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A Mathematical Weibull model for desensitization of gonadotropin responses to kisspeptin in the female rat Analyses of LH and FSH secretion at different developmental and metabolic states

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Abstract: *In this paper we present desensitization of gonadotropin responses to kisspeptin in the female rat analyses of LH and FSH secretion at different developmental and metabolic states using recent generations of the Weibull distribution. We conclude that continuous administration of Kisspeptin to female rats, with remarkable differences being detected between LH and FSH responses in different developmental and metabolic states. The physiological roles of kisspeptin in the dynamic regulation of gonadotropin secretion in the female rat. Finally by using these results we have arrived from the mathematical figures for the application part. This coincides with the mathematical result that the secretion of LH and FSH is monotonically increasing and decreases in the case of Kisspeptin -10 and libitum, when time increases.*

Keywords: *Gonadotropin, Kisspeptin, FSH, LH, Hazard rate function, Cumulative Failure rate function, Reliability function, Mean life time.*
Mathematical subject classification*: 60 G_{xx} ; 62H_{xx}; 62P_{xx}*

I. Introduction

In the context of reliability modeling, some well-known interrelationships between the various quantities such as pdf, cdf, failure rate function, cumulative failure rate function, and reliability function, for a continuous lifetime , can be summarized as

$$h(t) = \frac{f(t)}{1-F(t)} = \frac{f(t)}{R(t)} \quad ------(1)$$

$$H(t) = \int_0^t h(x)dx \quad ------(2)$$

$$R(t) = e^{-H(t)} \quad ------(3)$$

Note that all the cumulative failure rate functions must satisfy the following conditions:
i. $H(t)$ is nondecreasing for all
ii. $H(0) = 0$
iii. $\lim_{n\to\infty} H(t) = \infty$

Thus, knowing one of the three quantities, one can easily obtain the other two. In this short communication, we shall see how (3) facilitates the construct of Weibull-type lifetime distributions. The bathtub-shaped failure rate function plays an important role in reliability applications, such as human life and electronic devices. Many authors have proposed new distributions based on the traditional Weibull distribution function. Nadarajah & Kotz [14] recently made the point that the proposed distributions. Equation (3) above describes the relationship between the reliability function, and cumulative failure rate function considered a class of distributions generalizing the traditional Weibull model:

$$R(t) = \exp\{-\alpha G(t)\}, \alpha > 0 \quad ------(4)$$

where $G(t)$is a monotonically increasing function of t. Comparing (3) to (4) . Which implies that the class represented by (4) is a well-known general result in reliability literature.

II. Mathematical Recent Weibull Model

Nikulin & Haghighi [18] proposed a generalized power Weibull distribution with three parameters and its reliability function

$$R(t) = \exp\left\{1 - (1 + (t/\beta)^{\alpha})^{\theta}\right\}\ t \geq 0; \alpha, \beta > 0; \theta \geq 0 \quad ------(5)$$

Note that when $\theta = 1$, (5) reduces to a two-parameter Weibull; when $\theta = 1$, and , $\alpha = 1$ it reduces to the exponential. They also showed that is i) IFR if either $\alpha > 1$, and $\alpha > 1/\theta$; or $\alpha = 1$ and $\theta > 1$; ii) DFR if either $0 < \alpha < 1$, and $\alpha < 1/\theta$; or $\alpha\theta$ = 1, and $0 < \alpha < 1$;
iii) BT if $0 < \frac{1}{\theta} < \alpha < 1$; and iv) UBT if $\frac{1}{\theta} > \alpha > 1$ and Weibull failure rate , cumulative distributive function, probability density functions as

$$h(t) = \frac{K}{\lambda}\left(\frac{x}{\lambda}\right)^{(k-1)} \qquad ------(6)$$

$$F(t) = \left\{ \begin{matrix} 1 - e^{-\left(\frac{x}{\lambda}\right)^{t}}; x > 0 \\ 0 \qquad\quad ; x < 0 \end{matrix} \right\} \qquad ------(7)$$

$$f(x) = \left\{ \begin{matrix} \frac{k}{\lambda}\left(\frac{x}{\lambda}\right)^{(k-1)} e^{-\left(\frac{x}{\lambda}\right)^{k}}; x \geq 0 \\ 0 \qquad\qquad\qquad\quad ; x < 0 \end{matrix} \right\} \qquad ------(8)$$

III. Applications

The secretion of pituitary Gonadotropin LH and FSH is dictated by the pulsatile release of the hypothalamic decapeptide gonadotropin releasing hormone (GnRH) which is ultimately driven by the complex interaction of a plethora of excitatory and inhibitory signals of central and peripheral. Origin that are thought to integrate at the level of GnRH neurons [10,11]. Recently neuroendocrine networks controlling GnRH secretion has been substantially enlarged by the identification of the essential roles of kisspeptins, products of the KiSS-1 gene, and their receptor, G protein-coupled receptor 54 (GPR54), in the regulation of key facets of reproductive function in different mammalian species [19,21]. Thus genetic inactivation of GPR54 and KiSS-1 has been reported to cause sexual immaturity and hypogonadotropic hypogonadism [6,7,13,24]. In addition, hypothalamic KiSS-1 neurons have been shown to be essential elements for pubertal activation of the gonadotropic axis, through a complex maturational process that is likely to involve increased kisspeptin tone, enhanced GPR54 signaling efficiency, and the rise of the number of their appositions to GnRH neurons at the time of puberty [2, 5, 9, 15, 25].Moreover, the KiSS-1/GPR54 system has been implicated in the dynamic regulation of gonadotropin secretion in adulthood, playing key roles in conveying both positive and negative feedback effects of sex steroids and the metabolic control of the gonadotropic axis and its modulation by endogenous rhythms and environmental cues [3, 15, 21, 22, 26,27].

Moreover, the above analyses have only considered LH responses, whereas potential changes in FSH secretion after chronic kisspeptin administration remain totally unexplored. Considering the specific, somewhat differential, features of LH and FSH secretion in general [12], and their responses to kisspeptin in particular [16,17] ,and taking into account the obvious therapeutic interest of optimization of amenable protocols of pharmacological intervention of the female gonadotropic axis, the present work was undertaken to provide an integral analysis of gonadotropin (LH and FSH) responses to continuous intracerebral infusion of kisspeptin-10 in the female rat. Given that substantial changes in the functionality of the female gonadotropic axis are detected along sexual maturation and under different metabolic/nutritional conditions, our experiments were comparatively conducted in pubertal and adult cyclic females, either fed ad libitum or after chronic subnutrition. In the latter, considering the proven roles of leptin in signaling the state of energy stores to the centers governing the gonadotropic axis [1,8]and its particular role in the modulation of kisspeptin signaling [4,25], the effects of continuous infusion of kisspeptin-10 were compared with those of leptin, selectively in underfed animals.

Effects of continuous kisspeptin infusion on LH and FSH secretion in adult female rats. In an attempt to characterize the consequences of continuous administration of kisspeptin on the circulating levels of both gonadotropins in the female, a standard protocol of intracerebral infusion of kisspeptin-10 for 7 days was implemented in adult, regularly cyclic rats, starting on the day of diestrus-1. Of note, protocols of central administration were implemented in an attempt to achieve high effective doses of kisspeptin at the hypo-thalamus. In keeping with previous results of acute or repeated injection of the peptide to adult males [3,29] , final body weights remained unaltered in female rats after 7-day treatment with kisspeptin- 10 (258.4 $\pm$ 9.4 vs. 258.6 $\pm$6.6 g in vehicle-infused controls), and daily food intake was not modified .

In addition, chronic infusion of kisspeptin resulted in a marginal increase in uterus weight at the end of the treatment (172.9 $\pm$ 12.3 vs. 155.3 $\pm$ 5.8 mg/100 g body wt in vehicletreatedrats), which did not reach statistical significance.Regular (daily) blood sampling of kisspeptin-infused females demonstrated that serum LH levels were significantly enhanced 24 h (day 1) after initiation of chronic treatments remained elevated up to 48 h (day 2) after continuous kisspeptin administration and significantly dropped thereafter, with circulating LH concentrations below control values on day 3 and normalized levels from day 4 of infusion onwards (Fig. 3.1 A). Yet, despite the loss of LH stimulation after >2 days of chronic

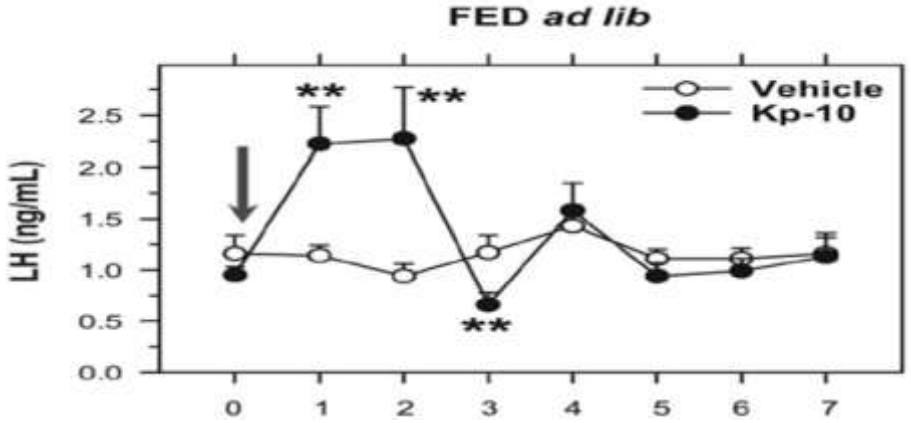

Fig. 3.1. A Pattern of LH secretion in adult, cyclic female rats after continuous intracerebroventricular infusion of kisspeptin-10 (Kp-10). Daily (9:00 –10:00) levels of LH, before (day 0) and during the course of the 7-day period of Kp-10 administration are presented in A.

LH secretion, FSH responses were monitored in the different experimental groups indicated above. In cyclic females fed ad libitum, daily blood sampling at 9:00 –10:00 showed the dynamic fluctuation of FSH levels across the cycle, with low levels at diestrus and proestrus and peaks of secretion on the morning of the corresponding estrus. Contrary to LH, chronic infusion of kisspeptin-10 resulted in a persistent elevation of FSH levels throughout the study period. Indeed, at the end of the kisspeptin infusion (corresponding to estrus), serum FSH concentrations were significantly higher than the endogenously elevated levels of the secondary surge of FSH (Fig. 3.2 A).

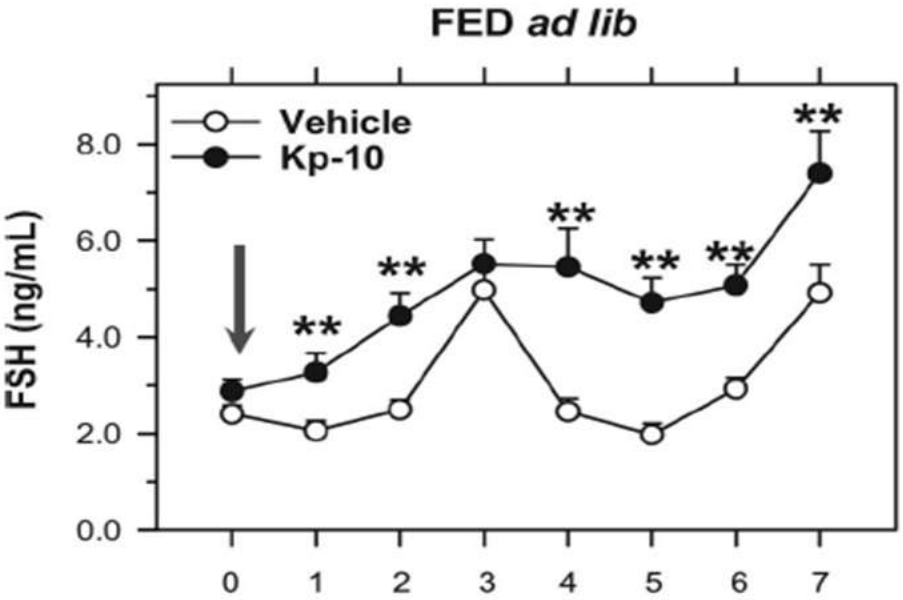

Fig. 3.2 A. Pattern of FSH secretion in adult, cyclic female rats after continuous intracerebroventricular infusion of Kp-10

IV. Discussion

In this paper, the recent identification of kisspeptins as very potent stimulators of gonadotropin secretion in a number of mammalian species, including the human, has raised the interesting possibility that the products of KiSS-1 gene and their putative receptor GPR54 might be suitable targets for therapeutic intervention of the gonadotropic axis [21] . Thus kisspeptins have been shown to potently elicit LH and FSH secretion even at very low doses and after systemic administration, thus providing a potential alternative to GnRH stimulation of gonadotropins [21]. Indeed, as kisspeptins primarily act by inducing the secretion of the releasable pool of endogenous GnRH, such a procedure seems more physiological and accordingly less prone to rapid desensitization than the pharmacological activation of the axis by an exogenous bolus of GnRH [30]. Nonetheless, evidence is mounting that continuous exposure to kisspeptins is also able to induce desensitization to their potent gonadotropin-releasing effects [20,23,28] . In any event, the loss of LH stimulation after chronic

administration of kisspeptin-10 in adult female rats cannot be attributed to degradation of the peptide or premature exhaustion of the pumps, as indirectly evidenced by persistent FSH responses in the very same animals (See Fig.3. 2A).

One of the most salient observations of our study is that, despite rapidly extinguished LH responses, chronic infusion of kisspeptin-10 did not obliterate, but rather persistently augmented, FSH secretion in the female rat.

These observations suggest that our protocol of leptin administration (1 nmol/day between days 30 and 37) was not sufficient to evoke a full activation of the KiSS-1 system in the hypo-thalamus at puberty, in keeping with the contention that leptin is a permissive metabolic factor, rather than the triggering signal, for puberty onset [8]. Admittedly, however, protracted protocols of leptin infusion (e.g., starting at weaning) have been reported to advance puberty onset in food restricted rats [31], suggesting that supraphysiological leptin stimulation might be sufficient to trigger puberty in rodents.

V. Mathematical Results

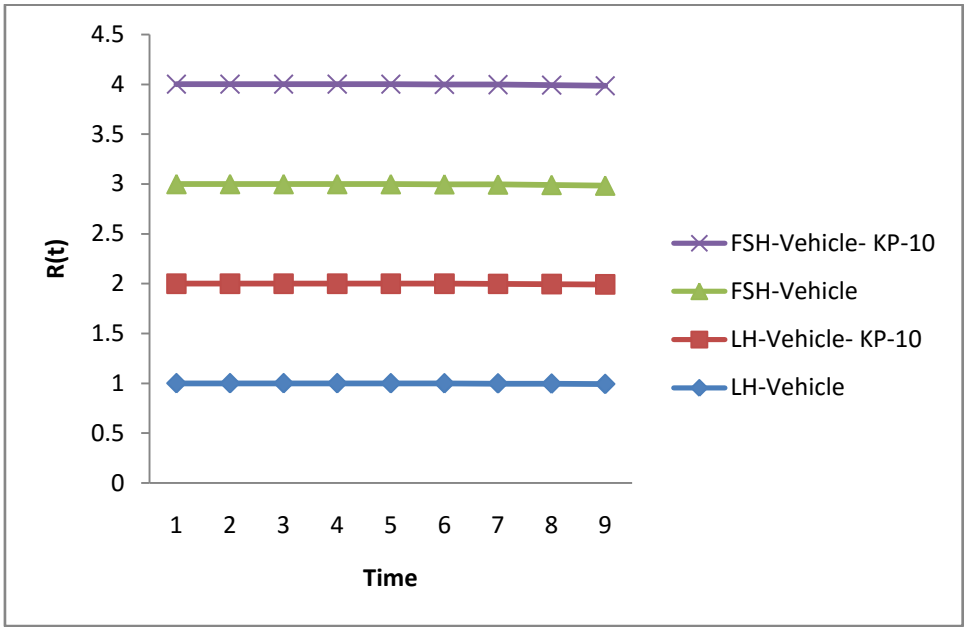

Fig 5.1 (A) The value of reliability function for FSH and LH corresponding to Figure(Reliability function)

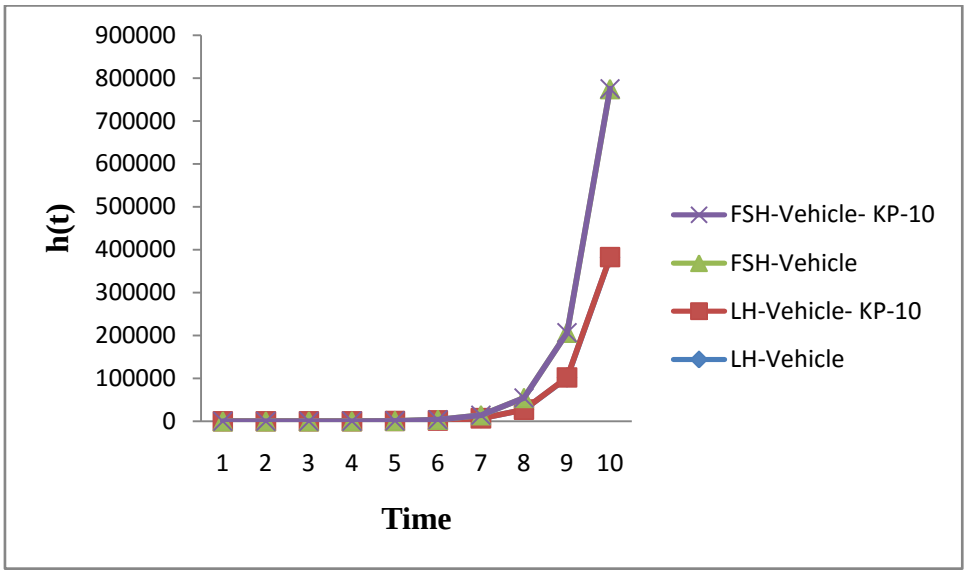

Fig 5.2 (B) The value of Hazard rate for FSH and LH corresponding to Figure(Hazard rate)

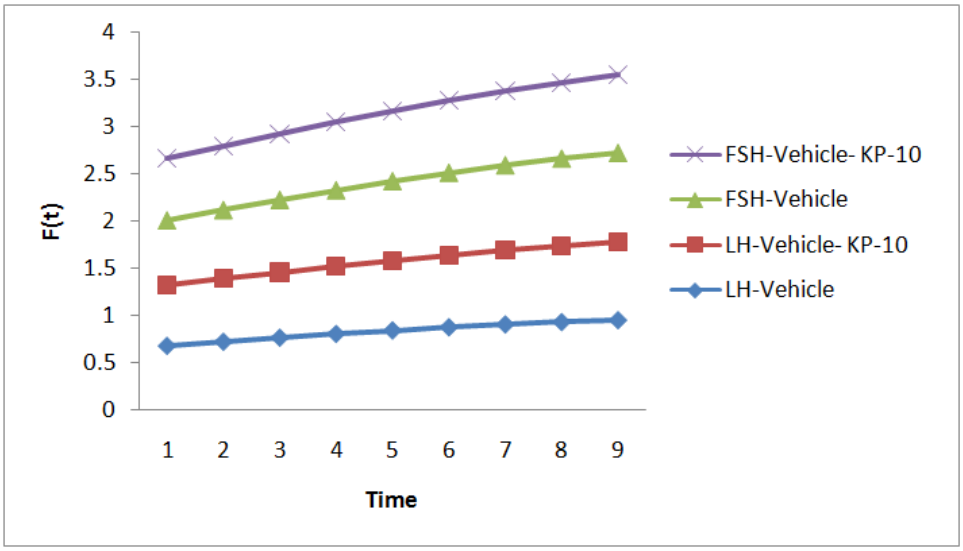

Fig 5.3 (C) The value of cumulative distribution function FSH and LH corresponding to Figure(Cumulative Distribution)

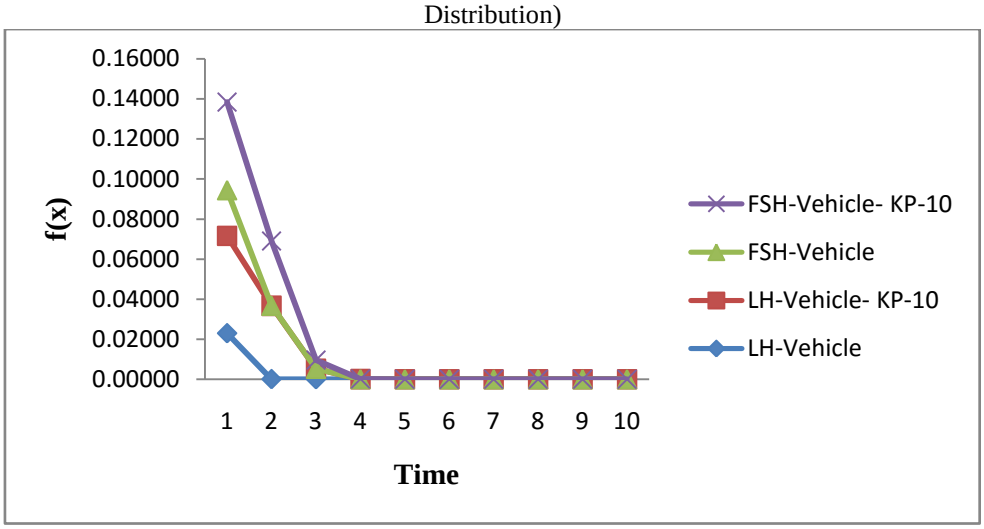

Fig 5.3 (D) Probability density function for FSH and LH responses, in different developmental and metabolic states corresponding to figure(Probability Density function)

VI. Conclusions

We present here in an integral study of the patterns of gonadotropin secretion after continuous administration of kisspeptin-10 in the female rat by the combined analysis of LH and FSH secretary responses at different developmental and metabolic states of the female gonadotropic axis, which contributes to provide a deeper insight in to the mechanisms where kisspeptin signaling may participate in the differential regulation of LH and FSH secretion in certain physiological (or) pathological conditions in the female. Finally by using these results we have arrived from the mathematical figures for the application part. This coincides with the mathematical result that the secretion of LH and FSH is monotonically continuous and decreases in the case of kisspeptin-10 and libitum, when time increases.

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