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A MATHEMATICAL SKEW-LOGISTIC MODEL FOR CIRCADIAN GENE EXPRESSION REGULATES PULSATILE GONADOTROPIN-RELEASING HORMONE (GNRH) SECRETORY PATTERNS IN THE HYPOTHALAMIC GNRH-SECRETING GT1-7 CELL LINE

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Abstract: In this paper we introduce the skew logistic distribution. It is observed that the probability density function of the skew logistic distribution is always unimodal The main idea is to introduce the skewness parameter, so that the generalized logistic distribution can be used to model data exhibiting a unimodal density function having some skewness present in the data, a feature which is very common in practice. We used the GT1-7 mouse hypothalamic cell line as a model for GnRH secretion, because these cells release GnRH in a pulsatile pattern similar to that observed in vivo. This effect persists in normal light/dark (LD) cycles, suggesting that a suprachiasmatic nucleus- independent endogenous clock in GnRH neurons is required for eliciting normal pulsatile patterns of GnRH secrection.finally we conclude that the application part overlaps with a mathematical model. In future, this paper will be advantageous in the medical field.

Keywords and Phrases: Skew logistic distribution, circadian, GnRH, secretion, Clock, GT1-7.

2020 Mathematics Subject Classification: 60G12, 60H12.

1. Introduction

If it has the following cumulative distribution function, the random variable Y has the logistic allocation

$$G(y,\theta,\alpha)=\frac{1}{1+e^{\frac{x-\theta}{\alpha}}},\quad -\infty<x<\infty \tag{1}$$

The probability density function corresponding to the equation (1) is for any arbitrary position parameter θ and for the scale parameter $\alpha>0$.

$$G(y,\theta,\alpha)=\alpha\left(1+e^{\frac{\frac{y-\theta}{\alpha}}{\frac{y-\theta}{\alpha}}}\right)^{2},\quad -\infty<x<\infty \tag{2}$$

Clearly,the probability density function given in (2) is symmetric about the position parameter θ. From now on the logistic distribution with the probability density function given in (2) will be denoted as $L(\theta,\alpha)$ [1, 15].

It is observed that the PDF of the skew logistic distribution can have different shapes with both positive and negative skewness depending on the skewness parameter [18, 19]. Although the PDF of the skew logistic distribution is unimodal. Moreover, it is observed that even when the location and scale parameters are known, the maximum likelihood estimator of the skewness parameter may not always exist [7, 8].

2. Applications

In order to induce gonadotropin release from the anterior pituitary, reproductive activity hinges on the episodic secretion of gonadotropinreleasing hormone (GnRH) from hypothalamic nerve terminals. This pulsatile GnRH secretion ultimately regulates critical reproductive process ranging from gametogenesis to ovulation. Although GnRH perikarya and nerve terminals are positioned with in the mediobasal hypothalamus to receive multiple neuronal and humoral signals and can respond to apparent that species-specific timing of GnRH pulse release is an intrinsic property of GnRH neurons. Studies using immortalized GT1-1 and GT1-7 cell lines reveal that these homogenous clonal cell population are capable of recapitulating GnRH pulse release patterns observed in vivo from rodents [10, 22].

In more recent work, pulsatile GnRH release was also observed from tissue explants of premigratory GnRH cells collected from embryonic primate olfactory placode [20], demonstrating that GnRH neurons do not require the complex array of afferent neuronal connections present in the mature hypothalamus to secrete GnRH in discretely timed pulses. Although the phenomenon of GnRH pulsatility has been well documented, mechanism mediating coordinated neurose-cretion

have proven elusive. In support of the aforementioned studies implicating biological clock function in GnRH surge generation, evidence suggests that the circadian clock may be involved in regulating basel GnRH pulse frequency as well. Hamsters harbouring the naturally occurring tau mutation, a mutated CKIε unable to fully phos-phorylate Per2 [10]. exhibit accelerated LH pulse frequencies [9]. Suggesting that the underlying GnRH pulsatility may be fundamentally altered by this circadian mutation. In addition, recent studies implicate proper molecular clock function as crucial to normal reproductive patency in Drosophila [4].

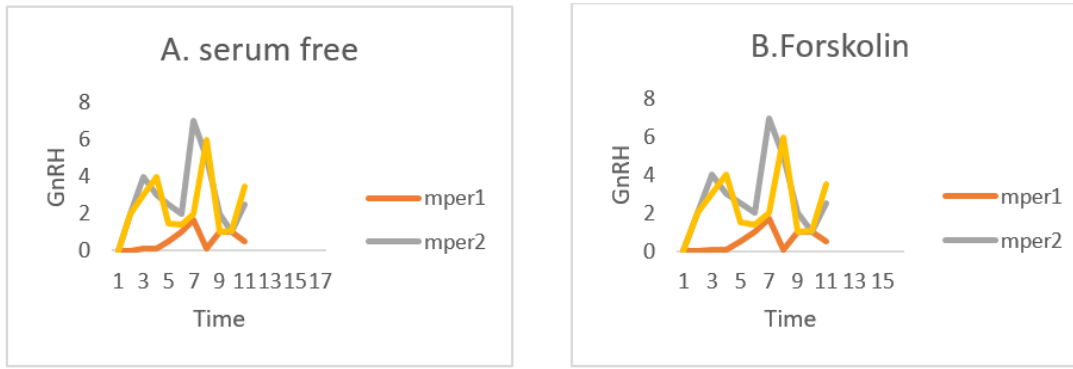

Figure 1: Multiple stimuli induce transient increases in expression and oscillation of circadian clock gene expression in cultured GT1-7 cells, as measured by RNase protection assay A, circadian gene expression of mPer1 and mPer2 oscillates in GT1-7 cells after a shift to SF media.

As shown in Figure 1A, mRNA levels of mPer1 and mPer2 oscillate with 20-24 hr periodicity in this cell line, as well as in NIH3T3 cells. After change to the conditions of SF media as well as after a 15-30 min exposure to 1.0 μm FSK (Figure 1B). Under both conditions,the peaks in expression levels, as observed previously in other cell lines [24]. Clock cycling serumshock and FSK activation have previously been characterized in rat-1 and NIH3T3 fibroblasts [3, 14]. A temporary down regulation of several clock genes accompanied by low amplitude cycling was associated with the neuronal SCN2.2 cell line, in which minor disruptions such as a depolarizing KCI concentration or low (2 percent) serum levels are necessary to trigger gene expression oscillation [1], has also been observed to have large pulses. Furthermore, RNA expression levels of mCry1 and mCry2 were found to oscillatein arhytm close to that of mPer1 and mPer2. In comparison to mCry1, mCry2 has substantially damped amplitudes. For the duration of the experiment, plates of GT1-7 cells cultured and harvested in 10% FBS DMEM (no disturbance) showed

no noticeable oscillations in mRNA accumulation.

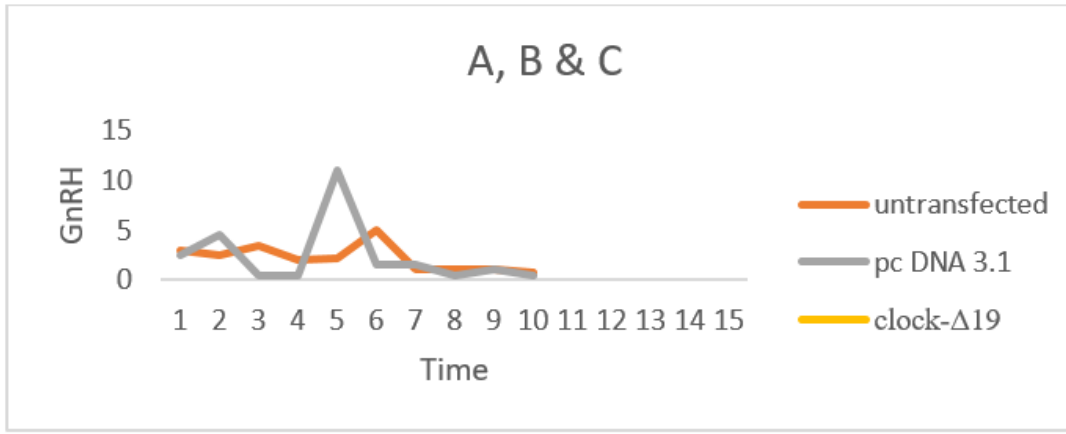

Figure 2: Perturbation of the circadian clock by expression of clock -Δ19 disrupts patterns of GnRH pulse release from perifused GT1-7 cells. A-C, representative GnRH pulse release profiles from perifused GT1-7 cells that were untransfected (A), transfected with the control vector pcDNA3.1(B), or transfected with clock-Δ19(c).

GT1-7 cells cultured on beads in a perifusion system were transiently transfected with clock-Δ19. 16-24 hr before column loading and fraction selection in order to investigate the impact of clock-19 expression on pulsatile GnRH secretion Cells were perifused in KRB for 6-12 hr after loading into columns, followed by either 1 or 5 min sample collection for an additional 12 hr, followed by either 1 or 5 min sample collection for an additional 1012 hr. GnRH significant pulse peaks were distinguished from baseline noise using parameters of cluster analysis to determine peak and nadir values and significant differences between peak and nadir values. Whereas GnRH secretion profiles of either untransfected (Figure 2)or pcDNA3.1 (control)-transfected (Figure 1A) GT1-7 cells displayed secretory interpulse intervals of approximately 30 minutes, similar to previously published reports [6], Transiently expressing clock cells 19 showed markedly disrupted secretion patterns,frequently characterized by large erratic GnRH release bursts followed by long quiet periods of minimal secretion.

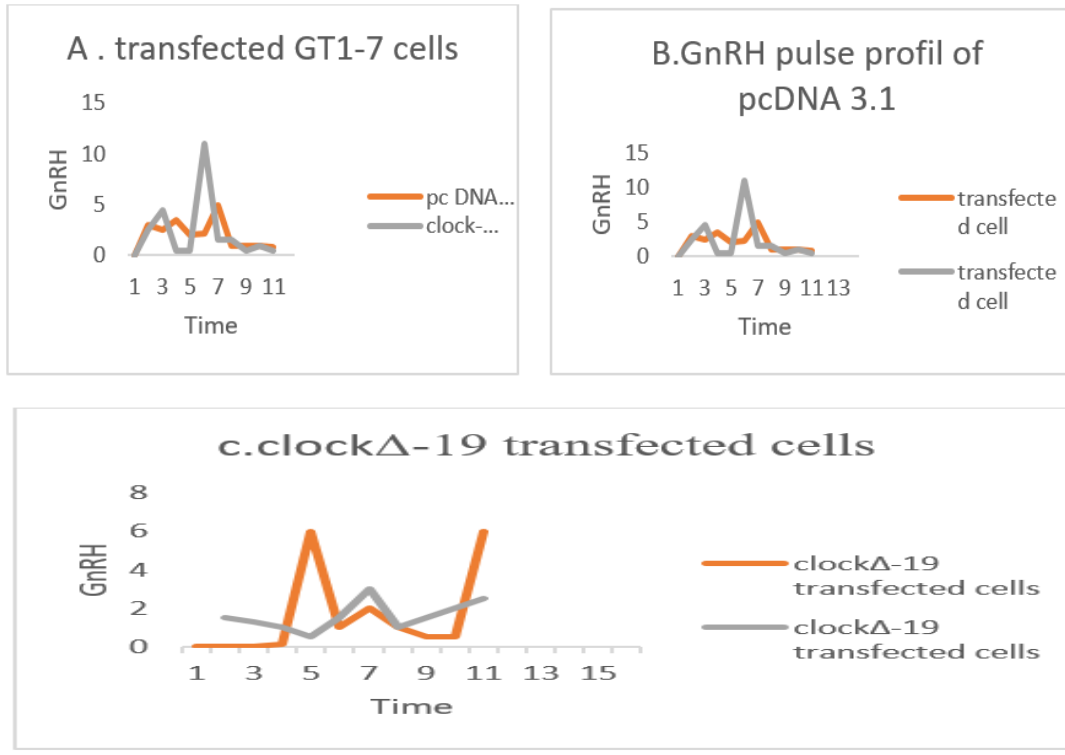

Figure 3: Expression of clock-Δ19 results in alteration of GnRH pulsatile secretory patterns. A, representative 5 min GnRH pulse profiles of perifused pcDNA3.1-transfected (top) and clock-Δ19 –transfected (bottom) GT1-7 cells. C, Representative 1 min GnRH pulse profiles of pcDNA3.1- transfected cells and clock-Δ19–transfected GT1-7 cell.

Although some clock perifusion columns-almost 19-transfected GT1-7 cells showed few observable pulses, others showed a high-amplitude burst lasting up to 25-30 minutes followed low amplitude secretion near the detection stage of the assay (Figure 3). These results suggest that cell configuration and proximity may also play a role in constructing patterns of GnRH pulse release such that pools of GnRH available for secretion may increase in dispersed cells transfected with clock-Δ19. GT1-7 cells overexpressing mCry1 exhibit significantly ($*p < 0.01$) higher mean pulse amplitude (77.6 ± 3.6 pg/ml) in comparision with cells transfected with the control vector (33.5 ± 3.1), without an appreciable difference in mean pulse frequency . because mCry1 levels oscillates in a circadian manner in many tissues in vivo, these results suggest that normal circadian increase in mCry1 protein GnRH neurons could potentially stimulate cellular neurosecretory mechanisms, possibly linking circadian clock cycling to GnRH surge secretion.

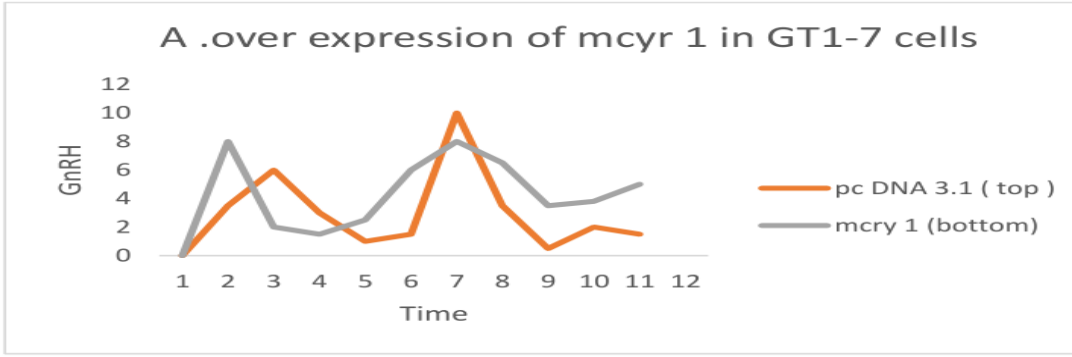

Figure 4: Over expression of mCry1 in GT1-7 results in a significant increase in mean GnRH pulse amplitude. A, representative GnRH pulse profile of perifused GT1-7 cells transiently transfected with a pcDNA3.1(top) or a Cry1 expression vector (bottom).

3. Mathematical Results

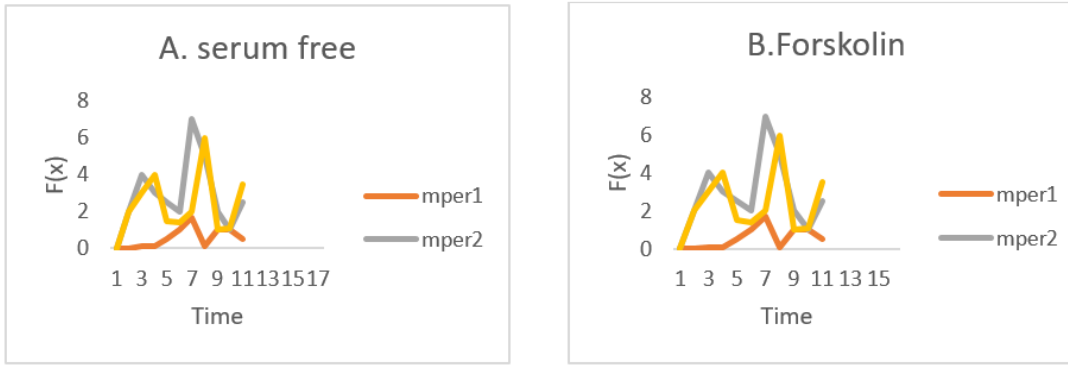

Figure 5

Figure 6

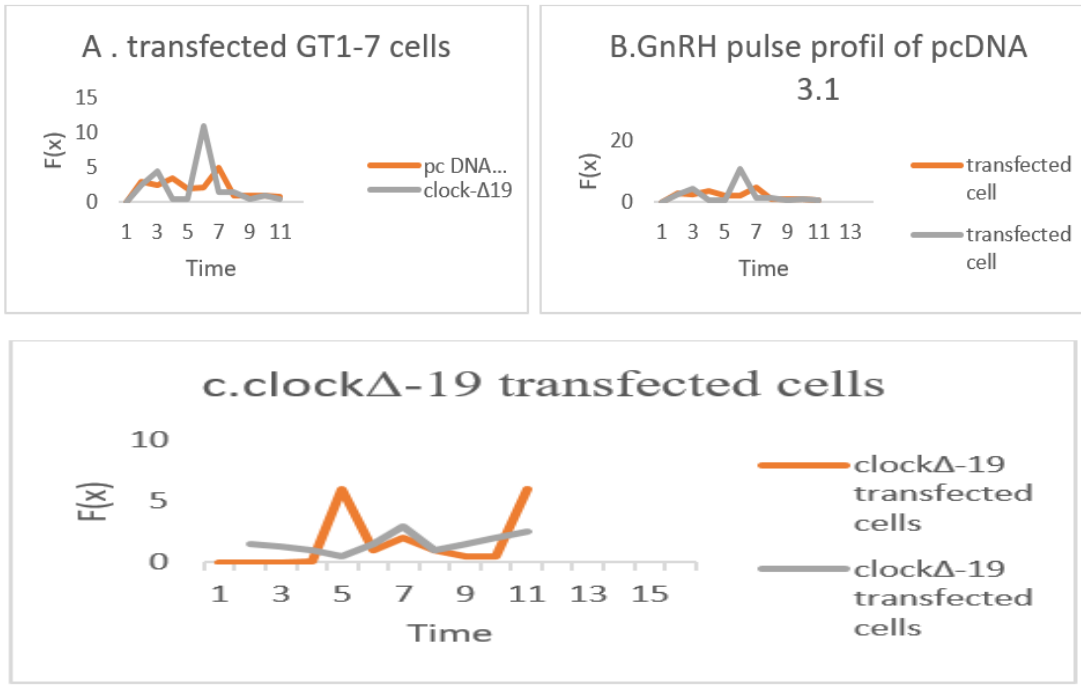

Figure 7

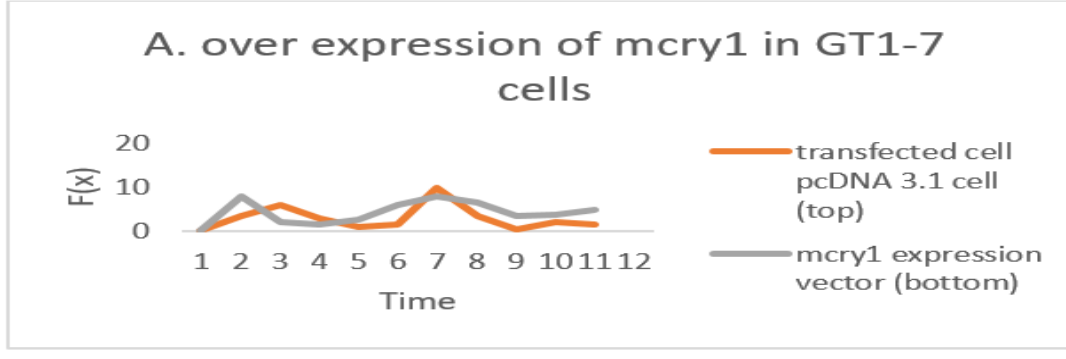

Figure 8

4. Conclusion

In sum, the results of the current study demonstrate that an endogenous circadian clock lays a role in regulating parameters of GnRH pulsatility. Although future studies are required to determine the extent and mode of this regulation,

these data provide insight into the fundamental mechanism underlying GnRH pulsatility, as well as presenting a direct influence of the circadian clock on primary neuronal components of the reproductive axis. Finally, we conclude that a mathematical report and medical report are well fitted.

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