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Stochastic Clearing System For Nicotine Self Administration Differentially Regulates Corticotropin Releasing Factor And Arginine Vasopressin Due To Stress

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ABSTRACT

Acute nicotine is a potent stimulus for activation of the stress responsive hypothalamic-pituitary-adrenal (HPA) axis. To identify underlying mechanisms, we investigated the effects of chronic nicotine self administration (SA) on the co-expression of corticotropin-releasing factor (CRF) and Arginine vasopressin (AVP) mRNAs. The phenotypic neuronal alterations may provide the pivotal mechanism underlying the capacity of chronically self administered nicotine to cross-sensitizes the HPA response to specific stressors, suggesting that nicotine may augment HPA responsiveness to specific stressors in human smokers. Schematic representation of paraventricular nucleus (PVN) neuroadaptive changes and HPA axis responses during nicotine SA is given in section 1. So we consider this as a special case of the general stochastic clearing system. The organ system receives an input (AVP secretion). overtime according to a non - decreasing continuous time stochastic process Z={z(t),t≥0} and z(t) is the cumulative input upto time t. At epochs $\tau_1 \leq \tau_2 \leq \tau_3 \leq \ldots\ldots$ the quantities accumulated are instantaneously cleared.

Keywords: Cumulative stress effect, Stochastic clearing system Arginine vasopressine, Correlated renewal process.
Classification: 60G

1. INTRODUCTION

Arginine vasopressin may play a critical role in regulating hypothalamic pituitary adrenal (HPA) responses to chronic stressors[1]. When chronically self-administered, nicotine appears to function as a stressor,e.g.,14-25d unlimited access nicotine self-administration (SA) persistently stimulated norepinephrine release, in both PVN [7].

Stress is a well known risk factor for the development and maintenance of smoking. However, whether smoking itself affects the response to stressors is controversial, because both reductions and increases in stress levels have been reported in smokers [3][4][11]. Data from several sources suggest that increased stress hormones secretion is in fact potentially dangerous, since, if it lasts too long or Is repeated too often, it may cause functional disturbances in various organs and organ systems which, in turn, may lead to disease. It seems reasonable to regard the duration of the response evoked by temporary disturbances in daily life as a key determinant of their potential harmfulness. Since every biological organ system is homeostatic, it is quite natural to assume that some reset due to relaxation, or rest takes place. Here, we have discussed the process in which magnitude of the stress effect i.e. Arginine vasopressin (A_n) and the corresponding time epoch T_n are independent. Consider a stochastic clearing system in which constant demand occurs at random epochs. If accumulated quantity of stress effects reaches the demand level before at random epochs, renewal for homeostatic system is needed and the demand is fulfilled when it occurs. On the other hand if the accumulated quantity is insufficient to satisfy the demand, a severe penalty may be imposed [12,14] .

Corticotropin Releasing Factor (CRF) and arginine vasopressin (AVP), both synthesized in PVN, are the primary hypothalamic neuropeptides regulating ACTH secretion during stress [8]. Under specific conditions, CRF and AVP are co-synthesized in parvocellular PVN (pcPVN) neurons and co secreted from median eminence terminals. Chronic exposure to homotypic stressors typically increased pcPVN AVP mRNA levels, whereas CRF mRNA showed varying responses depending on the stress paradigm [1]. Furthermore, repeated stress increased CRF neuronal numbers and terminals coexpressing AVP, which may increase the AVP/CRF ratio in pituitary portal circulation during response to a heterotypic stressor.

Based on evidence that chronically self-administered nicotine functions as a stressor, we hypothesized that chronic nicotine SA would affect CRF/AVP mRNA coexpression in pcPVN. Based on our finding that chronic nicotine SA enhanced ACTH response to a heterotypic stressor [2], we also postulated that chronic nicotine SA would augment activation of pcPVN neurons coexpressing CRF and AVP in response to a novel stressor.

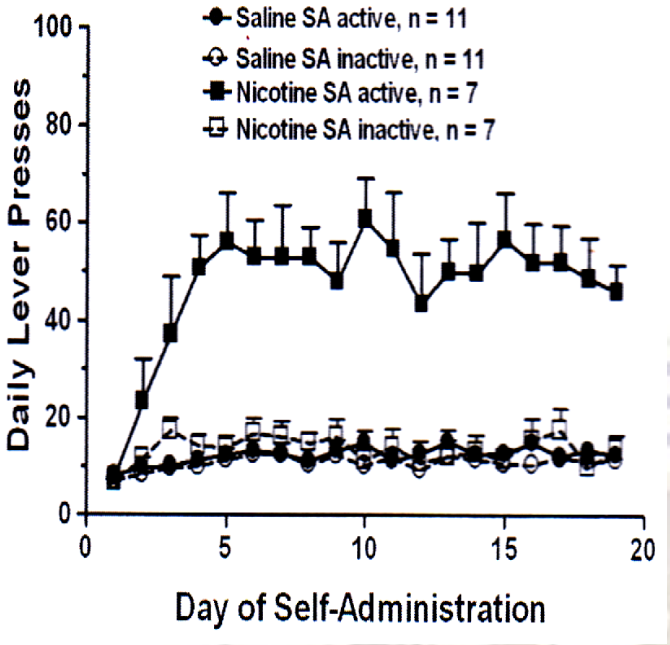

Figure 1.1 : Comparison of daily lever presses between adult male rat cohorts self administering nicotine (nicotine SA; 30 g/kg per injection) versus saline. The lever press records from the free-fed and pair-fed saline SA groups were combined, because active ($F(1,9)=1.8$, $p>0.05$) and inactive ($F(1,9)=1.3$, $p>0.05$) lever presses were similar in both groups. Rats self-administering nicotine pressed significantly more on the active lever than the inactive lever ($F(1,12)=28.6$, $p<0.001$) and also significantly more than the active level presses of control saline SA ($F(1,16)=52.1$, $p<0.001$). There were no significant differences between the active versus inactive lever presses of saline SA group ($F(1,20)=1.3$, $p>0.05$).

Lever presses and body weight gain during nicotine SA

Adult male rats acquired nicotine SA (0.03 mg/kg body weight per injection, i.v.) without previous training, priming, or food deprivation when the drug was available 23 h/d, as shown previously. Figure 1.1 illustrates the lever press record of all rats that self-administered nicotine versus saline in both experiments 1 and 3 (only unstressed groups); Additionally, active lever presses were greater in nicotine SA compared with saline SA ($F(1,16)=52.1$,$p>0.001$), but there was no difference in the inactive lever presses ($F(1,16)=1.8$, $p>0.05$).

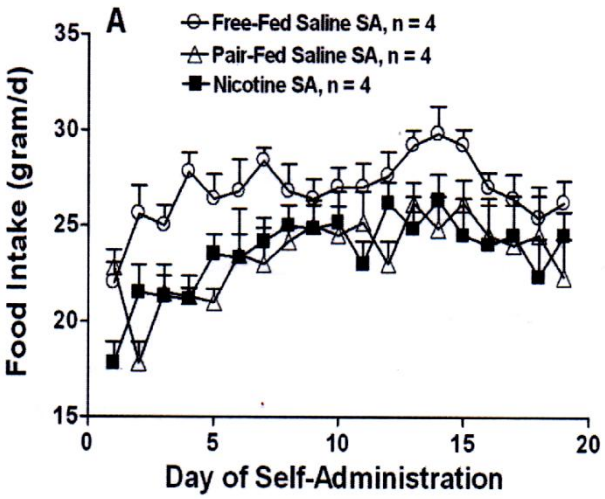

Figure 1.2: There was a significant effect of treatment on food intake, in that nicotine SA rats (and their matched pair-fed saline SA controls) ingested less food than free-fed saline SA rats ($F(1,6)=8.4$ and 17.7, respectively, $p<0.05$).

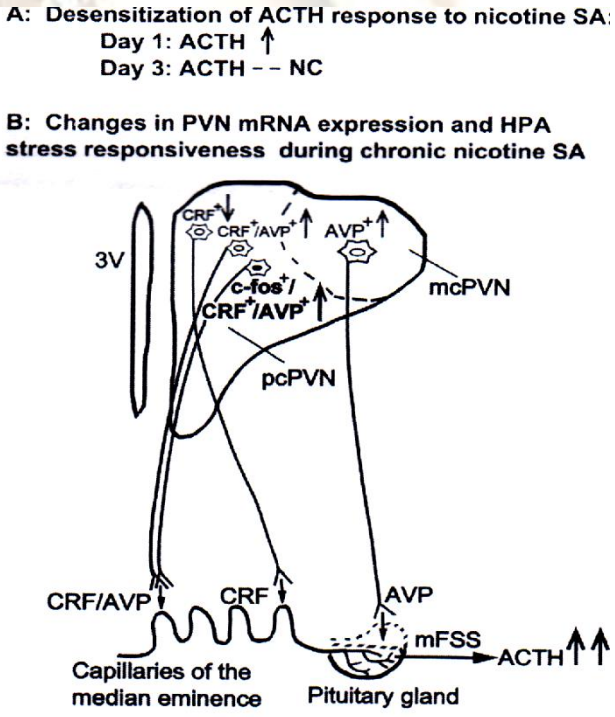

Figure 1.3: Schematic of PVN neuroadaptive changes and HPA axis responses during nicotine SA. A, Effects of nicotine SA per se on ACTH secretion during acquisition of the behavior on days 1 and 3 (NC, no change). B, Effects of chronic nicotine SAonthe PVN expression of CRF and AVP mRNAs in single- and double-positive neurons within pcPVN and mcPVN and on the ACTH response to mFSS. Chronic nicotine SA increased (1) the number of CRF+/AVP+neurons, the number of such neurons activated by mFSS (cFos+/CRF+/AVP+), and the ACTH response to mFSS.

2. NOTATIONS

A_n : The magnitude of AVP secretion at n^{th} Stochastic clearing epoch.

T_n : The time interval between two consecutive stress effects.

N(t) : Counting process associated with the renewal sequence $\{T_n\}_0^\infty$

Z = {z (t), t ≥ 0 }, such that z(0) = 0 : Non decreasing continuous time stochastic process.

$$V(t) = z(t) - z\tau_{N(t)} \qquad \tau_n = \sum_{i=0}^{n} T_i$$

$$M(t) = \max_{0 \le i \le N(t)} \{A_i\}$$

$F_{A,T}(a,t)$: Common cumulative distribution function of the correlated pairs of renewal sequences (A_n, T_n)

$F_T(t), F_A(a)$: The corresponding marginal distributions functions.

3. MATHEMATICAL MODEL

The organ system received an input overtime according to a non decreasing continuous time Stochastic process $Z = \{z(t), t \ge 0\}$ such that z(0) = 0 probability 1 and z(t) is the cumulative stress effect up to time t.

At epochs

$$\tau_1 \ge \tau_2 \ge \tau_3 \ge \ldots\ldots\ldots \left(\tau_n = \sum_{i=0}^{n} T_i\right)$$

The quantities accumulated are instantaneously cleared due to homeostatic organ system. (by relaxation and refreshment).

Let V(t) be the quantity in the system at time t.

$$V(t) = z(t) - z(\tau_{N(t)}), \qquad t \ge 0$$

Let $\{V(\bar{\tau}_n)\}_1^\infty$ be a renewal sequence. The renewal property for $\{V(\bar{\tau}_n)\}_1^\infty$ may be achieved by having the epochs to $\tau_1, \tau_2, \tau_3, \ldots\ldots\ldots$ to coincide with certain regeneration points of z. However, it should be noted that $V(\bar{\tau}_n)$ and T_n will be correlated. The maximum quantity cleared upto time t is

$$M(t) = \max_{0 \le i \le N(t)} \{A_i\}$$ with

$A_n = V(\bar{\tau}_n)$, n = 1,2, …

The following modified stochastic clearing system is of practical interest. The quantity of AVP accumulates constantly over time at a constant rate.

i.e.

$$V(\bar{\tau}_n), = T_n, \qquad n = 1,2\ldots\ldots\ldots$$

Due to the constraints imposed on external demands, it is assumed that the quantity that could be secreted used at each clearing is limited. Let this quantity called capacity (due to adaptation), be C_n at the n^{th} clearing epoch. Then the actual quantity that is put to productive use at the n^{th} clearing is

$A_n = \min \{V(\bar{\tau}_n), C_n\}$, n =1, 2….

If $\{C_n\}_1^\infty$ is a renewal sequence, so is $\{A_n\}_1^\infty$

Let

$$F_c(a) = P[C_n \le a]$$

Then

$$F_{A,T}(a,t) = F_T(t), \quad t < a$$

$$= F_T(a) + (F_T(t) - F_T(a))F_c(a), \quad t > a$$

Let W(z) = $\lim_{t\to\infty} P[V(t) \le z], \quad z \ge 0$ be the steady state probability distribution function of V(t). In this case, we can obtain the first passage time for the cleared quantity to exceed a level z.

4. SPECIAL CASE

Suppose both $F_T(.)$ and $F_c(.)$ are exponentially distributed with mean $(1/\mu)$ and $(1/\lambda)$ respectively.

Then

$$F_{A,T}(a,t) = 1 - e^{-\mu t}, \quad a \ge t$$

$$= 1 - e^{-(\lambda+\mu)a} - (1 - e^{-\lambda a})e^{-\mu t} \quad a < t$$

….. (4.1)

is a bivariate exponential distribution

The marginal distributions are

$$F_T(t) = 1 - e^{-\mu t}, \quad t \ge 0$$

$$F_A(a) = 1 - e^{-(\lambda+\mu)a}, \quad a \ge 0$$

…. (4.2)

Substituting

$$G_A^*(z,s) = \int_0^\infty e^{-st}[\partial/\partial t][F_{a,T}(z,t)]dt$$

$$= \frac{\mu\ [1 - e^{-(s+\lambda+\mu)z}]}{\mu + s}$$

in

$$w_z^*(s) = \frac{\overline{G_A^*}(z,s)}{1 - G_A^*(z,s)},\ \mathrm{Re}(s) \geq 0$$

$$= \frac{\mu\, e^{-(s+\lambda+\mu)z}}{s + \mu\, e^{-(s+\lambda+\mu)z}},$$

$\mathrm{Re}(s) \geq 0$

Then

$$\overline{w_z^*}(s) = (1/s)\{1 - w_z^*(s)\}$$

$$\overline{w_z^*}(s) = \frac{[1/(\mu+s)]}{1 - \frac{\mu\ [1 - e^{-(s+\lambda+\mu)z}]}{\mu + s}}$$

….. (4.3)

Inverting we can get the survival function.

5. RESULTS

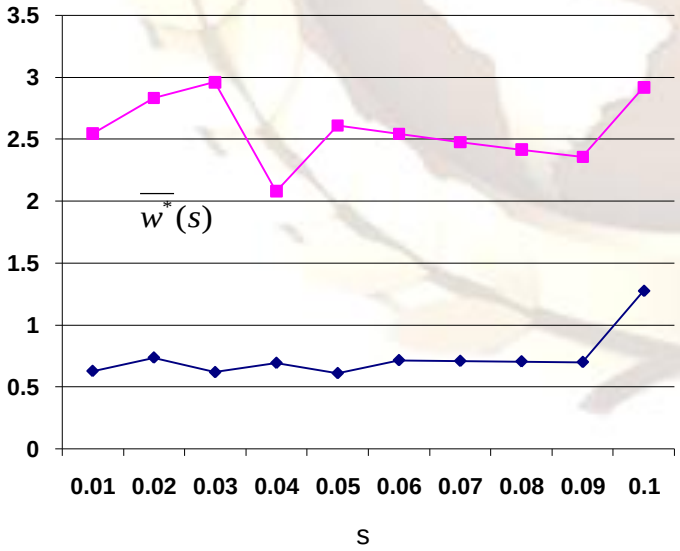

Fig 5.1: λ = 5.3971 μ=1.4330 ; λ = 5.5109 μ=0.32633

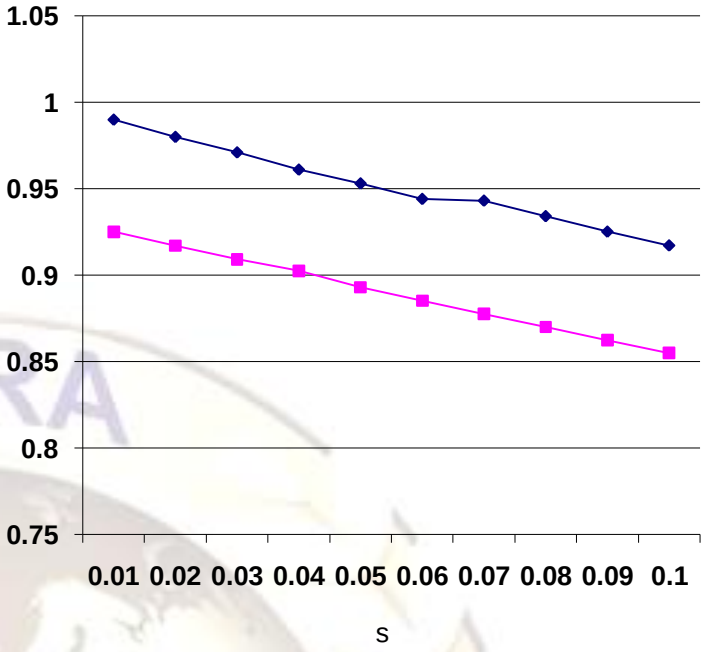

Fig 5.2 : λ = 5.2687 μ=1.0656 ; λ = 5.2471 μ=1.1408

6. CONCLUSION

In conclusion, chronic nicotine usage significantly decreased CRF and increased AVP, mRNA expression, increasing their co-localization in pcPVN. The phenotypic changes in pcPVN neurons may be involved in desensitization of HPA responses to nicotine stimulation. In the mathematical model, corresponding mean values of Daily lever presses in saline active and nicotine active are fitted with the model of stochastic clearing system. The plots of the survival function for various values of z, λ and μ are given in Fig 5.1 and 5.2. Therefore the survival function of the cumulative distribution of lever press in the case of nicotine active is always less than corresponding function of lever press of saline active. Similar cases for food intake also.

REFERENCES

1. Aguilera G.Rabadan –Diehl C (2000) Vasopressinergic regulation of the hypothalamic - pituitary-adrenal axis: implications for stress adaptation. Regul Pept 96:23-29.
2. Chen H. Fu. Y, Sharp BM (2007a) Chronic nicotine self-administration augments hypothalamic-pituitary-adrenal responses to mild acute stress-Neuropsychopharmacology 33:721-730.
3. Croghan IT, Bronars C, Patten CA, Schroeder DR, Nirelli LM, Thomas JL, Clark MM, Vickers KS, Foraker R, Lane K, Houlihan D, Offord KP, Hurt RD (2006) is smoking related to body image satisfaction

stress, and self-esteem in young adults? Am J Health Behav 30:322-333.

4. Finkelstein DM, Kubzansky LD, Goodman E (2006) Social status, stress, and adolescent smoking, J Adoles Health 39:678-685.
5. Frankenhaeuser. M. : Experimental approaches to the study of catecholamines and emotion in Levi.(Ed). Emotions-their parameter and measurement, *New York Raven Press.* (1975b). pp.209-234.
6. Fu Y, Matta SG, Brower VG, Sharp BM (2001) Norepinephrine secretion in the hypothalamic paraventricular nucleus of rats during unlimited access to self-administered nicotine: an in *vivo* microdialysis study. *J Neurosd* 21:8979-8989.
7. Fu Y, Matta SG, Kane VB Sharp BM (2003) Norepinephrine release in amygdala of rats during chronic nicotine self-administration: an in vivo microdialysis study. Neuropharmacology 45:514-523
8. Harbuz MS Lightman SL. (1992) Stress and the hypothalamo-pituitary-adrenal axis: acute, chronic and immunological activation. J Endocrinal 134:327-339.
9. Henry. J.P. : Understanding the early pathophysiology of essential hypertension. *Geriatrics 31*. (1976). Pp.59-72.
10. Kagan. A and Levi.L: Health and environment-psychosocial stimuli: A review. *Social Science and Medicine*. 8 (1974).pp.225-241.
11. Koval JJ, Pederson LL, Chan SS (2004) Psychosocial variables in a cohort of students in grades 8 and 11: a comparsion of current and never smokers. Prev Med 39:1017-1025.
12. Lakshmi S and Geetha T, *Journal of Indian Acad. Math*. Vol 29 No 1 (2007) pp 79-86.
13. Lakshmi. S.A.: Stochastic model for the time to get stress related disease dysfunction by two sources. *International Journal of Management and Systems*. Vol.17. No.1. Jan-April (2001).
14. Shanthikumar J.G., Sumitha.U: General shock models associated with correlated renewal sequences. J.Appl.Prob. 20,(1983) pp.600-614.
15. Theorell.T, Lind E.,Froberg J., C.G and Levi L .: Alongitudinal study of 21 subjects with coronary heart disease : Life changes, Catecholamine excretion and related biochemical reactions. *Psychosomatic medicine*, 34, (1972),pp. 505-516.