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Role of Lauric acid against Prenatal Sleep Deprivation-Induced-Stress rise in corticosterone and low birth weight in Rat offspring

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Abstract

Prenatal stress is known to affect the offspring later in life. Lauric acid is a known antioxidant shown to play a protective role in experimental animals. This study examines the role of Lauric acid on sleep deprivation-induced stress on serum corticosterone level and birth weight in male rat pups. Pregnant dams were sleep-deprived using the modified multiple water platform for 20hrs daily from gestational day 9-19. Animals in groups 1 and 2 served as normal and stressed controls respectively, groups 3,4 and 5 received Lauric acid of doses 125mg/kg, 250mg/kg and 500mg/kg respectively while group 6 received Vitamin C 300mg/kg. Male offspring birth weight was recorded and at PND 28-36, were sacrificed and blood was collected for corticosterone assay. Serum corticosterone was significantly higher ($p< 0.05$) in the sleep-deprivation-induced stress group. Its level was also significantly lower ($p<0.05$) in the LA and vitamin C treated groups. Birth weight was significantly lower ($p<0.05$) in the stressed and vitamin C (300mg/kg) groups while being significantly higher ($p< 0.05$) in LA 125mg/kg group. This finding suggest that Lauric acid protect against rise in serum corticosterone level and improves birth weight in male offspring of dams subjected to sleep deprivation.

Keywords: Corticosterone, Lauric acid, birth weight, HPA-axis, sleep deprivation.

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INTRODUCTION

Sleep deprivation (SD) which is the restriction in the amount of sleep time below the level of basal sleep need (Chasens *et al.* 2010), in women as a result of the trend in lifestyle, even when they are pregnant, is a serious concern as it can have damaging effect on the health of the fetus utero (Radhakrishnan, *et al*., 2015; Aswathy *et al*., 2018), by constituting a form of physical and emotional stressors, which can be linked to deleterious consequences to the mothers and their offspring (Pires *et al*., 2010). Stressful prenatal conditions are linked to developing psychiatric diseases later in the future in the life of the offspring, like, autism spectrum disorders (ASD), schizophrenia and attentional deficit/hyperactivity disorder (ADHD) (Kinney *et al*., 2008). With respect to timing of prenatal stress during pregnancy and birth outcomes, there is a lack of specificity (van den Bergh *et al*., 2017). Alterations in processes concerned with neurodevelopment during gestation can result in abnormalities in the offspring with about a reported incidence of 4 per 1000 births (Roeleveld *et al.*,1997). The negative effects of maternal stress during gestation on the offspring exist and the probable hypothesis that gestational perturbations alter the programming of the systems that are involved in stress response actions, not excluding the hypothalamic-pituitary-adrenal (HPA axis) (Keenan and Hipwell, 2015). The most cause of perinatal morbidity, death and neurodevelopmental alterations leading to abnormalities in newborns is low birth weight (WHO, 1995). It is important to initiate studies on the prevention of the negative effects of prenatal stress in humans. Neuroprotection as a potential plan has been supported by researches against neurodegenerative diseases (Albarracin *et al*., 2012).

Lauric acid (LA), a saturated fatty acid but a medium chain fatty acids, chemically known as dodecanoic acid is a major component of coconut oil, and can also be found in palm kernel oil, coconut milk, and human breast milk (Dayrit, 2015). Researches have shown that LA possess anti-oxidant (Alves *et al*., 2017), anti-inflammatory (Leiberman *et al.,* 2006) activities. No study has been done on the use of LA against the negative impact of prenatal stress on male offspring.

This study was aimed at assessing the effect of LA in male offspring of dams subjected to prenatal sleep deprivation induced-stress.

MATERIALS AND METHODS

Animals

A total of twenty (24) adult female Wistar rats weighing between 180-210 grams and thirty-six (36) male offspring rats from the dams that weigh between 40-60 grams were used for the study. Adult rats were purchased from the animal house of the Department of Human Physiology, Ahmadu Bello University Zaria and kept in standard cages. Their cages were kept clean on regular basis and they were fed on commercial feeds (Vital feeds) with tap water. Induction of estrus was done by exposing grouped adult nulliparous females to the bedding materials of the male rats for a period of three days (Bronson and Whitten, 1968). In the evening of the 3rd day, the rats were paired (one male and 2 females) for mating. Pregnancy was determined by daily vaginal smear examination. The day at which the smear was sperm positive (presence of sperm cells in the vaginal smear) or seminal (copulation) plug was first observed was considered as gestational day zero (GD 0) (Bernhardt *et al.* 2018). Pregnant rats were housed in groups, and had access to food and water *ad libitum* (Kvarik *et al*., 2016). The day of birth was considered as postnatal (P) day zero. Ethical approval on guidelines for care and use of laboratory animals in scientific research was obtained from the Ahmadu Bello

University Committee on Animal Use and Care (ABUCAUC) with ABUCAUC/2021/107 given as approval number.

Animal groups and treatments

Group 1 (normal control) received distilled water 1ml/kg, group 2 was untreated but received 1ml/kg Tween 80 + (sleep deprivation) SD, group 3 received lauric acid (LA) 125 mg/kg + SD, group 4 received LA 250mg/kg+ SD, group 5 received LA 500 mg/kg+ SD and group 6 received Vitamin C 300mg/kg + SD. SD (sleep deprivation), LA (lauric acid).

Sleep deprivation

Pregnant rats were exposed to sleep deprivation for 20hrs from gestational day (GD) 9 to GD19 (Clancy *et al*., 2007), with 4hr (7:00am-11:00am) rest each day using Modified Multiple Platform (MMP) method as described by Medeiros *et al*., (1998) and modified by Oh *et al*., (2012). The modified multiple platform method, which involves placing the rats in an acrylic water tank (123 x 44 x 44 cm) containing 14 circular platforms, 6.5 cm in diameter, with water up to 1 cm of their upper surface. The rats could move around inside the tank only by jumping from one platform to another. When they reach the paradoxical phase of sleep, muscle atonia will set in, and they will fall into the water and wake up. Food and water was provided ad libitum by placing chow pellets and water bottles on a grid located on top of the tank. The water in the tank was changed daily throughout the SD period.

Chemicals

Lauric acid (LA) was obtained from AK Scientific, USA. Tween 80 (Sigma-Aldrich), distilled water, Vitamin C (Ascorbic acid) (Central Drug House, New Delhi, India), Rat CORT ELISA, (Wuhan Fine Biotech Co., Ltd. Wuhan, China). Lauric acid was suspended in distilled water using Tween 80 and administered orally using the oral gavage (Patil *et al*., 2016) every morning before subjecting the pregnant rats to sleep deprivation. Offspring male Wistar rats from postnatal day 28-35 from each of the groups were used for this study. LA dosage administered was by the method of Dubo *et al.,* (2019).

Procedure

At the end of the experiment, the animals were sacrificed by cervical dislocation following anesthesia by a single intraperitoneal injection of ketamine (25 mg/kg) and xyaline (2.5mg/kg) (Molina *et al.,* 2015). Blood was collected by cardiac puncture using a 5ml syringe and transferred into plain tubes, centrifuged for 5 minutes at 1000x g at room temperature.

Corticosterone assay. The serum was collected after centrifugation, transferred and stored at -80^{o}C until analysis. Serum corticosterone concentrations was analyzed using enzyme-linked immunosorbent assay according to manufacturers' instructions (Fine Test, Wuhan, China).

Birth weight. Animals were weighed in grams at birth using the Electronic weighing machine (Salter, HoMedics Group Ltd. Production N0. IB1066-1011-03)

Statistical analysis

Data obtained from the study was expressed as mean ± SEM and statistical analysis was carried out using version 20 of IBM statistical package for social sciences (SPSS). One-way analysis of variance (ANOVA) was carried out followed by Tukey *post hoc* test to determine the differences among the groups. Values with $p< 0.05$ were considered statistically significant. Graph pad Prism 5.0 (GraphPad software, CA, USA) was used for charts.

RESULTS AND DISCUSSION

Results

Figure 1. Effect of LA administration on serum corticosterone level in male offspring of dams subjected to prenatal sleep deprivation. Result obtained from the study showed a statistically significant increase in serum corticosterone level in the SD untreated group compared with the normal control group: 638.36±11.64ng/ml vs 541.84±13.88ng/ml; [F (5, 24) =13.508; p= 0.0001]. Compared with the SD untreated group, the LA 125 mg/kg (638.36±11.64ng/ml vs 522.52±3.81ng/ml), LA 250 mg/kg (638.36±11.64ng/ml vs 510.60±4.08ng/ml), LA 500 mg/kg (638.36±11.64ng/ml vs 547.28±15.52) and vitamin C 300mg/kg (638.36±11.64ng/ml vs 544.08±17.53ng/ml) treated groups all showed a statistically significant decrease in the level of corticosterone in the serum.

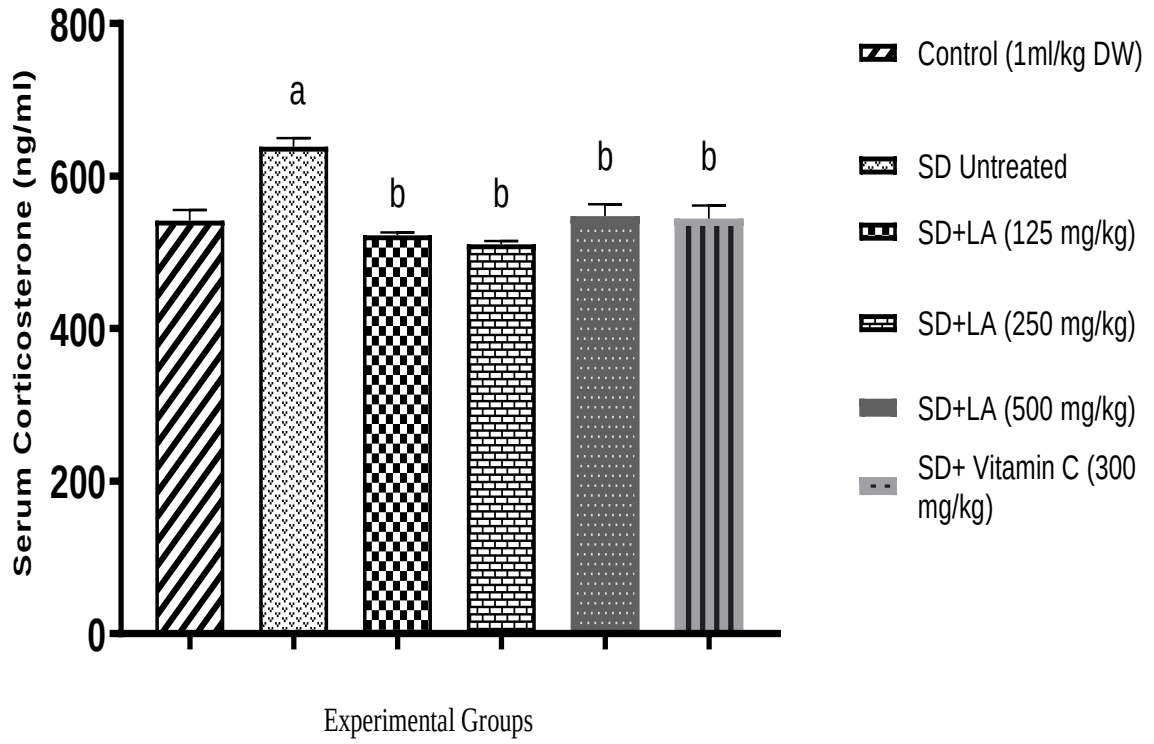

Figure 1: Serum corticosterone level (ng/ml) in male offspring of maternal sleep deprivation-induced-stress Wistar rats. Superscripts a,b indicate statistically significant difference ($p \leq 0.05$) compared to control and SD untreated respectively. DW- Distilled water, SD- sleep deprivation-induced-stress, LA- Lauric Acid

Figure 2. Effect of LA administration on birthweight in male offspring of dams subjected to prenatal sleep deprivation. Result from this study on revealed that the male offspring of dams subjected to sleep deprivation had a statistically significant lower birth weight compared with the control group: 6.04±0.14g vs 4.84±0.08g; [F (5, 24)= 7.151; p=0.0001]. Treatment with all doses of LA showed that birth weight was increased in a dose dependent manner in the male offspring of dams subjected to sleep deprivation compared to the offspring of dams subjected to sleep deprivation (SD untreated group). Only the LA 125mg/kg group showed statistical significant difference: 5.95±0.09g vs 4.84±0.08g; [F (5, 24)= 7.151; p=0.0001]. Male offspring of dams treated with Vitamin C (300mg/kg) showed a statistically significant decrease

(5.26±0.24g vs 5.95±0.09; [F (5, 24)= 7.151; p=0.0001]in the birth weight of the male offspring compared to the control group.

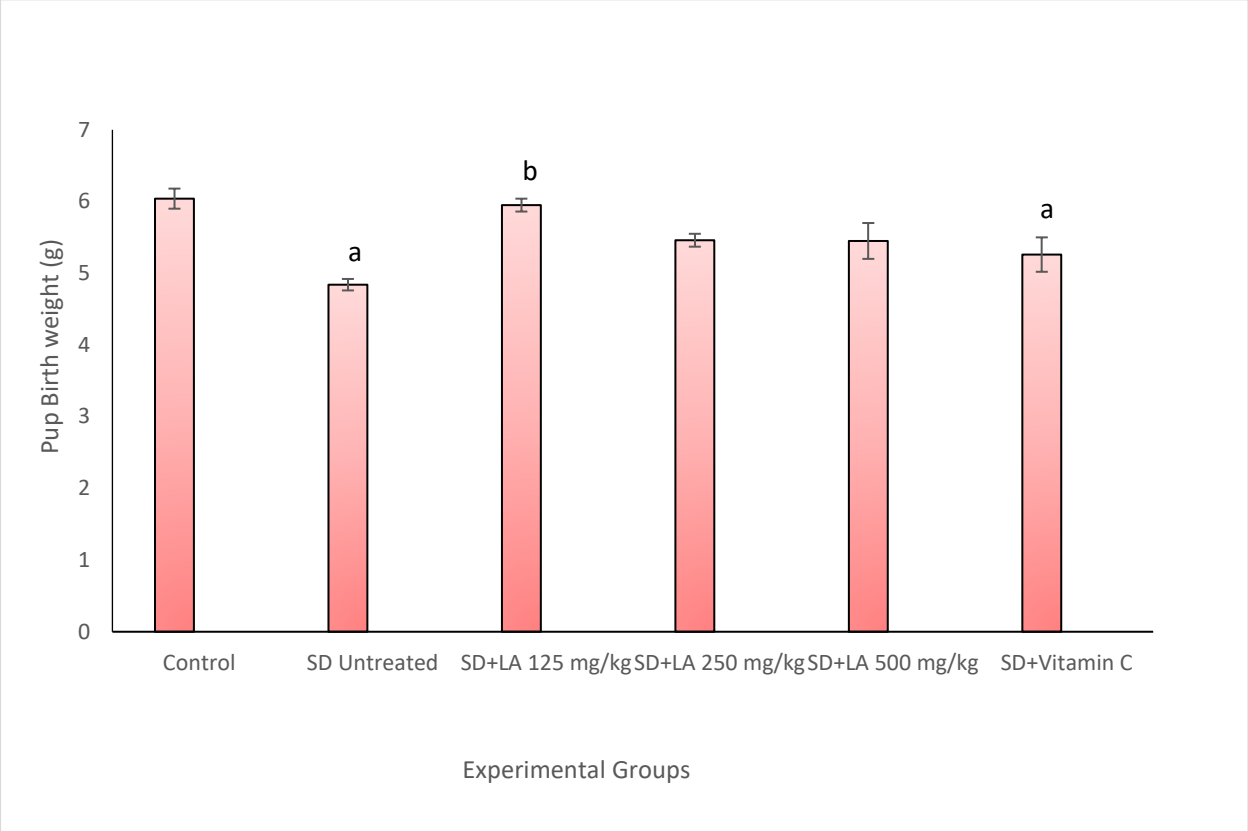

Figure 2: Body weight in male offspring of maternal sleep deprivation-induced-stress Wistar rats. Different superscripts a,b, indicate statistically significant difference ($p \leq 0.05$) compared to control and SD untreated. SD-sleep deprivation-induced-stress, LA- Lauric Acid

DISCUSSION

Corticosterone (CORT) is a liposoluble glucocorticoid (GC) that passes through the placenta and interacts with various cells and fetal tissue, affecting the development of the adrenal gland of the fetus (Mayer *et al*., 2011). Though important for fetal development, maternal stress during gestation can increase cortisol level by two to four times (Munck *et al.,* 1984; Mastorakos and Ilias, 2003). Exposure to excess maternal cortisol may cause neurotoxicity and impairment in the development of the brain (Kapoor et al., 2006). The result of significant increase in serum corticosterone level in the SD untreated group in this study in Figure 1, could be due to the ability of maternal stress to reprogram the HPA axis by increasing GC level due to persistence of the stress (Del Cerro *et al*., 2015; Soares-Cunha *et al.,* 2018) as seen from the duration of stress throughout our study, decrease placental protection which results in a rise in glucocorticoid level that affect neurodevelopment in the rat offspring via signaling pathways (Fatima *et al.,* 2017). The dysregulation of the HPA axis can stimulate an increase activation of corticotropin-releasing factor (CRF) firing neuron, an increase in peripheral glucocorticoids (GCs), and a suppression of the immune system (Arnett *et al*., 2016). The placental CRF stimulatory effect on HPA axis activity and the natural decrease in placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) activity (Vaughan *et al*., 2012), have been reported to be responsible for the higher CORT levels (Argeri, 2016). and this can predispose the developing brain to development of neurodevelopmental defects in the offspring (Buitelaar *et al*., 2003), laying credence that sleep deprivation from our study as a form of stressor. Treatment with LA from our study reversed significantly the increased serum level of CORT in the male offspring due to maternal sleep deprivation. Our result

suggests that the LA action may be due to it belonging to the medium chain fatty acid group that can help to prevent the development of stress (Yeap *et al.,* 2014), since supplementation with fatty acid have been reported to modify psychological responses to stressors (Keenan and Hipwell 2015).

Reduced birth weight with other negative birth outcomes has been linked to maternal distress before and during gestation (Su *et al*., 2015). The development of the offspring's brain development can be influenced by body weight at birth (Walhovd *et al.* 2012). The reduction in birth weight in the offspring of maternal sleep-deprived untreated group (Figure 2) in our study could be due to excess glucocorticoid exposure during critical times of development of the neuroendocrine system due to the prenatal stress (Matthews, 2002), and also alteration in the metabolism of offspring born to dams exposed to gestational stress by sleep deprivation (Fatima *et al*., 2019). Though the mechanism underlying the link between prenatal stress and low birth weight is scarcely known (Baker *et al.* 2008), there seem to be a direct relationship existing between maternal stress during gestation, low birthweight and intrauterine growth restriction which may be due to the release of catecholamines, which results in hypoperfusion of the placenta and consequently leading to deprivation in oxygen and nutrients availabilty to the fetus leading to impairment in fetal development and growth (Copper *et al*, 1996). The findings from our study is consistent with the research conducted by Akindele *et al*., (2016) that also reported a decrease in birth weight in offspring whose dams were subjected to sleep deprivation. Abnormal sleep patterns during pregnancy is linked to decrease birth weight and restriction of intrauterine growth (Micheli *et al*., 2011. Offspring with abnormal birth weight have been reported to have increase chance of psychiatric disorder and neurologic-associated disabilities, since evidences show that low weight at the time of birth is associated with schizophrenia (Holloway *et al.* 2013) and bipolar affective disorder (Zucchi *et al*., 2013).
From the result, the birth weight was observed to be increased in the LA treated groups and may be due to the antioxidant effect of LA in mitigating stress response in rats (Alex *et al*., 2019). This to the best of our knowledge, is the first study reporting the effect of a medium chain fatty acid (Lauric acid) in mitigating the effect of sleep deprivation on offspring birth weight.

CONCLUSION

Based on the findings from this research, lauric acid protected the male offspring from prenatal chronic sleep deprivation induced stress during gestation from low birth weight and rise in serum corticosterone concentration.

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