High-Dose of oral Montelukast Induces Monoamines Depletion and brain-Derived Neurotrophic Factor BDNF Upregulation in male Rat's Brain

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Abstract:

Background: Montelukast, a leukotriene D4 antagonist used for asthma and allergic rhinitis, has been increasingly linked to neuropsychiatric effects, including mood disorders and suicidality. ***Its*** impact on central monoamine neurotransmitters and neurotrophic factors remains unclear.

Objective: This study aimed to evaluate the impact of montelukast on monoamine neurotransmitters and brain-derived neurotrophic factor (BDNF) in rats, in conjunction with a histological analysis of brain tissue.

Methods: Thirty-five male albino rats were randomly assigned to five groups (n=7 each): a negative control, a positive control given reserpine (0.2 mg/kg, i.p.), and three groups receiving oral montelukast at 5, 10, and 20 mg/kg/day for 14 days. Monoamines (dopamine, serotonin, norepinephrine) and BDNF were measured using ELISA. Histopathological changes were examined with H&E staining.

Results: Montelukast treatment resulted in a dose-dependent decrease in dopamine, serotonin, and norepinephrine, akin to the monoamine depletion caused by reserpine. Notably, BDNF levels were markedly increased in both the reserpine group and the high-dose montelukast group (20 mg/kg). Histological analysis demonstrated normal neuronal morphology at low dose, but higher doses (10 and 20 mg/kg/day) resulted in moderate vascular congestion and neuronal edema without necrosis.

Conclusion: Montelukast causes considerable monoamine depletion and a counterintuitive increase in BDNF at elevated dosages, with initial neurotoxic histopathological alterations in the brain tissues of male rats. Further detailed studies are warranted to determine whether these modifications contribute to the neuropsychiatric side effects observed in clinical environments.

Key words: Montelukast, Reserpine, BDNF, Serotonin, Dopamine

جرعات عالية من المونتيلوكاست المعطى فمويا تُحدث استنزافًا للأحاديّات الأمينية مع زيادة في تنظيم عامل التغذية العصبية المشتق من الدماغ في ادمغة الجرذان الذكور

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الخلاصة:

يُعدّ المونتيلوكاست، وهو مضاد لمستقبل اللوكوترين د4 يُستخدم عادة في علاج الربو والتهاب الأنف التحسّسي، من الأدوية التي ارتبطت تدريجيًا بآثار جانبية نفسية-عصبية مثل اضطرابات المزاج والانتحار. ومع ذلك، فإن تأثيراته على الناقلات العصبية الأحادية الأمين المركزية والعوامل العصبية المغذّية لم تُفهم بالكامل بعد.

الهدف: كان الهدف من هذا البحث تقييم تأثير المونتيلوكاست على الناقلات العصبية الأحادية الأمين (الدوبامين، السيروتونين، النورأدرينالين) وعلى عامل التغذية العصبية المشتق من الدماغ في الجرذان، وذلك بالتوازي مع التحليل النسيجي لأنسجة الدماغ.

طرق العمل: تم توزيع خمسة وثلاثين جرذًا أبيض اللون ذكرً عشوائيًا إلى خمس مجموعات (7 جرذان لكل مجموعة): مجموعة ضابطة سالبة، مجموعة ضابطة موجبة عُولجت بالريزيربين (0.2 ملغم/كغم/يوم، حقن داخل الصفاق)، وثلاث مجموعات عُولجت فمويًا بالمونتيلوكاست بجرعات 5، 10، و20 ملغم/كغم/يوم لمدة 14 يومًا. جرى قياس مستويات الناقلات العصبية (الدوبامين، السيروتونين، النورأدرينالين) وعامل التغذية العصبي باستخدام تقنية المقايسة المناعية المرتبطة بالإنزيم، بينما جرى تقييم التغيرات النسيجية المرضية في عينات الدماغ بواسطة صبغة الهيماتوكسيلين والإيوزين.

النتائج: أدى علاج المونتيلوكاست إلى انخفاض يعتمد على الجرعة في مستويات الدوبامين والسيروتونين والنورأدرينالين، مشابهًا للاستنزاف الأحادي الأمين الناتج عن الريزيربين. ولوحظ بشكل لافت ازدياد كبير في مستويات وعامل التغذية العصبي في كل من مجموعة الريزيربين ومجموعة المونتيلوكاست عالية الجرعة (20 ملغم/كغم/يوم). أظهر التحليل النسيجي مورفولوجيا عصبية طبيعية عند الجرعات المنخفضة، بينما سببت الجرعات الأعلى (10 و20 ملغم/كغم/يوم) احتقانًا وعائيًا متوسطًا ووذمة عصبية دون حدوث تنخر.

الاستنتاجات: يؤدي المونتيلوكاست إلى استنزاف كبير في الناقلات العصبية الأحادية الأمين وزيادة تعويضية في مستويات وعامل التغذية العصبي عند الجرعات المرتفعة، مع ظهور تغيّرات نسيجية عصبية أولية سامة. قد تسهم هذه التعديلات في الآثار الجانبية النفسية-العصبية التي لوحظت سريريًا.

الكلمات المفتاحية: مونتيلوكاست، ريزيربين، عامل التغذية العصبية المشتق من الدماغ(BDNF) ، السيروتونين، الدوبامين

Introduction

Montelukast, a cysteinyl leukotriene receptor antagonist primarily prescribed for asthma and allergic conditions, has recently been associated with neuropsychiatric adverse events, including anxiety, depression, and sleep disturbances. Although several reports suggest that montelukast may influence neuroinflammatory signaling and glial activation, the underlying neurochemical mechanisms remain poorly defined. Previous studies have largely focused on inflammatory markers without directly evaluating whether montelukast alters central monoaminergic neurotransmission, a critical determinant of mood and behavior(1)

Therefore, the present study was undertaken to investigate whether montelukast exerts neurochemical effects comparable to monoamine-depleting agents and whether compensatory upregulation of brain-derived neurotrophic factor (BDNF) occurs as a homeostatic response to neurotransmitter depletion. By examining dopamine, serotonin, norepinephrine, and BDNF levels across graded montelukast doses, this study provides new insight into the potential

mechanistic link between leukotriene receptor blocker, monoamine modulation, and neurotrophic(2)

Montelukast is a leukotriene D4 inhibitor widely utilized in the management of asthma, allergic rhinitis, and various other respiratory disorders(3).Additionally, there are numerous efforts to repurpose the drug for other conditions, such as neurodegenerative diseases and rheumatoid arthritis(4,5). Conversely, there are several reports of neuropsychiatric adverse effects associated with montelukast use This issue has been prompted by a warning from the FDA on a potential correlation between montelukast and suicidal attempts in users of this medicine(6)

According to one research, montelukast may interfere with the production of hormones and neurotransmitters in the prefrontal cortex, which might be the source of the neuropsychiatric disorders linked to the drug, It affects the pathways of branched-chain amino acids (leucine, isoleucine, and valine), which are essential for the synthesis of neurotransmitters, including dopamine, adrenaline, noradrenaline, histamine, and serotonin (5-hydroxytryptamine, 5-HT(7).

Monoamine neurotransmitters, including norepinephrine (NE), serotonin (5-HT), and dopamine (DA), play a crucial role as bioactive signaling molecules within the central nervous system (CNS). Monoaminergic (MA-ergic) systems regulate the gastrointestinal, respiratory, and cardiovascular systems, while also modulating mood, cognition, sleep, nociception, temperature, perspiration, and additional processes(7). MA-ergic systems are involved in numerous physiological processes that modulate CNS inflammation, which may be triggered by factors including infection, traumatic brain injury, toxic metabolites, or autoimmune responses(8).

Any chemical or drug that dysregulates this system may lead to significant dysfunction in the activity of the central nervous system(9). By examining the monoaminergic pathway and serum BDNF, this research aims to demonstrate whether montelukast may induce mood disturbances.

Methods:

Statement of ethical principles.

All animal operations received approval from the Animal Ethics Committee of Mustansiriyah University, Baghdad, Iraq (Approval No: [54]). Rats were anesthetized by intraperitoneal administration of ketamine (100 mg/kg, 10%, Alfasan, Holland) and xylazine (10 mg/kg, 20 mg/ml, Kepro, Holland). Euthanasia was conducted at the experiment's end by an overdose of ketamine/xylazine. This process followed the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals (2020). All measures were taken to reduce animal suffering.

Materials.

The materials used included reserpine and montelukast powder from Sigma, Germany. Dimethyl sulfoxide and acetic acid were acquired from Mumbai, India. Corn oil was from Sigma Aldrich, Germany, and distilled water from Pioneer, Iraq. The xylazine vial (20 mg/ml) came from Kepro, Holland, and the ketamine vial (10%) from Alfasan, Holland. Hematoxylin and eosin were from Sigma, Germany.

Animals used in the study.

This experimental animal research used thirty-five albino male rats weighing between 150 and 200 grams. Rats were housed in ample, comfortable cages after being procured from the animal facility of the Iraqi Centre for Cancer and Medical Genetics Research (ICCMGR) at Mustansiriyah

University. They were allowed to acclimate for 21 days in a controlled setting. The schedule consisted of 12 hours of light and 12 hours of darkness, with a temperature maintained at 25 ± 1°C and humidity levels ranging from 40% to 50%. They possess unrestricted access to food and drink *ad libitum.* the dose of the drugs was administered at 8 a.m.m.

study groups

Rats were then randomly allocated into five groups. Each group has seven rats.

i. Group 1 (n=7): Negative control group; rats were administered a combination of distilled water, , maize oil, and 5% DMSO orally daily for 14 days(10).
ii. Group 2 (n=7): The positive control group of rats received an intraperitoneal administration of reserpine at a concentration of 0.2 mg/kg/day of body weight once daily for 14 days.
iii. Group 3 (n=7): rats orally received montelukast at a dosage of 5 mg/kg for a duration of 14 days.
iv. Group 4 (n=7): rats orally received montelukast at a dosage of 10 mg/kg/day for a duration of 14 days.
v. Group 5 (n=7): rats orally received a montelukast dosage of 20 mg/kg/day for a duration of 14 days(11).

Drugs preparations.

Preparation of medication and dosages to make 0.2 mg/kg of reserpine, we first made a working solution of 1 mg of reserpine that dissolved in 5 ml of diluted glacial acetic acid. The glacial acetic acid was at a 5% concentration, and we mixed it well in a glass tube by vortex until it was completely dissolved. This gave us a final concentration of 0.2 mg/1 ml of reserpine, from which we injected about 0.2 ml to 0.175 ml intraperitoneally.

Five milligrams of montelukast were put into a laboratory glass to make a 5% DMSO solution. Then, a little bit of DMSO was added, and the mixture was agitated until the montelukast was fully dissolved. Corn oil was then utilized as a diluent and a vehicle of administration, and 5 mg/ml of montelukast solution was delivered orally. The dose was split up depending on how much the animals weighed, and the Table (1)**: Montelukast per dosage group and their associated volume of delivery.** below shows how each group is represented.

Table (1): Montelukast per dosage group and their associated volume of delivery.

Group of animals	The volume of a drug administration
Group III (5mg/kg)	0.2ml
Group IV (10mg/kg)	0.4ml
GROUP V (20mg/kg)	0.8ml

On day 14, rats were allowed to undergo a 12-hour fast and after 4 hours from the last dose they were anesthetized with intraperitoneal injections of ketamine and xylazine at dosages of 100 and 10 mg/kg, respectively. After scarified blood samples were obtained from the apex of the heart (left ventricle) with a 5ml syringe, gauge 23, put in gel tubes, and let to clot for 15 minutes at ambient temperature(12). They were then centrifuged for 15 minutes at 3000 RPM. The collected serum was divided into Eppendorf tubes (1.5 ml). They were stored at −20 °C to measure blood concentrations of BDNF, serotonin, norepinephrine, and dopamine.

Dosing Rationale:

Montelukast doses of 5, 10, and 20 mg/kg/day were selected to model escalating exposure levels. Using standard body surface area conversion, these doses correspond to approximately 57, 113, and 227 mg/day for a 70-kg adult substantially higher than the therapeutic human dose of 10 mg/day. Thus, all doses represent toxicological exposures, due to rodent–human pharmacokinetic differences, reduced blood–brain barrier penetration at normal doses, and the need for supratherapeutic exposure to detect early neurochemical/histological effects support the use of high-dose modeling(13)

Vehicle and solubility rationale.

Montelukast is highly lipophilic and shows limited aqueous solubility; therefore, a mixed vehicle was used to ensure complete dissolution, uniform dosing, and consistent gastrointestinal delivery across the 14-day oral administration period. The vehicle components were selected for complementary roles for this DMSO (5%) was used as a co-solvent to facilitate initial dissolution of montelukast powder before dilution; with corn/maize oil which served as the primary oral carrier to improve dispersion of the lipophilic drug and maintain dose uniformity, Importantly, the negative control group received the same vehicle mixture without montelukast, so that any effects attributable to the vehicle were balanced across groups.

Collection of tissue:

Upon the experiment's conclusion (day 14), subsequent to euthanasia, the skull was dissected, and the brains of seven rats from each group were removed and washed with cold phosphate-buffered saline (PBS, pH 7.4) to remove remaining blood and debris. Subsequently, the tissue was dried using filter paper and then preserved in 10% neutral buffered formalin (NBF) for histological investigation, thereby protecting the tissue architecture from autolysis.

Enzyme-Linked Immuno-Sorbent Assay (ELISA).

We utilize the obtained blood serum from rats to determine brain-derived neurotrophic factor (BDNF) using the sandwich method, in accordance with the manufacturer's instructions (14), and to determine dopamine, serotonin, and norepinephrine using a competitive technique (15). The kit's origin and catalog number are shown below in Table (2), also, it is important to note that neurotransmitters and BDNF were quantified from serum samples rather than brain tissue. Serum concentrations do not directly represent central nervous system (CNS) levels because peripheral measurements are influenced by systemic metabolism, peripheral release, and blood–brain barrier dynamics. Therefore, the values obtained in this study should be interpreted as peripheral biochemical changes rather than direct indicators of brain neurotransmitter or neurotrophic activity.

Table (2): the used ELISA kits and their catalog no.

Elisa kit	Catalog no.	Manufacturer
Rat-BDNF	Elabscience	E-EL-R1235
Rat-SEROTONIN	Elabscience	E-EL-0033
Rat-NOREPINEPHRINE	Elabscience	E-EL-0047
Rat-DOPAMINE	Cloud-clone corp.	CEA851Ge

Histopathologic procedure

The brain of different groups was removed and fixed in 10% formol saline. Paraffin sections (5 µm thick) were stained with haematoxylin and eosin (Hx & E) , The severity of neuronal damage was scored using a semi-quantitative grading system(14).

Statistical analysis

Analyses were performed in SPSS v26 and GraphPad Prism v9 (Excel 2021 for data verification/graphics). Data are reported as mean ± SD in tables and mean ± SEM in figures. Two-tailed tests were used with $\alpha = 0.05$; exact p values are given where possible, and figures use $p < 0.05$, $p < 0.01$, $p < 0.001$. Assumptions were examined by Shapiro–Wilk tests and Q–Q plots (normality) and Levene's test (homogeneity).

Results

Neurotransmitter Levels

Analysis of serum neurotransmitter levels revealed alterations across treatment groups. As shown in Table (3) and figures (1,2,3and5), dopamine levels were significantly reduced in the reserpine group (9.74 ± 1.12 pg/ml) compared to the control (45.41 ± 8.47 pg/ml). Montelukast treatment produced dose-dependent reductions in dopamine, with levels of 31.49 ± 0.87 pg/ml, 23.55 ± 0.69 pg/ml, and 19.64 ± 4.77 pg/ml for the 5, 10, and 20 mg/kg doses, respectively. Also, because all measurements were obtained from serum, these findings should not be interpreted as direct CNS concentrations. Serum monoamine and BDNF levels may not accurately reflect changes within specific brain regions, and therefore, the present results represent peripheral alterations associated with treatment rather than definitive central neurochemical effects.

Table (3): serum level of monoamine neurotransmitter (Mean ± SD) in study groups.

Parameter	G1 (Control)	G2 (Reserpine)	G3 (MTK 5mg/kg)	G4 (MTK 10mg/kg)	G5 (MTK 20mg/kg)	p-value
Dopamine (pg/ml)	45.4 ± 3.2[a]	**9.7 ± 0.4[b]**	**31.5 ± 0.3[c]**	**23.6 ± 0.3[c]**	**19.6 ± 1.8[d]**	<0.001
Serotonin (ng/ml)	126.3 ± 4.5[a]	**60.6 ± 0.1[c]**	127.1 ± 9.9[a]	**103.3 ± 1.3[b]**	**75.5 ± 1.2[c]**	<0.001
Norepinephrine (ng/ml)	5.7 ± 0.6[a]	**1.9 ± 0.1[b]**	**6.2 ± 1.2[a]**	5.7 ± 0.4[a]	**2.6 ± 0.1[b]**	<0.001

Comprehensive Post-hoc Analysis: *Different superscript letters indicate significant differences ($p < 0.05$, Tukey HSD).*

Key Findings: *All monoamines significantly depleted at higher*

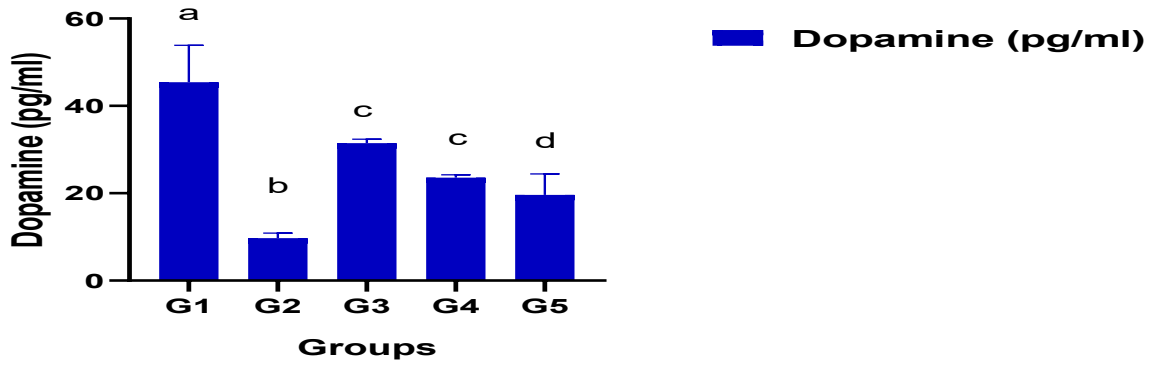

Figure (1): Serum Dopamine (Mean ± SD) across study groups One-way ANOVA with Tukey HSD post-hoc test. Different superscript letters indicate significant differences in p-value ($p < 0.05$, Tukey HSD) between the different groups

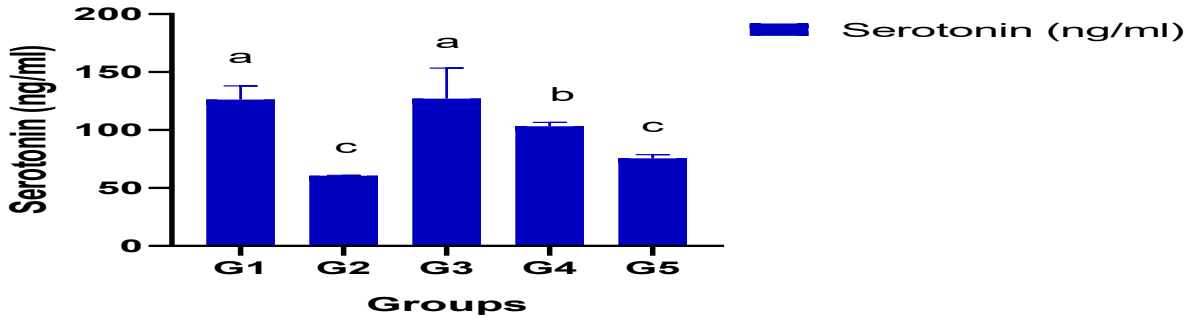

Figure (2): Serum Serotonin (Mean ± SD) across study groups One-way ANOVA with Tukey HSD post-hoc test. Different superscript letters indicate significant differences in p-value ($p < 0.05$, Tukey HSD) between the different groups

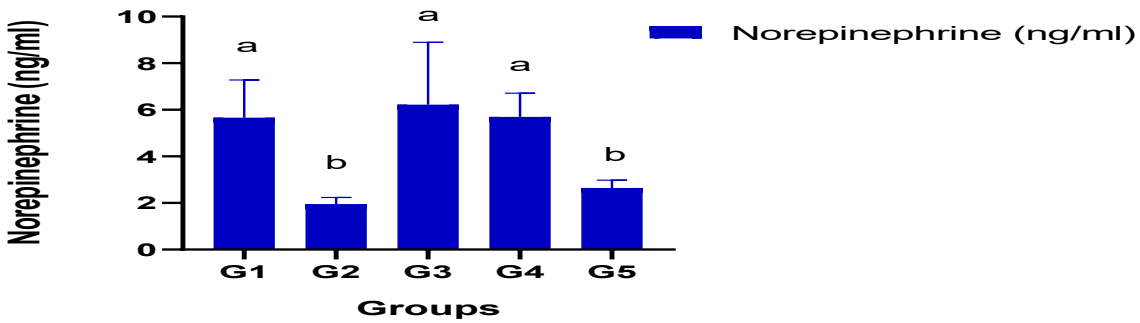

Figure (3:) Serum Norepinephrine level (Mean ± SD) across study groups One-way ANOVA with Tukey HSD post-hoc test. Different superscript letters indicate significant differences in p-value ($p < 0.05$, Tukey HSD) between the different groups

Serum Brain-derived neurotrophic factor (BDNF) levels showed significant variations among groups. The reserpine group exhibited elevated BDNF levels (566.33 ± 9.19 pg/ml) compared to control (392.42 ± 24.45 pg/ml). Montelukast treatment at 20 mg/kg also increased BDNF levels (493.57 ± 42.09 pg/ml) this can be notice in t Serum BDNF level (Mean ± SD) in study groups Table (4) and Figure (4) and (5).

Table (4): Serum BDNF level (Mean ± SD) in study groups.

Parameter	G1 (Control)	G2 (Reserpine)	G3 (MTK 5mg/kg)	G4 (MTK 10mg/kg)	G5 (MTK 20mg/kg)	p-value
BDNF (pg/ml)	392.4 ± 9.2[a]	**566.3 ± 3.5[d]**	**325.0 ± 12.6[b]**	387.2 ± 9.4[a]	**493.6 ± 15.9[c]**	<0.001

BDNF = Brain-derived neurotrophic factor; MTK = Montelukast; n=7 per group, ***Comprehensive Post-hoc Analysis:*** *Different superscript letters indicate significant differences ($p < 0.05$, Tukey HSD).* ***Key Findings:*** *BDNF protein paradoxically increased*

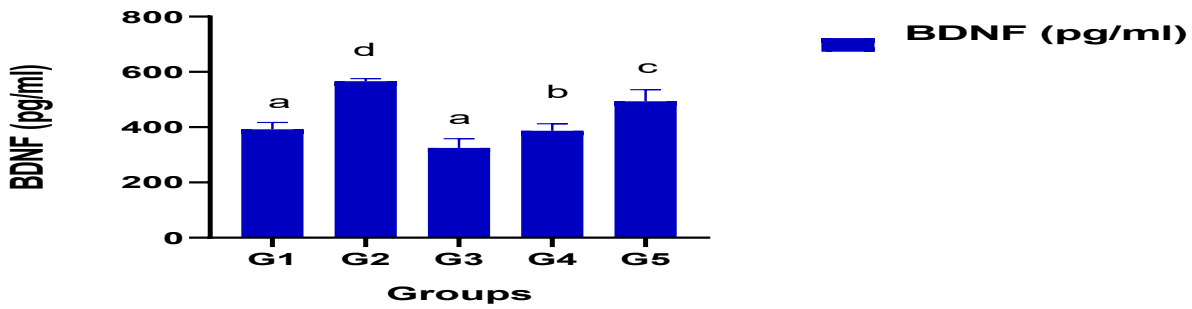

Figure (4): Serum BDNF (Mean ± SD) across study groups One-way ANOVA with Tukey HSD post-hoc test. Different superscript letters indicate significant differences in p-value ($p < 0.05$, Tukey HSD) between the different groups

Histopathology:

Group 1(negative control): *The figures of the basal ganglion showed normal appearance and arrangement of neurons and glial cells of the caudate nucleus, globus pallidus and putamen as presented in figure (6).*

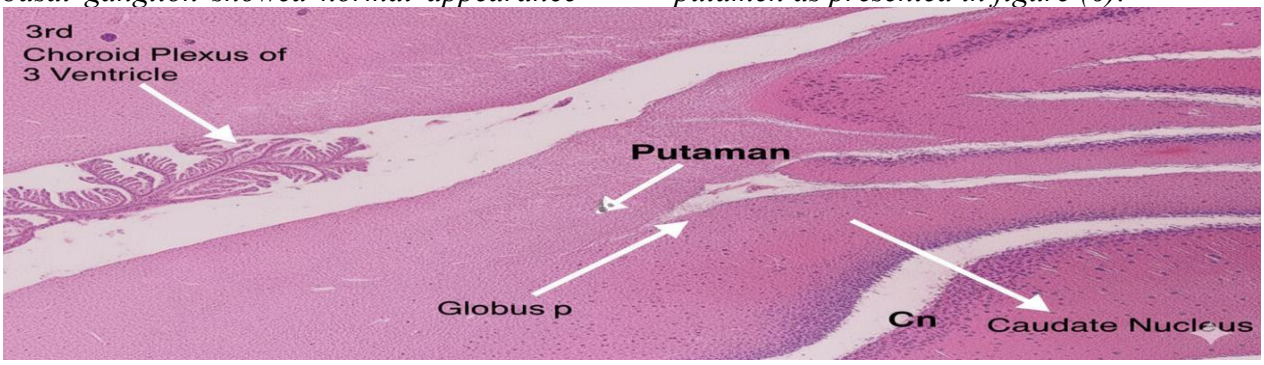

Figure (5): Basal ganglia (Control) show: normal appearance and arrangement of the neurons within caudate nucleus (Cn), globus pallidus (p), putamen (P) & normal choroid plexus of ventricle (3[rd]) H&E stain.40x

Group 2(positive control): The thalamus and 3rd ventricle showed severe congestion of choroid blood vessels and severe vacuolation of nervous tissue within thalamic massa (demyelination) as presented in figure (7).

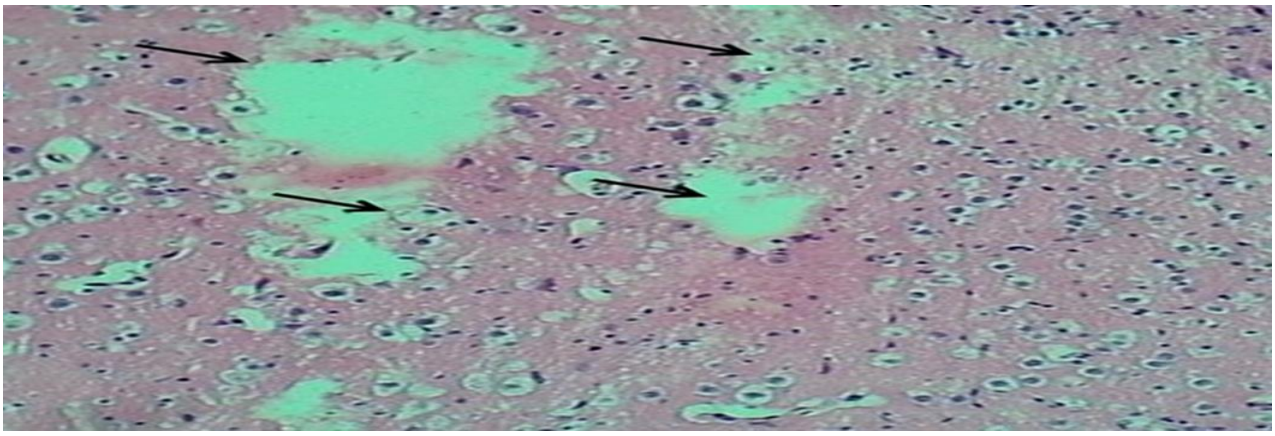

Figure (6): Thalamus (Control positive) shows: severe vacuolation associated with degeneration and necrosis of nervous tissue within (demyelination) & tissue depletion (black arrows). H&E stain.100x

Group3 (montelukast 5mg/kg): The basal ganglion caudate nucleus, globus pallidus, putamen had normal appearance of the myelin with normal neurons and glial cells in addition for choroid plexuses of 3rd ventricle as presented in figure (8).

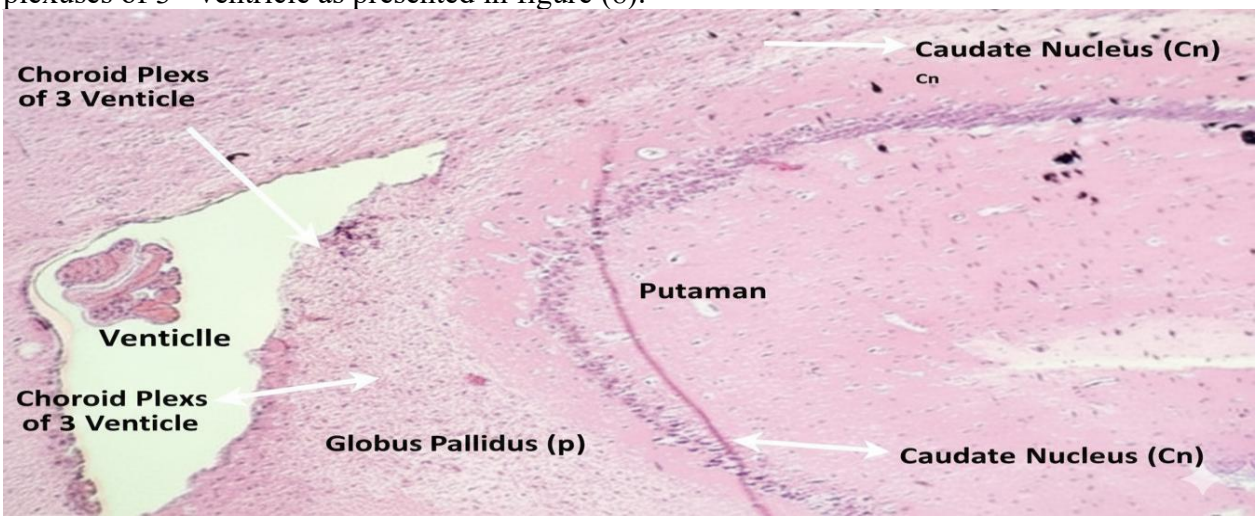

Figure (7): Basal ganglia (m1) show: normal appearance with arrangement of neurons & glial cells of basal ganglion (Cn) & putamen (p) & 3rd ventricle (3rd). H&E stain.40x

Group 4 (montelukast 10mg/kg): The basal ganglion caudate nucleus, globus pallidus, putamen had normal appearance of the myelin with normal neurons and glial cell. Figure (10) showed mild congestion of choroid blood vessels as presented in figure (9-10).

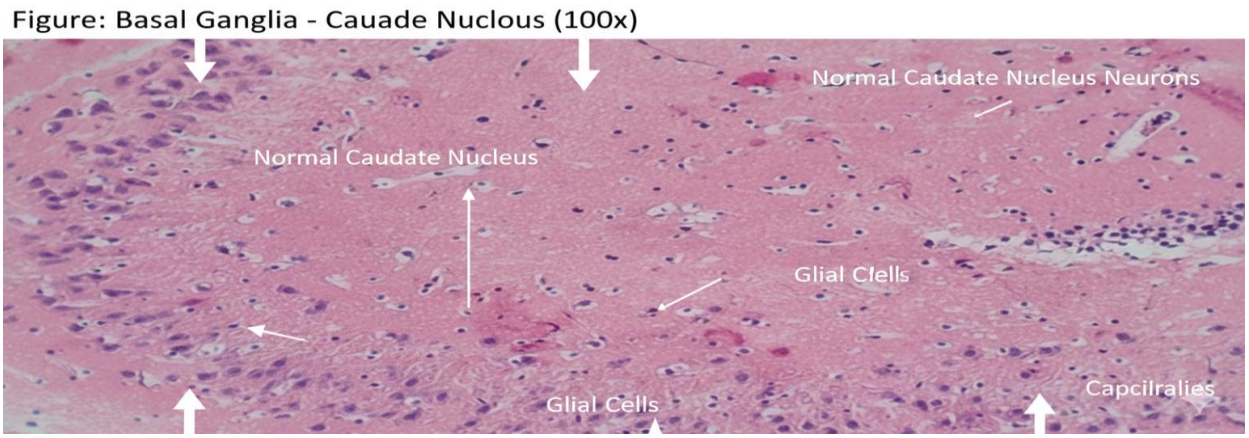

Figure (8): Basal ganglion show: normal appearance of the caudate nucleus neurons. H&E stain.100x

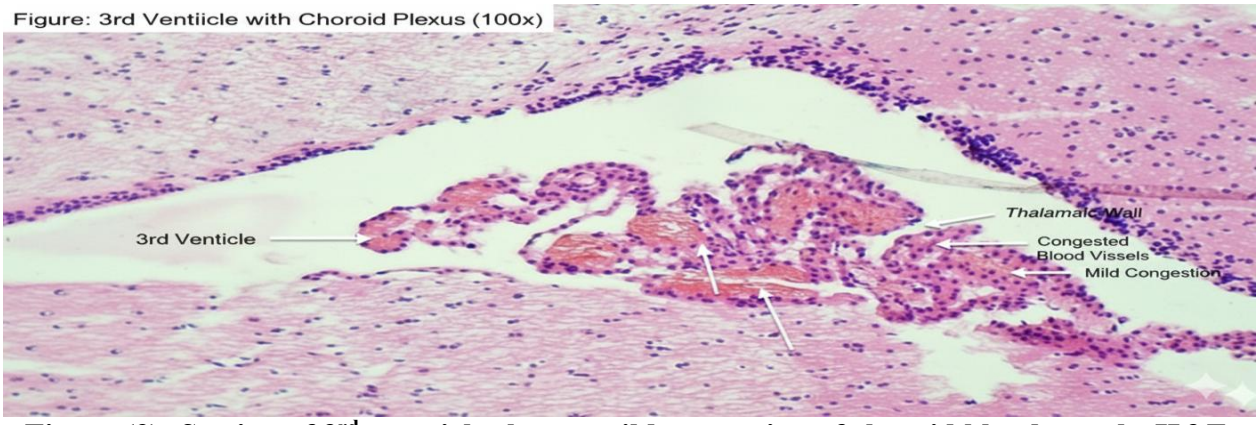

Figure (9): Section of 3rd ventricle shows: mild congestion of choroid blood vessels. H&E stain.100x

Group 5 (montelukast 20mg/kg): The figure (11) showed mild congestion with dilation of choroid plexus blood vessels of the 3rd ventricle. the figure (12) of the basal caudate nucleus revealed mild cellular swelling without necrosis

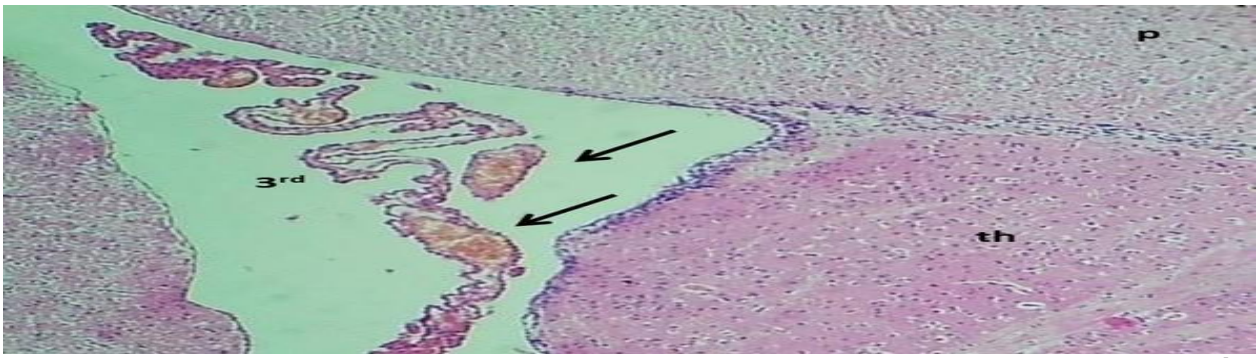

Figure (10): mild congestion with dilation of choroid plexus blood vessels (Arrows) of 3rd ventricle (3rd). H&E stain.100x

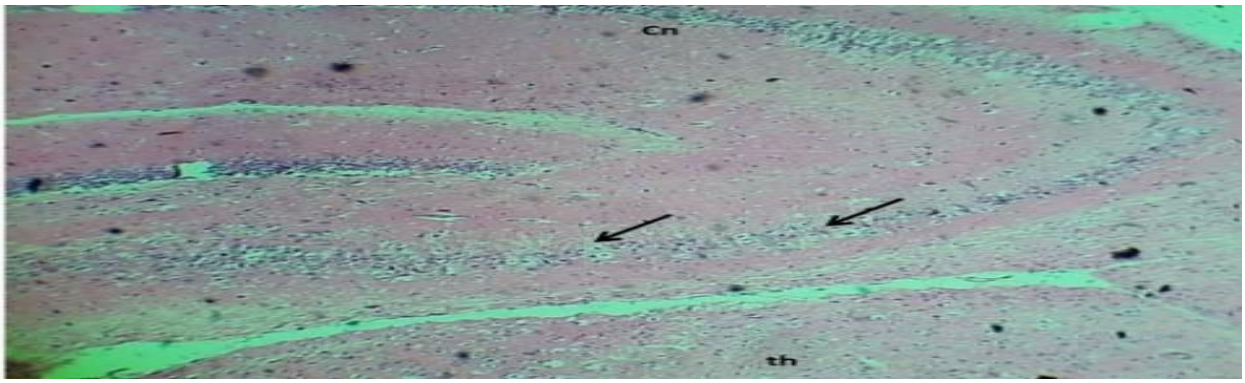

Figure (11): mild cellular swelling (Arrows) without necrosis of the neurons of basal ganglion caudate nucleus (Cn) & normal thalamic neurons (Th). H&E stain.40x

Histopathological analysis. standardized assessment of neuronal and vascular alterations. Three parameters were evaluated: (1) vascular congestion, (2) neuronal edema/swelling, and (3) neuronal degeneration. Each parameter was scored on a four-point scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. For each animal, at least three representative fields were analyzed. All slides were examined by a board-certified histopathologist who was blinded to the treatment groups to avoid assessment bias. Magnification levels were standardized across micrographs and reported consistently as 40× or 100×. Staining was performed using hematoxylin and eosin (H&E).

Table (5): Histopathological score Levels (Mean ± SD).

Parameter	**G1 (Control)**	**G2 (Reserpine)**	**G3 (MTK 5mg/kg)**	**G4 (MTK 10mg/kg)**	**G5 (MTK 20mg/kg)**	**p-value**
Neuronal degeneration	0.00	2.143±0.38	0.00	0.14 ± 0.38	0.43± 0.53	p<0.001
Congestion	0.00	2.29± 0.49	0.00	0.29 ± 0.49	1.00	NS
Edema	0.00	2.86 ± 0.38	0.00	0.29 ± 0.49	1.14± 0.38	p<0.001

MTK = Montelukast; n=7 per group, *Comprehensive Post-hoc Analysis: Different superscript letters indicate significant differences (p < 0.05, Tukey HSD)*

Key findings: The histological scoring of the basal ganglia demonstrated significant pathological changes following Reserpine administration and mild congestion with 20 mg/kg montelukast treated group.

Discussion:

This study evaluated the neurochemical and histopathological effects of escalating doses of montelukast in rats, focusing on peripheral monoamine neurotransmitters and serum BDNF levels. In the 5, 10, and 20 mg/kg treatment groups, we observed a dose-dependent reduction in serum dopamine, serotonin, and norepinephrine. At the highest dose, BDNF paradoxically increased. Although these are important preliminary insights, they must be interpreted cautiously, as all biochemical measurements were derived from serum rather than brain tissue. Reserpine, used as a positive control, produced the expected profound monoamine depletion by inhibiting the vesicular monoamine transporter (VMAT), consistent with classical monoaminergic dysfunction models (10). Interestingly, montelukast induced a similar but dose-dependent pattern of monoamine reduction.

This observation aligns with recent multi-omics and metabolic studies demonstrating that montelukast disrupts pathways involved in branched-chain amino acid metabolism critical precursors for neurotransmitter synthesis within the prefrontal cortex(7).Additional rodent studies also report depression-like behaviors and altered neurotransmitter metabolism following chronic montelukast exposure. Collectively, these data support the hypothesis that leukotriene receptor blockade may influence monoaminergic signaling; however, the present findings should be considered associative, as serum monoamine concentrations cannot be extrapolated directly to central neurotransmission(15).

A key finding of this study was the paradoxical increase in serum BDNF in both the reserpine and high-dose montelukast groups. Although monoamine depletion is frequently associated with reduced neurotrophic support, BDNF may also increase in response to neuronal stress, oxidative imbalance, or metabolic disruption(16,17) Several alternative explanations may account for this elevation, including physiological stress response. Both acute and chronic physiological stress have been shown to increase peripheral BDNF levels as part of an adaptive neuroprotective mechanism (9). Monoamine depletion itself may activate compensatory pathways that upregulate BDNF.

Finally, peripheral serum BDNF is primarily derived from platelets and vascular endothelial cells and does not reliably reflect CNS neurotrophic activity (9). Thus, the increase observed here may not correspond to enhanced BDNF expression in the brain.

This peripheral–central dissociation is critical for interpretation. BDNF does not freely cross the blood brain barrier. Its expression is highly region-specific within the CNS (e.g., hippocampus, cortex, amygdala) (9). Numerous neuropsychiatric disorders, including major depression and suicidality, show decreased brain BDNF but normal or elevated serum BDNF (ref 9). Therefore, the elevated serum BDNF in this study should not be interpreted as evidence of enhanced neurotrophic signaling in the brain(18)

Histopathological findings further contextualize the biochemical alterations. The 5 mg/kg group showed normal morphology. The 10 and 20 mg/kg groups demonstrated mild vascular congestion, choroid plexus dilation, and neuronal swelling without necrosis. These features indicate early structural or inflammatory stress. The observations correspond with biochemical indicators of neurostress and may reflect early tissue responses to high-dose montelukast exposure. Clinically, these findings may have relevance, given the increasing number of reports linking montelukast use to neuropsychiatric adverse effects such as

agitation, anxiety, depression, nightmares, and suicidal thoughts. Epidemiological studies, especially in children and adolescents, have identified a significant association between montelukast and neuropsychiatric outcomes (5).

In summary, the findings demonstrate a dose dependent association but not a causal relationship between high-dose montelukast exposure, serum monoamine depletion, elevated peripheral BDNF, and mild histopathological alterations. These results support emerging evidence that montelukast may exert systemic neurochemical effects at toxicological exposure levels. Further studies using clinically relevant doses, CNS-specific assays, and detailed behavioral evaluations are essential to clarify the neurobiological impact.

This study has several important limitations that should be considered when interpreting the findings. The sample size was limited to seven rats per group, which is typical for exploratory animal studies but may reduce statistical power and limit generalizability. In addition, no behavioral assessments such as the open field, elevated plus maze, or forced swim test—were conducted; therefore, the functional or behavioral consequences of the observed neurotransmitter depletion cannot be determined. The study also lacked measurements of oxidative stress and inflammatory biomarkers (e.g., MDA, SOD, catalase, GSH, TNF-α, IL-6), preventing a comprehensive understanding of the neurobiological pathways that may underlie the observed increase in BDNF. Furthermore, the use of only male rats limits translational relevance, as sex-specific differences in monoaminergic and neuroinflammatory responses are well established. The short treatment duration of 14 days may also be insufficient to capture neurochemical or structural changes associated with chronic montelukast exposure in humans. Finally, although no abnormalities were observed in the control group, the use of DMSO and acetic acid as vehicles introduces the possibility of confounding effects and warrants cautious interpretation of the results.

To strengthen the mechanistic interpretation of these findings, future studies should incorporate direct analyses of brain tissue rather than relying solely on serum measurements. Quantifying monoamines within discrete brain regions using high-performance liquid chromatography or LC-MS would allow confirmation of whether the peripheral neurotransmitter reductions observed here reflect true central deficits. Similarly, measuring BDNF protein and mRNA expression in brain tissue by Western blot or RT-PCR would clarify whether the serum elevation represents a compensatory neurotrophic response or a peripheral artifact. Further mechanistic insight would be gained by assessing neuroinflammatory mediators such as IL-6, TNF-α, and NF-κB, as inflammation is a key pathway linking montelukast to neuropsychiatric effects. Additionally, evaluating oxidative stress biomarkers including MDA, GSH, SOD, and catalase would help determine whether oxidative imbalance contributes to the neuronal swelling and vascular congestion observed histologically. Finally, behavioral assessments such as the forced swim test, open field test, and elevated plus maze should be included to determine whether biochemical and histological changes translate into functional alterations in mood, locomotion, or anxiety-like behaviors. Integrating these experiments would substantially enhance the mechanistic depth and translational relevance of future research.

Conclusion:

Montelukast administration resulted in a dose-dependent reduction in monoamine neurotransmitters, with dopamine, serotonin,

and norepinephrine showing progressive decreases in the 5, 10, and 20 mg/kg groups compared with controls. At the highest dose (20 mg/kg), montelukast was associated with an approximately 26% increase in BDNF levels, which may reflect a compensatory neurotrophic response rather than a definitive mechanistic effect. Histopathological examination revealed mild, dose related changes, characterized by normal morphology at 5 mg/kg, mild vascular congestion at 10 mg/kg, and mild neuronal swelling without necrosis at 20 mg/kg. Importantly, behavioral assessments, oxidative stress markers, and inflammatory parameters were not evaluated, precluding conclusions regarding functional outcomes or underlying mechanisms. Overall, these findings indicate a potential association rather than a confirmed causal relationship between high-dose montelukast exposure and neurochemical alterations, highlighting the need for further studies incorporating behavioral testing, mechanistic analyses, and clinically relevant dosing regimens.

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