion after RFRP administration in rats[28], along with the existence of a strong connection between GnIH neuron fibers and dopaminergic neurons in the arcuate of rhesus macaque[35], it is plausible that a GnIH surge increases prolactin secretion after orgasm via the inhibition of dopaminergic neurons.

An oxytocin surge occurs at the time of and immediately after orgasm in men [5,38; for a review, see39]. A recent study showed that intracerebroventricular injection of RFRPs increased the expression of Fos-protein in oxytocin neurons in the hypothalamus of rats and increased oxytocin plasma concentrations[40]. Also, it showed that the hypothalamic paraventricular and supraoptic nuclei expressed GPR147 mRNA, and applying RFRPs to the isolated supraoptic nuclei facilitated oxytocin release. Therefore, they concluded that RFRPs activate oxytocin neurons directly[40]. The pattern of oxytocin surge at the time of and after orgasm supports the surge secretion of GnIH in the current hypothesis.

Testing the Hypothesis GnIH expression is investigated in different species using different methods and techniques. For example, using immunohistochemistry in rodents[20], sheep[30], rhesus macaques[35], and humans[25]; using in situ hybridization in rhesus macaques[31], mice[41], and rats[42]; and using RT-PCR in rats[43,44]. It should also be noted that GnIH concentration has been investigated in hypothalamic portal blood vessels as an in-vivo method recently[36]. To test the current hypothesis, GnIH expression and its concentration in the portal system should be investigated before, during, and after orgasm. Another possible condition that may be useful for testing this hypothesis is the comparison of GnIH expression in animals with high and low libidos.

CONCLUSION This paper hypothesizes that, first, gonadotropin inhibitory hormone (GnIH) secretion, in addition to exhibiting a pulsatile pattern, shows a surge-like pattern of release at the time of orgasm, and second, the post-ejaculatory refractory period is due to high levels of secretion of this hormone after orgasm, which inhibits sexual functions. If this hypothesis stands, it can explain the reason behind sexual exhaustion and post-ejaculatory refractory period after orgasm. Therefore, using GnIH antagonists, low libido and sexual exhaustion in men could potentially be remedied. It should be noted that the refractory period ranges from 15 minutes for 18-year-old men to 20 hours for seniors[45]. In addition to decreasing erectile disfunction, sildenafil (Viagra™) reduces the post-ejaculatory refractory period, but its effect does not seem to involve an interaction with central monoaminergic control pathways[46]. On the contrary, a GnIH antagonist might affect the hypothalamic-pituitary-gonadal axis at the brain level and probably would result in the fewest side effects. Also, from a psychological point of view, this hypothesis can explain why men need to separate from post-coital connection. Although there exist some evolutionary hypotheses[47], there is no definite and objective explanation for this behavior yet.

Finally, it should be noted that in addition to the role of GnIH in the post-ejaculatory refractory period, it is also possible that alternative mechanisms through other neuronal and hormonal pathways, which are not mentioned here, may be in action.**H**

AUTHOR'S CONTRIBUTIONS FP contributed to the conception of the study; FP

and MSS wrote and revised the manuscript. Both authors read and approved the final draft of the manuscript.

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CONFLICTS OF INTEREST Authors declare no conflicts of interest.

ABOUT THE AUTHORS Farid Pazhoohi and Mohammad Saied Salehi are post-graduate students in animal physiology investigating neuroendocrinology of reproduction in animal models. Beside physiology, Farid Pazhoohi has conducted experiments in the fields of human perception, evolutionary psychology and physical anthropology.

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