

A Mathematical Model for the Enhancement of Stress Induced Hypoglycaemia by Antidepressant Treatment in Healthy Men using Multivariate Normal Distribution

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Abstract:The normal distribution is a very commonly occurring continuous probability distribution. In this paper the Multivariate Normal distribution is used for finding the mgf of the curve for the enhancement of stress induced Hypoglycaemia with consideration of the variables Prolactin, ACTH, Growth Hormone, Blood Pressure, Plasma Glucose, Plasma Renin, Epinephrine, Cortisol. These variables are treated with the drugs (citalopram and tianeptine) and the joint moment generating function for the variables in Citalopram, Tianeptine and Placebo cases are found out and are given as curves in the Mathematical Results.

Keywords: Adrenocorticotrophic Hormone (ACTH), Antidepressants, Growth Hormone (GH), Joint Moment Generating Function, Prolactin.

I. INTRODUCTION

The aim of the present study is to verify the hypothesis that (i) treatment with antidepressants inhibits hormone release in response to stressful stimulation in humans and (ii) drugs with opposing effects on brain serotonin (citalopram and tianeptine) exert similar modulatory effects on neuroendocrine activation during stress. As a stress stimulus, insulin – induced hypoglycaemia was selected because hypoglycaemia induces the release of a wide spectrum of hormones and the insulin tolerance test is a clinically useful one to assess pituitary function. This study shows that treatment with antidepressants in healthy men results in an augmentation of neuroendocrine response during stress of hypoglycaemia, manifested by increased release of ACTH, growth hormone and prolactin. Treatment with antidepressants should have induced an attenuation of the stress response. It was not due to altered intensity of the stress stimulus, as the degree of hypoglycaemia in antidepressant treated groups was not different from that in the control, placebo treated group. The Stress induced changes and its mechanisms are clearly showed in /the Mathematical figures to obtain the conclusion of the medical part.

II. MATHEMATICAL MODEL

2.1 Bivariate And Multivariate Normal Distribution:

Two random variables (X,Y) have a bivariate normal distribution $N(\mu_1, \mu_2, \sigma_1^2, \sigma_2^2, \rho)$ if their joint p.d.f

$$f_{X,Y}(x, y) = \frac{1}{2\pi\sigma_1\sigma_2\sqrt{1-\rho^2}} e^{-\frac{1}{2(1-\rho^2)}\left[\left(\frac{x-\mu_1}{\sigma_1}\right)^2 - 2\rho\left(\frac{x-\mu_1}{\sigma_1}\right)\left(\frac{y-\mu_2}{\sigma_2}\right) + \left(\frac{y-\mu_2}{\sigma_2}\right)^2\right]}; \quad (2.1.1)$$

for all x, y [6, 9].

The parameters μ_1, μ_2 may be any real numbers, $\sigma_1 > 0, \sigma_2 > 0, -1 \leq \rho \leq 1$. It is convenient to rewrite (2.1.1)

in the form $f_{X,Y}(x, y) = ce^{-\frac{1}{2}Q(x,y)}$, where $c = \frac{1}{2\pi\sigma_1\sigma_2\sqrt{1-\rho^2}}$ and

$$Q = (1 - \rho^2)^{-1} \left[\left(\frac{x-\mu_1}{\sigma_1}\right)^2 - 2\rho\left(\frac{x-\mu_1}{\sigma_1}\right)\left(\frac{y-\mu_2}{\sigma_2}\right) + \left(\frac{y-\mu_2}{\sigma_2}\right)^2 \right]; \quad (2.1.2)$$

Statement:

The marginal distributions of $N(\mu_1, \mu_2, \sigma_1^2, \sigma_2^2, \rho)$ are normal with random variables X and Y having density functions

$$f_X(x) = \frac{1}{\sqrt{2\pi}\sigma_1} e^{-\frac{(x-\mu_1)^2}{2\sigma_1^2}}, \quad f_Y(y) = \frac{1}{\sqrt{2\pi}\sigma_2} e^{-\frac{(y-\mu_2)^2}{2\sigma_2^2}}$$

Proof:

The expression for Q(x,y) can be rearranged as follows:

$$Q = \frac{1}{1-\rho^2} \left[\left(\frac{x-\mu_1}{\sigma_1} - \rho\frac{y-\mu_2}{\sigma_2}\right)^2 + (1-\rho^2)\left(\frac{y-\mu_2}{\sigma_2}\right)^2 \right]$$

$$= \frac{(x-a)^2}{(1-\rho^2)\sigma_1^2} + \frac{(y-\mu_2)^2}{\sigma_2^2} ; \tag{2.1.3}$$

where $a = a(y) = \mu_1 + \rho \frac{\sigma_1}{\sigma_2}(y - \mu_2)$. Hence

$$f_Y(y) = \int_{-\infty}^{\infty} f_{X,Y}(x,y) dx = ce^{-\frac{(y-\mu_2)^2}{2\sigma_2^2}} \times \int_{-\infty}^{\infty} e^{-\frac{(x-a)^2}{2(1-\rho^2)\sigma_1^2}} dx = \frac{1}{\sqrt{2\pi}\sigma_2} e^{-\frac{(y-\mu_2)^2}{2\sigma_2^2}}$$

Where the last step makes use of the formula $\int_{-\infty}^{\infty} e^{-\frac{(x-a)^2}{2\sigma^2}} dx = \sqrt{2\pi}\sigma$ with $\sigma = \sigma_1\sqrt{1-\rho^2}$

Corollaries

1. Since $X \sim N(\mu_1, \sigma_1^2), Y \sim N(\mu_2, \sigma_2^2)$ we know the meaning of four parameters involved into the definition of the normal distribution, namely

$$E(X) = \mu_1, Var(X) = \sigma_1^2, E(Y) = \mu_2, Var(Y) = \sigma_2^2$$

2. $X | (Y = y)$ is a normal variable. To verify this statement we substitute the necessary ingredients into the formula defining the relevant conditional density

$$f_{X|Y}(x | y) = \frac{f_{X,Y}(x,y)}{f_Y(y)} = \frac{1}{\sqrt{2\pi(1-\rho^2)}\sigma_1} e^{-\frac{(x-a(y))^2}{2\sigma_1^2(1-\rho^2)}}$$

In other words, $X | (Y = y) \sim N(a(y), (1-\rho^2)\sigma_1^2)$.

3. $E(X | Y = y) = a(y)$ or equivalently, $E(X | Y) = \mu_1 + \rho \frac{\sigma_1}{\sigma_2}(Y - \mu_2)$. In particular we see that $E(X|Y)$ is a linear function of Y [6].

4. $E(XY) = \sigma_1\sigma_2\rho + \mu_1\mu_2$.

Proof:

$$\begin{aligned} E(XY) &= E[E(XY | Y)] = E[YE(X | Y)] = E\left[Y\left(\mu_1 + \rho \frac{\sigma_1}{\sigma_2}(Y - \mu_2)\right)\right] \\ &= \mu_1 E(Y) + \rho \frac{\sigma_1}{\sigma_2} [E(Y^2) - \mu_2 E(Y)] = \mu_1\mu_2 + \rho \frac{\sigma_1}{\sigma_2} [E(Y^2) - \mu_2^2] \\ &= \mu_1\mu_2 + \rho \frac{\sigma_1}{\sigma_2} Var(Y) = \sigma_1\sigma_2\rho + \mu_1\mu_2. \end{aligned}$$

5. $Cov(X, Y) = \sigma_1\sigma_2\rho$. This follows from Corollary 4 and the formula $Cov(X, Y) = E(XY) - E(X)E(Y)$

6. $\rho(X, Y) = \rho$, in words ρ is the correlation coefficient of X, Y . This is now obvious from the definition $\rho(X, Y) = \frac{Cov(X, Y)}{\sqrt{Var(X)Var(Y)}}$.

Remark:

It is possible to show that the m.g.f of X, Y is

$$M_{X,Y}(t_1, t_2) = e^{(\mu_1 t_1 + \mu_2 t_2) + \frac{1}{2}(\sigma_1^2 t_1^2 + 2\rho\sigma_1\sigma_2 t_1 t_2 + \sigma_2^2 t_2^2)}.$$

2.2 Multivariate Normal Distribution:

Using Vector and Matrix Notation:

To study the joint normal distributions of more than two random variables it is convenient to use vectors and matrices. But let us first introduce these notations for the case of two normal random variables X_1, X_2 [8]. We set,

$$X = \begin{pmatrix} X_1 \\ X_2 \end{pmatrix}, x = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}, t = \begin{pmatrix} t_1 \\ t_2 \end{pmatrix}, m = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, V = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

Then m is the vector of means and V is the variance – covariance matrix.

Note that $|V| = \sigma_1^2\sigma_2^2(1-\rho^2)$ and $V^{-1} = \frac{1}{(1-\rho^2)} \begin{pmatrix} \frac{1}{\sigma_1^2} & \frac{-\rho}{\sigma_1\sigma_2} \\ \frac{-\rho}{\sigma_1\sigma_2} & \frac{1}{\sigma_2^2} \end{pmatrix}$

Hence $f_X(x) = \frac{1}{(2\pi)^{1/2}|V|^{1/2}} e^{-\frac{1}{2}(x-m)^T V^{-1}(x-m)}$ for all x . Also $M_X(t) = e^{t^T m + \frac{1}{2} t^T V t}$; (2.2.1)

We again use matrix and vector notation, but now there are n random variables so that X, x, t and m are now n -vectors with i^{th} entries X_i, x_i, t_i , and μ_i and V is the $n \times n$ matrix with i^{th} entry σ_i^2 and ij^{th} entry ($for\ i \neq j$) σ_{ij} . Note that V is symmetric so that $V^T = V$.

The joint p.d.f is $f_X(x) = \frac{1}{(2\pi)^{n/2}|V|^{1/2}} e^{-\frac{1}{2}(x-m)^T V^{-1}(x-m)}$ for all x . We say that $X \sim N(m, V)$.

We can find the joint m.g.f quite easily.

$$M_X(t) = E[e^{t^T X}] = \int_{-\infty}^{\infty} \dots \int_{-\infty}^{\infty} \frac{1}{(2\pi)^{n/2}|V|^{1/2}} e^{-\frac{1}{2}((x-m)^T V^{-1}(x-m) - 2t^T x)} dx_1 \dots dx_n; \tag{2.2.2}$$

We do the equivalent of completing the square, i.e we write

$$(x - m)^T V^{-1}(x - m) - 2t^T x = (x - m - a)^T V^{-1}(x - m - a) + b$$

for a suitable choice of the n -vector a of constants and a constant b . Then

$$M_x(t) = e^{-b/2} \int_{-\infty}^{\infty} \dots \int_{-\infty}^{\infty} \frac{1}{(2\pi)^{n/2} |V|^{1/2}} e^{-\frac{1}{2}(x-m-a)^T V^{-1}(x-m-a)} dx_1 \dots dx_n = e^{-b/2}; \quad (2.2.3)$$

We just need to find a and b . Expanding we have

$$\begin{aligned} ((x-m)-a)^T V^{-1}((x-m)-a) + b &= (x-m)^T V^{-1}(x-m) - 2a^T V^{-1}(x-m) + a^T V^{-1}a + b \\ &= (x-m)^T V^{-1}(x-m) - 2a^T V^{-1}x + [2a^T V^{-1}m + a^T V^{-1}a + b] \end{aligned}$$

This has equal to $(x-m)^T V^{-1}(x-m) - 2t^T x$ for all x . Hence we need $a^T V^{-1} = t^T$ and $b = -[2a^T V^{-1}m + a^T V^{-1}a]$. Hence $a = Vt$ and $b = -[2t^T m + t^T Vt]$.

Therefore $M_x(t) = e^{-b/2} = e^{t^T m + \frac{1}{2} t^T V t}$.

Results obtained using the m.g.f:

1. Any (non-empty) subset of multivariate normals is multivariate normal. Simply put $t_j = 0$ for all j for which X_j is not in the subset.

For example $M_{X_1, \dots, X_n}(t_1, 0, \dots, \dots, 0) = e^{\mu_1 t_1 + \frac{1}{2} \sigma_1^2 t_1^2}$.

Hence $X_1 \sim N(\mu_1, \sigma_1^2)$. A similar result holds for X_i . This identifies the parameters μ_i and σ_i^2 as the mean and variance of X_i . Also

$$\begin{aligned} M_{X_1}(t_1) &= M_{X_1, X_2}(t_1, t_2) = M_{X_1, X_2, \dots, X_n}(t_1, t_2, 0, \dots, \dots, 0) \\ &= e^{(\mu_1 t_1 + \mu_2 t_2) + \frac{1}{2}(\sigma_1^2 t_1^2 + 2\sigma_{12} t_1 t_2 + \sigma_2^2 t_2^2)}, \end{aligned} \quad (2.2.4)$$

Hence X_1 and X_2 have bivariate normal distribution with $\sigma_{12} = Cov(X_1, X_2)$. A similar result holds for the joint distribution of X_i and X_j for $i \neq j$. This identifies V as the variance – covariance matrix for X_1, X_2, \dots, X_n .

2. X is a vector of independent random variables iff V is diagonal (i.e. all off-diagonal entries are zero so that $\sigma_{ij} = 0$ for $i \neq j$).

Proof:

From the above result (result 1) if the X 's are independent then $t^T V t = \sum_{j=1}^n \sigma_j^2 t_j^2$ and hence

$$M_x(t) = e^{t^T m + \frac{1}{2} t^T V t} = \prod_{j=1}^n e^{\mu_j t_j + \frac{1}{2} \sigma_j^2 t_j^2} = \prod_{j=1}^n M_{X_j}(t_j) \quad (2.2.5)$$

By the uniqueness of the joint m.g.f X_1, X_2, \dots, X_n are independent.

3. Linearly independent linear functions of multivariate normal random variables are multivariate normal random variables. If $Y = AX + b$, where A is a $n \times n$ non-singular matrix and b is a (column) n -vector of constants, then $Y \sim N(Am + b, AVA^T)$.

Proof:

Use the joint m.g.f

$$\begin{aligned} M_Y(t) &= E[e^{t^T Y}] = E[e^{t^T (AX+b)}] = e^{t^T b} E[e^{(A^T t)^T X}] = e^{t^T b} M_X(A^T t) \\ &= e^{t^T b} e^{(A^T t)^T m + \frac{1}{2} (A^T t)^T V (A^T t)} = e^{t^T (Am+b) + \frac{1}{2} t^T (AVA^T) t} \end{aligned}$$

This is just the m.g.f for the multivariate normal distribution with vector of means $Am+b$ and variance – covariance matrix AVA^T . Hence, from the uniqueness of the joint m.g.f

$Y \sim N(Am + b, AVA^T)$. Note that from (2) a subset of the Y 's is multivariate normal.

III. APPLICATION

Stress is generally considered to be one of the factors involved in the pathogenesis of affective disorders. Neuroendocrine activation includes profound changes in central neurotransmitter systems as well as increased release of stress hormones, such as cortisol, catecholamines, adrenocorticotrophic hormone (ACTH), growth hormone (GH), prolactin or angiogenesis II. The relationship between antidepressants and stress is further substantiated by their effects on stress hormone release. Acute administration of antidepressants leads to a rise in hormone secretion, whereas prolonged treatment can be associated with inhibitory effects. Thus, decreased levels of plasma corticosterone and ACTH were observed after chronic treatment with several antidepressants.

The aim of the present study is to verify the hypothesis that (i) treatment with antidepressants inhibits hormone release in response to stressful stimulation in humans and (ii) drugs with opposing effects on brain serotonin (citalopram and tianeptine) exert similar modulatory effects on neuroendocrine activation during stress. As a stress stimulus, insulin – induced hypoglycaemia was selected because hypoglycaemia induces the release of a wide spectrum of hormones and the insulin tolerance test is a clinically useful to assess pituitary function [7]. The study was designed as a randomized, double – blind, placebo – controlled trial in a total of 31 healthy male volunteers in the age group of 20 – 27 years. All treatments were given three times daily (one of active drugs or placebo) with the main meals for 7 days. The subjects were treated with tianeptine (37.5 mg p.o daily divided in three doses) or citalopram (20 mg p.o daily in one dose in the morning while placebo was given at noon and evening) given in the same manner as the active drugs. Hypoglycaemia was induced by

administration of insulin. An appropriate dose of insulin was diluted in 5 ml of isotonic saline and injected in to the catheter inserted in a cubital vein within 1 min. After 7 days of drug treatment, the observations started the following morning at 07.30 h after an overnight fast. Each subject was asked to take his last dose of treatment. An indwelling catheter was inserted into a cubital vein. The first blood sample was taken at least 30 minutes after catheter insertion and exactly 45 min after the last drug administration. Insulin was injected 60 min after the drug and blood samples were collected at 30, 45, 60 and 90 min after insulin injection.

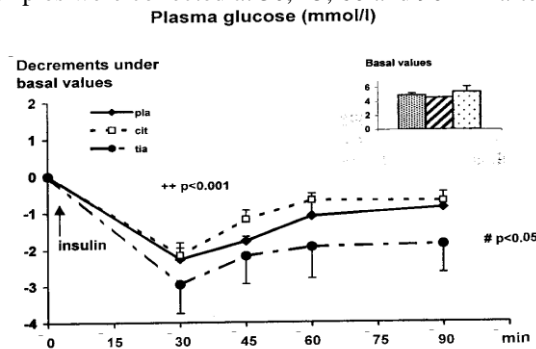


Figure – 3.1

Decrease in plasma glucose levels induced by insulin infusion in citalopram, tianeptine or placebo treated subjects. Statistical significance: effect of time $++p < 0.001$; effect of treatment $p < 0.05$; post hoc treatment tianeptine versus citalopram $\#p < 0.05$

As expected insulin administration induced a decrease in blood glucose, which the nadir at 30 min and the returned towards the control levels (Fig.3.1). No significant differences in blood glucose concentrations were found between placebo and any of the antidepressant treated groups. Insulin induced hypoglycaemia was somewhat more prolonged in subjects treated within tianeptine compared to the values in citalopram but not placebo treated group.

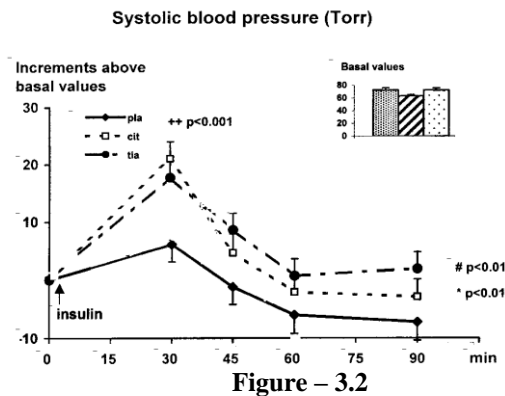


Figure – 3.2

Enhancement of systolic blood pressure response during stress of hypoglycaemia by treatment with citalopram or tianeptine in comparison to placebo. Statistical significance: effect of time $++p < 0.001$; post hoc test, citalopram versus placebo $*p < 0.01$; tianeptine versus placebo $\#p < 0.01$

When respect to cardiovascular responses, changes in systolic blood pressure reached statistical significance for both time and treatment. Stress induced rise in systolic blood pressure was significantly higher in the citalopram and tianeptine groups compared to that in subjects treated with placebo (Fig.3.2). Diastolic blood pressure decreased in time, but no statistically significant differences among groups were observed.

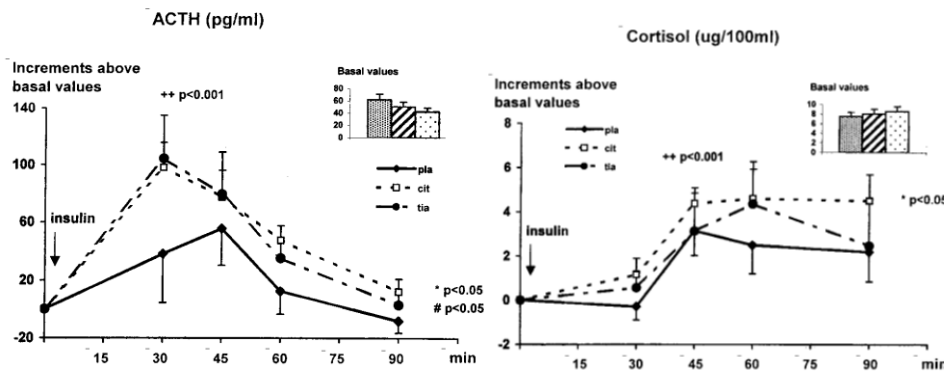


Figure – 3.3 Figures – 3.4

Elevation of plasma ACTH and cortisol levels during stress of hypoglycaemia in subjects treated with citalopram (cit), tianeptine (tia) or placebo (pla) for 7 days. Statistical significance: effect of time ++ $p<0.001$; post – hoc test (treatment), citalopram versus placebo * $p<0.01$; tianeptine versus placebo # $P<0.01$

ACTH levels increased significantly in response to insulin hypoglycaemia (Fig.–3.3). ACTH responses were enhanced in subjects treated with both antidepressants compared to those treated with placebo. The differences between the values in placebo versus citalopram, as well as placebo versus tianeptine – pretreated groups, were found to be significant. The changes in cortisol levels were less pronounced in (Fig.3.4). Stress of hypoglycaemia was associated with a similar rise in cortisol levels in the control and tianeptine – pretreated groups. In subjects treated with citalopram, the elevation in cortisol levels was more pronounced and prolonged compared to that in the control group.

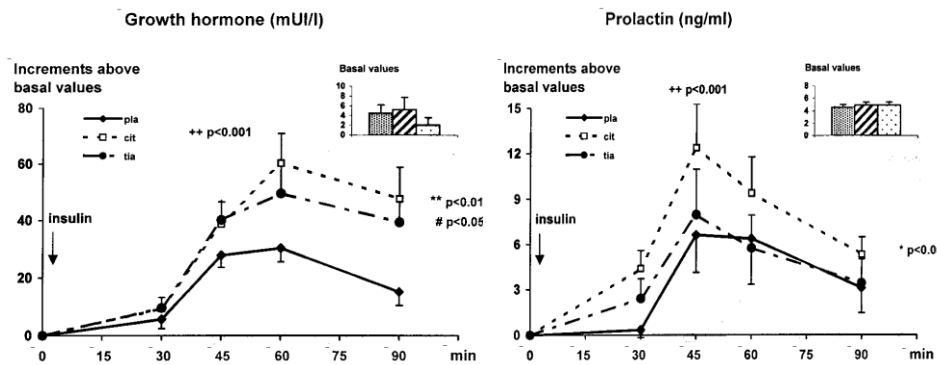
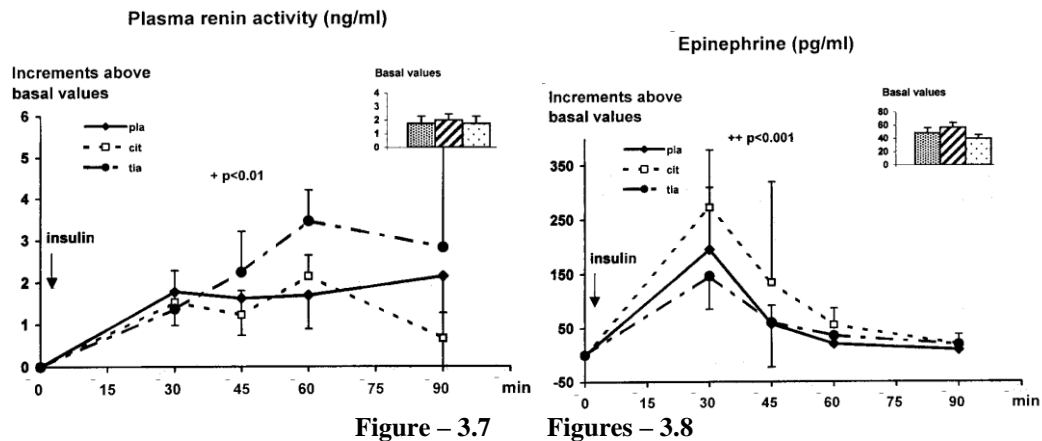


Figure – 3.5 Figure – 3.6

Enhancement of growth hormone response during stress of hypoglycaemia by treatment with citalopram (cit), tianeptine (tia) in comparison to placebo (pla). The rise in plasma prolactin levels was potentiated in citalopram treated subjects only. Statistical significance: effect of time ++ $p<0.001$; post – hoc test (treatment), citalopram versus placebo * $p<0.05$, ** $p<0.01$; tianeptine versus placebo # $p<0.01$.

Release of Growth Hormone induced by insulin hypoglycaemia was significantly potentiated by both citalopram and tianeptine treatments. Significant differences were found for both time and treatment. Thus, the rise in growth hormone release during stress was higher in subjects treated with citalopram as well as with tianeptine compared to those treated with placebo(Fig. – 3.5) . There were no differences between the groups treated with citalopram or tianeptine. Similarly, changes in prolactin levels showed significant differences for both time and treatment(Fig.–3.6). However, a potentiation of stress – induced prolactin release was found in citalopram – pretreated volunteers, while this hormone levels were similar in tianeptine and placebo treated groups.



Increase of plasma renin activity and epinephrine levels during stress of hypoglycaemia in subjects treated with citalopram (cit), tianeptine (tia) or placebo (pla) for 7 days. Statistical significance: effect of time +p<0.01, ++p<0.001

Plasma Renin activity rose in response to insulin – induced hypoglycaemia in all groups. With respect to treatment, no significant differences were observed. Concentrations of epinephrine in plasma increased significantly in a similar manner in all treatment groups (Fig.–3.7, 3.8).

This study shows that treatment with antidepressants in healthy men results in an augmentation of neuroendocrine response during stress of hypoglycaemia, manifested by increased release of ACTH, growth hormone and prolactin. Treatment with antidepressants should have induced an attenuation of the stress response. It was not due to altered intensity of the stress stimulus, as the degree of hypoglycaemia in antidepressant treated groups was not different from that in the control, placebo treated group. Stress induced changes as well as the mechanisms involved are affected by several factors particularly by the character of stress stimulus [5]. Patients with major depression were found to exhibit decreased responses of ACTH or prolactin to the stress of hypoglycaemia [4], attenuated beta – endorphin responses in Trier’s social stress test and lower cardiovascular activation in response to a cognitive challenge [3]. A similar modulation of acute stress responses by antidepressants in depressed patients remains to be confirmed.

Some drugs such as tianeptine, cause a reduction of serotonin availability in the brain, which is opposite to the action of most widely used group of antidepressants acting as specific serotonin reuptake inhibitors [1]. On the basis of the present findings showing the ability of both citalopram and tianeptine to enhance neuroendocrine activation during stress. Single intravenous infusion of citalopram is known to increase plasma cortisol and prolactin levels in healthy individuals. Repeated oral treatment with citalopram has no effect on vassal hormone levels (prolactin, growth hormone, ACTH, cortisol). The same was true for tianeptine treatment. On the other hand, neuroendocrine activation during stress was found to be potentiated by both treatments. The actions of citalopram and tianeptine were similar.

The only exception was observed in stress – induced prolactin release, which was enhanced by citalopram but not tianeptine administration. It should be noted that prolactin levels were not modified by tianeptine treatment [2]. The present data further indicate that cortisol is not an optimal indicator of ACTH release as the changes in ACTH levels were much more evident than those in cortisol secretion. However, the observation period of 90 minutes was not long enough to reveal any possible differences in the duration of the cortisol response, which might be induced by the drug treatments used.

The repeated antidepressant treatment in healthy men does not inhibit, but enhances neuroendocrine activation during stress. Such effects were observed after treatment with antidepressants having opposing actions on brain serotonin. Stress induces both protective and damaging effects on the body. It is suggested that an enhancement of neuroendocrine activation to acute stress stimuli may be of benefit for patients with depression, in which an attenuated stress response has been reported.

IV. MATHEMATICAL RESULTS

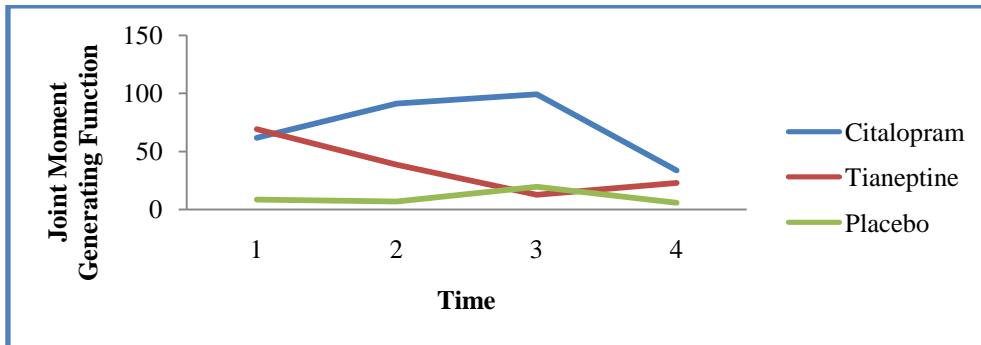


Figure 4.1

Moment Generating Function for the enhancement of stress induced by insulin infusion for the four variables Prolactin, ACTH, Cortisol and Epinephrine for the Citalopram, Tianeptine and Placebo cases.

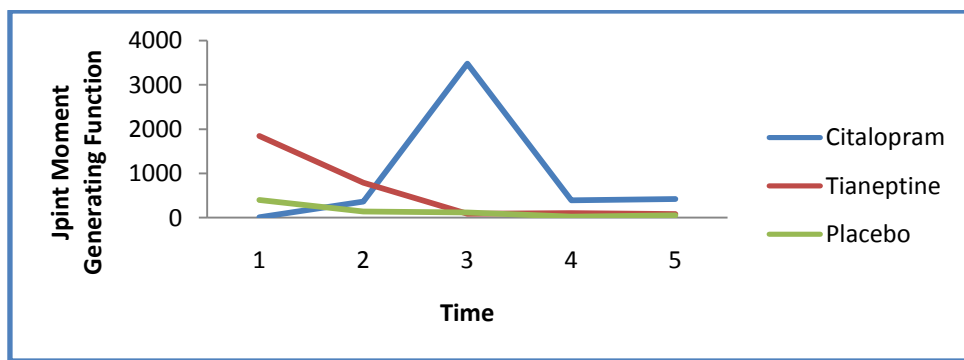


Figure 4.2

Moment Generating Function for the enhancement of stress induced by insulin infusion for the five variables Prolactin, ACTH, Cortisol, Plasma Renin and Epinephrine for the Citalopram, Tianeptine and Placebo cases.

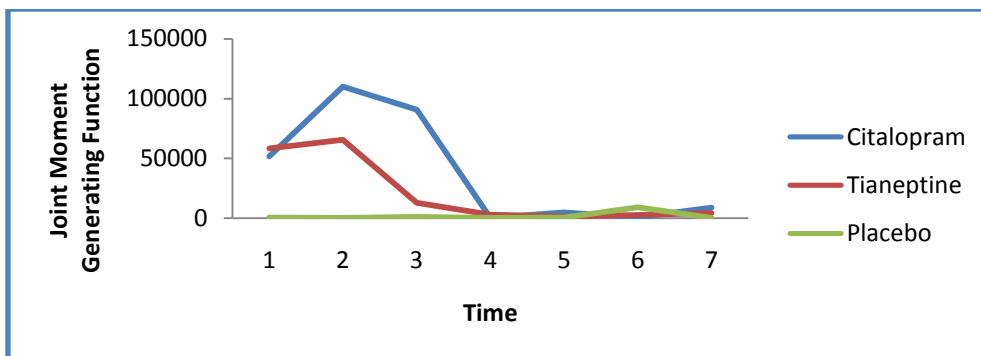


Figure 4.3

Moment Generating Function for the enhancement of stress induced by insulin infusion for the seven variables Prolactin, ACTH, Cortisol, Plasma Renin, Blood Pressure, Plasma Glucose and Epinephrine for the Citalopram, Tianeptine and Placebo cases.

V. CONCLUSION

In this paper the multivariate normal distribution is used for the treatment with depressants inhibits hormone release in response to stressful stimulation in humans. The curves for moment generating function of stress induced by insulin infusion for the i.) Four Variables - Prolactin, ACTH, Cortisol and Epinephrine for the

Citalopram, Tianeptine and Placebo cases are given in Fig.4.1. In this, the mgf of citalopram is found to be maximum than tianeptine and placebo in the time period 30 minutes to 1 hour. ii.) Five variables Prolactin, ACTH, Cortisol, Plasma Renin and Epinephrine for the Citalopram, Tianeptine and Placebo cases are given in Fig.4.2. In this, the mgf of citalopram is found to be maximum than the other two cases and reach the peak value in the time period of 45 minutes exactly. iii.) Seven variables Prolactin, ACTH, Cortisol, Plasma Renin, Blood Pressure, Plasma Glucose and Epinephrine for the Citalopram, Tianeptine and Placebo cases are given in Fig.4.3. In this, the mgf of citalopram is found to be maximum when compared to the mgf of tianeptine and placebo has no more effect. Here citalopram increases in the time interval of 0 to 15 minutes and decreases from the 15th minute.

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