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A Mathematical Model for the Release of Vasopressin using Fuzzy Step-Stress Approach

S. Mohankumar[1*] A. Venkatesh[2]
1.Oxford Engineering College, Trichirapalli, Tamilnadu, Pin: 620 009
2.A. V. V. M. Sri Pushpam College, Poondi, Thanjavur (Dt), TamilNadu, Pin:613503
* E-mail: mohanmath_13@yahoo.co.in, a_venkatesh03@yahoo.co.in

Abstract
The theoretical study was to investigate the release of the hormones Vasopressin and Oxytocin from explants of the hypothalamoneurohypophysial system (HNS). A mathematical model using fuzzy constant step –stress approach was developed and used this model to calculate the mean values of the release of Vasopressin and Oxytocin. The result shows that a synergistic effect of metabotropic glutamate receptor activation of Vasopressin and Oxytocin.
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1. Introduction

In accelerated life testing (ALT), by testing products at higher than normal levels of stress, information on the life testing of the product can be quickly and economically obtained. The relationship between lifetime and stress level under accelerated conditions is then extrapolated to normal working condition. ALT consists of a variety of test methods for shortening the life of products of hastening the degradation of their performance. The aim of such testing is to obtain data quickly, which properly modeled and analyzed, yield the desired information on product life or performance under usual use. There are basically two types of accelerated life test schemes; the constant-stress test, and the step-stress test, a time dependent stress test. The former puts each experimental unit to only one of the stress levels. In the step-stress test, initial low stress is applied to all test units. If a unit does not fail in a specific time, the stress is increased .There can be more than one change of stress level. If there is a single change of stress, this is a simple step –stress test. The objective is to choose times to change or minimize a normal stress level.

The problem of modeling data from ALT and making inference from such data from ALT and making inference from such data has been studied by many authors. Chernoff [1] considered an optimal life test for estimation of model parameters based on data from ALT. Meeker and Nelson[2] obtained optimum ALT plans for the Weibull and extreme –value distribution with censored data. Nelson and Kiepinski [3] further studied optimum ALT plans for S-normal and log normal life distribution based on censored data. Nelson [7] is the first to propose the step stress scheme, with the cumulative exposure model and method of analysis. Miler and Nelson [8] obtained the optimum simple step-stress accelerated life test plan for the case where the test units exponentially distributed life times. In industrial experiments, the mean times to failure of product can often be too large under typical operating condition, so that failure under conventional life-tests can become scarce. To overcome this problem in life time reliability analysis, experimenters resort to accelerated testing, where in the experimenters resort to accelerated testing, where in the experimental units are exposed to higher stress levels than usual to reduce the time to failure. The data obtained from such an accelerated test are then transformed to estimate the distribution of failure under typical condition.

Vasopressin (VP) is a man-made form of a hormone called “anti-diuretic hormone” that is normally secreted by the pituitary gland. In the body, vasopressin acts on the kidneys and blood vessels. It is produced and released in the posterior pituitary gland, which causes the kidneys to retain water, thus increasing the water content of the body. In high concentrations, it causes the constriction of blood vessels throughout the body and consequent elevation of blood pressure. VP hormone, related to oxytocin that is secreted by the posterior lobe of the pituitary gland. The vasopressin hormone secreted and the VP release have been studied by many authors, including Sladek CD and Armstrong WE[9], Sladek CD and Joynt RJ [6], Sladek CD and Knigge KM [5], Swenson KL and Sladek CD [10], among others.

Stress is defined as anything that throws the body out of homeostatic balance. Maintenance of the homeostasis in a constantly changing environment is a fundamental process of life. Stress plays some role in the development of every disease and that failure to cope with stress can result in “diseases of adaptation” such as ulcers, high blood pressure and the many other diseases that are caused or complicated by stress Hans Selye[4]. Cortisol is the primary hormone responsible for the stress response. Stress is a normal part of your life and does serve its purpose, but too much of it causes problems. Stress is the result of changes that take place in our body when we are faced with a threat. Understanding the biochemical interactions that constitute the stress response requires a definition of stress**.** There are 3 types of stress symptoms, i.e., Physical, mental and emotional. In the

current studies, various metabotropic glutamate receptor (mGluR) agonists and antagonists were evaluated by using fuzzy step-stress model for the effects on Vasopressin and oxytocin (OT) release from explants of the hypothalamoneurohypophysial system (HNS).

2. Notations

N	:	Number of test units
θ_1, θ_2	:	Scale Parameters of the lifetime distribution model
β	:	Shape parameter of the model.
r	:	Number of observed failures .
E(T)	:	Mean value of life time distribution
$\bar{E}(T)$	:	Fuzzy Mean value of life time distribution
τ	:	The time to change stress

3. A Mathematical model using fuzzy step-stress approach

The stress levels x_1 and x_2 are assumed to follow a lifetime distribution with scale parameter θ_1 and θ_2 with common shape parameter β . At any constants stress x_i; i=0, 1, 2, 3….k . The cdf of life time of a test unit is $F_i(t) = F(t/\theta_i)$, $t > 0$ the Stress-response relationship θ_i is a function of x_i.

The cumulative exposure model for the step-stress is given by

$G(t) = F_1(t)$ for $0 \le t \le \tau_1$ and $G(t) = F_2(t-\tau_1+s)$ for $\tau_1 \le t \le \alpha$

$F_i(t) = F(t/\theta_i)$ for i=1, 2

$S = \tau_1 \theta_2/\theta_1$

Fuzzy constant step stress- mean value of life time distribution is

$$\bar{E}(T) = \left[\bar{E}_L(T), \bar{E}_U(T)\right]$$

$$\bar{E}(T) = n \binom{n-1}{r-1} (\psi_{4,A} - \psi_{4,B} + \psi_{4,C})$$

$$\psi_{4,A} = \sum_{i=0}^{r-1} \frac{\psi(i,r)\bar{\theta}_2^2}{(n-r+i+2)\bar{\theta}_2 - \bar{\theta}_1}$$

$$\psi_{4,B} = \sum_{i=0}^{r-1} \frac{\psi(i,r)\bar{\theta}_1^2}{(n-r+i+2)^2((n-r+i+2)\bar{\theta}_2 - \bar{\theta}_1)}$$

$$\psi_{4,C} = \sum_{i=0}^{r-1} \frac{\psi(i,r)\bar{\theta}_1}{(n-r+i+2)^2(n-r+i+1)}$$

$$\psi_{i,r} = (-1)^i \binom{r-1}{i}$$

where $\bar{\theta}_1 \in \bar{\theta}_1[\alpha]$ *and* $\bar{\theta}_2 \in \bar{\theta}_2[\alpha]$

4. Application

The explants were perifused for 4 hours before use of any pharmacological agent or change in osmolality to permit the explants to equilibrate and to establish a basal rate of hormone release. Subsequent hormone discharge was normalized to the basal discharge of that explants at the end of the calibration period and is expressed as a percentage of this basal value. The effect of metabotropic glutamate receptor activation on Vasopressin and Oxytocin discharge was evaluated using explants of the hypothalamoneurohypophysial system. Metabotropic Glutamate Receptors (mGluRs) are classified into three groups based on sequence homology, pharmacology, and effectors. Group I include mGluR1 and mGluR5 that are positively linked to phospholipase C (PLC), group II include mGluR2 and mGluR3, and group III includes mGluR 4, 6, 7, 8. Both groups II and III are negatively linked to adenylate cyclase. Electrophysiological, immunocytochemical, and in situ hybridization data support the presence and involvement of the mGluRs on both the presynaptic terminals in the supraoptic nucleus (SON) and the postsynaptic membranes of the magnocellular neurons of SON (5, 6, 11, 12, 22, 24). This strongly implicates a role of these receptors in VP and OT release, but the effect of mGluRs on release has yet to be examined directly.

In the current studies, various mGluR agonists and antagonists were evaluated for effects on VP and OT

release from explants of the hypothalamoneurohypophysial system (HNS). The purpose was to widen the previous electrophysiological observations by examining the role of mGluRs in a neuropeptide hormone release. The effects of t-ACPD (a group I and II mGluR agonist), DHPG (a specific group I agonist), and L-AP4 (an mGluR group III agonist) were evaluated. Level x_1 and Level x_2 are considered as a percentage of the VP release and OT release respectively.

A sample of 7 experimental units is placed under the simple step-stress life testing. Assume that the VP release is level x_1 and OT release is level x_2. In level x_1 and x_2 we take N=7. From the Table-1, the scale parameter of two levels is obtained as θ_1=153.5, θ_2=107.8 and the common shape parameter is 4.1 and assume that number of observed failures are r = 3 in both cases. From the above data, we find the mean values for various alpha values and are given in Table-2.

Fuzzy trapezoidal numbers for the corresponding scale parameters are given by

θ_1 = (150.2, 151.5, 153.5, 155.6)

θ_2 = (103.8, 105.2, 107.8, 109.3)

and its alpha cuts are

$\overline{\theta_1}(\alpha)$ = (150.2+1.3α, 155.6-2.1 α)

$\overline{\theta_2}(\alpha)$ = (103.8+1.4 α, 109.3-1.5 α)

5. Conclusion

Here we proposed a case to study, the mean value of the release of VP and OT level due to the postsynaptic effects of t-ACPD and DHPG to depolarize magnocellular neurons by using fuzzy step stress model. The membership function shows that a synergistic effect of metabotropic glutamate receptor activation on Vasopressin and Oxytocin.

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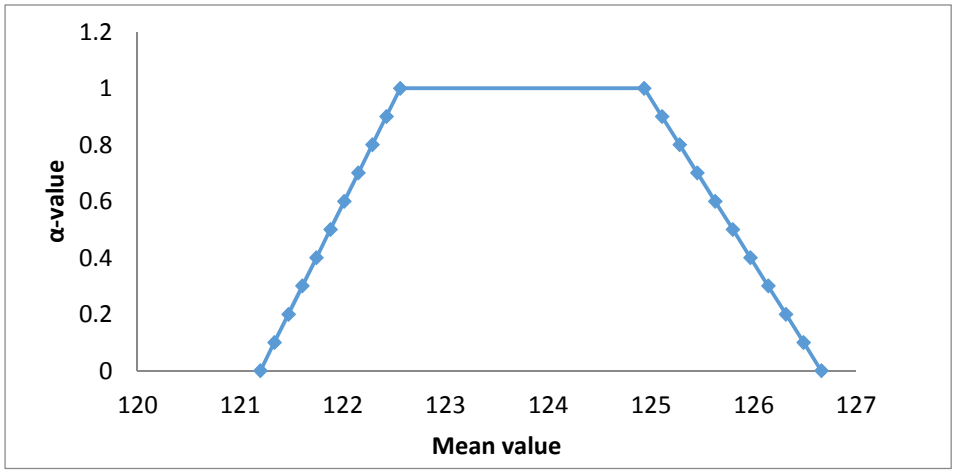

Figure 1. Fuzzy membership function value

Time(hrs)	4	5	6	7	8	9	10
% of VP release	100	190	180	110	130	155	110
% of OT release	100	150	100	85	80	90	80

Table-1. Percentage of VP and OT release

α	$\bar{E}_L(T)$	$\bar{E}_U(T)$
0	121.2	126.66
0.1	121.33	126.49
0.2	121.47	126.31
0.3	121.6	126.14
0.4	121.74	125.97
0.5	121.88	125.8
0.6	122.01	125.62
0.7	122.15	125.45
0.8	122.29	125.28
0.9	122.42	125.11
1	122.56	124.93

Table-2. The mean values of Fuzzy constant step stress model

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