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EFFECT OF TAURINE AND CAFFEINE ON SPATIAL MEMORY IN ADULT MALE WISTAR RATS

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ABSTRACT

There is an increase in the production and consumption of caffeine and taurine beverages tagged as energy drinks. This study was therefore undertaken to investigate the effect of co-administration of caffeine and taurine on memory in Wistar rats. Fifty-four adult Wistar rats were divided into nine groups of six animals and treatments were as follows: Group 1 (10 ml/kg normal saline), Group 2 (100 mg/kg taurine), Group 3 (200 mg/kg taurine), Group 4 (taurine plus furosemide; 20 mg/kg), Group 5 (taurine plus nifedipine; 10 mg/kg), Group 6 (taurine plus caffeine), Group 7 (7.5 mg/kg caffeine), Group 8 (15 mg/kg caffeine) and Group 9 (taurine plus nifedipine plus furosemide plus caffeine). Treatment was once daily for 21 days, after which long term spatial memory of pretreatment training in Morris Water Maze was tested. Histological study was done using haematoxylin and eosin stains on hippocampus tissues harvested from the brain of one animal in each group. The results showed that there was a significant ($p<0.05$) decrease in time taken to find and mount the escape platform compared with the control. This was with the exception of the group co-treated with caffeine and taurine. Histological studies showed normal cell morphology, arrangement and distribution in the hippocampus. There was increased in the number of cells in the hippocampus of the animals given taurine (200 mg/kg) plus caffeine (15 mg/kg), and caffeine (15 mg/kg). In conclusion, at the doses used, co-administration of caffeine and taurine has no significant effects on spatial memory, however the separate use of caffeine or taurine proved to have capacity to enhance spatial memory.

Keywords: *Caffeine, Taurine, Memory, Hippocampus, Rats*

INTRODUCTION

It is not uncommon to find various carbonated beverages especially the energy drinks and its cohort to contain caffeine or taurine. The alarming rate of consumption of these caffeinated and taurine added drinks had instigated many scientists to research into possible health benefits and adverse health consequences of both caffeine and taurine.

Caffeine is a xanthine alkaloid that is believed to be one of the most commonly used psychoactive substances in the world (Richard 2005; Yang et al. 2010). Naturally, caffeine is found in beans, leaves and fruit of over 60 plants where it acts as a pesticide that paralyzes and kills certain insects feeding upon such plants (Nathanson 1984). In addition to these sources, various beverages, food and drinks have now been caffeinated for adult consumption. Furthermore, caffeine is believed to be a major promoter of wakefulness, alertness and stimulatory effects that are associated with most caffeinated energy drinks and food (Lieberman et al. 2002; Frary

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Table 1: Effect of Taurine and Caffeine on Recalling Latency in Wistar Rats Using Morris

Group (n = 6)	Recalling Latency (s)
Normal saline 10ml/kg	15.69 ± 0.14
Taurine 100mg/kg	10.71 ± 0.09*
Taurine 200mg/kg	10.49 ± 0.13*
Caffeine 7.5mg/kg	10.63 ± 0.06*
Caffeine 15mg/kg	13.53 ± 0.12*
Taurine 200mg/kg + Caffeine 15mg/kg	15.68 ± 0.14

Value is mean ± SEM; *p < 0.05 compared with control

et al. 2005; Haskell et al. 2005). When taken, caffeine is completely absorbed in the stomach and small intestine within few minutes of ingestion and metabolized in the liver by the cytochrome P_{450} oxidase enzyme system into paraxanthine, theobromine and theophylline. It is distributed throughout all tissues of the body and is eliminated by first-order kinetics (Newton et al. 1981). In healthy adults, caffeine's half-life is about 3-4 hours. This increase to 5-10 hours in women taking oral contraceptives and approximately 9-11 hours half-life in pregnant women (Ortweiler et al. 1985; Meyer et al. 1991). The half-life in infants and young children may be longer than in adults. In a newborn baby for instance, the half-life may be as long as 30 hours (Bolton et al. 1981).

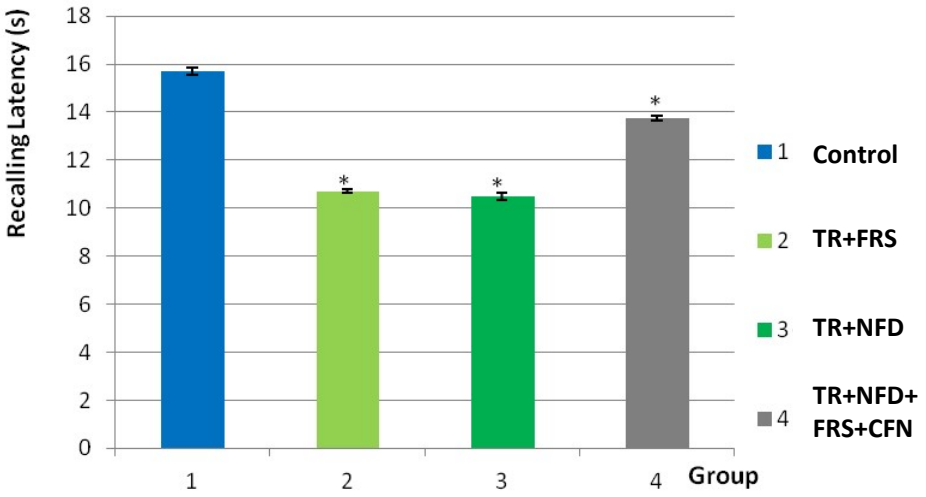

Fig.1. Effect of Taurine on Recalling Latency in Calcium Blocker Treated Wistar Rats using Morris Water Maze. Each value is the mean ± S.E.M. (n = 6); *p < 0.05 compared with control. TR+FRS, Taurine plus Furosemide; TR+NFD, Taurine plus Nefidipine plus Furosemide; TR+NFD+FRS+CFN, Taurine plus Nefidipine plus Furosemide plus Caffeine

Caffeine has multiple mechanism of actions that involved both receptors and channels at the cell membrane, as well as intracellular action on calcium and cyclic adenosine monophosphate pathways. However, its major mode of action is an antagonist of adenosine (A1 and A2A) receptors in the brain (Dunwiddie and Masino 2001; Fisone et al. 2004). As an antagonist of adenosine receptors, caffeine molecule binds to adenosine receptors on the surface of cells without activating them. The decline in adenosine activity results in increased activity of the neurotransmitter dopamine, as well as epinephrine (possibly via a different mechanism). These resulting consequences largely account for the stimulatory effects of caffeine (Graham et al. 1994). Therefore, caffeine has both neural and vascular effects depending on the ratio of A1 and A2A receptors it binds to in different brain regions (Chen and Parrish 2009; Laurienti et al. 2003).

Caffeine had been documented to have various effects in the body. Its remarkable effects on attention, mood and alertness had been widely reported (Ruijter et al. 2000a; Ruijter et al. 2000b; Rogers et al. 2010; Rogers and Smith 2011). Clinically, it is used as an analgesic adjuvant to treat premature neonatal apnea (Migliardi et al. 1994; Schmidt et al. 2007). In non habitual subjects, caffeine can cause diuresis and bronchodilatation, as well as a rise in systolic blood pressure (Benowitz 1990; Mosqueda-Garcia et al. 1993). Patients with anxiety and panic disorder can experience aggravated anxiety which can precipitate panic attacks when they consume caffeine (Charney et al. 1985; Lee et al. 1985; Bruce et al. 1992; Nardi et al. 2009). Growing evidence showed that genetic diversity can influence a response to caffeine and its consumption pattern in many ways (Yang et al. 2010).

Unlike caffeine, taurine is an endogenous sulphur containing amino acid and the next most abundant amino acid after glutamate (De Belleroche and Bradford 1973; Martínez-Páramo et al. 2013). Structurally, it is similar to the neurotransmitters glycine and gamma-aminobutyric acid (GABA) (Simon and Wen 2010). Despite this similarity, taurine has been considered as a low affinity ligand which can bind to glycine or GABA receptors (Xu et al. 2004; Jia et al. 2008). Following its discovery in 1827, studies showed that taurine has

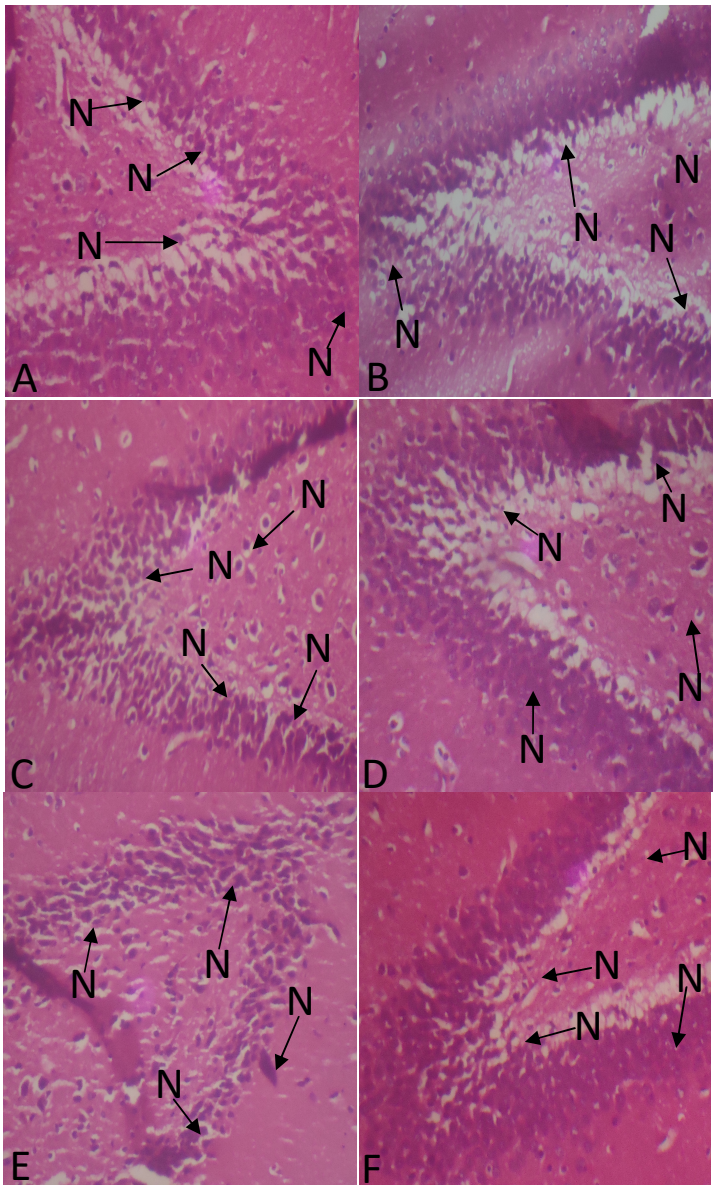

Fig. 2: Effect of Taurine and Caffeine on Hippocampus Cells in Rats (A) - Control group, (B) Taurine (100mg/kg) group, (C) - Taurine (200mg/kg) group (D) - Taurine (200mg/kg) plus caffeine (15mg/kg) group, (E) - Caffeine (7.5mg/kg) group, (F) – Caffeine (15mg/kg) group. N - Neural cell. Hippocampus (x160) using H&E stain

various physiological functions and play an essential role in neural development (Schaffer et al. 2010). Also, studies showed that taurine is helpful in forestalling the age-related decline in cognitive functions (El Idrissi et al. 2013), and also in the treatment of alcoholism, fatigue and myotonia (Trip et al. 2006; Soyka and Roesner 2006). Taurine deficiency was linked with depression, anxiety, hyperactivity and epilepsy (Kong et al. 2006). Maternal intake of taurine during late pregnancy period causes insulin resistance and obesity in the offspring of rats (Hultman et al. 2007).

At low dose, caffeine has been supported by enormous evidences to improve learning and memory in both disease (Alzheimer) (Dall'Igna et al. 2007) and normal (Angelucci et al. 2002) states. Also, studies on taurine supplementation have shown that it improves learning and memory in normal animals (Lu et al. 2012) or metal-induced intoxicated animals (Lu et al. 2015). There is paucity of information on effects of co-administration of caffeine and taurine on spatial memory. Thus, the present study was designed to investigate this.

MATERIALS AND METHODS

Animal Preparation

Fifty four adult Wistar rats with an average weight of 120-140 g were used for this study. The rats were obtained from the animal holding of the Department of the Biological Sciences, University of Ilorin, Nigeria. Nine groups of six animals were formed and housed separately in an equal size cage of 47 x 26 x 20 cm throughout the duration of the study. These cages have good ventilation and were in turn housed in the animal house of the Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, Nigeria. All animals used had free access to rat pellet (feeds) and clean water. Ethical guidelines specified for animal's experiment were closely followed as laid down by the Ethical Committee of College of Health Sciences, University of Ilorin, Nigeria. These guidelines are similar to what is available internationally.

Drug Preparation

The taurine used was a product of Titan Biotech LTD, India (BHIWADI -301 019, Raj.) while caffeine was obtained from Sigma-Aldrich Co. USA (NO. 63103). Nifedipine and furosemide were obtained as products of Jiangxi Xier Kangtai Pharmaceuticals Co Ltd, China (Batch No: 120820) and Tianjin Pharmaceutical Group Xinzheng Co Ltd, China (Batch No: 1211081), respectively. Stock solution for each of the drug was prepared by dissolving it in saline separately. In accordance with the animal grouping, appropriate doses of the drugs were injected intraperitoneally using hypodermic syringe produced by El-Salmat Pharmaceutical Co LTD, Nigeria (Batch No. 161). However, furosemide and nifedipine (calcium blockers) were administered orally 30 minutes before injecting taurine or/and caffeine. Finally, the control group also received appropriate dose of normal saline (i.p).

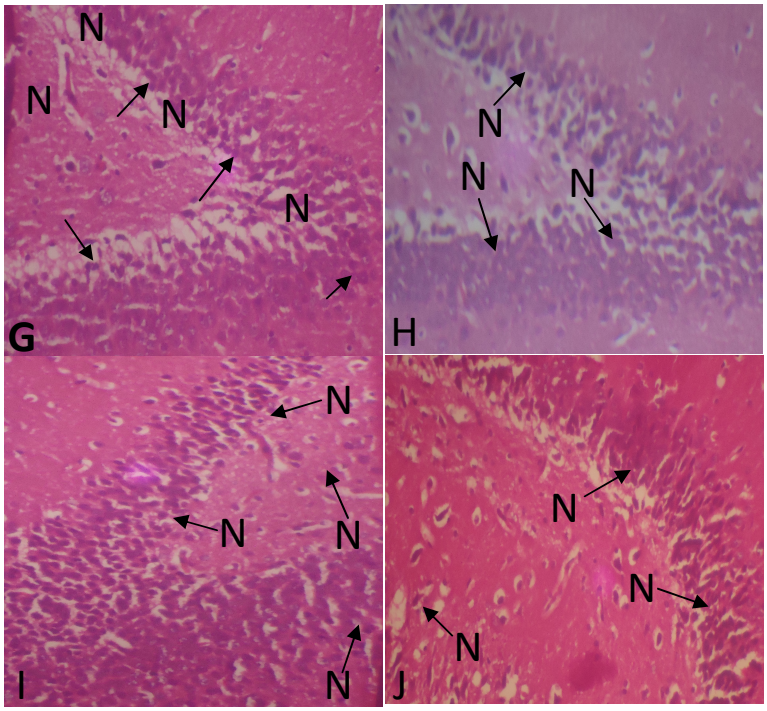

Fig. 3: Effect of Taurine and Caffeine on Hippocampus Cells in L-type Calcium Channel-Blocked Rats. (G) - Control group, (H) - taurine plus furosemide (20mg/kg) group, (I) - taurine plus nifedipine (10mg/kg) group (J) - Taurine plus nifedipine plus furosemide plus caffeine group. N - Neural cell. Hippocampus (x160) using H&E stain

Group 1, (Control) was administered 10 ml/kg of normal saline, Group 2 was administered 100 mg/kg of taurine, Group 3 was given 200 mg/kg of taurine, Group 4 received taurine plus furosemide (20 mg/kg), Group 5 took taurine plus nifedipine (10 mg/kg), Group 6 took taurine plus caffeine, Group 7 was administered with 7.5 mg/kg caffeine, while Group 8 was given 15 mg/kg of caffeine and Group 9 given taurine plus nifedipine plus furosemide plus caffeine. The treatments were repeated once daily for twenty-one (21) days.

Memory Test - Morris Water Maze

This maze was modified from the paradigm described by Morris (Morris 1984). Morris Water Maze is widely used in behavioural neuroscience for the study of psychological processes (Pierre and Debouzie 2000) and spatial learning and memory (Oyewole and Owoyele 2014). It has been claimed that this maze is advantageous over the conventional mazes because cues like scent traces and fixed escape formula is usually eliminated (Pierre and Debouzie 2000). The equipment used is as described by Oyewole and Owoyele (2014). Briefly, the water maze used was 1.2 m in diameter and 0.6 m in depth. Water was filled to 0.3 m depth and was whitened with powder milk to hide the 10 cm diameter escape-platform from the animals. The escape-platform was also painted white to blend it with the water. The rats were trained to navigate to escape-platform within the maze for three days with two trials per day. The training was to create spatial memory on specific location of escape-platform. Learning and spatial memory in each animal was confirmed on the third day by accessing the number of time the animal searched for the escape-platform around the spot that it was initially placed. At the end of 21 days of repeated administration of test drugs and saline, spatial memory formed during the pretreatment training was tested and documented as the time taken for each animal to locate and mount on the escape-platform using a stop watch.

Histological Examination

After the memory test in Morris water maze, representative sample of rats in each group were sacrificed by cervical dislocation for histological study using haematoxylin and eosin (H&E) stains.

Statistical Analysis

Collated data were analysed using SPSS 17 (SPSS Inc., Chicago, IL, USA). One-way analysis of variance was used to carry out the analysis followed by least significant difference (LSD) post hoc test. Statistical comparisons of control and treated groups were done at significance level of $p < 0.05$ and values were expressed as mean ± standard error of mean.

RESULTS

Effect of Taurine and Caffeine on Recalling Latency in the Morris Water Maze

There was significant ($p<0.05$) decrease in time taken to find and mount the escape platform in all the treated groups compared with the control except in the group co-treated with taurine (200 mg/kg) plus caffeine (15 mg/kg), (Table 1).

Effect of Combined Taurine and Caffeine on Recalling Latency in L-type Calcium Channel-Blocked Rats

In the rats placed on calcium blockers, the results showed a significant ($p<0.05$) increase in spatial memory in all treated groups compared to the control group (Figure 1). This is indicated by the significant decrease in the time taken for the animals in these groups to find and mount the escape platform compared to the animals in the control group.

Effect of Taurine and Caffeine on Hippocampus Cells in Rats

Hippocampal cells of the animals in the control group showed normal cell staining, morphology, arrangement and distribution (Figure 2A). However, hippocampal cells of the animals in the caffeine (15 mg/kg) group stained hyperchromic with the H&E. Although cell morphology, arrangement and distribution were normal but appeared to have high density in the hippocampus of these animals (Figure 2F). In the group treated with taurine, 100 mg/kg and 200 mg/kg plus caffeine, 15 mg/kg, hippocampal cells stained normally (normochromic) with H&E and cells showed normal morphology, arrangement and distribution, although cells in these groups were relatively dense compare to the hippocampal cells in the control group (Figure 2B & 2D). In the taurine (200 mg/kg) treated group, hippocampal cells stained normally with normal cell morphology, arrangement and distribution (Figure 2C), while that treated with caffeine (7.5 mg/kg) also had normal cell morphology, arrangement and distribution but stained hypochromic with H&E and was characterised with few cells compared to the control group (Figure 2E).

Effect of Taurine and Caffeine on Hippocampus cells in L-type Calcium Channel-Blocked Rats

The results of histological study in the group administered nifedipine and/or furosemide (Figure 3) showed that the group treated with taurine plus nifedipine plus furosemide plus caffeine (Figure 3J) display a close similarity to what was observed in the control group (Figure 3G) that stained normally with H&E and hippocampal cells of the animals in this group showed normal cells morphology, arrangement and distribution. Animals in the taurine plus nifedipine (10 mg/kg) group appeared to have more hippocampal cells that stained normally (normochromic) with H&E with normal morphology, arrangement and distribution compare to the hippocampal cells of control group (Figure 3I). In the group treated with taurine plus furosemide (20 mg/kg), hippocampal cells stained hypochromic with H&E, the cells however showed normal morphology, arrangement and distribution (Figure 3H).

DISCUSSION

In the last few decades, consumption of caffeine and taurine from various drinks, beverages and food has increased drastically. This persistent surge in consumption of both caffeine and taurine stimulated our interest in the search for the effect of these substances on long term spatial memory.

In this study, it was observed that when caffeine and taurine were used separately in normal rats, the pretreatment spatial memory formed from the training navigation and mounting of escape-platform was enhanced after 21 days of repeated treatment. It was observed that the navigation time to the escape-platform was shortest in the taurine (200 mg/kg) treated group than any other group. With the exception of the group that concurrently received taurine and caffeine, taurine was able to maintain, shortened the retrieval time and improve long term spatial memory. This observation contrasts Sase et al. (2013) report that performance of taurine treated rats did not improve in the Morris water maze. Also, it was documented that acute administration of taurine to humans and mice, and subacute oral supplementation of taurine to rats has no effect on learning ability and memory (Sakata et al. 2005; Bichler et al. 2006; Sakata et al. 2006; Ito et al. 2009). It was reported by Ito et al. (2012) that while taurine administered peripherally has no influence on spatial memory, intracerebroventricularly taurine-administered in rats caused suppression and delayed the ability of learning and memory. At the doses used, this study was able to establish that orally administered taurine can maintain and enhance long term spatial memory.

On the other hand, except when co-treated with taurine, all doses of caffeine used in the caffeine treated group animals were also able to shorten the time taken to navigate and mount the escape-platform in the Morris water maze. This is not surprising since this fact had been established in literature (Angelucci et al. 2002). Caffeine is an antagonist of adenosine receptor A1 and A2A. Adenosine A1 receptors are distributed throughout the brain but has the highest expression levels in hippocampus, cerebral and cerebella cortex (Haller et al. 2014). Hippocampus is documented as the part of the brain where spatial memory is formed and stored (Phelps 2004). Thus, blocking of adenosine receptors in the hippocampus will increase its neural activities and thereby strengthen the spatial memory formed. The positive role of caffeine on cognition (Duarte et al. 2012; Vila-Luna et al. 2012), spatial memory (Angelucci et al. 2002) and on improving impaired memory (Leite et al. 2014) was established in various literatures. Our data appeared to be supported by the histological study we carried out. Especially in the group administered 15 mg/kg of caffeine, hippocampal cells stained hyperchromic with H&E stain suggesting a likely increased in secretion and activities within the hippocampus cells.

Pharmacological blockade of calcium channels followed by taurine treatment appeared to enhance spatial memory. The same trend was observed in the group that was concurrently administered calcium blockers, furosemide and nifedipine, followed by caffeine and taurine. This observation contribute to the understanding that taurine moderate intracellular Ca^{2+} hence the balance of neurotransmitters. This is because previous reports indicated that taurine has homeostatic ability on intracellular Ca^{2+} and Na^{+} concentration, as well as balancing of

neurotransmitters (Guizouarn et al. 2000; Parcell 2002; Gupta et al. 2005). Neural excitation is necessary for the formation, maintenance and retrieval of spatial memory and intracellular Ca^{2+} is needed for the release of neurotransmitter necessary for this neural excitation. Thus, the significant decreased difference observed in the retrieval time of the animals in the groups administered calcium blockers compared with that of control group showed that Ca^{2+} is needed for neural excitation and was probably transported into the hippocampal cells through other means different from L-type calcium channel. This is because the furosemide and nifedipine calcium blocker used were documented to selectively block L-type calcium channel (van Mil et al. 1997; Spafford et al. 2006). Histological assessment of hippocampus reveals no adverse structural alteration in the hippocampus as the morphology, arrangement and distribution of the cells appeared normal.

In conclusion, except when co-administered which showed no difference, the separate use of caffeine or taurine in normal and calcium channel blocker rats is beneficial to spatial memory.

Conflict of Interest

None declared.

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