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Post-conceptional melatonin administration mitigates changes in neurobehaviour and cerebral cortex histomorphology in prenatal sodium valproate-exposed rats

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Abstract

The effects of post-conceptional melatonin administration on prenatal-sodium valproate (SV)- induced changes in behaviour and cerebral cortex histomorphology in rats were examined in this study. Twenty-five rats (150-200 g) were mated with age-matched males and pregnancy confirmed by presence of vaginal plug. Pregnant dams were assigned into five groups. group A (Control) administered distilled water (10 ml/kg) and intraperitoneal (i.p) injection of saline (2ml/kg), B SV control, received distilled water and i.p SV (150 mg/kg). Groups C-E were administered i.p SV and melatonin (5, 10, and 20 mg/kg) via oral gavage. Distilled water and melatonin were administered from post conceptional day (PCD) 1-10, while single i.p injection of saline and SV was administered on PCD 12. Pregnant dams delivered on PCD 21 and cared for their offspring till weaned on postnatal day (PND) 21. Weaned rat pups were exposed to behavioural paradigms (open-field arena, social interaction test, elevated plus maze and Y-maze) on PND 35. On PND 36, pups were euthanized, and brains were processed for general histology. Results showed a decrease in self grooming, spatial memory and social interaction while an increase in locomotor activity and rearing was observed with SV. Post-conceptional melatonin increased, self-grooming, spatial memory and social interaction and decreased rearing and locomotor activity. Administration of SV caused neuronal loss in the cerebral cortex, while melatonin was associated with protection against SV-induced neuronal injury. In conclusion, melatonin mitigated against maternal SV-induced behavioural and structural changes in the cerebral cortex of offspring.

Keywords: Autism Spectrum Disorders, Animal models, Melatonin, Prenatal, Post-conceptional

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social interaction, repetitive behaviours, and sensory abnormalities [1, 2]. The increasing global incidence of autism disorder (particularly males), poor understanding of its pathophysiology/pathology, lack of practical diagnostic criteria (due to disease heterogeneity) and limited therapies continue to drive autism research [3]. There is ample evidence that prenatal exposure to environmental factors including sodium valproic acid (SV), is a significant risk factor for ASD [4]. Sodium valproate commonly prescribed as an anticonvulsant and mood stabilizer, readily crosses the placental barrier, disrupting foetal brain development [4]. This exposure is associated with altered brain biochemistry, reduced neuronal viability, and behavioural deficits, including impaired social interaction, repetitive behaviours, increased anxiety, and changes in motor activity [5]. These effects are further exacerbated by elevated levels of neuroinflammation and oxidative stress [5]. Sodium valproate is effectively absorbed from the gastrointestinal tract, with bioavailability ranging from 81% to 89%, is influenced by the specific formulation and food intake. Delayed- and extended-release formulations are designed to extend the drug's action [6, 7]. The absorption of SV is enhanced by food, especially fatty

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meals, which can increase bioavailability by up to 35%. SV binds strongly to plasma proteins (about 90%), but this binding decreases as concentration increases [7]. Sodium valproate crosses the blood-brain barrier, with cerebrospinal fluid (CSF) concentrations at 10%–20% of plasma levels. [8]. It is excreted into breast milk [9-11]. Its ability to readily cross the blood brain barrier Sodium valproate has also been reported to cross the placenta, posing significant teratogenic risks [12, 13]. Its use as a chemical model of autism is based primarily on the readiness with which it crosses the placental barrier and blood brin barrier. Investigating these mechanisms have been suggested to be of crucial importance in the development of novel interventions for autism management [4].

The high incidence of sleep disorders including parasomnias, difficulty initiating sleep and insomnia in children with autism are among the initial indications for melatonin use in these children [14, 15]. Autism research has also demonstrated reduced plasma levels of melatonin and its metabolites as well as decreased urine excretion rates of melatonin sulphate [15]. Although studies have implicated also abnormalities in the circadian rhythm and melatonin physiology in ASDs [14]. In recent times better understanding of melatonin's influence as a multifunctional signalling molecule and its antioxidant and immune modulating properties [16, 17] as well as reports of its neuromodulatory and neuroprotective potential in the management of various neurocognitive and neurodegenerative disorders [18, 19] has led to suggestions that it could have more value in autism disease management above its use as a sleep aid. Melatonin's effects extend beyond sleep, influencing anxiety, sadness, pain, and gastrointestinal dysfunctions, therefore enhancing the well-being of individuals with ASD. [20)

There have been reports suggesting that melatonin has the ability to modulate neuronal plasticity in utero, it also plays a significant role in placental homeostasis and immunity [20]. Melatonin-induced neuroplasticity has been linked to its ability to traverses the placenta and deliver photoperiodic information to the foetus thereby facilitating the establishment of a regular sleep cycle, which is crucial for proper neurodevelopment [20, 21].

The objective of this study was to examine the neuroprotective effects of early postconceptional melatonin supplementation in a sodium valproate model of autism spectrum disorder in rats.

2. Materials and Methods

2.1 Chemicals and Drugs

Melatonin (10 mg, Bedford Square, Bloomsbury, London, UK), Sodium Valproate (200 mg, Sanofi, Berkshire, UK).

2.2 Animals

Healthy Wistar rats used in this study were purchased from Empire Breeders, Osogbo, Osun State, Nigeria. Rats were housed in wooden cages, located in temperature-controlled quarters (22-25 degrees Celsius) with 12 hours of light daily (lights on at 7.00 a.m.). During the behavioural tests. All procedures were conducted by the approved institutional protocols and within the provisions for animal care and use prescribed in the scientific procedures on living animals, European Council Directive (EU2010/63)

2.3 Experimental Methods

Adult female Wistar rats weighing 150 -200g were used for the study. The female rats were placed in the same cage with an age-matched male rat of proven fertility. Females were the checked daily for presence of vaginal plug. Rats with a vaginal plug were assigned as Day 0 of pregnancy and were used in this study. Pregnant dams were assigned into five groups. group A (Control) administered distilled water (10 ml/kg) and intraperitoneal (i.p) injection of saline (2 ml/kg), B was SV control, received distilled water and i.p, SV (150 mg/kg) according to a previous study [22]. Groups C-E were administered i.p SV and melatonin at 5, 10, and 20 mg/kg via oral gavage [23]. Distilled water and melatonin were administered from post conceptional day (PCD) 1-10, while single i.p injection of saline and SV was administered on PCD 12. Pregnant dams delivered their pups on PCD 21 and were allowed to care for their offspring till weaned on postnatal day (PND) 21. Weaned rat pups were exposed to behavioural paradigms (open-field arena, social interaction test, elevated plus maze and Y-maze) two weeks after weaning (PND 35). On PND 36, pups were euthanized, and brains were dissected, sectioned and fixed in neutral-buffered formolsaline. The cerebral cortex was then processed for paraffin-embedding, cut at 5 µm and stained with haematoxylin and eosin and cresyl fast violet for general histological study.

2.3 Behavioural Testing

Behavioural tests were conducted in the following sequence: Open field, Elevated plus maze, Y- maze and social interaction tests.

2.4.1 Open field Novelty induced Behaviours

Open-field responses in rats encompass a variety of behaviours, including arousal, inhibition, exploratory actions, and anxiety-related responses. Stereotypic behaviours like grooming are also commonly observed. These behaviours are generally considered central to the rodent's exploratory capacity. In this study, grooming, rearing, and horizontal locomotion were monitored and scored over ten minutes in the open-field box. The open field apparatus is a rectangular arena made of white-painted wood, measuring 36 x 36x 26 cm. The floor is made of hardwood and divided by permanent blue markings into 16

equal-sized squares. The rats were placed in the centre of the field and covered by a small dome for (5 seconds), which was removed at the beginning of the 10-minute countdown. Generally, spontaneous motor activity was monitored in the open field as previously described. [18, 19, 23]. Each rat was introduced into the field and the total horizontal locomotion (number of floor units entered with all paws), rearing frequency (number of times the animal stood on its hind legs either with its fore-arms against the walls of the observation cage or free in the air) and frequency of grooming (number of body cleaning with paws, picking of the body and pubis with the mouth, and face-washing actions, indicative of a stereotypic behaviour) within the 10 minutes was recorded.

2.4.2 Spatial working memory (Y maze)

Memory Y-maze was used to measure general activity spatial working memory and anxiety-related behaviour. Spontaneous alternation behaviour (SAB) was used to measure spatial working memory. SAB comprises the tendency for rodents to alternate their (conventionally) non-reinforced choices of Y-maze arms on successive opportunities. Spontaneous alternation was assessed using a Y-maze as previously described [18, 19, 23].

2.4.3 Anxiety-related behaviour (Elevated plus maze)

The elevated plus maze is a plus-shaped apparatus with four arms at right angles to each other. The two open arms lie across from each other measuring 25 x 5 x 5 cm and perpendicular to two closed arms measuring 25 x 5 x 16 cm with a centre platform (5 x 5 x 0.5 cm). The closed arms have a high wall (16 cm) to enclose the arms whereas the open arms have a low side wall. Weaned rats were placed in the central platform facing the closed arm, and their behaviour was recorded for 5 min as previously described [18, 19, 24].

2.4.4 Social Interaction test

The 3-chamber sociability box was used to evaluate social interaction and novelty preference in a two-phase test. At the start of each session, the test rat was placed in the apparatus, and after testing, was returned to its home cage. The apparatus was then cleaned with 70% ethanol, wiped dry, and left for at least 5 minutes to ensure it was dry and odour-free. Behavioural parameters were scored by two independent observers blinded to groupings. The social interaction novelty test, was assessed as previously described [25]. Briefly, rats were introduced into a cage with three interconnected compartments each measuring 70 cm in width and 30 cm in in two phases. In the first phase, the test rat (belonging to any of the treatment groups) was placed in the central compartment, while a familiar littermate was restricted by a wire cage with a 5.5 cm radius to the left compartment. After an initial 5-minute period of habituation, sociability measured as the rate of interaction between test rat and familiar rat over a 10-minute period of observation. In the second phase, an unfamiliar rat from a different control litter was introduced into the right compartment and also restricted under a similar wire cage. The test rat was then returned to the centre compartment. Over another 10 minute-period, the preference for engaging with the familiar or unfamiliar rat versus time spent in the unoccupied compartment was calculated [26].

2.5 Photomicrography

Cerebral cortex slides were examined using a Sellon- Olympus trinocular light microscope with a digital camera attached and images were captured.

2.6 Statistical Analysis

Data were analysed using Chris Rorden's ANOVA for Windows (version 0.98). Analysis of data was by One-way analysis of variance (ANOVA), and a post-hoc test (Tukey HSD) was used for comparisons. All results were expressed as mean ± S.E.M. and $p < 0.05$ was taken as the accepted level of significant difference from control.

3. Results

3.1 Effect of postconceptional melatonin on horizontal locomotion

Figure 1 shows the effect of melatonin on open-field horizontal locomotion measured as number of lines crossed. There was a significant ($p < 0.001$) increase in line crossing with Sodium valproate (SV), SV+ melatonin (MEL) at 5 and 10 mg/kg compared to control. Compared to SV, locomotor activity decreased significantly with SV+ MEL) at 5, 10 and 20 mg/kg.

3.2 Effect of postconceptional melatonin on rearing behaviour

Figure 2 shows the effect of melatonin on open-field vertical locomotion measured as number of rears. There was a significant ($p < 0.001$) increase in rearing with SV, SV+ MEL at 5, 10 and 20 mg/kg compared to control. Compared to SV, rearing decreased significantly with SV+ MEL at 5, 10 and 20 mg/kg.

3.3 Effect of postconceptional melatonin on self-grooming behaviour

Figure 3 shows the effect of melatonin on open-field self-grooming behaviour measured as number of grooming episodes. There was a significant ($p < 0.001$) increase in grooming with SV, SV+ MEL at 5, 10 and 20 mg/kg compared to control. Compared to SV, self-grooming

increased significantly with SV+ MEL at 5, 10 and 20 mg/kg.

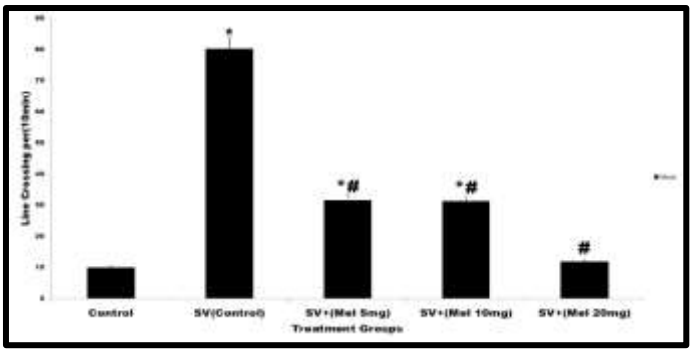

Figure 1: Effect of post-conceptional melatonin on line crossing. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from Mel, number of rats per treatment group =10. SV: Sodium Valproate, Mel: Melatonin

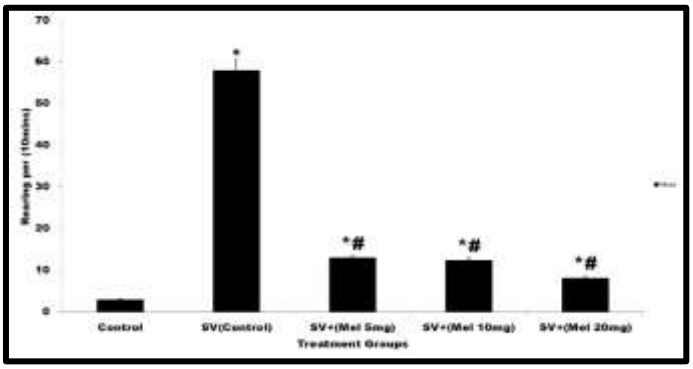

Figure 2: The Effect of Post-Conceptional Melatonin on rearing activity. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from Mel, number of rats per treatment group =10. SV: Sodium Valproate, Mel: Melatonin.

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3.4 Effect of postconceptional melatonin on Y-maze spatial working memory

Figure 4 shows the effect of melatonin on Y maze spatial working memory measured as % alternation/5 minutes. There was a significant ($p < 0.001$) increase in spatial working memory scores with SV+MEL at 10 and 20 mg/kg compared to control. Compared to SV, spatial working memory increased significantly with SV+MEL at 5, 10 and 20 mg/kg.

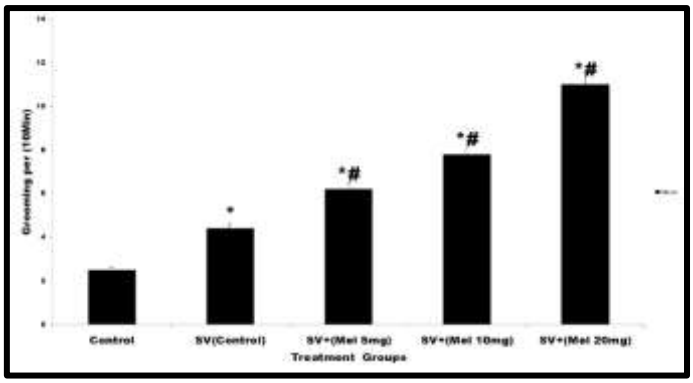

Figure 3: The Effect of Post-Conceptional Melatonin on self-grooming Behavior Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from Mel, number of rats per treatment group =10. SV: Sodium Valproate, Mel: Melatonin.

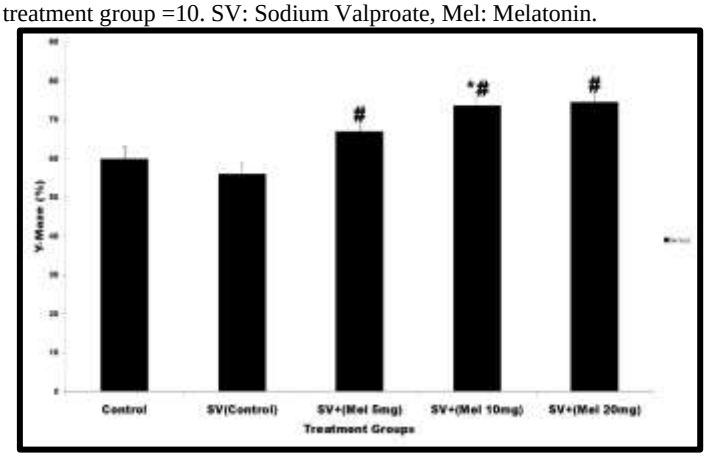

Figure 4: Effect of post-conceptional melatonin in Y-maze Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from Mel, number of rats per treatment group =10. SV: Sodium Valproate, Mel: Melatonin.

3.5 Effect of postconceptional melatonin on open arm time

Figure 5 shows the effect of melatonin on anxiety-related behaviours measured as time spent in the open arm of the elevated plus maze. There was a significant ($p < 0.001$) increase in open arm time with SV+ compared to control. Compared to SV, open arm time decreased significantly with SV+MEL at 5, 10 and 20 mg/kg.

3.6 Effect of postconceptional melatonin on closed arm time

Figure 6 shows the effect of melatonin on anxiety-related behaviours measured as time spent in the closed arm of the elevated plus maze. There was a significant ($p < 0.001$) increase in open arm time with SV+ compared to control. Compared to SV, open arm time decreased significantly with SV+MEL at 5, 10 and 20 mg/kg.

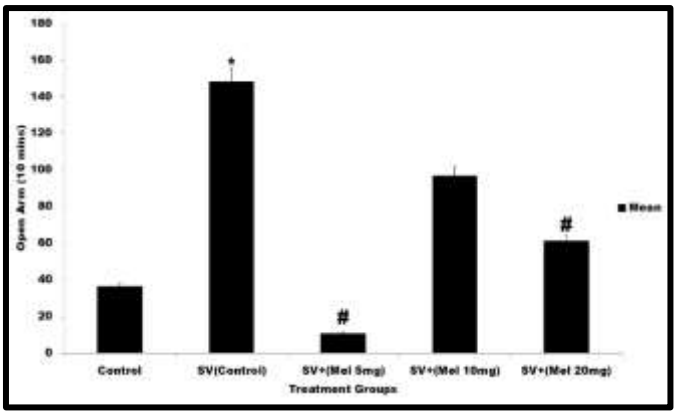

Figure 5: Effect of post-conceptional melatonin on time spent in the open arm of the elevated plus maze. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from Mel, number of rats per treatment group =10. SV: Sodium Valproate, Mel: Melatonin.

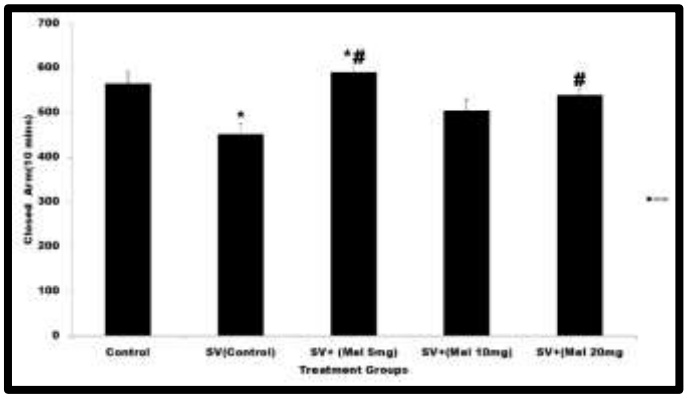

Figure 6: Effect of post-conceptional melatonin in the closed arm of the elevated plus maze. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from Mel, number of rats per treatment group =10. SV: Sodium Valproate, Mel: Melatonin.

3.7 Effect of postconceptional melatonin on social interaction

Figure 7 shows the effect of melatonin on social interaction measured as time spent in the empty or stranger rat compartment. There was a significant ($p < 0.001$) increase in time spent in the empty compartment and a decrease in time spent in the stranger compartment with SV compared to Control. Compared to SV, there was a decrease in time spent in the empty compartment and an increase in time spent in the stranger compartment with SV+MEL at 5, 10 and 20 mg/kg.

3.8 Effect of postconceptional melatonin on Frequency of Compartment Entries

Figure 8 shows the effect of melatonin on the number of entries into empty or stranger rat compartments. There was a significant ($p < 0.001$) decrease in the number of entries into empty or stranger compartments with SV compared to control. Compared to SV, there was an increase in the number of entries into the empty and stranger rat compartment with SV+MEL at 5, 10 and 20 mg/kg.

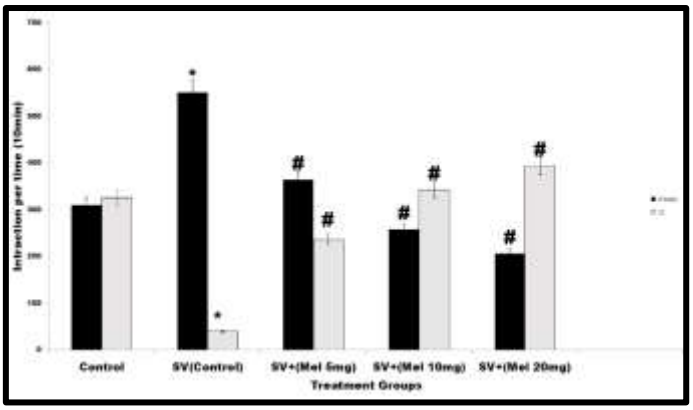

Figure 7: Effect of post-conceptional melatonin on sociability in the social interaction test chamber. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from Mel, number of rats per treatment group =10. SV: Sodium Valproate, Mel: Melatonin.

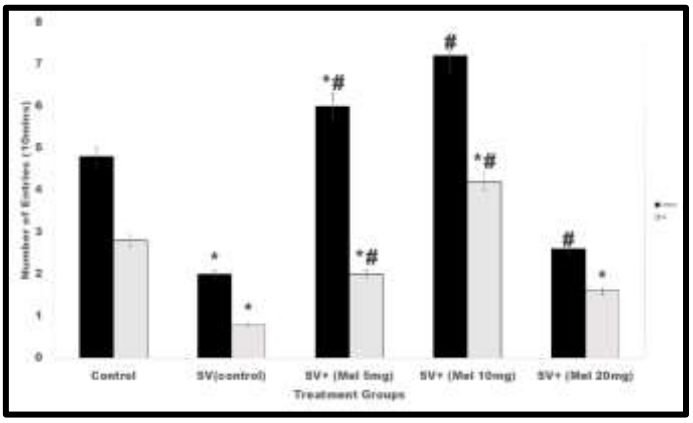

Figure 8: Effect of post-conceptional melatonin in frequency of compartment entries. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from Mel, number of rats per treatment group =10. SV: Sodium Valproate, Mel: Melatonin.

3.9 Effect of postconceptional melatonin on cerebral cortex histomorphology

Plates 1 (A–E) and 2 (A–E), depict representative sections of the rat cerebral cortex stained with haematoxylin and eosin (H&E) and cresyl fast violet (CFV) stains respectively. Examination of the H&E-stained sections from the vehicle-treated rats (Plate 1A) revealed well-defined cortical layers, with multipolar pyramidal cells characterized by large vesicular nuclei scattered within the neuropil. The neuropil, appearing pink in the H&E slides, was well-preserved in the CFV-stained sections (Plates 2A) of groups administered SV/MEL at 5 mg, 10 mg, and 20 mg. Normal-shaped pyramidal cells were interspersed with granule and neuroglial cells in Plates 1A and 2A. In contrast, sections from the group administered SV (Plates 1B, 2B) showed numerous neuroglial cells alongside degenerating pyramidal and granule cells

interspersed among normal cells. Evidence of neuronal degeneration and injury included the presence of pale-staining neurons with shrunken nuclei. In groups administered SV with melatonin at 5, 10 and 20 mg/kg varying degrees of preservation of neuronal cells was observed

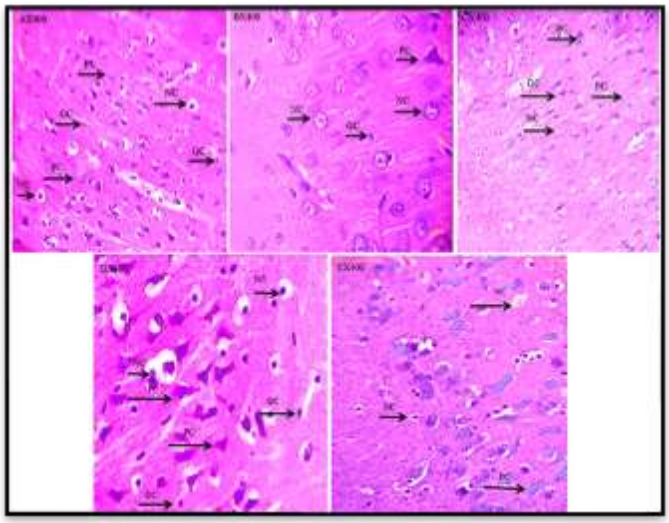

Plate 1: Effect of Melatonin on cerebral cortex morphology of rats stained with haematoxylin and eosin stain. Photomicrographs showed the presence of numerous granule cells (GC), pyramidal cells (PC), and neuroglia cells (Nc) Mag. X 400.

4. Discussion

This study explored the neuroprotective effects of postconceptional melatonin administration on behavioural and structural changes in the cerebral cortex of offspring of dams exposed to sodium valproate prenatally. The findings demonstrated prenatal SV exposure a decrease in self-grooming, spatial memory and social interaction while an increase in locomotor activity and rearing was observed with SV. Post-conceptional melatonin increased, self-grooming, spatial memory and social interaction and decreased rearing and locomotor activity. Administration of SV caused neuronal loss in the cerebral cortex, while melatonin was associated with protection against SV-induced neuronal injury.

Several studies [26-28] have associated prenatal exposure to sodium valproate was associated with the development of behavioural changes including memory and learning disabilities, low verbal intelligence quotient and poor social interaction which are features common to autism spectrum disorders. In this study prenatal SV exposure was associated with central excitatory effects in horizontal locomotion and rearing, spatial working memory loss and reduced social interaction. These observations corroborate the result of studies that had not associated prenatal SV exposure with behavioural deficits but also advanced its use as a rodent model of neurodevelopmental disorders particularly autism [5, 11, 26-29]. Sodium valproate exposure was also associated with a visual decease in stereotypy corroborating the result of Podgorac et al [30]. A decreased in anxiety response was also observed in this study, while a study by Podogorac et al [30] had reported sex differential effects of SV exposure with increased anxiety in males and decreased anxiety response in females; duration of exposure continuous versus single dose administration in this study could also be pivotal to the development or not of anxiety response in SV exposed rat pups. Behaviours in the open field including locomotor activity, grooming and rearing have been attributed to changes in neurotransmitter systems [30]. While the dopaminergic system (mesolimbic) has been implicated in the modulation of locomotor activity; the modulation of self-grooming behaviours has been reported to be dependent on the nigrostriatal dopaminergic inputs [30, 31]. Development of structural brain changes have also been associated with exposure to SV [32-34].in this study, disorganisation of the neuropil, neuronal loss and presence of degenerating pyramidal and granule neurons were observed in the cerebral cortex of rat pups exposed to SV alone. While the mechanisms responsible for SV-induced structural changes are still being investigated, there have been suggestions that diminished neurogenesis, oxidative stress, neuroinflammation and disruption of synaptic transmission are possible mechanisms [35]. Impairments in verbal, non-verbal communication and poor social interaction skills are among the main features of ASD [9, 36]. In this study SV exposure was associated with a decreased in sociability and social interaction. The deficits in social interaction observed in this study corroborate the result so fa number of studies that and also reported reduced social interaction skills in rat pups prenatally exposed to SV [36, 37].

The neuroprotective effects of melatonin have been reported severally [16-20, 38]. In this study, pre-treatment of rat dams with melatonin resulted in a reversal of a number of the behavioural including sociability and social interaction locomotor response, rearing, grooming and working memory score. Also, melatonin mitigated a number of the structural changes observed in the cerebral cortex of SV exposed rats. The behavioural effects of melatonin supplementation are corroborated by Xu et al [39] who examined the impact of melatonin supplementation in a genetic model of ASD and observed that melatonin supplementation reversed autism-like behaviours including. impaired social interaction, typical patterns of social interaction, repetitive and restrictive and behaviours. The beneficial effects of melatonin were attributed to its ability to modulate the sleep wake cycle amongst other mechanisms.

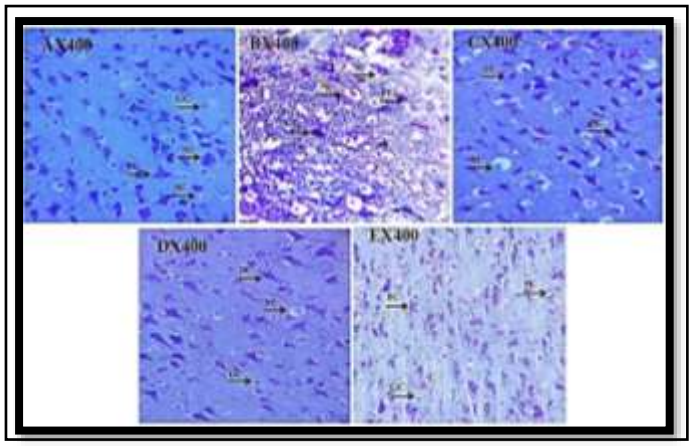

Plate 2: Effect of Melatonin on cerebral cortex morphology of rats stained with cresyl fast violet. Photomicrographs showed distinct layers of the cerebral cortex, with the presence of numerous granule cells (GC), pyramidal cells (PC), neuroglia cells (Nc), and Nissl (NS). Mag. X 100.

Conclusion

This study demonstrated the ability of post-conceptional melatonin administration in mitigating the adverse effects of prenatal sodium valproate (SV) exposure in rat offspring. The findings reveal that melatonin effectively reduces the risk of autistic-like features, counteracting sodium valproate -induced changes in social interaction hyperlocomotion, decreased stereotypic behaviours, memory loss and structural changes in the cerebral cortex. However, continued research is required to further elucidate its clinical applications and evaluate long-term outcomes.

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None

Declaration of Ethical approval

Ethical approval for this study was granted by the Ethical Committee of the Faculty of Basic Medical Sciences (ERC/FBMS/025/2024), LAUTECH.

Competing interests

All authors of this paper declare that there is no conflict of interest related to the content of this manuscript.

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