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COMPARATIVE STUDY OF DIFFERENT ANTIDEPRESSANTS IN NORMAL, SLEEP DEPRIVED AND DIABETIC MICE

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Abstract

According to WHO report, approximately 450 million people suffer from a mental or behavioral disorder. Worldwide, depression is the most common affective disorder and a major cause of disability and premature death. The prevalence of depression is higher in diabetic and hypertensive patients than in the general population. There is an increasing evidence that sleep may be important for learning and memory where as sleep deficit results in performance impairment (depression) both in rodents and humans. Hence, the study was prompted to investigate whether the conventionally used dose of antidepressants are effective in (disorded and diseased) sleep deprived and diabetic depressive patients.

LIST OF ABBREVIATIONS USED

5-HIAA	5-HydroxyIndoleAcetic Acid
5-HT	5-hydroxytryptamine= Serotonin
ACTH	Adrenocorticotrophic Hormone
ANOVA	Analysis of Variance
BDNF	Brain-Derived Neurotrophic Factor
BW	Body Weight
CPCSEA	Committee for the Purpose of Control and Supervision of Experimentation on Animals
CRF	Corticotropin-Releasing Factor
CRH	Corticotropin-Releasing Hormone
DA	Dopamine
DSM-IV	Diagnostic and Statistical Manual of mental disorders-Fourth edition
EDTA	Ethylene diamine tetra acetate
GH	Growth Hormone
GMC	Gauhati Medical College
GMCH	Gauhati Medical College and Hospital
GR	Glucocorticoid Receptor
GRs	Glucocorticoid Receptors
Hb1Ac	Glycosylated hemoglobin
HPA	Hypothalamo-Pituitary-Adrenocortical axis
i.p./ip	intraperitoneal
IDDM	Insulin Dependent Diabetes Mellitus
MAO	Monoamine Oxidase
MHPG	3-Methoxy-4-HydroxyPhenylGlycol
MRs	Mineralocorticoid Receptors
NA	Noradrenaline
NE	Norepinephrine

NIDDM	Non Insulin Dependent Diabetes Mellitus
NIPER	National Institute of Pharmaceutical Education and Research
NMDA	N-methyl-D-aspartic acid
p.o./po	per os
PRL	Prolactin
SEM/S.E.M.	Standard Error of the Mean
SLA	Spontaneous Locomotor Activity
SNARI	Selective Noradrenaline Reuptake Inhibitor
SNERI	Selective Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STZ	Streptozotocin
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TCA	Tricyclic Antidepressant
TST	Tail suspension Test
VMAT	Vesicular Monoamine Transporter
WHO	World Health Organisation

Aim of the study: To compare different antidepressants in Normal, Sleep deprived and Diabetic mice and find out the right category of antidepressants in different abnormal conditions.

Materials and methods: The efficacy of three categories of antidepressants-Paroxetine (an SSRI), Nortriptyline (an SNERI) and Amitriptyline (a non selective NA/5-HT reuptake inhibitor) was compared using Tail Suspension Test and Spontaneous Locomotor Activity in normal, sleep deprived and diabetic mice.

Results: In Normal and Diabetic mice, Paroxetine significantly reduced the duration of immobility and increased the spontaneous locomotor activity than the other two drugs and in sleep deprived mice, amitriptyline markedly reduced duration of immobility and increased spontaneous locomotor activity .

Conclusion: In normal and diabetic depressive patients, Paroxetine, an SSRI would be a better option than Nortriptyline and Amitriptyline while in sleep deprived condition , only amitriptyline (a non selective NA/5-HT reuptake inhibitor) is much better than the other two drugs.

Introduction

According to WHO report1, approximately 450 million people suffer from a mental or behavioral disorder. Yet only a small minority of them receive even the most basic treatment. This amounts to 12.3% of the global burden of disease, and will rise to 15% by 20202. Psychiatric illness is often associated with suicide and there are between 10 and 20 million suicide attempts every year. The complexity of daily life in modern society frequently leads to varying degree of anxiety and depression. Positive or negative events can trigger depression for instance death of a loved one,Promotion ,major illness such as cancer ,diabetes, Which results in changes of life-Style (weight loss ,psychomotor depression ,diminished sexual desire).

The coexistence of diabetes and depression is associated with significant morbidity, mortality, and increased healthcare cost. It is well established that depression and anxiety are common among patients with diabetes3,4,5. Diabetes mellitus is accompanied by hormonal and neurochemical changes that can be associated with anxiety and depression. Furthermore, the prevalence of depression was unrelated to the type (IDDM or NIDDM) of diabetes6. The prevalence of depression is ~18% higher in diabetic patients than in the general population.

Large number of people suffer from sleep deprivation who mainly work in night shifts tight schedules . There is an increasing evidence that sleep may be important for proper learning and memory where as sleep deficit results in performance impairement both in rodents and humans. Thus, the present study in diabetic and sleep deprived

animals may be useful to investigate whether conventionally used dose of antidepressants are effective in the (disorded and diseased) sleep deprived and diabetic depressive patients.

Aim and Objectives

Aim

To compare different classes of antidepressants in normal, disordered and diseased mice.

Objectives

1. To compare the efficacy of different antidepressants (an SSRI, an SNERI and a non selective 5-HT,NE reuptake inhibitor) in normal, sleep deprived and diabetic mice by using tail suspension test and spontaneous locomotor activity.
2. Main objective of this study is to compare and know the effect of different antidepressant drugs to the zenith

Materials and methods

Animals

Swiss albino mice of either sex weighing 18-22g bred at the animal house of NIPER-Guwahati were used in the experiments. All animals were housed in polypropylene cages in a temperature controlled room maintained at 24±1 ◦C, 0700 to 2000 hr light and 55% relative humidity and received humane care according to the guidelines of the Committee for the Purpose of Control and Supervision of Experimentation on Animals (CPCSEA) under the Ministry of Environment & Forests(Animal Welfare Division), Govt. of India. They were given standard pellet diet and tap water ad libitum throughout the course of the study. All behavioural observations were performed between 0800 and 2000 hr each day. Each animal was
used only once.

Drugs and treatments

The drugs and used in the study were Paroxetine Hydrochloride (Sigma Aldrich), Nortriptyline Hydrochloride (Sigma Aldrich), Amitriptyline Hydrochloride (Sigma Aldrich), and Streptozotocin (Sigma Aldrich).

The former three drugs were dissolved in distilled water and administered p.o. 50 mins before the administration of test drugs. Drugs were administered both p.o. and i.p. in a volume of 0.1ml/10g of body weight. The doses of the drugs were calculated from the conventional human dose as per the table of Paget & Barnes31.

Dose of drug for a mice of 20 g = absolute human dose*0.0026 Absolute human dose (dose of the drug for an adult human of 70 kg/day) was taken from Indian Drugs Review32 and IP-199633,34.
Paroxetine - Selective Serotonin (5-HT) Reuptake Inhibitor (SSRI)
Nortriptyline - Selective Norepinephrine Reuptake Inhibitor (SNERI)
Amitriptyline - Non selective 5-HT and NE reuptake Inhibitor

Table 3.2.1. Dosing schedule in Normal mice

Name of the main group	Name of the sub group	No.of animals per group	treatment
Normal	**control**	**6**	**vehicle**
	Paroxetine	**6**	**6.5mg/kg,p.o**
	Nortriptyline	**6**	**13 mg/kg,p.o**
	amitriptyline	**6**	**9.75mg/kg,p.o**

Table 3.2.2. Dosing schedule in Diabetic mice

Name of the main group	Name of the sub group	No.of animals per group	treatment
diabetic	control	6	vehicle
	Paroxetine	6	6.5mg/kg,p.o
	Nortriptyline	6	13 mg/kg,p.o
	amitriptyline	6	9.75mg/kg,p.o

Diabetes is induced by injecting STZ (in citrate buffer of pH 4.5) (250 mg/kg ip) and the antidepressant tests were conducted after 14 days (during this time the mice will become diabetic with a blood glucose level of ≥ 200mg/dL).

Table 3.2.3. Dosing schedule in sleep deprived mice

Name of the main group	Name of the sub group	No.of animals per group	treatment
Sleep deprived	control	6	vehicle
	Paroxetine	6	6.5mg/kg,p.o
	Nortriptyline	6	13 mg/kg,p.o
	amitriptyline	6	9.75mg/kg,p.o

The same design and number of animals were used for both Tail Suspension Test and Spontaneous Locomotor Activity study.

Tail Suspension Test (TST)

The Tail Suspension Test was performed as described by Steru et al27. Each animal is acoustically and visually isolated from other animals during the test and each animal is used only once. Drug is administered p.o. according to BW 50 mins before the test. Individual mice were suspended 58 cm above the edge of the working bench with an adhesive tape placed 1 cm away from the tip of the tail for 6 min. Immobility duration is recorded for the last 4 min of the total 6 min test period. Mice are considered to be immobile when they hung passively or are completely motionless. (Fig. 3.3.1).

Fig. 3.3.1. Tail Suspension Test

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Fig. 3.4.1. Spontaneous Locomotor activity measurement using Photoactometer

Spontaneous Locomotor Activity (SLA)

Spontaneous Locomotor Activity of mice was measured using a digital actophotometer. Each mouse was placed individually in the actophotometer for a habituation period of 1 hr. Drug is administered p.o. according to BW 50 min before the test. Total activity counts were automatically recorded for 10 min. (Fig. 3.4.1)

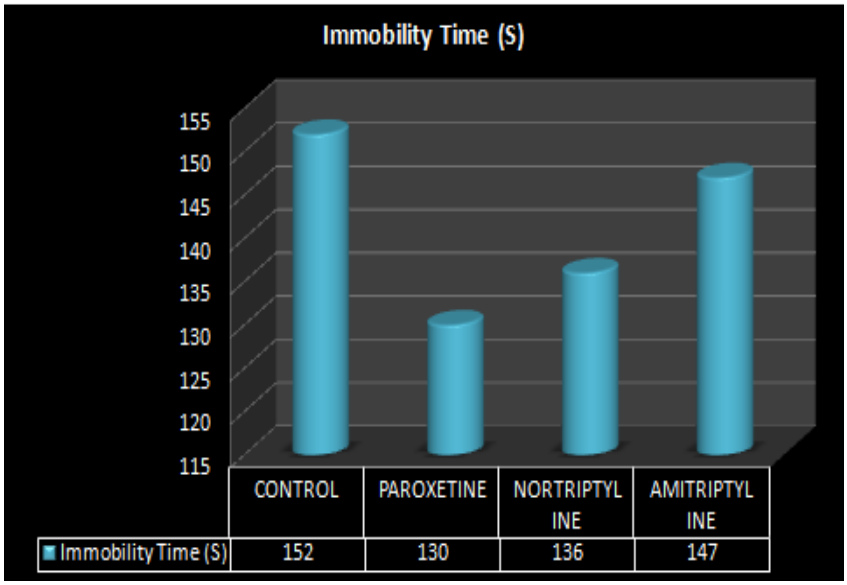
Calculation of Results

Average absorbance values for each set of controls, samples (Paroxetine, Nortriptyline and Amitriptyline) were calculated. A standard curve was constructedby plotting the mean absorbance obtained from each standard against its concentration with absorbance value on the vertical (Y) axis and concentration on the horizontal (X) axis. Concentrations of the samples were interpolated from the standard curve using nonlinear regression method using **GraphPad Prism 5.04**

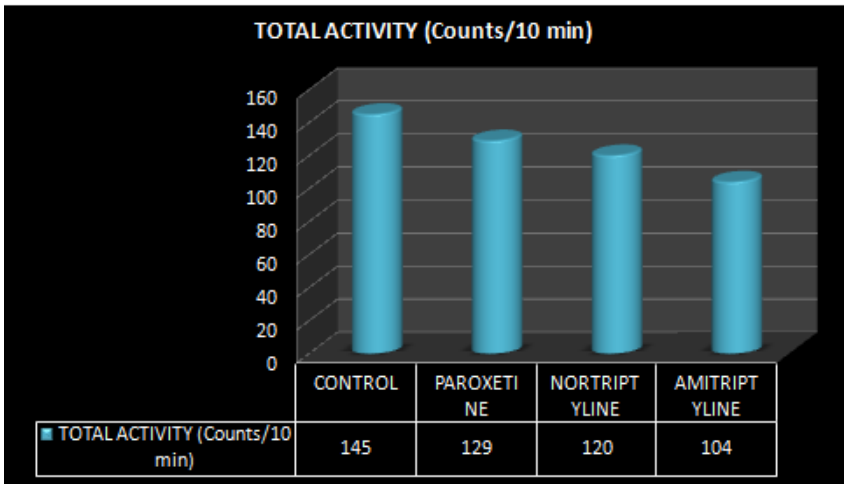
Statistical Analysis

The data were expressed as means ± SEM in the form of tables and vertical column bar graphs. Significant differences were determined by two-way analysis of variance (ANOVA) for factorial comparisons and the Bonferroni test for multiple comparisons. P-values less than 0.05 were considered significant.

NORMAL MICE - TST



NORMAL MICE - SLA



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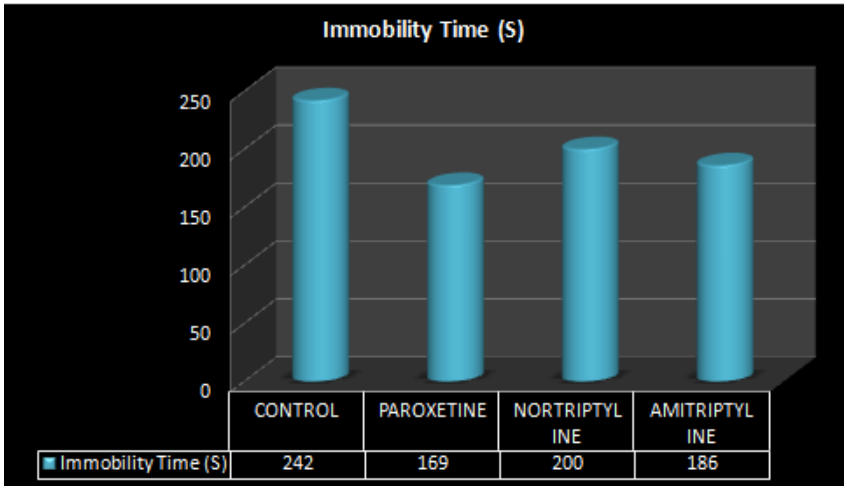
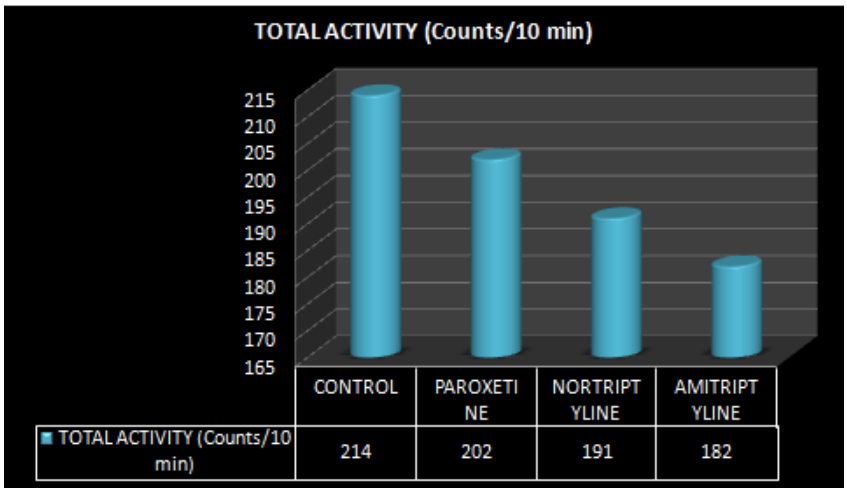
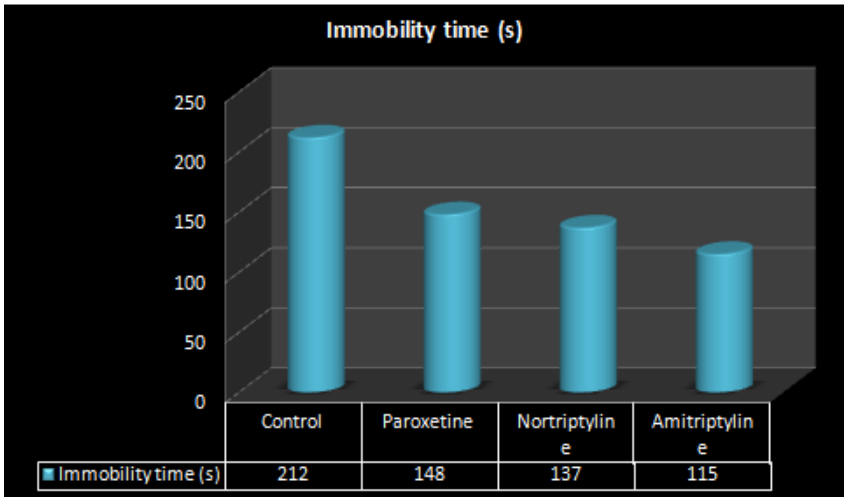
DIABETIC MICE- TST



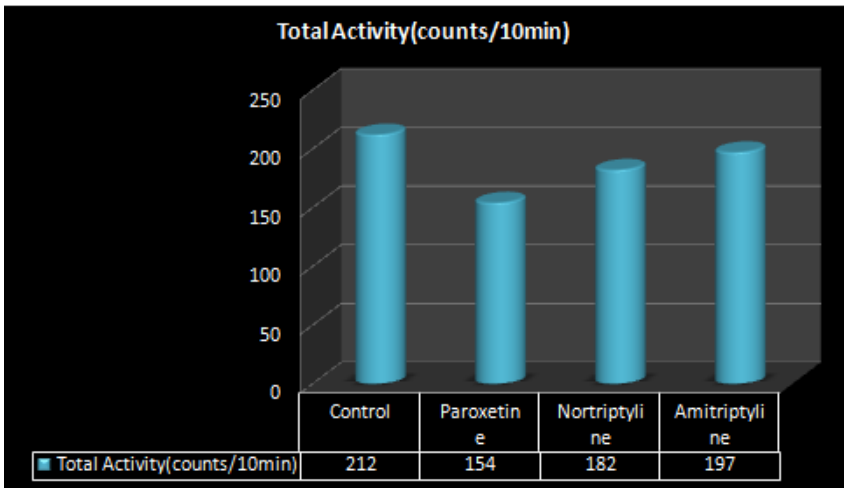
DIABETIC MICE - SLA



SLEEP DEPRIVED MICE - TST



SLEEP DEPRIVED MICE - SLA



Conclusion

In the present study, different antidepressant - Paroxetine (6.5 mg/kg), an SSRI; Nortriptyline (13 mg/kg), an SNERI and Amitriptyline (9.75 mg/kg), a nonselective NA/5-HT reuptake inhibitor were administered orally according to their body weight to compare their efficacy in Normal, Diabetic and sleep deprived mice on Tail Suspension Test and Spontaneous Locomotor Activity. TST was performed as Per Steru et al and it is a valid test for a broad spectrum of antidepressants.

It is possible that drugs reducing the duration of immobility in tail suspension test increase the total activity counts in spontaneous locomotor activity . Therefore, in Normal mice the graph for the TST and SLA are exactly mirror images to each other. i.e., Paroxetine reduced the immobility time in TST significantly than Nortriptyline and

Amitriptyline and Paroxetine increased the total activity counts in SLA significantly than Nortriptyline and Amitriptyline.

It has been recognised that patients with either type 1 or type 2 diabetes have a higher prevalence of major depression and depressive symptoms than the general population7. It is well known that 5-HT systems in brain play a major role in the pathogenesis and treatment of depression . In the rat microdialysis studies, the extracellular 5-HT levels in the hypothalamus and in hippocampus are decreased by STZ-induced diabetes . In the present study, in diabetic mice also, in TST, Paroxetine (an SSRI) is markedly effective than amitriptyline and Nortriptyline, indicating that behavioural changes in diabetic mice are likely to be related to, atleast in part, the changes in 5-HT systems, such as 5-HT neuronal activities and 5-HT receptor responses, caused by diabetes. Both amitriptyline and Nortriptyline were equally effective in terms of their activity, but however inferior to that of paroxetine.Diabetes, though affected the immobility time, did not affect the spontaneous locomotor activity compared to that of Normal mice and hence the activity of antidepressants on locomotor activity in diabetic mice is almost similar that of in normal mice. Therefore, SSRIs are useful agents to reduce the severity of depression in diabetic patients.

Type 1 and type 2 diabetes cause hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis in humans and animals . In consistent with these previous reports, in our present results, diabetic mice showed the increase in plasma corticosterone levels. Long-term corticosterone treatment induced dysfunction of 5-HT1A receptors to 8-OH-DPAT in behavioral and electrophysiological studies Therefore, it is possible that the dysfunction of 5-HT1A receptors, partly responsible for mediating antidepressant-like effect, may be due to the chronic high corticosterone levels in diabetic mice. From the corticosterone levels, it is clear that the drug treated groups showed lesser corticosterone level compared to that of the respective control, however significant difference is not observed among the drug-treated groups. If Normal, Diabetic and sleep deprived groups are viewed as a whole, the corticosterone level of Diabetic is more.

In normal and diabetic depressive patients, Paroxetine, an SSRI would be a better option than Nortriptyline and Amitriptyline while in sleep deprived condition , only amitriptyline (a non selective NA/5-HT reuptake inhibitor) is much better than the other two drugs.

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