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*Full-Length Research Article*

# Effect of Caffeine and Adrenaline on Memory and Anxiety in Male Wistar Rats

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**Summary:** The present study was designed to investigate the effects of caffeine and adrenaline administration on memory and anxiety in male rats. Rats weighing about 140-200g were used for the study. They were divided into three groups (4 animals per group). Study groups 1; a,b,c,d were healthy rats administered normal saline, 5,10 and 15mg/kg bw caffeine intraperitoneally (i.p.), respectively for 6 weeks. Study groups 2; a,b,c,d administered normal saline, 0.1, 0.2 and 0.31mg/kg bw adrenaline (i.p.), respectively for 6 weeks. Study groups 3; a,b,c,d administered normal saline, 5mg/kg caffeine (i.p.) + 0.1mg/kg adrenaline (i.p.), 10mg/kg Caffeine (i.p.) + 0.2mg/kg Adrenaline (i.p.) and 15mg/kg Caffeine (i.p.) + 0.3mg/kg Adrenaline (i.p.) respectively for 6 weeks. The result showed no significant difference in spatial memory across all animals in study groups 1: b,c,d when compared to control (a). Study groups 2: (b, c) showed increase in spatial memory when compared to control (a). 2(d) showed a significant ($p<0.05$) decrease. Study groups 3: b, c, d showed no significant difference in spatial memory when compared to control (a). Study groups 1: b, c showed significant ($p<0.05$) reduction in duration for the short and long-term memory test when compared to control. Study groups 2 showed reduction in duration for both the long- and short-term memory test when compared to control Study groups 3 no significant ($p<0.05$) difference in short and long term memory test across all animals in the group. It was also observed that adrenaline enhanced short and long term memory and only high dose of adrenaline distorted spatial memory. Study groups 1; (b,c) showed significant ($p<0.05$) increase in the number of entries to the open arm of the elevated plus maze when compared to control (a). Study groups 2; (b), showed significant ($p<0.05$) increase in the frequencies of entries to the closed arm of the elevated plus maze when compared to control (a). Study groups 2; (d), showed a significant ($p<0.05$) decrease in the frequency of entries to the open and closed arm when compared to control (a). The study revealed that co- administration of caffeine and adrenaline led to elevation of mood, increased activity and reduction of anxiety in Wistar rats. In addition, it was observed that only high dose of adrenaline increased anxiety. It was also observed that caffeine and adrenaline enhanced short and long term memory and only high dose of adrenaline distorted spatial memory.

**Keywords***: adrenaline, anxiety, behavioural tests, caffeine, memory, Wistar rats.*

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## INTRODUCTION

Memory is a process which involves storage of information or experiences in the brain. Encoding information is one of the processes involved in remembering episodes (McDermott and Roediger, 2022) and allows information that is from the outside to get into the senses in the forms of chemical and physical stimuli. The process of memory consolidation is in stages: Sensory memory, which is the ability to see an item and remember what it looked like within few seconds of observation. Short term memory is a type of memory that allows recall for a period of several seconds to about a minute without rehearsal as seen in recalling an eleven-digit telephone number. Long-term memory can store much larger information for potentially unlimited time or duration, sometimes it takes a whole life span. The hippocampus is the major organ responsible for acquisition of new information and also for memory consolidation of information from short term to long-term memory. If there is a damage or problem with the hippocampus, the ability to make new information and memories are not possible to be stored into long-term memory (Anand and Dhikav, 2012). Long-term memory can be categorised into declarative and non-declarative memories (Camina and Guell, 2017). Declarative memory requires conscious recall and it can be sub-divided into semantic memory and episodic memory. Semantic memory allows the encoding of abstract knowledge about the continents (Binder and Desai, 2011). Episodic memory is more for personal memories, such as the sensations, emotions, and personal associations with a particular place or time. Some factors e.g. odour can affect memory and can also be used to re-activate new memories in the brains of people when sleeping and the individuals would remember better when they are awake (Shanahan et al., 2018). Emotion is also a major link to recall. Interference can hamper memorisation and retrieval. Sometimes, retroactive interference can occur where learning new information leads to hard recall of old information and proactive interference, where previous learning interferes with the recall of new information (Sosic-Vasic et al., 2018).

Caffeine (1,3, 7 trimethylxanthine), a bitter, white crystalline purine has been discovered as a CNS stimulant and also classified as an organic molecule called methylxanthine (Fiani et al., 2021). Caffeine counteracts adenosine that normally circulates at high levels throughout the body and especially in the nervous system. Adenosine acts as an inhibitory neurotransmitter that suppresses activity in the central nervous system. It produces a certain alertness of short duration (Camargo and Camargo, 2019), increases wakefulness, focus, and better general body coordination. Low doses (20±200 mg) produce positive feelings (e.g. heightened energy, ability to concentrate, liking (Lieberman et al., 1987), while higher doses have been associated with feelings of severe anxiety, nervousness and agitations which can increase in severity with dose (Walter, 2022). Herz (1999) reported that psychoactive dose of caffeine does not impair or enhance memory, even though it produced a significant mood elevation in arousal. It has been proposed that arousal elevation sufficient to alter memory encoding must impact on β-adrenergic systems (Cahill and McGaugh, 1998) and 5 mg/kg caffeine may not have produced this effect.

Adrenaline, also called epinephrine, is a stress hormone produced from the adrenal glands of the kidneys and in some neurons of the central nervous system. It helps in preparing the body for a fight-or-flight reaction in threatening environments. Evidence suggests that adrenergic hormones modulate the consolidation of long-term memory for experiences that induce their release. For example, post-training injection of adrenergic drugs or hormones enhances memory consolidation in many species (Segal et al., 2012; Villain et al., 2016; Schramm et al., 2016). Adrenergic hormones, released by emotional arousal modulate memory consolidation of the events (McGaugh, 2013). The relationship between the effects of adrenaline and the anxiety state is further emphasised by the emotive action of adrenaline (Richter, 1940).

This study was aimed at investigating the effect of caffeine and adrenaline on memory and anxiety in male Wistar rats. The objective of this study is to administer caffeine and adrenaline singly and in combination to evaluate its synergistic effects on spatial memory, long and short-term memory, and anxiety.

## MATERIALS AND METHODS

**Experimental Animals:** Male albino rats of Wistar strain weighing between 140-200g were obtained from the animal holding of the Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. The animals were fed on rats pellet (Premier Feed Limited, Apapa, Lagos, Nigeria) and water *ad libitum.* All animals were maintained under standard laboratory conditions of temperature (22±2ºC) and natural photoperiod of about 12h light: dark cycle with relative humidity of 40-50%. Ethical approval was obtained from the University of Ilorin Ethical Review Committee with ethical approval number (UERC/ASN/2016/487).

**Study design:** The rats were grouped into study groups A, B and C. Study groups 1; a,b,c,d were healthy rats administered normal saline, 5,10,15mg/kg bw caffeine intraperitoneally (i.p.), respectively for 6 weeks. Study groups 2; a,b,c,d administered normal saline, 0.1, 0.2, 0.31mg/kg bw adrenaline (i.p.), respectively for 6 weeks. Study groups 3; a,b,c,d administered normal saline, 5mg/kg caffeine (i.p.) + 0.1mg/kg adrenaline (i.p.), 10mg/kg Caffeine (i.p.) + 0.2mg/kg Adrenaline (i.p.), 15mg/kg Caffeine (i.p.) + 0.3mg/kg Adrenaline (i.p.) respectively for 6 weeks. At the end of six weeks of administration, the animals were subjected to series of behavioural tests which include spatial learning and memory and anxiety.

**Spatial learning and memory test using morris water maze**: The methods of Morris (1984) and *D'Hooge, and De Deyn (2001) were used for this study.* The animals were subjected to 5days training in the Morris water maze prior to the learning test and memory test. During this period, 10cm platform was visible i.e. 1cm above the water level in the maze. This was followed by the learning and memory test at the end of the drug administration where the hidden platform was 1cm bellow the water.
Each rat was placed in the Morris water maze at a designated start point of a quadrant and allowed to swim freely to locate the hidden platform within a maximum duration of 1minute.

**Anxiety test using elevated plus maze:** Following the drug administration, animals were placed in the central platform facing the closed arm and their behaviour recorded for 5 min. based upon the study by Montgomery, (1958). The duration of time spent in the arms was calculated as time in open arms or closed arm, the number of entries into the arms was calculated as number of entries into open or closed arms/total number of entries.

**Spatial memory test using y-maze:** Each rat was placed in the centre of the arm compartments and was allowed to move freely until its tail completely enters a particular arm. The sequence of arm entries was manually recorded, the arms being labelled A, B, or C. An alternation is defined as entry into all three arms consecutively, for instance if the animal makes the following arm entries; A,C,B,C,A,B,C,A,C,A,B,C,A, in this example, the animal made 13 arm entries 8 of which are correct alternations. The number of maximum spontaneous alternations is the total number of arms entered minus two, and the percentage alternation is calculated as {(actual alternations /maximum alternations) x 100}. For each animal the Y-maze testing was carried out for 5 minutes. The apparatus was cleaned with 5% alcohol and allowed to dry between sessions (Onaolapo *et al*., 2012).

**Open field test:** The procedure followed the method of Danenberj, (1969). Each rat was placed in the center of the open field maze and allowed to move freely for the duration of 5minutes. Each line crossing frequency, centre square frequency and center square duration was recorded. Rearing frequency was also recorded. Time spent moving, cleaning/grooming was also noted.

**Statistical analysis**
Results obtained are expressed as the mean ± standard error of mean (SEM). The test for significance was done using one-way ANOVA, Student's t-test and Duncan *post-hoc* test. Differences were considered statistically significant at

p<0.05. Data analysis was performed using statistical packages for social sciences (SPSS) version 16.

## RESULTS

### Memory test

### Y-maze test

**Effect of caffeine administration on spatial memory in male Wistar rats:** There was no significant difference across all animals administered caffeine when compared to control group in the spatial memory test using Y-Maze as indicated in Figure 1

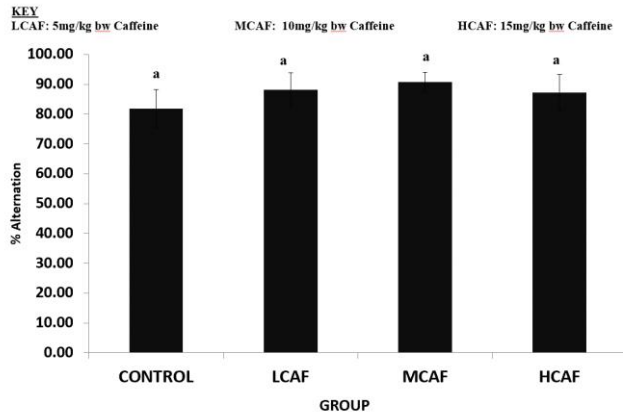


**Figure 1:**
Effect of caffeine administration on spatial memory in male Wistar rats. Bars with different letters are significantly (p<0.05) different

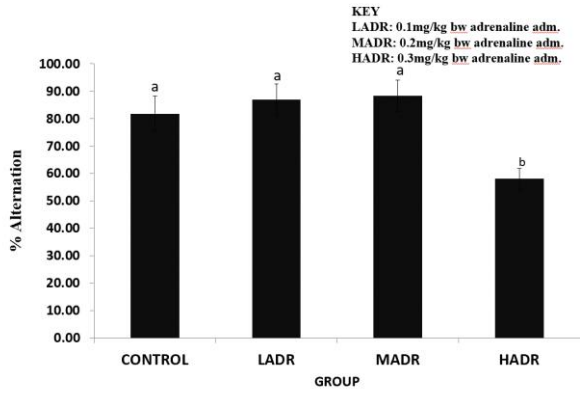


**Figure 2:**
Effect of adrenaline administration on spatial memory in male Wistar rats. Bars with different letters are significantly (p<0.05) different.

**Effect of adrenaline administration on spatial memory in male Wistar rats:** Only high dose of caffeine showed significant decrease in the measure of spatial memory (correct alternation (%) in Y-Maze) when compared to control, other animals showed no significant difference as shown in figure 2.

**Effect of combined administration of caffeine and adrenaline on spatial memory in male Wistar rats:** There was no significant difference across all the caffeine and adrenaline co-administered animals when compared to control (Figure 3).

### Morris water maze

**Effect of caffeine administration on short and long-term memory of male Wistar rats:** Caffeine animals (10 and 15mg/kg bw) showed significant (p<0.05) reduction in duration for the short and long term memory test when compared to control. Low dose of caffeine (5mg/kg bw) only showed significant (p<0.05) reduction in duration for long term memory test when compared to control as shown in Figure 4.

**Effect of adrenaline administration on short and long-term memory of male Wistar rats:** All doses of adrenaline group showed reduction in duration for both the long and short term memory test when compared to control as shown in Figure 5.

**Effect of combined administration of caffeine and adrenaline on short and long-term memory of male Wistar rats**: No significant (p<0.05) difference in short and long term memory test across the animals as shown in Figure 6.

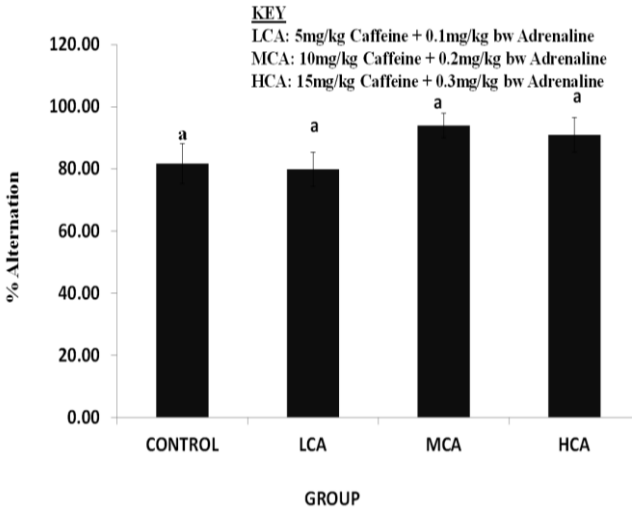


**Figure 3:**
Effect of combined administration of caffeine and adrenaline on spatial memory in male Wistar rats. Bars with different letters are significantly (p<0.05) different.

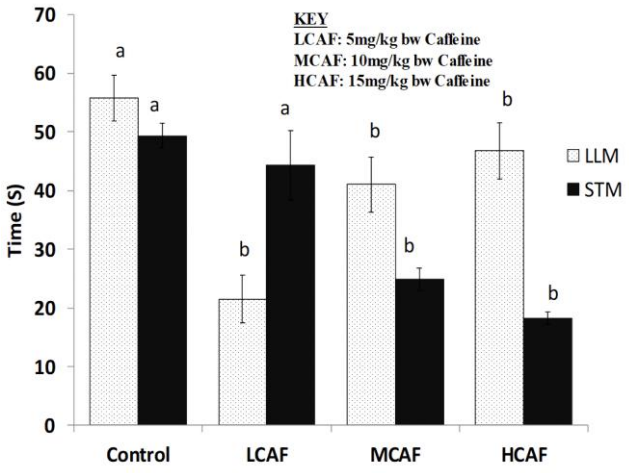


**Figure 4:**
Effect of caffeine administration on short and long-term memory of male Wistar rats. Bars with different letters are significantly (p<0.05) different.

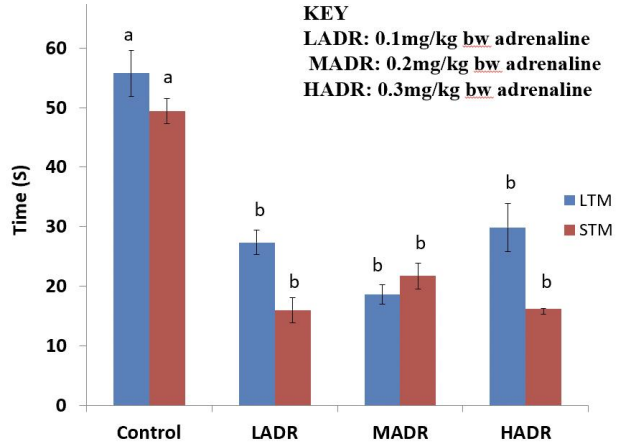


**Figure 5:**
Effect of adrenaline administration on short and long-term memory of male Wistar rats. Bars with different letters are significantly ($p<0.05$) different.

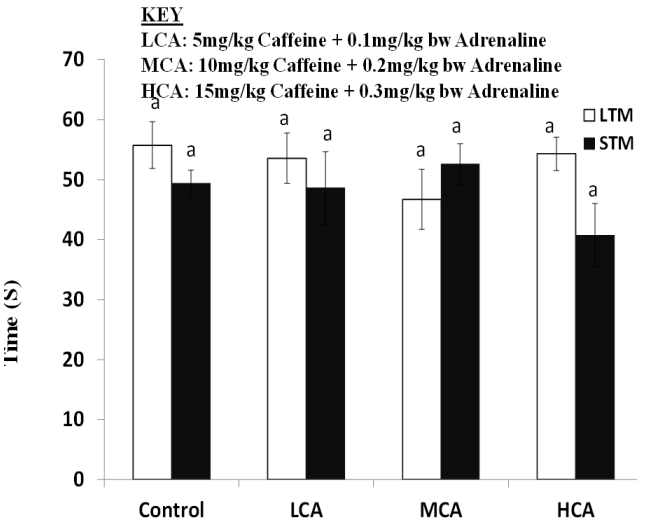


**Figure 6:**
Effect of combined administration of caffeine and adrenaline on short and long-term memory of male Wistar rats. Bars with different letters are significantly ($p<0.05$) different

**Anxiety Tests Using Elevated Plus Maze**

**Open and closed arm entry frequencies**

**Effect of caffeine administration on anxiety of male Wistar rats**: Animals administered caffeine 5mg/kg bw and 10mg/kg bw showed significant ($p<0.05$) increase in the number of entries to the open arm of the elevated plus maze when compared to control as shown in Figure 7.

**Effect of adrenaline administration on anxiety of male Wistar rats:** Adrenaline group administered 0.1mg/kg bw showed significant ($p<0.05$) increase (LADR, 3.88±0.611) in the frequencies of entries to the closed arm of the elevated plus maze when compared to control with no significant ($p<0.05$) difference in the open arm entry frequency. Group administered 0.2mg/kg bw adrenaline showed no significant ($p<0.05$) difference in frequencies of entries to the open and closed arm when compared to control. However administered 0.3mg/kg bw adrenaline showed a significant ($p<0.05$) decrease in the frequency of entries to the open and closed arm when compared to control, group as shown in Figure 8.

**Effect of combined administration of caffeine and adrenaline on anxiety of male rats:** Only the moderate dose of caffeine+adrenaline showed a significant ($p<0.05$) increase in the number of entries to the open arm and closed arm of the elevated plus maze when compared to control. Moderate and high dose caffeine + adrenaline showed no significant difference in number of entries to the open arm when compared to control as shown in Figure 9.

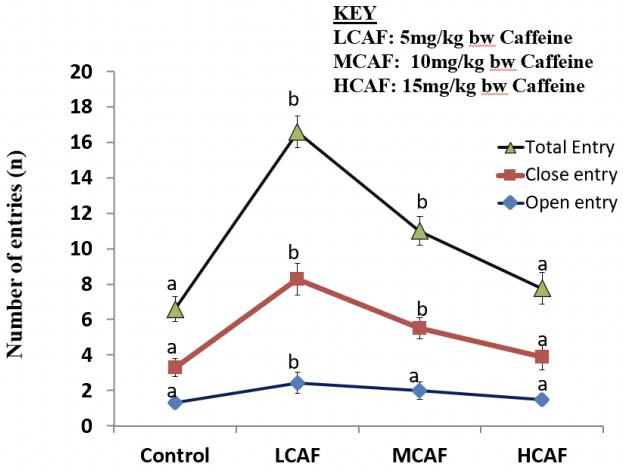


**Figure 7:**
Effect of caffeine administration on anxiety of male Wistar rats. Groups with different letters are significantly ($p<0.05$) different.

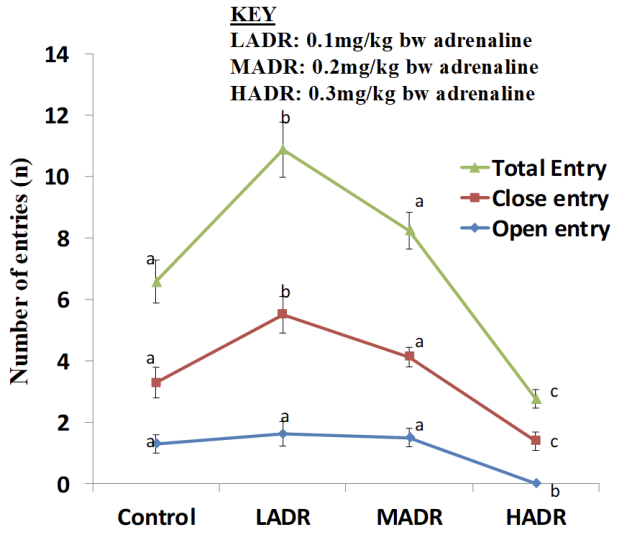


**Figure 8:**
Effect of adrenaline administration on anxiety in male Wistar rats. Groups with different letters are significantly ($p<0.05$) different.

**Opened and closed arm duration (seconds)**

**Effect of caffeine administration on anxiety of male Wistar rats:** There was no significant ($p<0.05$) difference in the closed arm duration in all animals administered caffeine when compared to control. Moderate dose of caffeine showed significant ($p<0.05$) increase in open duration when compared control as shown in Figure 10.

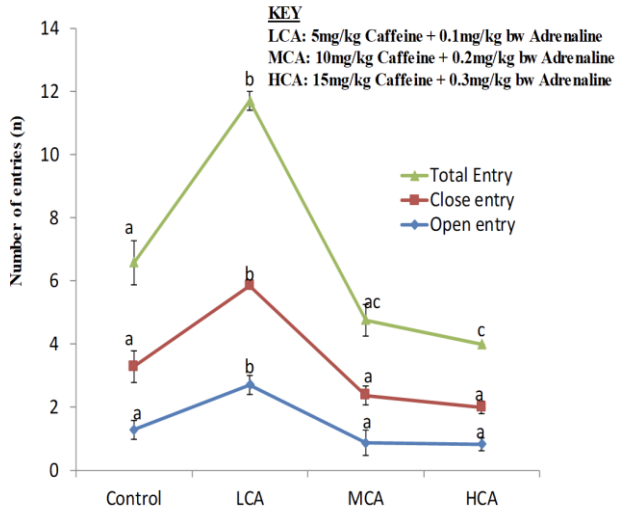


**Figure 9:**
Effect of combined administration of caffeine and adrenaline on anxiety in male Wistar rats. Groups with different letters are significantly ($p<0.05$) different.

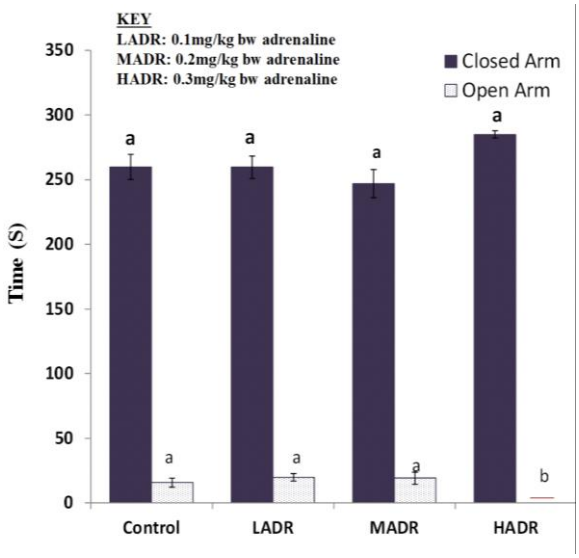


**Figure 11:**
Effect of adrenaline administration on anxiety of male Wistar rats. Bars with different letters are significantly ($p<0.05$) different.

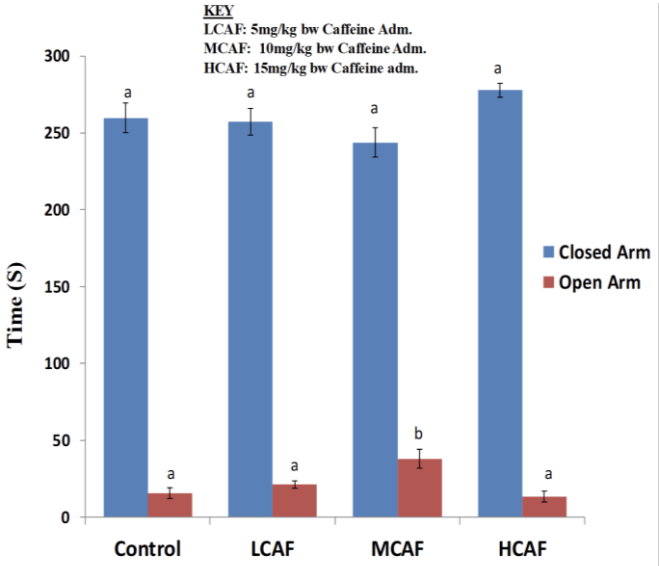


**Figure 10:**
Effect of caffeine administration on anxiety of male Wistar rats. Bars with different letters are significantly ($p<0.05$) different.

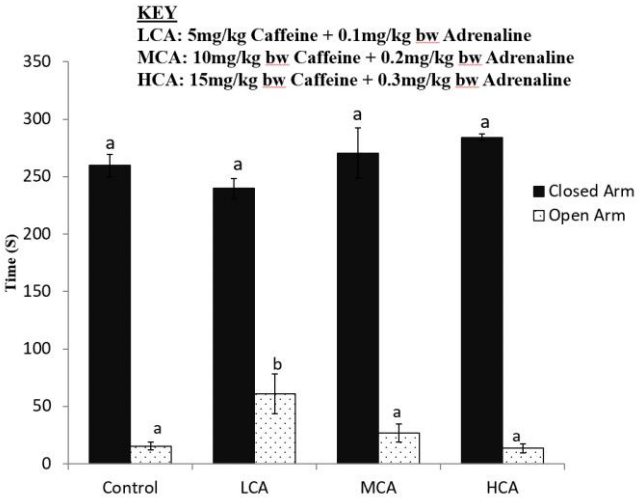


**Figure 12:**
Effect of combined administration of caffeine and adrenaline on anxiety of male Wistar rats. Bars with different letters are significantly ($p<0.05$) different.

**Effect of adrenaline administration on anxiety of male Wistar rats:** There was no significant ($p<0.05$) difference in the closed arm duration in animals administered adrenaline (0.1 and 0.2 mg/kg bw) when compared to control. Only group administered 0.3mg/kg bw adrenaline showed significant ($p<0.05$) reduction in open arm when compared to control as shown in Figure 11.

**Effect of combined administration of caffeine and adrenaline on anxiety of male Wistar rats:** There was no significant ($p<0.05$) difference in the closed arm duration in all animals co-administered caffeine and adrenaline when compared to control. Only low dose of caffeine and adrenaline showed significant ($p<0.05$) increase in open arm duration when compared to control as shown in Figure 12.

## Anxiety test using open field maze

**Effect of caffeine, adrenaline and their combination on rearing frequency in the open field of male Wistar rats**: There was no significant ($p<0.05$)difference in rearing frequency of animals administered 15mg/kg bw caffeine and 0.3mg/kg bw adrenaline when compared to control, all other animals showed significant ($p<0.05$) increase in rearing frequency when compared to control as indicated in Table 1.

**Effect of caffeine, adrenaline and their combination on grooming duration (S) in the open field of male Wistar rats:** There was significant ($p<0.05$) reduction in grooming time of animals administered 0.1 and 0.2mg/kg bw adrenaline when compared to the control. Other animals showed no significant ($p<0.05$) difference when compared to control (Table 1).

**Table 1:**
Effect of caffeine, adrenaline and their combination on rearing, grooming, center duration and movement time in the open field maze

| Animals | Rearing Frequency | Grooming Duration (s) | Center duration (s) | Edge duration (s) | Active movement time (s) |
|---|---|---|---|---|---|
| CONTROL | 7.29±1.36$^{a}$ | 30.71±2.12$^{ac}$ | 5.14±1.10$^{a}$ | 293.57±0.81$^{a}$ | 105.57±5.34$^{a}$ |
| LCAF | 14.86±1.55$^{c}$ | 24.57±2.43$^{ab}$ | 9.14±1.05$^{b}$ | 291.14±1.18$^{bc}$ | 118.29±3.08$^{b}$ |
| MCAF | 15.43±1.11$^{c}$ | 26.43±1.84$^{abc}$ | 10.42±0.48$^{b}$ | 289.85±0.67$^{c}$ | 155.00±2.79$^{e}$ |
| HCAF | 9.57±1.04$^{ab}$ | 24.71±1.$^{98ab}$ | 6.71±0.57$^{a}$ | 293.29±0.57$^{ab}$ | 143.14±2.69$^{cd}$ |
| LADR | 12.57±0.84$^{bc}$ | 18.00±1.73$^{d}$ | 10.14±0.51$^{b}$ | 289.85±0.51$^{c}$ | 151.86±2.37d$^{e}$ |
| MADR | 13.86±0.94$^{c}$ | 22.00±2.31$^{bd}$ | 10.14±0.46$^{b}$ | 289.86±0.46$^{c}$ | 157.85±4.21$^{e}$ |
| HADR | 9.86±0.51$^{ab}$ | 24.57±2.30$^{ab}$ | 6.57±0.65$^{a}$ | 293.43±0.65$^{a}$ | 113.57±2.11$^{ab}$ |
| LCA | 12.14±0.60$^{bc}$ | 30.86±2.05$^{ac}$ | 5.71±0.87$^{a}$ | 294.89±0.87$^{a}$ | 135.86±4.15$^{c}$ |
| MCA | 20.42±2.34$^{d}$ | 31.43±1.60$^{c}$ | 11.00±0.87$^{b}$ | 289.00±0.87$^{c}$ | 138.57±2.31$^{c}$ |
| HCA | 11.57±0.75$^{bc}$ | 26.14±2.20$^{abc}$ | 5.86±0.80$^{a}$ | 294.14±0.33$^{a}$ | 109.29±4.49$^{ab}$ |

*Animals with different letters are significantly different.LCAF=5mg/kg caffeine, MCAF=10mg/kg caffeine, HCAF=15mg/kg caffeine, LADR=0.1mg/kg adrenaline, MADR=0.2mg/kg adrenaline, HADR=0.3mg/kg adrenaline, LCA=5mg/kg caffeine + 0.1mg/kg adrenaline, MCA=10mg/kg caffeine + 0.2mg/kg adrenaline, HCA=15mg/kg caffeine + 0.3mg/kg adrenaline*

**Effect of caffeine, adrenaline and their combination on center area duration (S) in the open field of male Wistar rats:** There was no significant ($p<0.05$) difference in center time duration of animals administered 15mg/kg bw caffeine, 0.3mg/kg bw adrenaline when compared to control. Also no significant ($p<0.05$) difference in center time duration of animals administered 5mg/kg bw caffeine + 0.1mg/kg bw adrenaline and 15mg/kg bw caffeine + 0.3mg/kg bw adrenaline (Table 1).

**Effect of caffeine, adrenaline and their combination on edge duration (S) in the open field of male Wistar rats:** Animals administered15mg/kg bw caffeine, 0.3mg/kg bw adrenaline, 5mg/kg bw caffeine + 0.1mg/kg bw adrenaline and 15mg/kg bw caffeine+0.3mg/kg bw adrenaline showed no significant ($p<0.05$) different in the edge duration when compared to control while other animals showed significant ($p<0.05$) decrease in edge duration when compared to control as shown in Table 1.

**Effect of caffeine, adrenaline and their combination on active movement time (S) in the open field of male Wistar rats:** Animals administered 0.3mg/kg bw adrenaline and 15mg/kg bw caffeine + 0.3mg/kg bw adrenaline showed no significant ($p<0.05$) different in the active movement time duration when compared to control while other animals showed significant ($p<0.05$) increase in movement duration when compared to control as shown in Table 1.

## DISCUSSION

The aim of the present study was to evaluate the cognitive effects of caffeine, adrenaline and their combination. Caffeine has been widely studied, some reports states that in moderate doses, caffeine typically does not affect learning and memory. Other studies reported that low dose caffeine has a greater effect on activation of brain and improves cognitive functions (Zhang et al., 2020).

All doses of caffeine, and adrenaline used in this study enhanced both short and long term memory although adrenaline showed more profound memory enhancement. The CACA however, did not have any effect on memory of the animals. Spatial memory tested using Y-maze was not altered following caffeine and adrenaline administration, except for the high dose of adrenaline that seems to impair spatial memory.

Studies suggest that caffeine improves memory consolidation of long-term memory in humans and that it can also improve memory retrieval in a task specific for the spatial/relational memory system that models the human hippocampal memory system (Angelucci et al., 2002; Borota et al., 2014).

While many studies suggest that caffeine produces improvement in memory either in animal (Munawar, 2022; Villanueva-Garcia et al., 2020) or in human (Borota et al., 2014; Sherman et al., 2016; Hartney, 2020) models of learning and memory, other studies report that caffeine does not affect memory (Nehlig, 2010) or even its craving impairs memory (Palmer et al., 2017). Some studies reported that long-term consumption of caffeine could inhibit hippocampus-dependent learning and memory partially through inhibition of hippocampal neurogenesis (Han et al., 2007).

According to Gold, low-to-moderate doses of adrenaline facilitate memory, while high doses impair memory (Gold 2014; Roozendaal and Hermans 2017). Considerable evidence suggests that adrenergic hormones modulate the consolidation of long-term memory for experiences that induce their release. For example, post-training injection of adrenergic drugs or hormones has been reported to enhance memory consolidation in many species (Segal et al., 2012; Villain et al., 2016; Schramm et al., 2016).

The brain's response to stress, or any kind of emotional arousal, is in part mediated by the release of the hormone adrenaline. This type of stress memory, or adrenaline-mediated memory formation, is important because it could explain the pathological memory formation that is commonly seen in phenomena such as Post Traumatic Stress Disorder (Samuelson, 2011).

The results of this study showed that low to moderate dose of caffeine reduce anxiety and elevated mood with an increase in general activity. Low dose of adrenaline produced elevated mood and increase motor activities. Anxiety is increased with high dose of adrenaline, which also led to moody state in the animals with no to minimal general activities.

CACA in this study eradicated the observed anxiety following high dose of adrenaline. Low dose of CACA reduced anxiety to a greater extent, it also showed an elevated mood with increased general activity, although activity is reduced following high dose of caffeine and adrenaline. Therefore, caffeine and adrenaline has dose-

dependent anxiolytic effect and could be used to lighten mood. It was reported that caffeine increases anxiety in some individuals and patients with panic disorder (Richards and Smith, 2015; Klevebrant and Frick, 2022). Caffeine has also been shown to have anxiogenic- like behaviour in animals (Rogers et al., 2010). On the other hand, caffeine has also been reported to have anxiolytic effect in rats (Pedraza et al., 2018; Hughes et al., 2014). Increase alertness by caffeine is associated with a high core body temperature (McHill et al., 2014). Also adrenaline has been reported to induce somatic symptoms as well as mental anxiety (Argyropoulos and Nutt, 2003).

The part played by adrenaline in the major emotions of anger and fear has been generally recognized since the classical work of Cannon, who obtained evidence of a liberation of adrenaline from the adrenals and showed that the main somatic accompaniments of anger and fear could be attributed to the action of adrenaline (Richter, 1940).
Anxiety has also been reported to increase the body's metabolism, and being anxious increases body temperature (Folk and Folk, 2016). This study reported increased memory in rats administered caffeine and adrenaline.

In conclusion, the study revealed that CACA led to elevation of mood, increased activity and reduction of anxiety in Wistar rats. In addition, it was observed that only high dose of adrenaline increased anxiety. It was also observed that caffeine and adrenaline enhanced short- and long-term memory and only high dose of adrenaline distorted spatial memory. This finding most likely revealed the underlying mechanism to enhance memory, elevate mood and increase anxiety and increased activity in the Wistar rats.

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