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RESEARCH ARTICLE

EFFECTS OF SALBUTAMOL ADMINISTRATION ON THE MORPHOLOGY AND CYTOARCHITECTURE OF THE CEREBELLUM AND HIPPOCAMPUS OF ADULT WISTAR RATS

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Abstract

Background: Salbutamol is the most preferred and widely used drug for treating bronchial asthma and bronchospasm. Its abuse has however been reported amongst users. Most of the side effects reports on salbutamol are clinical based such as headache, tremor, weakness etc. This study, therefore, investigated the sub-acute effect of oral salbutamol on the general morphology of the cerebellum and hippocampus of adult Wistar rats.

Method and Material: Twenty adult Male Wistar rats (125 – 224g) were divided into four groups of five rats each. The control (distilled water); the 20mg/kg salbutamol, the 30mg/kg salbutamol, and the 40mg/kg salbutamol groups. Drugs were administered orally for 21 days. The body weight of each animal was monitored throughout the experiment. On day 22, animals were euthanized, brains excised, fixed in 10% buffered formal-saline, cerebelli and hippocampi were identified and processed with Haematoxylin and Eosin staining techniques. Data were analysed by ANOVA at $p \leq 0.05$ level of significance using SPSS and results presented as mean ± SEM

Results: Results showed that the animals that received 30mg/kg and 40mg/kg salbutamol had significant weight loss. The cerebellum of the 40mg/kg group showed eroded granule cell layer. Hippocampus also revealed pyknotic cells in the pyramidal cell layers at 30mg/kg and 40mg/kg.

Conclusions: This study showed that salbutamol at relatively higher doses caused significant weight loss; degeneration of cerebellum granule cells, which might affect motor coordination; and pyknosis of hippocampal pyramidal cells which may affect learning and memory.

Keywords: Salbutamol, weight loss, brain, degeneration.

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INTRODUCTION

Salbutamol (trade name Ventolin) is the most preferred and widely used drug prescribed for the treatment of Asthma because of its longer duration of action and its low cost of purchase.[1] Salbutamol is a short-acting beta-2 adrenergic receptor agonist and it activates adenylate cyclase and increases cyclic AMP synthesis that leads to a relaxation of bronchial smooth muscle.[2] The receptor for the binding of salbutamol for its mechanism of action is the beta 2 receptor cells which are present in the lungs and the brain.[3] It has an inhibitory effect on some inflammatory cells such as mast cells, eosinophils, and cytokines.[4] Biotransformation of salbutamol occurs in the liver by the phenylsulfotransferase enzyme.[5] When salbutamol is conjugated with the sulfatase enzyme, 4'-O-sulfate salbutamol is produced, and this has higher water solubility. The minor metabolic pathway is via the cytochrome P450 enzyme system. Salbutamol is actively eliminated by renal excretion in both its conjugated and parent forms.[6] The recommended dosage of oral salbutamol for adult is 4mg administered three to four times daily and it is being used for the therapeutic treatment of bronchospasm in bronchial asthma, chronic bronchitis, and emphysema. Salbutamol, a moderately selective beta (2)-receptor agonist is widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases. Recently, salbutamol abuse is becoming a common cause of hospital admission among patients. Salbutamol overdose intake has been associated with its low cost of purchase, low pharmacological response, and wide availability.[7] Marchant-forde2 reported that the body weight of pigs fed with 2 mg/kg (R)-salbutamol for 4 weeks significantly increased compared with those of the control, the 4 mg/kg and the 8 mg/kg groups. Some side effects of salbutamol such as headache, tremor, anxiety, dry mouth, palpitation, and muscle cramps have been established.[8] Emerging research indicates that individuals with asthma suffer from higher rates of cognitive and memory impairment compared to the healthy population[9] across their life span. However, biological correlates of these behavioral deficits remain unknown. The primary neural region involved in memory is the hippocampus, a structure integral for encoding episodic memory and memory consolidation.[10]

The cerebellum is a vital component in the human brain as it plays a role in motor movement regulation and balance control. The cerebellum coordinates gait, maintains posture, controls muscle tone and voluntary muscle activity. Damage to this area in humans resulted in a loss of the ability to control fine movements; maintain posture and motor learning.[11] The hippocampus is the predominant neural structure involved in memory, and alterations in the hippocampal metabolic profile are observed in individuals with mild cognitive impairment.[12] Most of the data available in the literature on the effects of salbutamol abuse are clinical based side effects. Experimental research reports on the histological effects of salbutamol abuse on the organs of the body, especially the brain are rather too scarce. Thus, this study was designed to investigate the sub-acute effect of oral administration of salbutamol on the histology of cerebellum and hippocampus of adult Wistar rats.

METHODOLOGY

The study was conducted in the Department of Medical Laboratory Science, Faculty of Pure and Applied Sciences, Kwara State University over a period of three weeks. Twenty (20) adult-male Wistar rats weighing between 125 – 224g were used. They were housed in transparent plastic cages with wood shavings as beddings, and within a freely ventilated and naturally illuminated animal house. The rats were fed with standard rat feed and allowed free access to drinking water according to guidelines and regulations of Organization for Economic Cooperation and Development.[13]

Procurement and preparation of salbutamol

The Salbutamol used was manufactured by Alpha Laboratories limited (Pigdamber, India) with batch number TE9107 and was obtained from a reputable Pharmacy in Ilorin, Kwara State, Nigeria. The stock solution of the drug dosage was prepared according to guidelines on dosage calculations and stock solution preparation in experimental animals' studies after which the drug dose for each animal was calculated based on OECD guideline of 10ml/kg.[14]

Animal Grouping and Dosages

The rats were randomly divided into four groups of five (5) animals per group.

- ✓ **Control group** - This group was allowed free access to distilled water.
- ✓ **20mg/kg body-weight group** - The group was administered oral salbutamol of 20mg/kg body weight for 21 days.
- ✓ **30mg/kg body-weight group** - The group was administered oral salbutamol of 30mg/kg body weight for 21 days.
- ✓ **40mg/kg body-weight group** - The group was administered oral salbutamol of 40mg/kg body weight for 21 days.

The rats were allowed access to feed and water ad-libitum.

The weights of the rats were taken fortnightly of the experiment with electronic weighing balance (Model: RS 225, Range: 0-600g, Make: Citizen). The difference between the initial body weight (at day 1) and the final body weight (at day 21) were calculated to determine weight gain or loss.

Ethical approval

Ethical approval to carry out the study was sought and obtained from the Kwara State University Centre for Research and Development with reference number KWASU/CR&D/REA/2022/0003.

Data Analysis

Data collected was analysed by Statistical Package for Social Sciences (SPSS) version 20 using one-way analysis of variance (ANOVA) followed by Tukey Post-hoc test for multiple comparison. Data were presented as Mean ± SEM and the level of statistical significance was taken at $p<0.05$.

RESULTS

(A) Morphological observations

Physical observation

The rats were observed to be restless within a short period after administration of salbutamol but later became docile.

Body Weight

The rats in the control group had increase in body weight while the groups that received 20mg/kg, 30mg/kg and 40mg/kg body weight of oral salbutamol had reduced body weights. However, only the rats in 30mg/kg and 40mg/kg groups had significant reduction in their body weights after sub-acute consumption of salbutamol for 21 days, compared with the control group (see Table 1).

(B) Histology of the Cerebellum

The three layers of the cerebellum: granule cell, Purkinje cell and molecular cell layers appeared normal without any pathological changes in the control group. A similar presentation was observed in the groups that received 20mg/kg and 30mg/kg salbutamol. However, in the group of 40mg/kg salbutamol, the Purkinje cell and molecular cell layers had normal appearance similar to the control and other groups, but the granule cell layer appeared degenerated (figure 1).

Histological section of the hippocampus revealed that the control group had normal pyramidal cell layer with the pyramidal cells appearing healthy and normal. The 20mg/kg salbutamol group showed evidence of pyknosis, a characteristic shrinkage or condensation in the nucleic substance (red arrow). Similarly, the groups that received 30mg/kg and 40mg/kg oral salbutamol show more evidence of pyknotic cells (red arrow) (see figure 2).

DISCUSSION

The docilely mood of the animals shortly after receiving the drugs may suggest that the drug initiates muscle weakness in the animals[8] and subsequently reported muscle tremor as one of the side effects of salbutamol.

The result of the body weight revealed that, consumption of salbutamol at 30mg/kg and 40mg/kg caused significant reduction in the body weights of the Wistar rats compared with the control group. This depicted that salbutamol consumed at 30mg/kg and 40mg/kg was detrimental to the body weight of the experimental animals. The reduction in body weight of the animals caused by salbutamol at 30mg/kg and 40mg/kg may be hinged on low consumption of feed by these animals due to anxiety or restlessness. This agrees with the previous submission that salbutamol caused anxiety as its side effects in human.[8] Contrarily, [2] in their study found a significant increase in body weight of pigs fed with 2mg/kg (R)-salbutamol for 4 weeks compared with those of the control, the 4mg/kg and the 8mg/kg groups.

The result of the histology revealed that salbutamol, consumed at 40mg/kg body weight for a period 21 days led to the pyknosis

of the cells in the granular layer of the cerebellum. This indicated that abuse of salbutamol (incessant consumption at abnormally higher dosages) within the sub-acute period of 21 days is deleterious to the normal structure of the cerebellum, and this may consequently affect the function of the cerebellum in muscular coordination, balancing and equilibrium. This is in consonance with the findings of[8] who reported that oral consumption of salbutamol posed some side effects like tremor and muscle cramps.

Similarly, the hippocampus is involved in coordinating spatial memory, cognition, and learning. The damage caused by salbutamol overdose consumption on the hippocampus pyramidal cells may be an indication that the drug would retard spatial memory, cognition, and learning. This finding corroborates the report of [12] who found out that more frequent use of rescue inhaler (short-acting bronchodilator) was related to lower levels of hippocampus metabolites and affected hippocampus chemistry - an indication of poorer cognitive function and impaired spatial memory and learning.

CONCLUSION

We were able to establish, from this study, that oral administration of salbutamol at 30mg/kg and 40mg/kg resulted in loss of body weight and damaged the cerebellum and hippocampus of adult Wistar rats. This might lead to serious complications involving memory loss, cognition defects, learning deficits and motor coordination disorder.

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ANNEX

TABLE 1. Body Weights of the Rats following Administration of Salbutamol

Groups/ Dosage of salbutamol	Initial Body Weight (g) (n=5)	Final Body Weight (g) (n=5)	Weight Difference (%)
Control	103.00±7.11	105.00±10.86	+1.94
20mg/kg	137.40±8.62	132.00±7.65	-3.94
30mg/kg	154.80±5.72	142.80±6.91	-7.79*
40mg/kg	186.20±29.34	170.60±34.16	-8.38*

Asterisk (*) indicates significant decrease at p≤0.05 when compared to the control.

FIGURE 1. Section of the Cerebellum of the Wistar rats: H&E (X400). Control (Distilled water); ML = Molecular layer; PL = Purkinje cell layer; GL = Granular layer; DG = Degeneration.

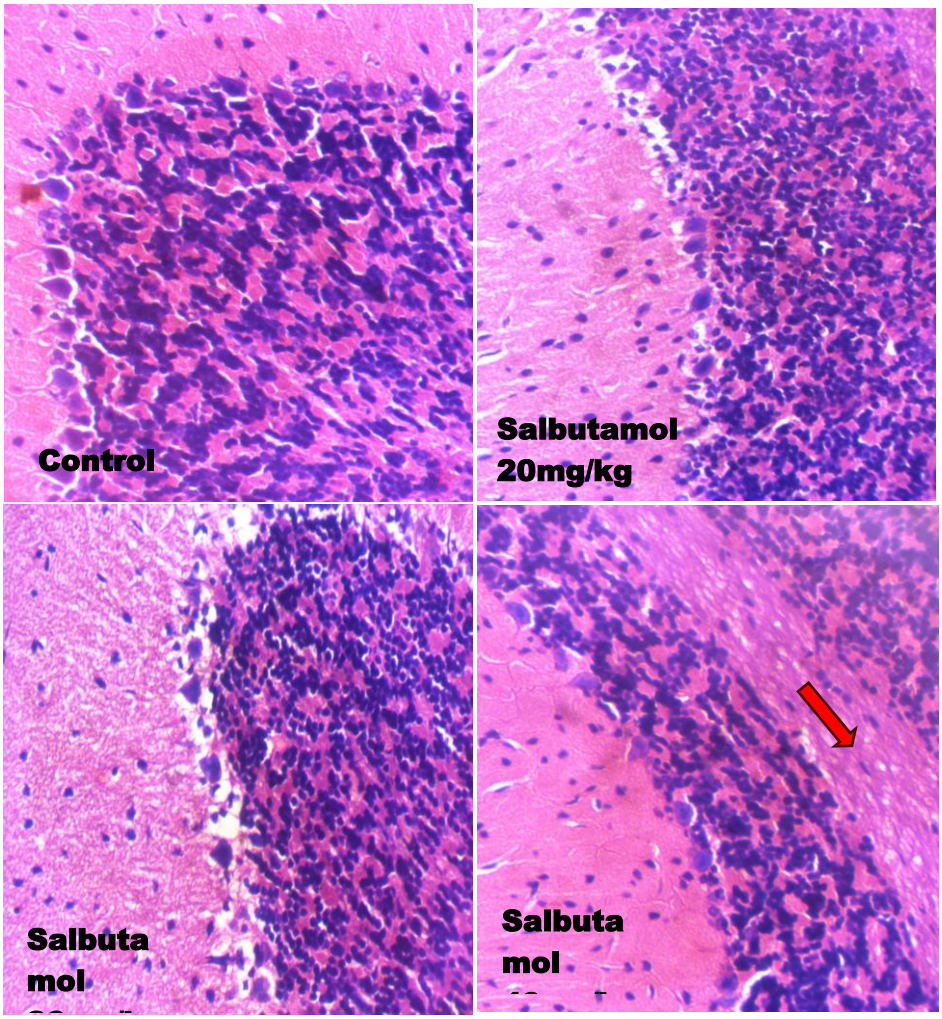

Figure 2. Section of the Hippocampus of the Wistar rats: H&E (X400). Control = Distilled water, ML= Molecular layer; PC = Pyramidal cell layer; PL = Polymorphic layer; Red arrows = Pyknotic cells.