THE EFFECT OF LAURIC ACID ON HIPPOCAMPAL ANTIOXIDANTS LEVEL IN OFFSPRING OF RATS EXPOSED TO GESTATIONAL CHRONIC SLEEP DEPRIVATION

Momoh, I. J.,[1,2*] Alhassan, A.,[2] Dawud, F. A.,[2] Abubakar, S. A.,[3] Abba, S.[4] Ogohi, D. A.[5] Haruna, S. O.[1] Jonah, A. C.[1]

[1] Department of Human Physiology, Faculty of Basic Medical Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria

[2] Department of Human Physiology, Faculty of Basic Medical Sciences, Ahmadu Bello University, Zaria, Kaduna State, Nigeria

[3] Department of Surgery, Ahmadu Bello University Teaching Hospital, Shika, Kaduna State, Nigeria

[4] Department of Human Anatomy, Faculty of Basic Medical Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria

[5] Department of Biochemistry, Faculty of Natural Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria

***Corresponding Author:** Momoh Ibrahim Joseph;
E-mail: momoh.ij@ksu.edu.ng, +2347038187256

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ABSTRACT

Background: Stress is part of the daily life and during pregnancy. Sleep deprivation in women especially during pregnancy is a serious concern. The developing brain can be damaged from increased levels of reactive oxygen species.

Aim: This study aims to examine the effect of Lauric acid against the hippocampal oxidative biomarkers in male rat offspring caused by maternal chronic sleep restriction.

Methodology Pregnant female Wistar rats were deprived of sleep for 20hrs daily using the modified multiple water platform from day 9-19. Group 1 received distilled, group 2 were stress controls, and groups 3,4 and 5 were administered lauric acid at 125mg/kg, 250mg/kg and 500mg/kg respectively. Group 6 were treated with Vitamin C 300mg/kg.

Results: The level of MDA in the hippocampus was significantly ($p<0.05$) elevated while SOD, CAT and GSH levels were significantly lowered in the stress untreated group. Treatment using lauric acid and Vitamin C significant ($p<0.05$) reversed the oxidative changes due to prenatal stress.

Conclusion: This study suggests that lauric acid may possess antioxidant action against oxidative stress alterations in male rat offspring whose mothers were exposed to maternal chronic sleep deprivation-induced-prenatal stress.

Key words: Sleep deprivation, Lauric acid, oxidative stress, antioxidants

INTRODUCTION

Stress is part of the daily life and during pregnancy. The negative effects on offspring developmental neurobehavior is a topic for research (Bernhardt *et al.,* 2018). Disruption to lipids, proteins and DNA, which has been associated with many pathologies has been reported to be due to oxidative stress (Schieber and Chandel, 2014). The damage which can be in the developing brain may be linked to overproduction of oxidants. A balance between the oxidants and the antioxidants seems to play a very critical role (Weinstock, 2005) during prenatal development.

Sleep restriction/deprivation in women as a result of their modern lifestyle, especially during pregnancy, has been reported to have deleterious consequences on the developing fetal health (Radhakrishnan, *et al*., 2015). In a study by Suchecki & Palermo, (1991), sleep deprivation as a biological stressor (Gabriel *et al*., 2015) during pregnancy caused reduction in the weight of the adrenal gland and also increased susceptibility to harmful agents, kidney tissues alterations, hypertension (Thomal *et al.*, 2010), increase in the inflammatory parameters, homocysteine levels and fetal outcome at birth, suppression of proliferation of neurons (Kawamura *et al*., 2006), neurobehavioral and oxidative metabolic changes in the offspring (Calegare *et al.*, 2010).

Related studies have shown that stress especially during pregnancy, has long-lasting effects on the in the offspring hypothalamo-pituitary adrenal axis (O'Keane *et al*., 2012). Chronic gestational stress induces a high cortisol level of maternal blood, which can enter the developing fetal brain and cause oxidative damage (Bernhardt *et al.*, 2018). Fatima *et al*. (2019) using the chronic unpredictable mild stress for 21 days reported a significant decrease in sucrose preference indicating a depression-like behavior, increase in lipid peroxidation, reduced GSH in the prefrontal cortex of neonates of prenatally stressed mothers.

Many studies have reported the mechanisms underlying neurobehavioral deficits associated with prenatal stress in offspring, limited researches to minimize or ameliorate these adversaries exist (Bernhardt *et al*., 2018). Antioxidant supplementation has been demonstrated to be an effective strategy for preventing stress-induced alterations (Liu and Mori, 1999).

Dodecanoic acid or lauric acid (LA), is a medium chain saturated fatty acid, found in human breast milk, coconut oil, coconut milk and palm kernel oil (Aly *et al.*, 2013; Uday *et al.*, 2014). Studies have demonstrated that LA has anti-inflammatory (Lieberman *et al.*, 2006) and antioxidant action (Alves *et al.*, 2017). The antihypertensive properties of coconut oil (Uday, 2014; Alves *et al.*, 2017) as well as the stimulation of insulin secretion (Garinkel *et al.*, 1992) has been associated with LA.

This study assessed the protective activity of lauric acid on the level of some biomarkers of oxidative stress in the hippocampus of male offspring whose mothers were exposed to sleep deprivation induced-stress during pregnancy.

MATERIALS AND METHODS

Materials

Lauric acid (AK Scientific, 98%, Union City, CA, USA. CAS#: [143-07-7] Lot#: AG37411), Tween 80 (Sigma-Aldrich), Vit C (Central Drug House, New Delhi, India, CAS No.99.99-0; 029395).

Animals

Twenty (24) female Wistar rats (180-210 g) and fifty (50) adult male Wistar rats weighing 40-60 g were used in the study. The adult rats were bought, mated, and housed in normal cages in the animal house of the department of Human Physiology, Ahmadu Bello University Zaria. Commercial foods (Vital feeds) and tap water were provided, and their cages were routinely cleaned. Vaginal smear tests were used every day to check for pregnancy. Gestational day zero (GD 0) was the day the smear revealed sperm or the seminal (copulation) plug was first noticed (Kvarik *et al*., 2016).

Ethical Approval

Ethical approval was sought and obtained from the Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC) (ABUCAUC/2021/107)

One day following parturition, litters were reduced to 6 pups per mother (picked randomly) to avoid differences during lactation. Litters were housed together with their mothers until weaning at postnatal day 21 after which they were housed with same sex littermates in groups.

A total of 6 male pups per group (at least one per cage in from each group) were selected randomly and used for the study.

Animal groups

Table 1: Groups, treatment, number of dams and offspring

Groups	Treatment	Number of Dams	Number of Pups (offspring)
Normal Control (distilled water)	1ml/kg	4	6
Sleep Deprivation (SD)	Untreated	4	6
SD + LA	125mg/kg	4	6
SD+ LA	250mg/kg	4	6
SD+ LA	500mg/kg	4	6
SD+ vit C	300mg/kg	4	6

SD -sleep deprivation, LA -lauric acid

The rats in the treatment group were given oral lauric acid suspension (dissolved) in distilled water using Tween 80 each morning prior to being denied sleep (Patil *et al*., 2016). From postnatal day 28 to 35, young male Wistar rats from the different groups were sacrificed for antioxidant studies.

Induction of stress (Sleep deprivation)

From gestational day (GD) 9 to 19, the pregnant Wistar rats were subjected to a 20-hour sleep deprivation (Clancy *et al*., 2007) using the Modified Multiple Platform (MMP) approach adapted by Oh *et al*. (2012) and reported by Medeiros *et al*. (1998). They were rested for 4-hour period each day between 7:00am-11:00am. The rats were kept in a 123 x 44 x 44 cm acrylic water tank with 14 circular platforms, each measuring 6.5 cm in diameter, with water up to 1 cm from their upper surface, using the modified multiple platform approach. As a result, the rats could leap from one platform to another to move around inside the tank. Muscle atonia will set in when they enter the paradoxical phase of sleep, causing them to fall into the water, wake up and climb back to the top of the platform. Food and water were available *ad libitum*. The water in the tank was changed daily throughout the SD period.

Estimation of oxidative stress in the hippocampus

Male pups were sacrificed by decapitation after anesthesia. The rat brain tissue was quickly removed rinsed thoroughly using ice cold phosphate buffer solution (PBS) (0.01 M, pH= 7.4), the hippocampus was gently dissected, separated and homogenized in the PBS. The tissue homogenate was then centrifuged for 5 minutes at 5000×g and then the supernatant was separated and analyzed for oxidative stress biomarkers.

Determination of Lipid peroxidation

The method described by Uchiyama and Mihara, (1978) with little modification was adopted. About 0.25 ml of hippocampal homogenate was added to 25 µl of 10 mM butylated hydroxytoluene (BHT). About 3.0 ml phosphoric acid (1%) and 1 ml of 0.67% thiobarbituric acid (TBA) were added and mixture was incubated at 95 °C for 1 h. The absorbance was determined at 535 nm. The level of lipid peroxidation was shown as micro-moles of thiobarbituric acid reactive substance (TBARS) formed/h/g of hippocampal tissue using a molar extinction coefficient of $1.56 \times 105\ M{-}1\ cm{-}1$.

Determination of Reduced glutathione (GSH)

The hippocampal GSH levels was determined calorimetrically using Ellman's reagent (DTNB) as total 'acid soluble sulfydryl' concentrations at 480 nm according to the protocol modifed by Jollow *et al*., (1974). Using sulphosalicylic acid (4.0%) in the ratio of 1:1, the homogenate was precipitated. The samples were stored at 4 °C for 1 hour and then centrifuged at 4000 rpm for 15 min at 4 °C. The total assay mixture contained 0.4 ml supernatant, 2.2 ml of 0.1 M sodium phosphate buffer (pH 7.4) and 0.4 ml of 10 mM DTNB making a total volume of 3 ml using the spectrophotometer, the optical density (OD) of reaction product was read

immediately at 412 nm and results were calculated using the molar extinction coefficient (ε) 1.36 × 104 M−1 cm−1, the results were expressed as nmol GSH/g tissue. 2.6 ml phosphate buffer and 400 µl DTNB was taken as blank.

Determination of Superoxide dismutase (SOD) activity.

The method of Misra and Fridovich (1972) was adopted for the determination of SOD activity. The assay mix was made up of 0.2 ml of supernatant (prepared in glycine buffer), 0.8 ml glycine buffer (50 mM, pH 10.4), and 20 µl of 2% epinephrine in a final volume of 1.02 ml. SOD activity can be measured kinetically at 480 nm. The activity was assayed by the oxidized product of epinephrine (adreno-chrome). The activity of SOD was expressed as nmol of (−) epinephrine that is protected from oxidation by the sample compared with the corresponding reading in the blank. This was done by using its ε 4.02 × 103 M−1 cm−1 and results were expressed as nmoles of epinephrine protected from oxidation/min/mg protein.

Estimation of Catalase (CAT) activity.

Catalase activity was determined using the method of Claiborne, (1985) with little modifcations. 1.0 ml of 0.05 M hydrogen peroxide, 50 µl hippocampal homogenate and 1.95ml of 0.1 M phosphate buffer (pH 7.4) was added in a 3 ml cuvette. The total volume for the estimation was 3ml. Using the spectrophotometer, OD was taken via kinetic method at 240 nm. The activity was calculated by using its ε 39.6 M−1 cm−1 and expressed as µmoles of H_2O_2 consumed/min/mg protein.

RESULTS

Effect of prenatal sleep deprivation-induced-stress on hippocampal MDA level of male offspring

The result as seen in figure 1, indicated a statistically significant rise in the hippocampal MDA level of SD group untreated when compared with the distill water control group; 54.56±2.05Umol/L vs 29.48±2.25Umol/L; [*F* (5, 24)= 23.761; p<0.0001]. The result from the all the groups treated with LA, all indicated a statistically significant reduction in MDA in the tissue when compared distil water group and the sleep deprivation untreated group; 54.56±2.05 Umol/L vs 38.16±0.93Umol/L; 54.56±2.05Umol/L vs30.42±2.62Umol/L; 54.56±2.05Umol/L vs 29.20±2.27Umol/L; 54.56±2.05Umol/L vs 29.20±2.27Umol/L; 54.56±2.05Umol/L vs 29.26±1.89Umol/L respectively; [*F*(5, 24)= 23.761; p<0.0001]. The treatment with LA revealed a dose dependent pattern.

Effect of prenatal sleep deprivation-induced-stress on hippocampal superoxide dismutase (SOD) level of male offspring

The result (figure 2) indicated a statistical significant decrease in the hippocampal SOD level in the SD group untreated when compared with the distill water control group: 21.22±0.40U/ml vs 35.26±1.18U/ml; [*F*(5, 24)= 14.569; *p*=0.0001]. It also showed a statistical significant decrease in LA 125mg/kg did not indicate any statistical significant change compared with the SD untreated group 26.48±0.90U/ml vs 21.22±0.40U/ml, but indicated a statistical significant decrease when compared with the distill water control groups 35.26±1.18U/ml vs 26.48±0.90U/ml; [*F*(5, 24)= 14.569; *p*=0.0001].

The result showed a statistically significant increase in the LA 250mg/kg, LA 500mg/kg and Vitamin C 300mg/kg groups when compared with the SD untreated group: 34.24±1.50U/ml vs 21.22±0.40U/ml; 28.30±0.93U/ml vs 21.22±0.40U/ml; 30.42±2.38U/ml vs 21.22±0.40U/ml respectively; [*F*(5, 24)= 14.569; *p*=0.0001]. The result for LA 250mg/kg also indicated a statistically significant elevation in the SOD level compared with LA 125mg/kg group.

Effect of prenatal sleep deprivation-induced-stress on hippocampal glutathione (GSH) level of male offspring

The GSH level in the hippocampus from figure 3, indicated a s tatistically significant drop in the SD untreated group when compared to the normal control: 70.38±1.52U/L vs 33.48±0.87U/L;

[*F*(5, 24)=43.737; *p*=0.0001]. The result also showed that all the LA and vitamin C treated groups statistically significantly elevated the GSH hippocampal level compared with the SD group in a dose dependent manner: 57.86±2.57U/l vs 33.48±0.87U/L; 76.76±5.00U/L vs 33.48±0.87U/L; 85.68±2.83U/L vs 33.48±0.87U/L; 78.02±2.50U/L vs 33.48±0.87U/L respectively; ; [*F*(5, 24)=43.737; *p*=0.0001]. The result interestingly showed that LA 250mg/kg, LA 500mg/kg and Vitamin C groups statistical significantly increase the hippocampal GSH when compared with the LA 125mg/kg group: 76.76±5.00U/L vs 57.86±2.57U/L; 85.68±2.83U/L vs 57.86±2.57U/L; 78.02±2.50U/L vs 57.86±2.57U/L respectively; [*F*(5, 24)=43.737; *p*=0.0001].

Effect of prenatal sleep deprivation-induced-stress on hippocampal catalase (CAT) level of male offspring

The result of the level of CAT in the hippocampus of prenatally sleep-deprived offspring from figure 4, showed a decrease in the SD group compared with the distill water control group. Though the difference was not statistically significant: 8.36±0.33U/L vs 7.76±0.50U/L. The result also indicated a statistically significant rise in all the LA and vitamin C groups when compared with the SD group and the distill water control: 20.30±0.48U/L vs 7.76±0.50; 16.82±1.43U/L vs 7.76±0.50U/L; 18.74±0.47U/L vs 7.76±0.50U/L; 13.20±0.60U/L vs 7.76±0.50U/L respectively; [*F*(5, 24)= 52.577; *p*=0.0001]. Furthermore, the result showed a statistically significant decrease in the LA 250mg/kg and Vitamin C 300mg/kg treatment groups when compared with the LA 125mg/Kg treatment group: 16.82±1.43U/L vs 20.30±0.48U/L; 13.20±0.60U/L vs 20.30±048U/L respectively; [*F*(5, 24)= 52.577; *p*=0.0001]. Interestingly, the result also showed a statistically significant decrease in the Vitamin C 300mg/kg treated group when compared with the LA 500mg/kg treated group: 13.20±0.60U/L vs 18.74±0.47U/L; [*F*(5, 24)= 52.577; *p*=0.0001].

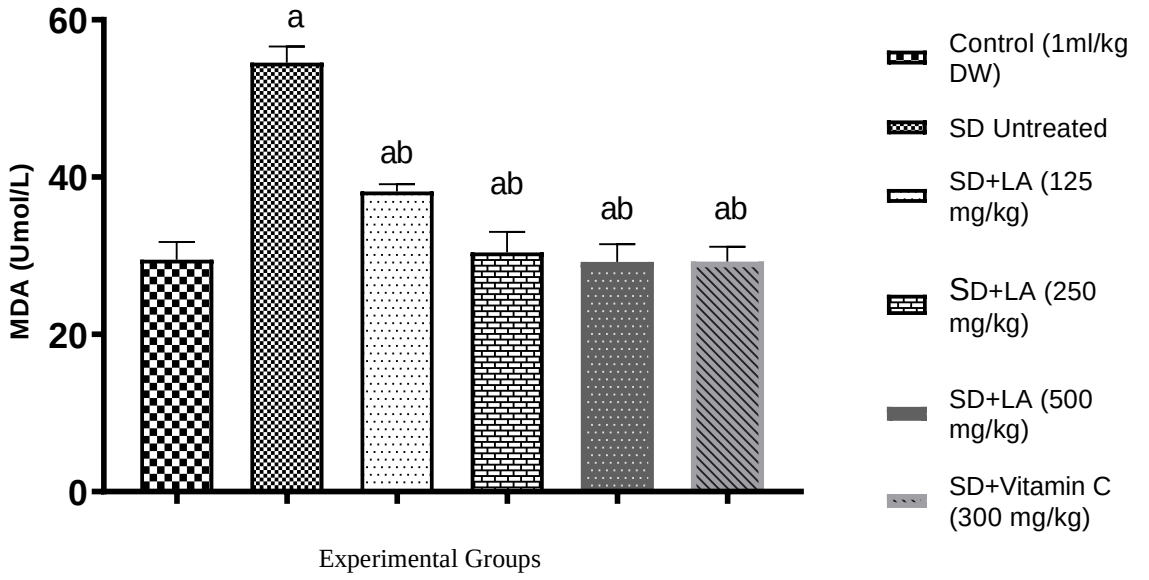

Figure 1: Hippocampal Malondialdehyde (MDA) level (pg/ml) in male offspring of maternal sleep deprivation-induced-stress Wistar rats. Different superscripts a,b, indicate statistically significant difference (p≤ 0.05) compared to control and SD untreated respectively. DW- Distilled water, SD- sleep deprivation-induced-stress, LA- Lauric Acid

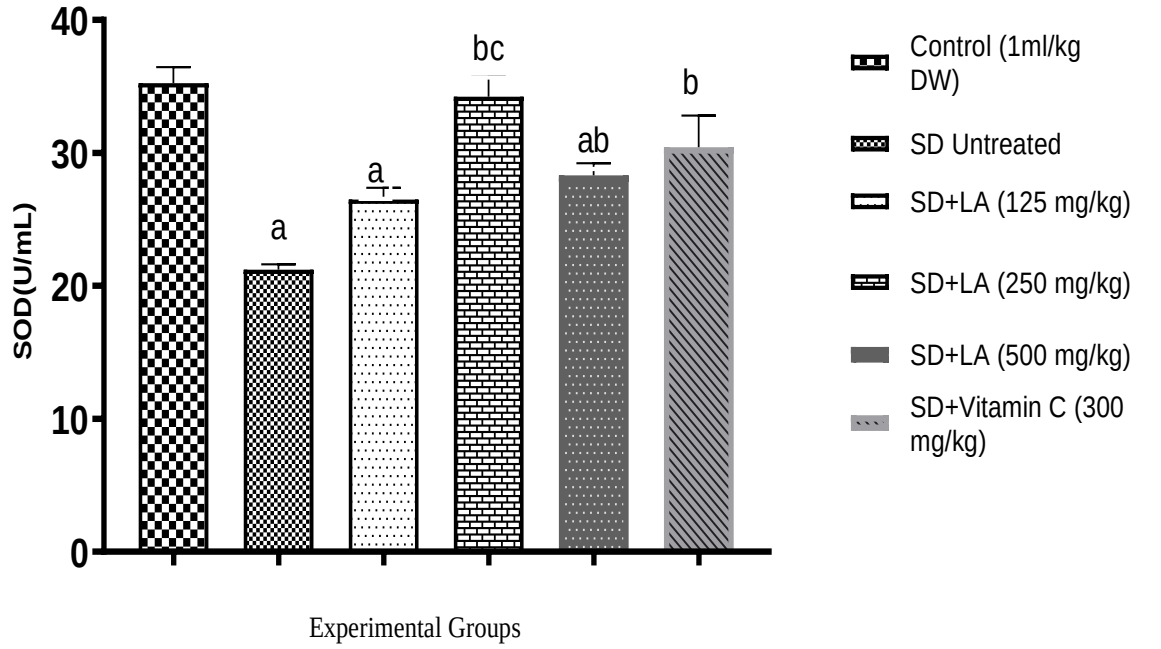

Figure 2: Hippocampal SOD level (U/ml) in male offspring of maternal sleep deprivation-induced-stress Wistar rats. Different superscripts a,b,c, indicate statistically significant difference (p≤ 0.05) compared to control and SD untreated respectively. DW- Distilled water, SD- sleep deprivation-induced-stress, LA- Lauric Acid

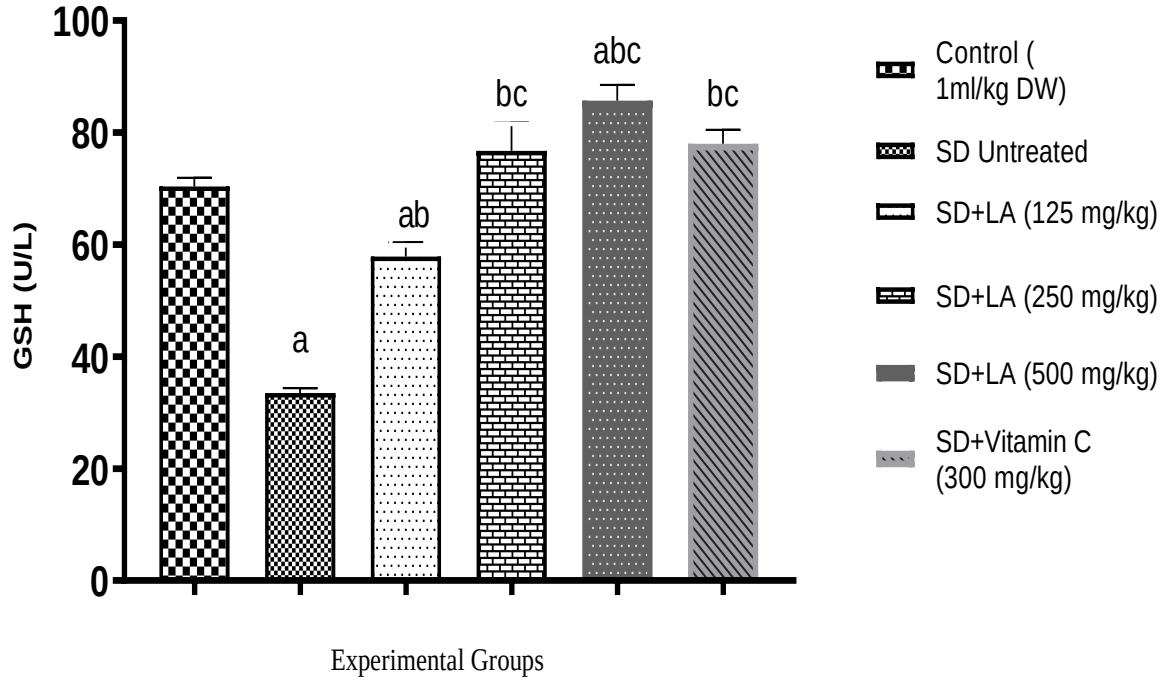

Figure 3: Hippocampal GSH level (U/ml) in male offspring of maternal sleep deprivation-induced-stress Wistar rats. Different superscripts a,b,c, indicate statistically significant difference (p≤ 0.05) compared to control and SD untreated, LA 125mg/kg respectively. Distilled water, SD- sleep deprivation-induced-stress, LA- Lauric Acid

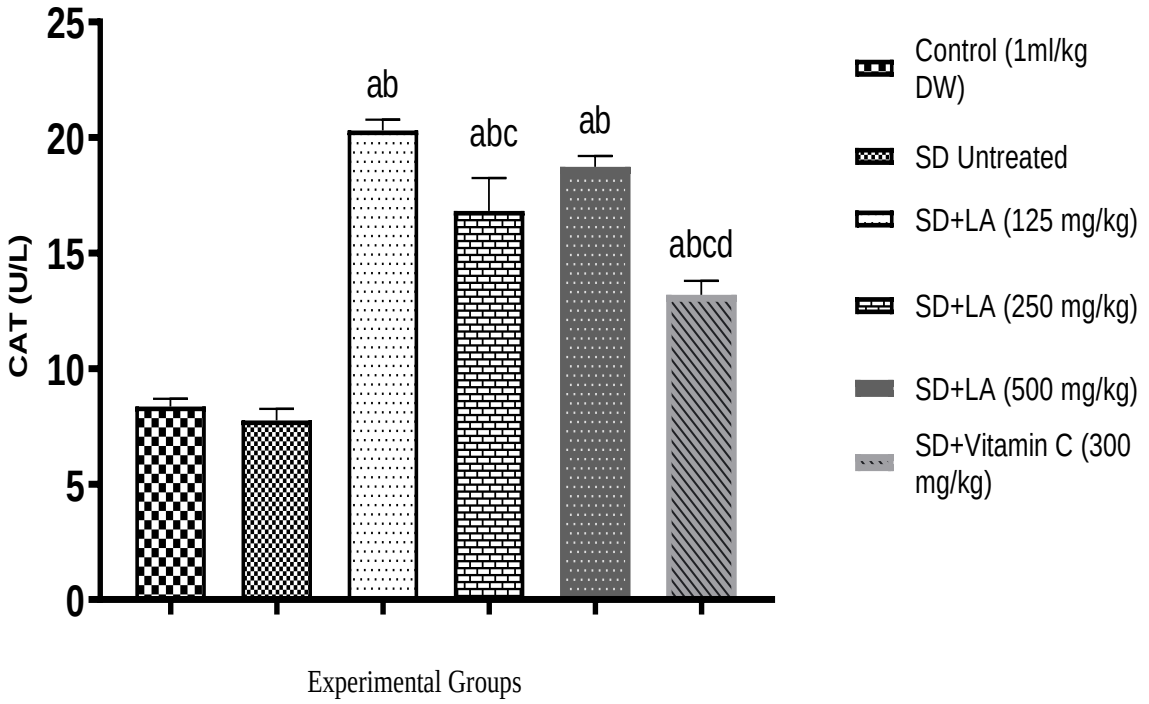

Figure 4: Hippocampal CAT level (U/ml) in male offspring of maternal sleep deprivation-induced-stress Wistar rats. Different superscripts a,b,c,d indicate statistically significant difference (p≤ 0.05) compared to control and SD untreated, LA 125mg/kg and 250mg/kg respectively. DW- Distilled water, SD- sleep deprivation-induced-stress, LA- Lauric Acid

DISCUSSION

Malonialdehyde (MDA) is one of the parameters mostly used as a marker of lipid peroxidation, been one of the major pathway of cell and membrane destruction (Hasim *et al*., 2020). This biomarker is increased under conditions of oxidative stress (Muñiz *et al*., 2014). Increased ROS in the hippocampus of rat offspring has been reported to be implicated with prenatal stress (Zhu *et al*., 2004). The increased in the hippocampal lipid peroxidation level in the male pups as seen from our result, is an index for oxidative stress which alter the intracellular signaling pathways and elevate redox signaling that may lead to mood distortions (Filho *et al.,* 2015; Fatima *et al.*, 2019) and lay credence to restriction of sleep as a stressor that can cause an increase in oxidation in the tissue. Prenatal stress has been shown to increase the level of MDA in the liver and brain of offspring (Al-Amin *et al.,* 2016; Emiliano *et al.*, 2019). Though MDA levels was indicated to be decreased significantly in diabetic rats administered LA (Alex *et al.*, 2019), our study is among the earliest works to report the action of LA on male offspring of pregnant Wistar rats exposed to chronic sleep restriction. The superoxide dismutase is a radical scavenging enzyme considered to act as the first line of defense against the damaging action of oxygen radicals intracellularly. It acts by scavenging ROS through catalyzing the dismutation of O^{2-} radical to H_2O_2 and O^{2-} which leads to decreasing the likelihood of superoxide anion reacting with nitric oxide to form reactive peroxynitrite (Singh *et al*., 2012). The SOD level, as shown in this study to be significantly lowered in the SD untreated group corroborate the study by Bernhardt *et al*. (2017) that showed a decrease in the SOD level in offspring exposed to early and late gestational stress.

Prenatal stress can also lower the activity of the brain SOD level (Al-Amin *et al.,* 2016; Liu *et al.,* 2020).

The decreased in the SOD in our study may be as a result of an increased ROS generation which overwhelmed the ability of the SOD enzyme to counteract its effects (Singh *et al.*, 2012).

The treatment with higher doses of LA and Vitamin C (300mg/kg) indicated an increase in the tissue SOD level of the male offspring. N-acetylcysteine has been shown to increase the brain SOD level in offspring whose mothers were subjected to gestational stress (Bernhardt *et al*., 2017).

Glutathione is required for detoxification of ROS in brain cells (Dringen and Hirrlinger, 2003). The GSH level from our study was shown to be significantly lowered in the SD group. Prenatal stress has been reported to lower GSH levels in the brains of offspring (Al-Amin *et al*., 2016; Bernhardt *et al.*, 2017). The decrease may be as connected to the reduced action of glutathione reductase that is needed to restore the level of GSH. Despite the SD-induced oxidative alterations, our results showed that LA at 500 mg/Kg significantly improved the hippocampal GSH level compared to the SD group and the distil water control group. It is possible as a result of the activity of glutathione over lipid peroxidation as it has been implicated to lower the peroxidized cholesterols and phospholipids levels (Thomas *et al*., 1990). The reduction in hippocampal GSH level seen in this study may be as a result of its high rate of utilization caused by oxidants (Sahin and Gümüşlü, 2004). Higher levels of ROS lead to more decreased glutathione (GSH) to change to its oxidized state (GSSG) (Ou *et al*., 1996). It could also result from a reduced action of the glutathione reductase (Costagliola, 1989) needed to restore the GSH level. Despite the SD-induced oxidative alterations, our result showed that the Lauric acid at the highest dose of 500mg/kg and the Vitamin C (300mg/kg) treatment improved the GSH level compared with the SD group. This indicating that Lauric acid at higher doses can increase the activity of the GSH.

Catalase is distributed in all body tissues and can protects the body tissue from hydroxyl radicals (Onyeka *et al*., 2012). Result from this study, showed that the hippocampal CAT level was decreased in the SD group compared with the distill water group.

The study conducted by Ehichioya and Jaja (2020) reported a significant lowering in the level of CAT in the heart tissue in offspring of sleep deprived pregnant Wistar rats between GD 14 to GD 20 compared with the control group. Our study indicated a significant increase in all the LA administered groups with the greatest effect seen with the LA 125 mg/Kg

It was found from this study that sleep deprivation-induced prenatal stress significantly reduced the antioxidant enzymes Catalase, SOD, GSH in the hippocampus and raises the level of lipid peroxidation, indicating oxidative stress (Schafer and Buettner, 2001). Oxidative stress in humans is believed to be involved in the development of many diseases or exacerbation of their symptoms (Whitworth *et al*., 2000). Oxidative stress is associated with prolonged exposure to glucocorticoids (Iuchi *et al*., 2003; Momoh *et al.*, 2022).

CONCLUSION

Sleep deprivation induced prenatal stress caused an increase in the peroxidation of lipids, lowered level of SOD, CAT and GSH in the hippocampus of male offspring of Wistar rats. These oxidative alterations were reversed by oral administration of lauric acid by enhancing the antioxidant system activity, thus indicating its protective action against oxidative enzyme disruptions.

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