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## Behavioural and Motor Responses to Induced Fear in Wistar Rats

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### ABSTRACT

This study investigated the behavioral and motor responses of induced fear in Wistar rats. Twenty-five wister rats used in this experiment were divided into five groups with each group comprising of five rats. Group I received low dose of glutamate receptor antagonist (GRA), Group II received high dose of GRA, Group III were given low dose of adrenaline, Group IV were given high dose of adrenaline while Group V (control group) were given normal saline. These animals were made to undergo two sets of tests viz; One, Induced Fear and Emotional Reactivity (IFER) Test using light/dark automatic reflex conditioned box to test for their threshold for fear shortly after induction using foot-shock method. The degree of passivity, grooming and escape attempt were noted and recorded and their respective cognitive recovery potentials were measured. Two, the Elevated Plus Maze (EPM) Test was employed to assess their level of fear expression under drug influence. The results and extrapolations suggested that groups administered with glutamate receptor antagonist in both low and high concentrations expressed less enhanced alertness, mental cognition and general awareness in both the light and dark compartments on a short time basis with activities characterized with passivity, grooming and attempt to escape when compared with those sets of observations in the adrenaline-administered groups both in short and long term durations with much significant influence ( $p < 0.05$ ). The results of the elevated maze plus (EPM) test followed the same pattern. The present results indicate that induced fear significantly interfered with cognitive activities and normal patterned behaviour in animals and the consequence of this psychic interference played out apparently in after-fear potential (a set of relatively new set of behavioural patterns. The cognitive recovery potential was significantly ( $p < 0.05$ ) slowest in the glutamate antagonist groups and fastest ( $p < 0.05$ ) in the adrenaline groups. These observations suggest that excitatory agonists like thiopental (glutamate receptor antagonist) may lack the ability to ameliorate stress-laden influence on brain cognitive circuitry but stress hormones such as adrenaline do in extremely significant fashion.

**Keywords:** Motor responses, glutamate receptor antagonist, emotional reactivity, foot-shock, passivity.

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## INTRODUCTION

All animals including human beings have inherent ability to respond to events or actions as well as environmental changes which are sometimes severe or life-threatening. The behavioral and motor responses constitute the physical manifestations of the complex mechanism initiated and coordinated in the brain and effected via the peripheral and musculo-skeletal systems. Behavioral and motor response is a component of emotional reactivity of an individual to several stimuli or event. Failure to regulate emotions is implicated in a range of psychological disorders (Gross, 2002).

Rats have been used to study the acquisition and extinction of induced or conditioned fear responses (Morgan & Ledoux, 1995) and its effect on various aspects of neuronal structure and function.

It was conventionally believed that rats exhibit a freezing reaction whenever they are confronted with a threat. This behavior was first noted in 1899 by an experimental psychologist named Willard Stanton Small who analyzed rats' response to fear (Willard, 1901). Recently, Shansky observed that male rats stand their ground and freeze, whereas female rats make a run for it – but it's actually the female rats that control their fear better than the males.

It's known that introduction of an animal to an aversive stimulus such as bright light, electric shock, strange environment induces both exploratory and fear responses resulting in a set of normal pattern motor and behavioural changes. The organism however, may develop approach behaviour due to the exploratory tendency or an aversive behaviour resulting from the fear response (Trullas and Skolnick, 1993)

Fear is a reaction caused by the perception of actual danger (Forkman, et al., 2007; Sherman and Mills, 2008). It is a feeling caused by perceived danger or threat to survival or well-being, this occurs both in animals and humans and brings about a change in metabolic and organ functions and eventually a change in behaviour such as fleeing, hiding or freezing from perceived traumatic events. Fear can be induced in experimental animals using various forms of aversive stimuli like the introduction to a strange environment, bright light, and electric shock or by the generation of loud sound. The other form of fear may be caused in the organism's natural environment by the presence of a predator or a natural disaster etc.

Depending on the nature or extent, fear is classified as rational/appropriate or irrational/inappropriate. An irrational fear is called a phobia. Distinction between fear and anxiety is not clear. While some authors believe there is a difference, others think otherwise. Ohman said that

fear is intimately related to, but should be differentiated from anxiety, which occurs due to threats that seem to be unmanageable or unavoidable (Öhman, 2000).

## MATERIALS AND METHOD

This research was carried out using albino wistar rats in the pre-clinical department of the University of Port Harcourt, Port Harcourt Rivers State, Nigeria. During the study, the recommendations from the 52nd Annual Assembly of the World Medical Association held in Edinburgh in October, 2000 on ethical guidance for biomedical research were generally followed. The project conforms to the guideline of the care and use of animals in research and teaching (NIH Publication No. 8593, revised 1985).

### **Laboratory animal**

Twenty-five albino wistar rats were used in this experiment and were obtained from the animal house of department of physiology, faculty of Basic Medical Sciences, University of Port Harcourt, Nigeria.

### **Acclimatization**

The animals were housed in a wire mesh cage within conditions of temperature between 25 and 29°C, 12 hours light/darkness cycle for two (2) weeks so as to acclimatize to the environmental conditions of the University of Port Harcourt. The animals were fed with normal rat chows and water ad libitum throughout the experiment except otherwise stated.

### **Experimental Design and Administration**

The experimental animals were randomized into five groups comprising of five rats in each group. Group I received low dose of glutamate receptor antagonist (GRA) (sodium thiopental), Group II received high dose of GRA (sodium thiopental), Group III were given low dose of Adrenaline, Group IV were given high dose of Adrenaline, and Group V (control group) were given normal saline. The drugs and normal saline were administered through the intraperitoneal route.

### **Navigational Maze**

This is a complex system of inter-communicating pathways or passages. In the navigational maze, the animal is expected to enter the path (about 50 cm in length) and meander its way out through the exit. The rapidity of completion of task is a measure of spatial memory and the more qualitative the spatial memory the more intelligent the rat.

### **Elevated Plus Maze (EPM)**

It is a cross (+) shaped apparatus with two open and two enclosed arms fixed at a height of about 38cm. It is used to measure (fear) anxiety level as well as cognition in laboratory animals

especially using rodents and as a tool in neurobiological anxiety research such as Post-Traumatic Stress Disorders and Traumatic Brain Injury (Ojo and Mouzon, 2016). It is also been used as a behavioural assay to examine the brain sites (e.g., limbic regions, hippocampus, amygdala, dorsal raphe nucleus, etc.) (Gonzalez and File, 1997). The rat was placed at the central platform like a cross, facing 2 open arms, and 2 closed arm, and the latency for the rat to move from the open arms to one of the closed arm was recorded, the number of head dips on the open arm was recorded. Following entry into the arm, the rat was allowed to explore the apparatus for 5 minutes. An increase in open arm activity (duration/or entries) reflects anti-anxiety behaviour.

### Histological Examination of the Hippocampus

The hippocampi of both the experimental and control groups of the rats were harvested. The tissues were processed and analyzed in the Histopathological Anatomy department of the University of Port Harcourt. The purpose of this tissue processing was to provide a solid support medium for tissue during section cutting and to aid microscopic examination. After processing the tissues manually, microscopic examination of the slides was done using. E-microscopic software and digital pictures were taken, which are shown in the result.

### Statistical Analysis

Statistical analysis was done using SPSS version 20.0 and the results were expressed as mean  $\pm$  SEM and relative percent change. One way Analysis of Variance (ANOVA) and Dunnet Post Hoc (multiple comparisons) Test was used to compare the mean and P-Value  $\leq 0.05$  was accepted as statistically significant. Results were presented in tables, charts and plates.

## RESULT AND DISCUSSION

**Table 1 Response pattern in the light compartment of the Light-Dark Box.**

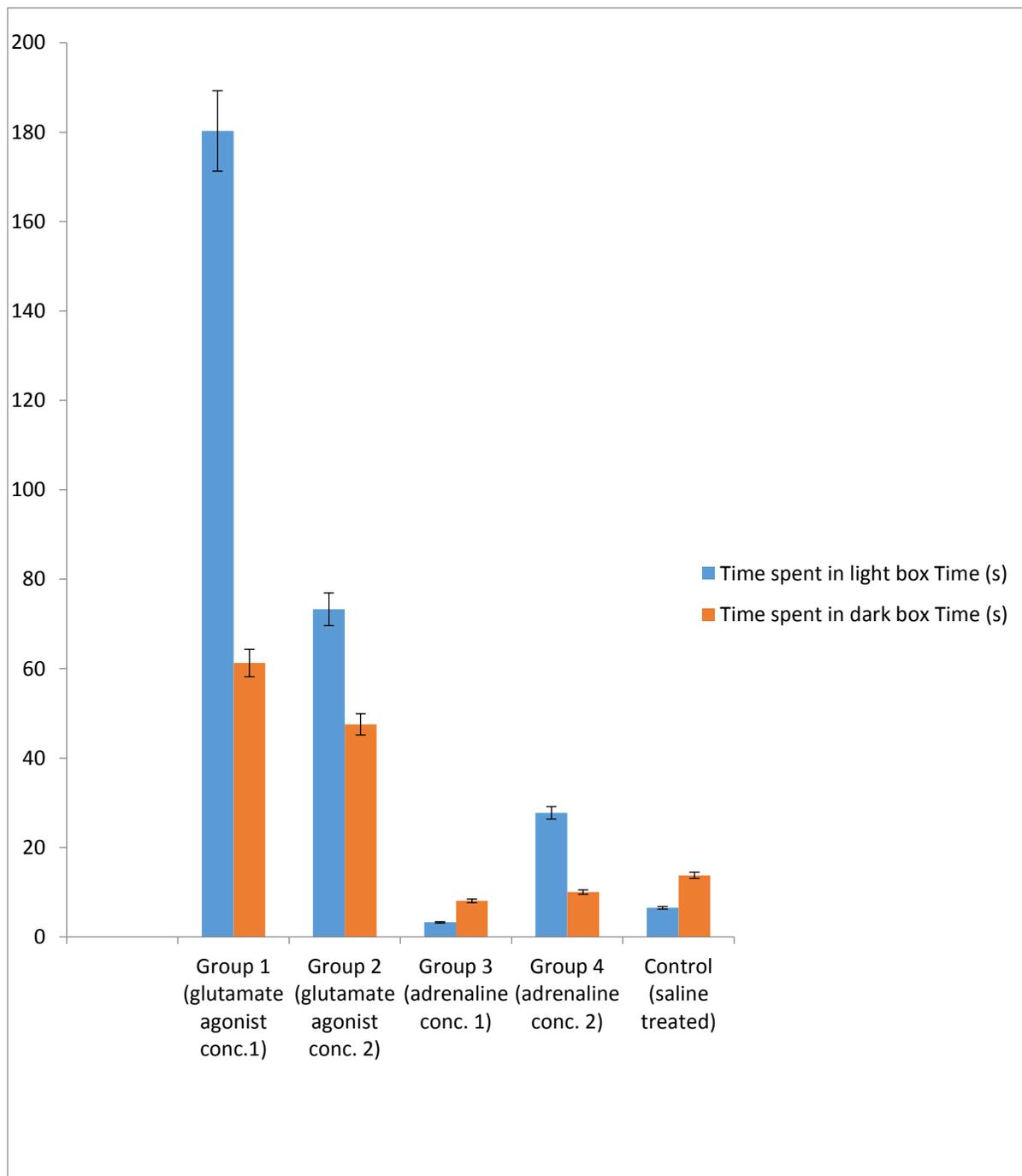
Groups	Time spent in light box Time (s) (Mean $\pm$ SEM)	Behavioural response & Activity Before shock treatment in the light area (Score $\pm$ SEM)		
		Attempt to escape	Grooming	Passivity
Control (saline treated 1ml)	6.5 $\pm$ 0.15	3.01 $\pm$ 0.11	2.12 $\pm$ 0.01	3.21 $\pm$ 0.02
Group 1 (Glutamate receptor antagonist{STP}0.2mg/120g)	180.3 $\pm$ 0.32*	3.22 $\pm$ 1.02	0.10 $\pm$ 0.01	3.50 $\pm$ 1.03
Group 2 (STP0.5mg/120g)	73.25 $\pm$ 0.45*	3.08 $\pm$ 0.25	0.15 $\pm$ 0.02	3.25 $\pm$ 1.25
Group 3 ( Adren 0.02mg/120g)	3.25 $\pm$ 0.65*	2.54 $\pm$ 1.22	2.25 $\pm$ 0.28	0.16 $\pm$ 0.10
Group 4 (Adren 0.05mg/120g )	27.75 $\pm$ 0.15*	2.22 $\pm$ 1.03	2.65 $\pm$ 1.30	0.08 $\pm$ 0.01

Values are presented as mean  $\pm$  Standard error of mean (SEM). n = 5. \* means values are statistically significant compared to the control.

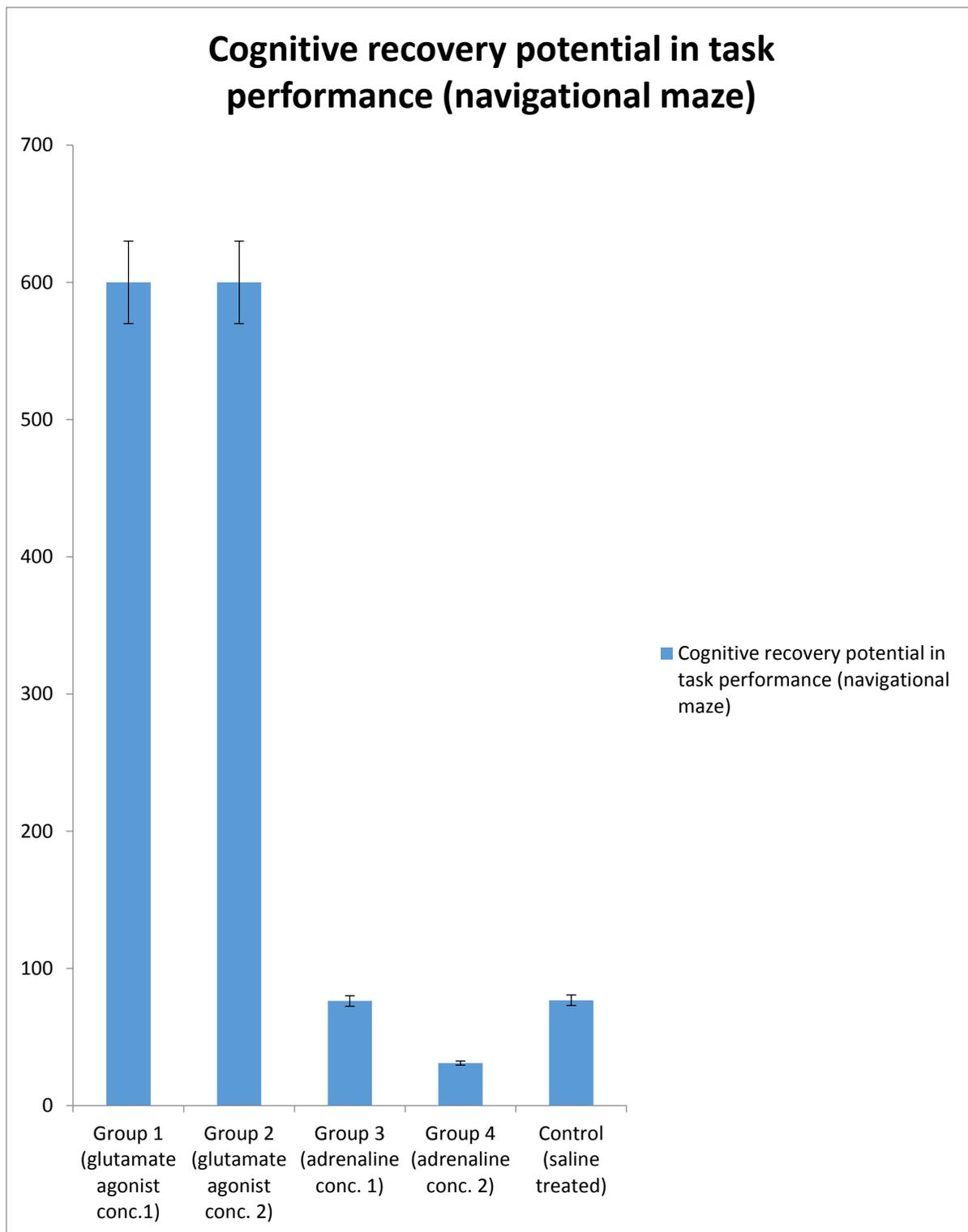
**Table 2 Response pattern in the dark area of Light-Dark Box**

Groups	Time spent in dark box Time (s) (Mean±SEM)	Behavioural response & Activity After Shock treatment in the dark area (Score ± SEM)		
		Attempt to escape	Grooming	Passivity
Control (saline treated 1ml/120g)	13.75 ± 0.38	1.06 ± 0.02	0.13 ± 0.01	3.23 ± 1.22
Group (Sodium thiopentone{STP} 0.2mg/120g)	61.25 ± 2.06	1.02 ± 0.00	0.21 ± 0.02	4.26 ± 2.10
Group 2 (STP 0.5MG/120g)	47.5 ± 1.23	0.07 ± 0.01	0.11 ± 0.00	0.29 ± 0.01
Group 3 (Adren 0.02mg//120g)	8.05 ± 0.51	2.28 ± 1.20	2.43 ± 1.22	1.25 ± 0.21
Group 4 (Adren 0.05mg/120g)	10.03 ± 0.18	2.30 ± 0.55	2.22 ± 0.25	3.82 ± 1.28

Values are presented as mean ± Standard error of mean (SEM). n = 5. \* means values are statistically significant compared to the control.



**Figure 1: Comparative result for the time spent in the Light and the Dark Area**



**Figure 2: Time spent in recovery after task performance**

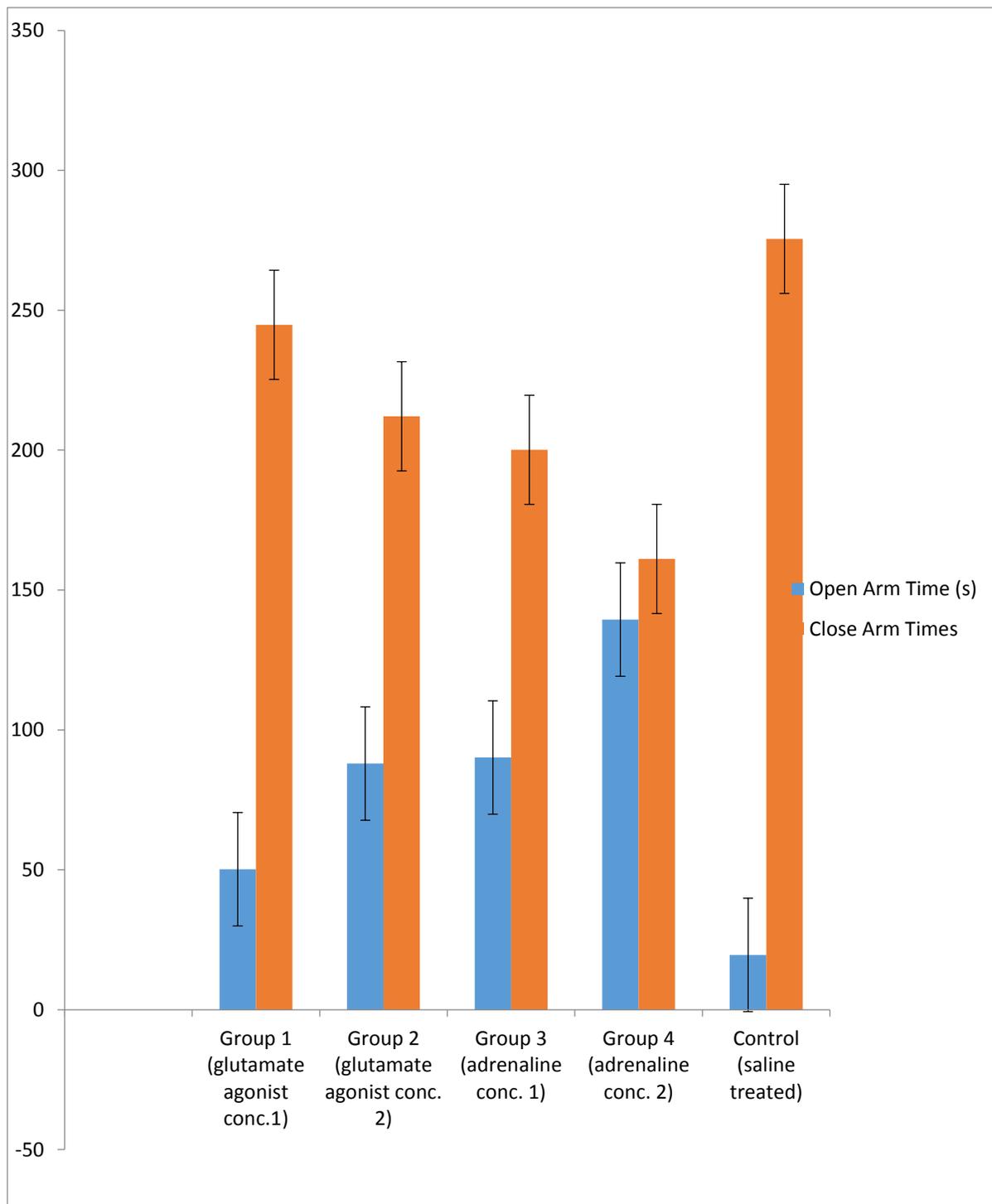
**Table 3 Behavioural Response in the Open arm of the Elevated Plus Maze**

Groups	Open Arm Time (s) Mean $\pm$ SEM	Behavioural Response and Activity in the open arm of EPM (Score $\pm$ SEM)		
		Attempt to Escape	Grooming	Passivity
Control (saline treated 1ml/120mg)	19.60 $\pm$ 4.17	0.15 $\pm$ 0.01	1.15 $\pm$ 0.03	3.67 $\pm$ 1.33
Group 1 (Glutamate rec antagonist {STP} 0.2mg/120g)	50.25 $\pm$ 8.35*	1.05 $\pm$ 0.01	2.58 $\pm$ 0.56	2.55 $\pm$ 0.35
Group 2 (STP 0.5mg/120g)	88.02 $\pm$ 11.21*	1.65 $\pm$ 0.55	2.55 $\pm$ 1.22	2.65 $\pm$ 1.22
Group 3 (adren 0.02mg/120g)	90.19 $\pm$ 15.23*	3.58 $\pm$ 2.01	0.05 $\pm$ 0.01	0.02 $\pm$ 0.01
Group 4 (adren 0.05mg/120g)	139.46 $\pm$ 25.67*	3.90 $\pm$ 1.32	0.01 $\pm$ 0.00	0.03 $\pm$ 0.01

Values are presented as mean  $\pm$  Standard error of mean (SEM). n = 5. \* means values are statistically Significant compared to the control.

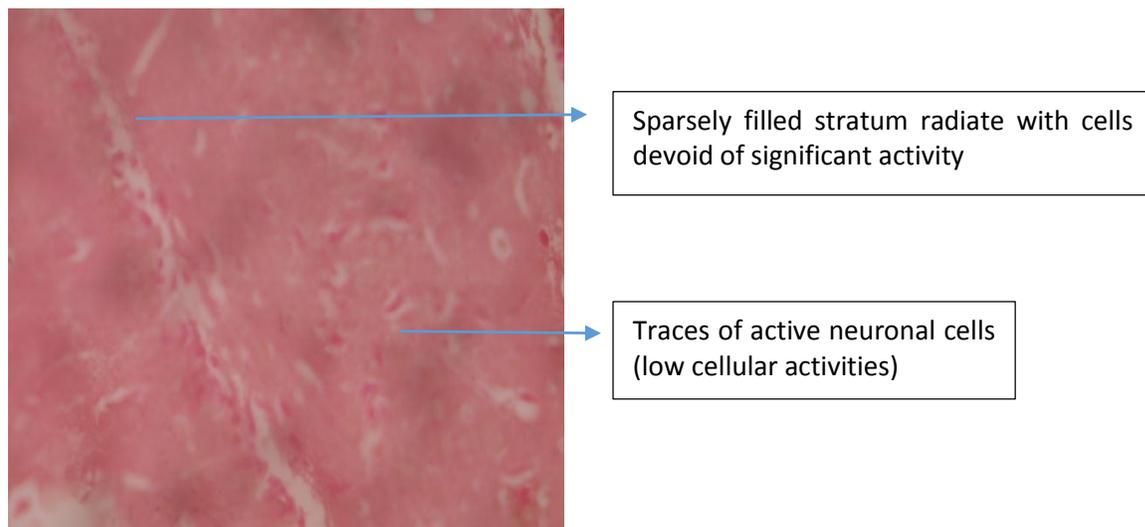
**Table 4 Behavioural Response in the close arm of Elevated Plus Maze**

Groups	Closed Arm Time (s) Mean $\pm$ SEM	Behavioural Response and Activity in the close arm (Score $\pm$ SEM)		
		Attempt to Escape	Grooming	Passivity
Control (saline treated 1ml)	275.51 $\pm$ 36.17	0.01 $\pm$ 0.00	3.29 $\pm$ 1.21	3.56 $\pm$ 2.15
Group 1 (Glutamate rec antagonist {STP} 0.2mg)	244.82 $\pm$ 28.12	1.05 $\pm$ 0.12	1.25 $\pm$ 0.10	2.58 $\pm$ 1.15
Group 2 (STP 0.5mg)	212.08 $\pm$ 65.15	1.03 $\pm$ 0.01	1.23 $\pm$ 0.13	2.75 $\pm$ 1.52
Group 3 (adrenalin 0.02mg)	200.15 $\pm$ 34.19	3.57 $\pm$ 2.17	1.11 $\pm$ 0.01	0.25 $\pm$ 0.01
Group 4 (adrenalin 0.05mg)	161.15 $\pm$ 35.21	3.95 $\pm$ 1.56	1.00 $\pm$ 0.01	0.12 $\pm$ 0.02

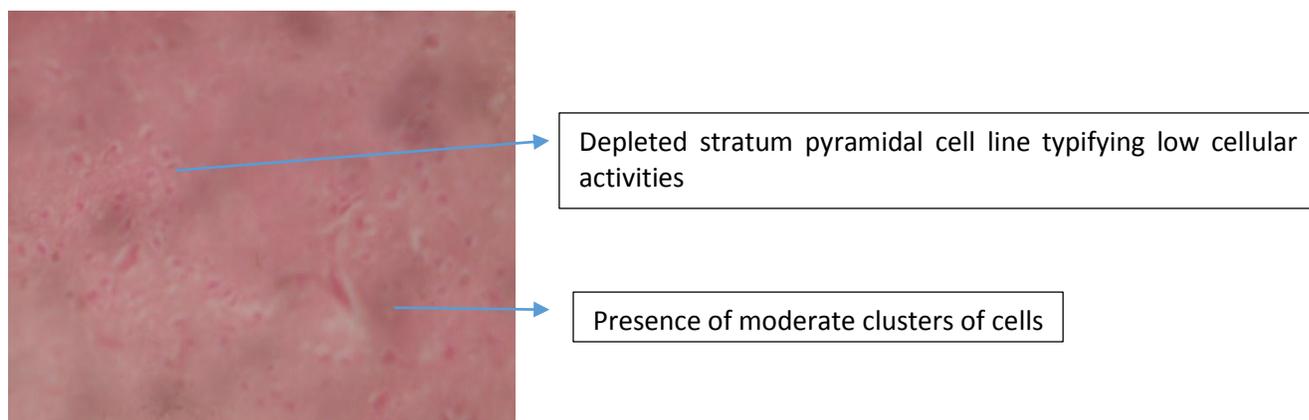


**Figure 3: Comparative result of the time spent in the open arm and the close arm**

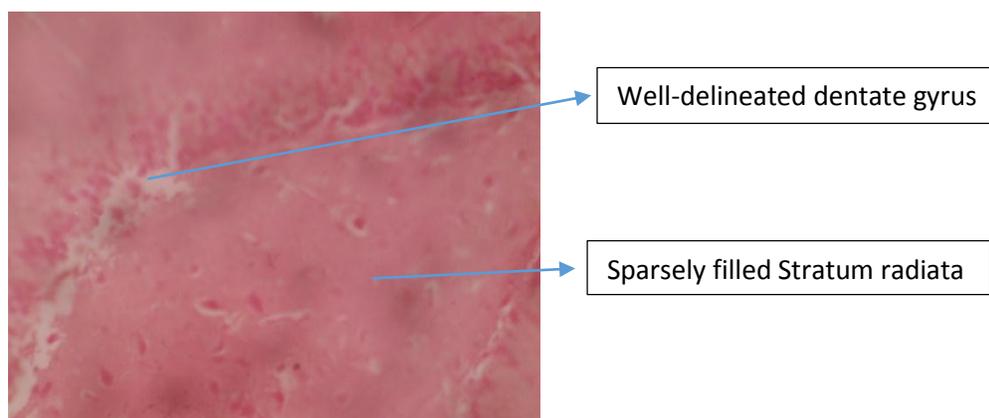
Results Of Histological Sections Of The Rats' Hippocampus Of The Experimental And Control Groups



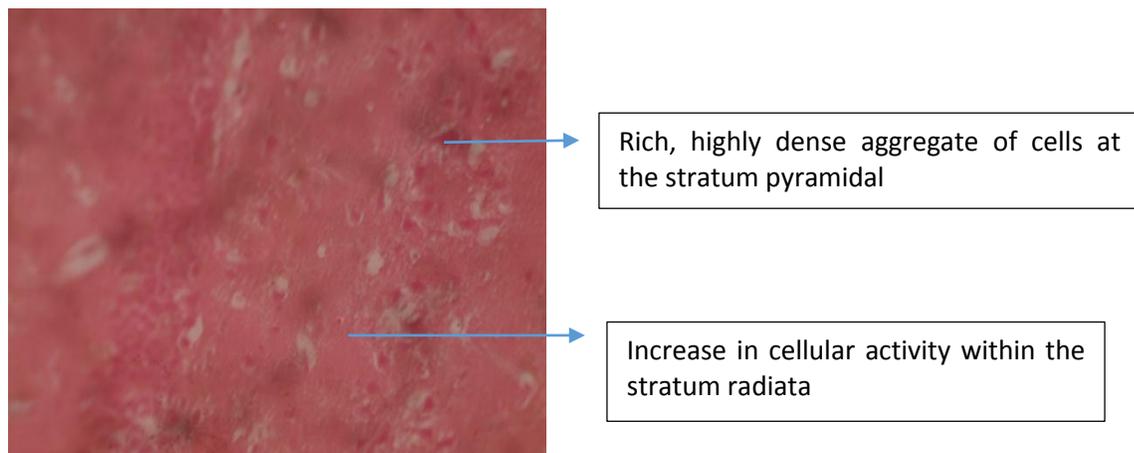
**Plate 1 Photomicrograph of the Hippocampus of Group 1 treated with glutamate receptor antagonist (Thiopental, low dose) (H&E × 400)**



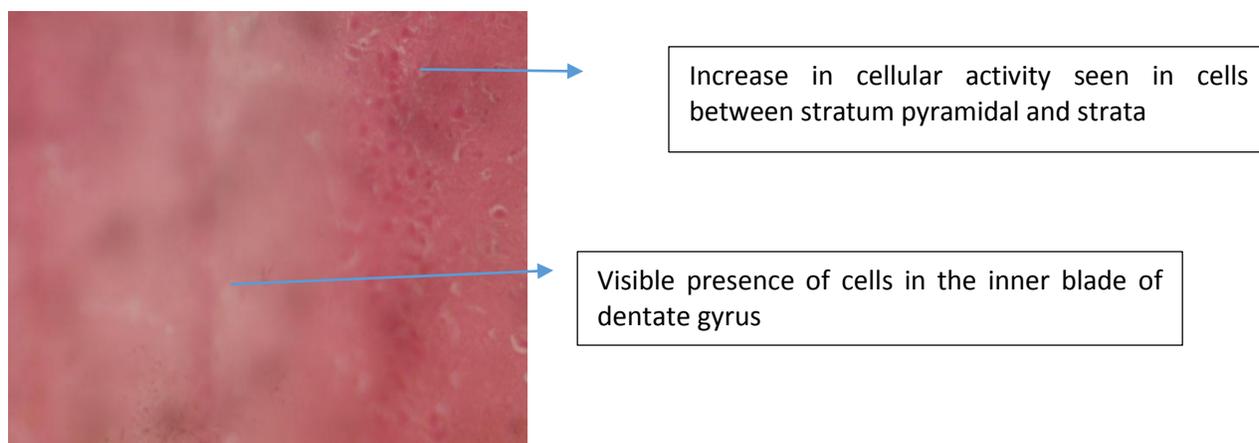
**Plate 2 Photomicrograph of the Hippocampus of group 2 treated with Glutamate receptor antagonist (Thiopental, high dose) (H&E × 400)**



**Plate 3 Photomicrograph of the Hippocampus group 3 treated with Adrenaline (low dose) (H&E × 400)**



**Plate 4 Photomicrograph of the Hippocampus of group 4 treated with Adrenaline (high dose) (H&E × 400)**



**Plate 5 Control (saline treated) (H&E × 400) Photomicrograph of the Hippocampus group 5**

This study investigated the behavioural and motor responses of induced fear in wistar rats. The extrapolations from the study indicated that temporary disruptions caused by transition from dark to light compartment worsens cognitive recovery ability in rats despite drug administration leading to exaggerated fear expressions and reduced defensive behaviours immediately after foot shock. Interestingly, these results are consistent with previous reports though in slightly different scenarios (Gisquet-Verrier *et al.*, 1999).

The result for the light and dark box test as presented in table 1 showed that there was significant increase ( $P \leq 0.05$ ) in the time spent in light box for Group 1 and Group 2 which were administered with glutamate receptor antagonist (sodium thiopental) when compared with the control group. This observation was in line with the report that the time rats spend within the light compartment was increased by anti-anxiety agents while anxiogenic drugs increase exploratory tendency of the environment and increase the time at the dark area (Borsini, *et al.*, 2002). These groups also demonstrated a high passivity and attempt to escape from the light region before shock

treatment, grooming was noticed to be low though. These indicated that the glutamate receptor antagonist groups have enhanced fear expression and cognitive awareness.

Again, groups 1 and 2 administered with glutamate antagonist were observed to spend more time in the dark box compared with the control group. Ordinarily, nocturnal animals like rats feel more secured in dark environment than in illuminated area. Group 2 administered with higher dose showed a poor attempt to escape after shock treatment in the dark box, grooming was low and passivity high.

This is similar to the observation with lower glutamate antagonist dose and is suggestive of a non-dose dependent drug effect. The time for a second attempt towards the dark box after the induced fear when compared with the control group was noticed to be insignificantly increased in groups 1 and 2. The rats in both groups, despite the shock (danger) still had a second attempt to the dark box in keeping with their preference to dark environment as seen in the night. This observation agrees with the report that active defense includes attack or threat while active avoidance can be expressed as hiding (making itself undetectable or noticeable), escape or flight (running away from danger). Passive avoidance can be expressed as immobility or freezing (Hashimoto, *et al*, 1999).

Group 3 which was administered with lower dose of adrenaline showed significant decrease ( $P \leq 0.05$ ) in time spent in the light box while group 4 administered with higher dose of adrenaline demonstrated significant increase in time spent in the light box compared with the control group. Attempt to escape from the light box and grooming was observed to be high in both higher and lower dose groups while passivity was found to be low.

There was an insignificant reduction in the time spent in dark box in low dose of adrenaline as well as in high dose when compared with the control group while the time was remarkably increased in both groups 1 and 2. Attempt to escape after shock treatment in dark box was high in both low and high dose of adrenaline, grooming was high and passivity low in groups 1 & 2. These observations implied that the rats treated with adrenaline had increased level of alertness, preparedness and motor activity upon introduction to aversive stimuli. Adrenaline is the prominent hormone and plays an important role in the fight-or-flight response following exposure to danger and makes the organism better prepared to face or avoid the threat. These findings support the reports by Moser *et al* as well as Lieberman *et al* who revealed that emotional and fear response are mediated by the sympatho-adrenal system neurotransmitters and these mediators include adrenaline and nor-adrenaline which are released in large amount and increase the organisms level of alertness and preparedness (Moser *et al.*, 1968; Lieberman, 2013).

The time for a second attempt towards dark box after shock treatment for group 3 and 4 was observed to be decreased; however this decrease was statistically insignificant.

A faster cognitive recovery potential ( $p \leq 0.05$ ) in task performance determined by the time spent by the rats to go through the navigational maze (from the entry to the exit point) was observed in both groups 3 and 4 administered with adrenaline compared with both the control and glutamate receptor antagonist groups, however, recovery was noticed to be fastest in group 4 administered with higher dose of adrenaline. This justifies the statement that the brain itself responds to stress partly by the release of adrenaline which is known to affect memory and emotional reactivity. Several experiments have shown the enhancing effect of adrenaline on memory (Gold, 1989; Gold and van Buskirk, 1976; Gold *et al.* 1982). Adrenaline does not cross the blood-brain barrier but when released peripherally results in vagal stimulation which is believed to trigger the release of nor-adrenaline within the brain especially the hippocampus where it binds to receptors and influence long-term potentiation (Georgia, 2014).

On the other hand, cognitive recovery potential in task performance after the shock treatment showed significant delay ( $P \leq 0.05$ ) in time in groups 1 and 2 which was administered with lower and higher doses of glutamate receptor antagonist respectively. This observation was consistent with the work of Osborn *et al* which showed that thiopental impaired short term memory in their human subjects during sedation in a dose-dependent manner without affecting long term memory (Osborn *et al*, 1967).

The above observations summarily suggested that groups administered with glutamate receptor antagonist in both lower and higher concentrations showed enhanced alertness, mental cognition and general awareness in the light compartments with activities devoid of grooming and indolence. These sets of observations were equally enhanced in the adrenaline-administered groups but in both light and dark compartment with significant influence ( $p \leq 0.05$ ).

The result of the elevated plus maze (EPM) test as demonstrated in table 3 and 4 showed that groups 1 and 2 administered with glutamate receptor antagonist in lower and higher doses respectively showed a significant increase ( $P \leq 0.05$ ) in time spent in the open arm when compared with the control group however, the animals spent more significant time in the close arm than in the open arm. Attempt to escape from both the open and close arm was poor, grooming was observed to be high in the open arm and low in the close arm while passivity was high in both. It is in keeping with the nocturnal lifestyle of rats and the fact that it tend to feel more secured in an enclosed area as against an open region.

Group 3 and 4 administered with lower and higher doses of adrenaline respectively was observed with significant increase ( $P \leq 0.05$ ) in time spent in the open arm compared with the control; group 3 was observed with a high attempt to escape from the open arm and group 4 was experienced to have a very high attempt to escape from the open arm. Grooming and passivity were found to be low in both groups. This is in line with the research which reported that when an organism is exposed to stress or trauma high levels of anti-stress hormones like catecholamines (adrenaline and nor-adrenaline) and glucocorticoids (cortisol in humans and corticosterone in rodents) are released into the system. These hormones help to prepare the individual to confront or escape the situation. The hippocampus is prone to long term stress due to the fact that it has high concentrations of stress hormone glucocorticoid receptors than other brain sites (Joels, 2008).

Apparently, the thiopental-administered groups had enhanced expression of fear when compared with adrenaline-administered groups that spent much longer time in the open arm. The degree of exploratory tendency was also better in the former groups as well.

The histological studies of the hippocampus of group 1 rats treated with glutamate antagonist (thiopental, lower dose) revealed sparsely-filled stratum radiata, of the hippocampus with cells void of significant activity and also traces of active neuronal cells which depicted low cellular activities.

In the same manner, the study revealed depleted stratum pyramidal cell line (typifying low cellular activity) and moderate clusters of cells in the hippocampus of the animals treated with glutamate antagonist in higher dose. This showed that glutamate antagonist tend to decrease cellular activities in the hippocampus. It agrees with the idea that thiopental has effects on brain electrical activity, cerebral blood flow, cerebral metabolic rate and intracranial pressure (Piatt & Schiff, 1984; Michenfelder & Theye, 1973).

Thiopental enhances the electrophysiological recovery of the CA1 and dentate regions from rat hippocampal slices after a short period of anoxia (Kass *et al*, 1992). It reduces NMDA- and AMPA-induced neuronal damage. This may result from its effect on depolarization or blockade of voltage-dependent ion channels (Collins & Anson, 1987; Cai & McCaslin, 1993). Results indicate that barbiturate protection against cerebral ischemia or anoxia may be due in part to the blockade of NMDA- and AMPA-mediated glutamate excitotoxicity (Zhu, *et al.*, 1997).

The result of the histological studies of the hippocampus after the experiment showed that the hippocampus of rats in group 3 administered with adrenaline (lower dose) have well delineated dentate gyrus and sparsely-filled stratum radiata as demonstrated in plate 4.1 which shows that the activity within the stratum radiata was not significantly increased.

Plate 2 demonstrated a rich, highly dense aggregate of cells at the stratum pyramydial and a significant increase in cellular activity within the stratum radiata in the hippocampus of group 4 rats treated with higher dose of adrenaline and therefore, adrenaline in high dose increases cellular activities within the hippocampus. This is in keeping with several reports that established that hippocampal cellular activity is enhanced through  $\beta$ -adrenergic receptor activation (Stanton & Sarvey, 1985; Madison & Nicoll, 1986; Heginbotham & Dunwiddie, 1991; Gereau & Conn, 1994).

## CONCLUSION

The present study indicated that the induced fear significantly interfered with cognitive activities by down-regulating it alongside normal patterned behaviours in rats and the consequence of this psychic interference played out apparently in after-fear behavioural and motor activity.

Cognitive recovery potential depicts the ability of the rats to form learned pattern of behavior which is purely adaptive and will make the animals better poised in handling threat-induced fear, react emotionally matured and better prepared. The cognitive recovery potential was significantly ( $p < 0.05$ ) slow in the glutamate antagonist groups and faster ( $p < 0.05$ ) in the adrenaline groups. These observations suggested that excitatory agonists like glutamate receptor antagonist do not ward off or ameliorate threat-induced influences on brain cognitive circuitry but stress hormones such as adrenaline do in extremely significant fashion.

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