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Regional neurochemical profile following co-administration of apomorphine and buspirone in an animal model of addiction

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Abstract: Although dopamine is the primary neurotransmitter mediating the reinforcing outcomes of abused drugs, serotonin (5-hydroxytryptamine; 5HT) also performs an important function in addiction pathophysiology. Increased dopamine levels in the nucleus accumbens mediate the final effects of various drugs of abuse, regardless of their exceptional preliminary binding sites. Repeated administration of apomorphine has been reported to supersensitize 5HT-1A receptors, and buspirone could attenuate these effects. The present study applied the conditioned place preference (CPP) test to screen apomorphine's reinforcing outcomes and their attenuation by means of co-administration of buspirone. Associated adjustments in 5-HT and dopamine metabolism in various brain regions were monitored using HPLC-EC. Withdrawal from apomorphine administration (1.0 mg/kg on 12 alternate days) brought about reinforcement as observed in the CPP paradigm. Serotonin and dopamine metabolism, mainly in the ventral and dorsal striatum, became additionally altered. The effects propose that desensitization of presynaptic dopamine receptors is concerned in apomorphine-induced reinforcement. Desensitization of somatodendritic 5HT-1A receptors, ensuing in expanded availability of 5HT at 5HT-2C receptors, could attenuate apomorphine-brought about reinforcement. These findings may additionally potentiate the therapeutic applicability of apomorphine.

Keywords: Apomorphine; Buspirone; Dorsal striatum; Hippocampus; Hypothalamus and prefrontal cortex; Mid brain; Prefrontal cortex; Ventral striatum

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INTRODUCTION

Current addiction research focuses to deepen our knowledge of the underlying physiological, cellular, and molecular mechanisms (Darcq and Kieffer, 2024). It has been shown that the improvement of dependency is encouraged by vulnerabilities to environmental, drug-induced, and genetic factors (Koijam *et al*., 2024). Additionally, early life experiences play a substantial role in shaping later neurobehavioral development (Tromp *et al*., 2024), and stress is identified as a key factor that could cause relapse (Wang *et al*., 2024).

Despite the diverse initial mechanisms and goals of drugs of abuse, several common features share their final mechanism of action (Negus, 2024). There is an increasing amount of evidences that serotonin, along with dopamine, performs a vital function in the pathophysiology of dependency. It has been reported that Dorsal raphe inputs to CA1 region take into account of drug-related contexts and drug-seeking through 5-HT1B receptors, while they inhibit consolidation of non-drug contexts via 5-HT1A receptors. Therefore, treatment approaches that modulate 5-HT-structured memory mechanisms in CA1 in the course of early abstinence may be beneficial in sustaining long-term abstinence (Kohtz *et al*., 2024). Alcohol abuse is recognized as a persistent, relapsing situation impacting the critical apprehensive system. The serotonergic system, broadly speaking through its effect on the mesolimbic dopaminergic praise pathway, is thought to be crucial in the mechanism of alcohol dependence. An association between the rs6295 polymorphism of the 5HTR1A gene, alcohol abuse, and persona tendencies has been determined in women with alcohol dependence (Boron *et al*, 2024). These findings endorse a pivotal role of 5HT-1A receptors in the pathophysiology of addiction.

Drug dependence arises from routine drug use, and unexpected discontinuation can cause physical withdrawal symptoms, complicating the mechanism of quitting. Psychostimulant withdrawal symptoms can consist of slight tremors, anxiety, hyperreflexia, seizures, and severe convulsions. The severity of withdrawal responses can rely upon the length and quantity of drug use (Yuan *et al*., 2024; Jones *et al*., 2024). The present study was designed to investigate the metabolism of biogenic amines in various brain regions of experimental animals after the establishment of reinforcement induced by repeated administration of apomorphine. By inspecting those metabolic modifications, we aim to make contributions to a higher understanding of the neurochemical underpinnings of addiction and the capability for healing interventions.

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MATERIALS AND METHODS

Animals

The experimental protocol commenced following approval from the Institutional Animal Ethics Committee (IAEC). Male Albino Wistar rats (180±20 g) were purchased from the HEJ Research Institute of Chemistry, University of Karachi, and housed in transparent Perspex cages. The animals were kept in a room with a 12:12 hour light/dark cycle (lights on at 6:00am). A 7 day acquisition period allowed the rats to acclimate to their new surroundings.

Drug and doses

Apomorphine (Sigma, St. Louis, USA) and buspirone (Sigma, St. Louis, USA) dissolved in saline (0.9% NaCl) and injected intra-peritoneally at the dose of 1.0 mg/kg to respective animals (Ikram *et al*., 2024). The drugs were freshly prepared each day before starting the experiment. Saline was injected to respective animals at the dose of 1.0 ml/kg.

Experimental protocol

Twenty four male Albino Wistar rats (180-220 g) had been randomly assigned to four groups each containing six animals: (i) saline-saline-, (ii) saline-apomorphine- (iii) buspirone-saline-, (ii) buspirone-apomorphine injected rats. The animals were injected with apomorphine on alternate days (i.e., day 2, 4, 6, 8, 10 & 12) and sequestered within the apomorphine-paired compartment of conditioned place preference equipment.

Saline was injected on day 1, 3, 5, 7, 9 &11 and rats were sequestered in the saline-paired compartment. Buspirone was injected daily and was not paired to any of the compartments. On day 13, entries and time spent in the compartments was monitored for 10 min. Rats were then decapitated and brain regions were isolated and stored at -70ºC until neurochemical analysis by HPLC-EC.

Behavioral procedures

Phase I: Pre-conditioning place preference test

The test was conducted as described earlier (Ikram *et al*., 2021). Each compartment was of equal length (26x26x26cm) with a shuttle compartment (12x12cm) between them. The compartments differed in their sensory properties. Walls of one compartment had horizontal grids, while other had vertical grids. Basal values for all rats were monitored with entrances among compartments open.

Phase II: Conditioning phase

During conditioning entrance between compartments was closed, and rats were sequestered in respective compartments for 20min each after drug/saline administration.

Phase III: Post-conditioning place preference test

On test day (day 13) entrance between compartments was open. Number of entries and time spent in compartments were monitored.

Regional brain dissection

The dissection process was basically similar to the one described in some other research work from our group. After decapitation, fresh brain was dipped in ice-cold saline and located with its ventral side up in the molded space of brain slicer. Sharp razor/blade was inserted among the slots to collect specific brain slices containing unique brain regions (i.e., prefrontal cortex, dorsal striatum, ventral striatum, mid brain, hippocampus, hypothalamus and prefrontal cortex). The brain regions were stored at -70°C until assessment by HPLC-EC.

HPLC-EC estimation of DA, 5-HT and metabolites

Biogenic amines and metabolites were extracted with perchloric acid ($HClO_4$; 70%) from brain tissue. 5 times volume of the extraction medium was added to the brain tissues. Samples were homogenized by using electrical homogenizer and subjected to ultracentrifugation at 6000 rpm for 20min at 4°C. The supernatant was transferred to Eppendorf tubes and injected to HPLC-EC for neurochemical assay. HPLC-EC determination was carried out as described earlier (Ikram *et al*., 2023).

Statistical analysis

Results are supplied as means±SD. Statistical analysis carried out via 2-way or 3-way ANOVA (analysis of variance) using SPSS software ver 21. Subsequent comparisons amongst groups had been done by means of the Tukey's test. Values of $p<0.01$ have been taken into consideration to be substantial.

RESULTS

Fig. 1 shows effects of repeated apomorphine-buspirone coadministration on time spent in compartments of conditioned place preference apparatus. Analysis of the data on pre-conditioning values (Fig. 1a) as analyzed by three-way ANOVA (df= 1, 20) showed non-significant effect of compartments (F= 1.34; p= 0.85), apomorphine (F= 1.13; p= 0.001) and interaction between the two (F= 1.51; p= 0.001). Post hoc analysis by Tukey's test showed no difference among groups. Analysis of the data on post-conditioning values (Figure 1b) as analyzed by the Three-way ANOVA (df= 1, 20) showed significant effect of compartments (F= 91.16; p= 0.001), apomorphine (F= 87.74; p= 0.001) and interaction between the two (F= 96.16; p= 0.001). Post hoc analysis by Tukey's test showed that saline-apomorphine injected rats spent decreased ($p<0.01$) time in saline-paired compartment as compared to second saline injected rats.

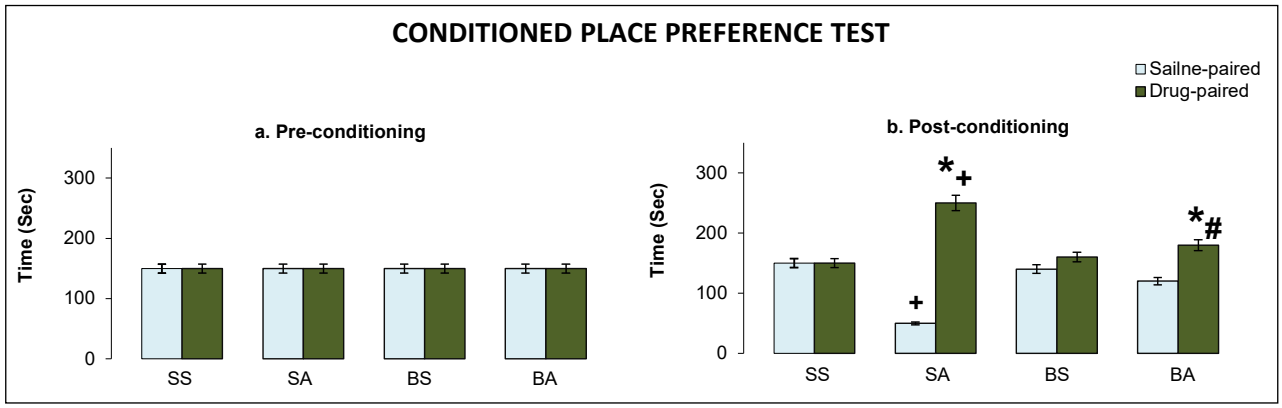

Fig. 1: Effects of repeated apomorphine-buspirone coadministration on time spent in compartments of conditioned place preference apparatus. SS= saline-saline; SA= saline-apomorphine; BS= buspirone-saline; BA= buspirone-apomorphine. Values are means±SD before and after treatment (day 0 and day 13). Significant differences by Tukey's test: *p<0.01 as compared to respective saline-paired compartment; +p<0.01 as compared to respective second saline injected rats; #p<0.01 as compared to respective first saline injected rats following three-way ANOVA.

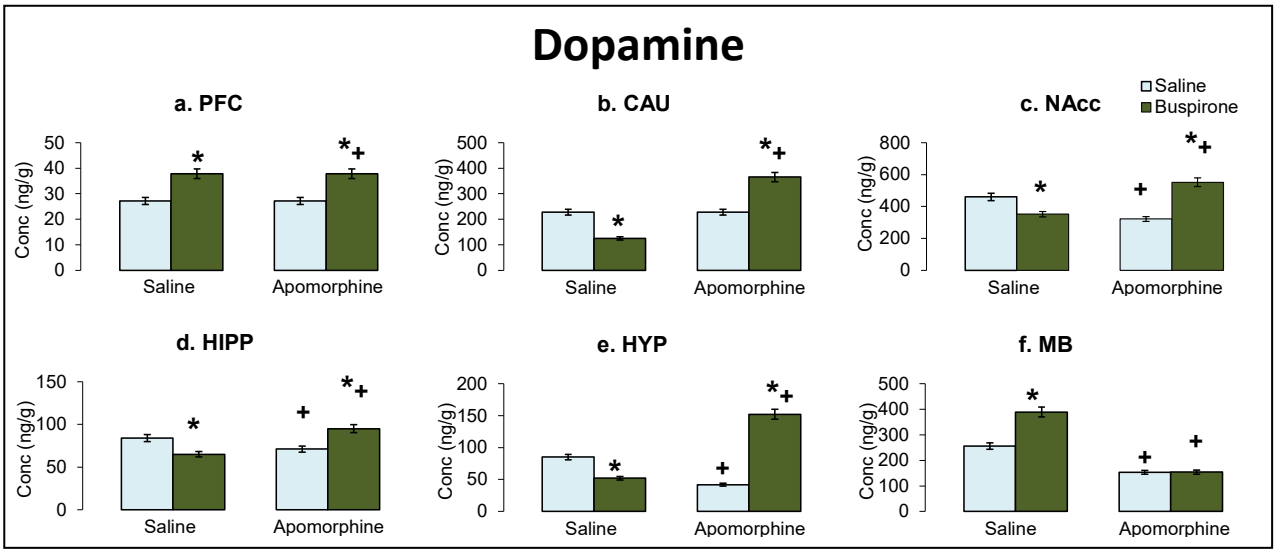

Fig. 2: Effects of repeated apomorphine-buspirone coadministration on dopamine levels in: PFC= prefrontal cortex, DS= dorsal striatum, VS= ventral striatum, HIPP= hippocampus, HYP= hypothalamus and MB= mid brain. Values are means±SD (n=6). Significant differences by Tukey's test: *p<0.01 from respective saline injected rats following two-way ANOVA.

Buspirone-apomorphine injected rats spent more (p<0.01) time in drug-paired compartment as compared to respective saline compartment values but this time in drug-paired compartment was decreased as compared to respective first saline injected rats.

Effects of repeated apomorphine-buspirone coadministration on levels of dopamine, DOPAC, HVA, 5HT and 5HIAA were analyzed by two-way ANOVA in brain regions: PFC= prefrontal cortex, DS= dorsal striatum, VS= ventral striatum, HIPP= hippocampus, HYP= hypothalamus and MB= mid brain. Significant effects of the treatment. Summarized results obtained by ANOVA are given in table 1. fig. 2-6 show diagrammatic representation of the data with post-hoc analysis done via Tukey's test.

DISCUSSION

The conditioned place preference (CPP) paradigm is commonly used to explore the motivational cues of drugs of abuse. Cues within the environment might also turn out to be paired with these motivational effects of the medication and later bring about drug seeking. As many of these drug-paired cues are visual, this could be a beneficial model to observe visible cue-associated drug seeking behavior. CPP, rats were tested for their basal preference for any of the two compartments of the CPP apparatus.

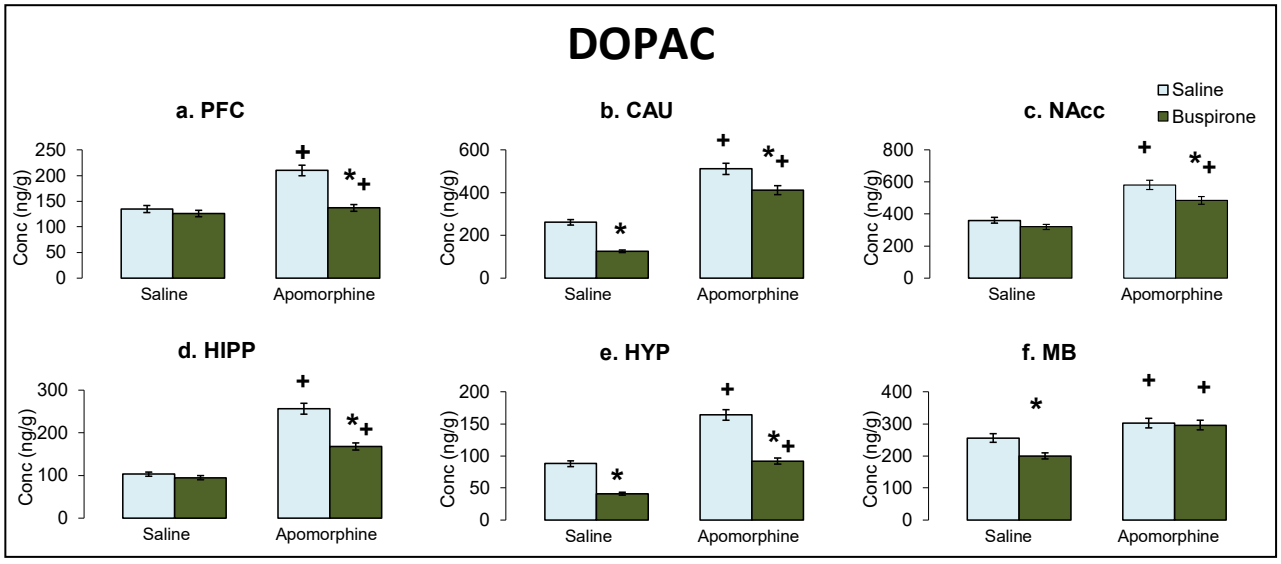

Fig. 3: Effects of repeated apomorphine-buspirone coadministration on DOPAC levels in: PFC= prefrontal cortex, DS= dorsal striatum, VS= ventral striatum, HIPP= hippocampus, HYP= hypothalamus and MB= mid brain. Values are means±SD (n=6). Significant differences by Tukey's test: *p<0.01 from respective saline injected rats following two-way ANOVA.

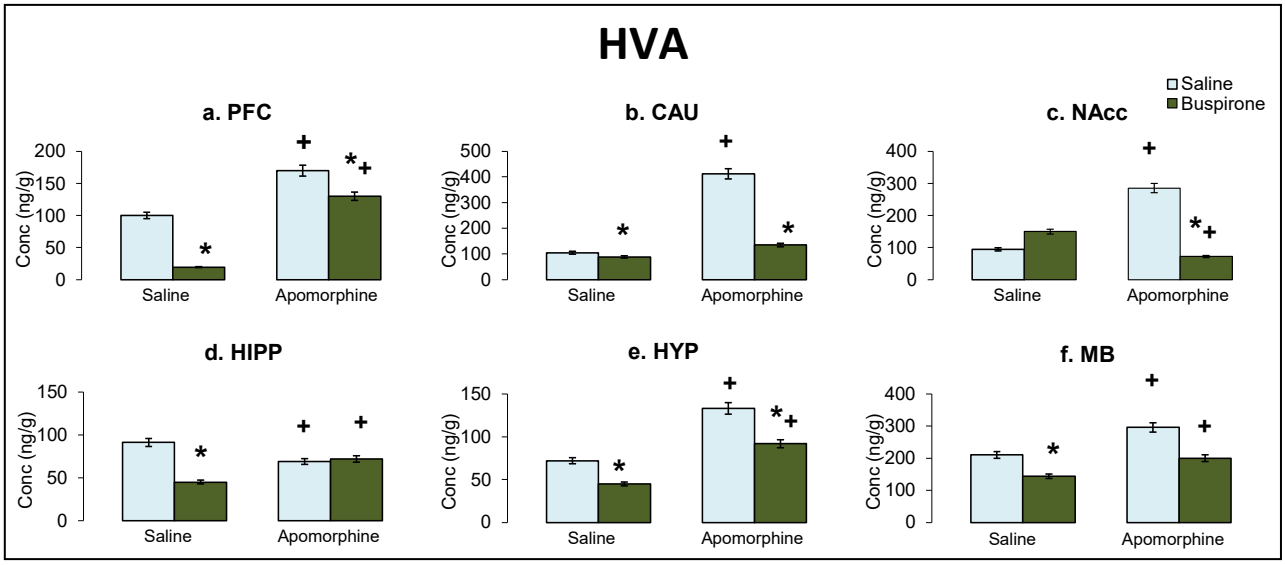

Fig. 4: Effects of repeated apomorphine-buspirone coadministration on HVA levels in: PFC= prefrontal cortex, DS= dorsal striatum, VS= ventral striatum, HIPP= hippocampus, HYP= hypothalamus and MB= mid brain. Values are means±SD (n=6). Significant differences by Tukey's test: *p<0.01 from respective saline injected rats following two-way ANOVA.

Rats were found to prefer no compartments during this session (Fig. 1a). This has been validated that social context and environmental stimuli modulate motivation and learning via associative reward, shaping the conditioning process (Monari *et al*., 2024). Throughout the conditioning/ training phase, animals discover ways to accomplice apomorphine injection with placement in drug paired compartment and saline injection with placement in both drug- or saline paired compartment. In the postconditioning phase, apomorphine injected animals exhibited more entries as well as greater time spent in the drug paired compartment (Fig. 1). Whilst buspirone turned into no longer paired with any of the compartments.

Sensitization to apomorphine (1.0 mg/kg) is mentioned following its repeated administration and is recommended to be mediated by stimulation of dopamine autoreceptors. Reinforcing outcomes of apomorphine might be monitored in a CPP paradigm, following withdrawal from its repeated

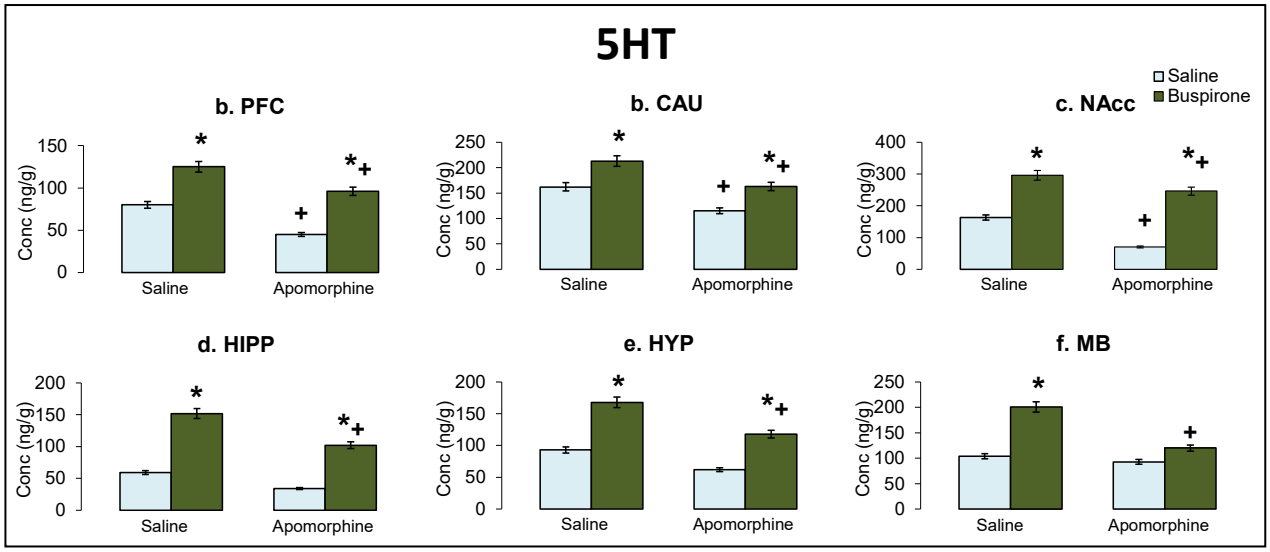

Fig. 5: Effects of repeated apomorphine-buspirone coadministration on 5HT levels in: PFC= prefrontal cortex, DS= dorsal striatum, VS= ventral striatum, HIPP= hippocampus, HYP= hypothalamus and MB= mid brain. Values are means±SD (n=6). Significant differences by Tukey's test: *p<0.01 from respective saline injected rats following two-way ANOVA.

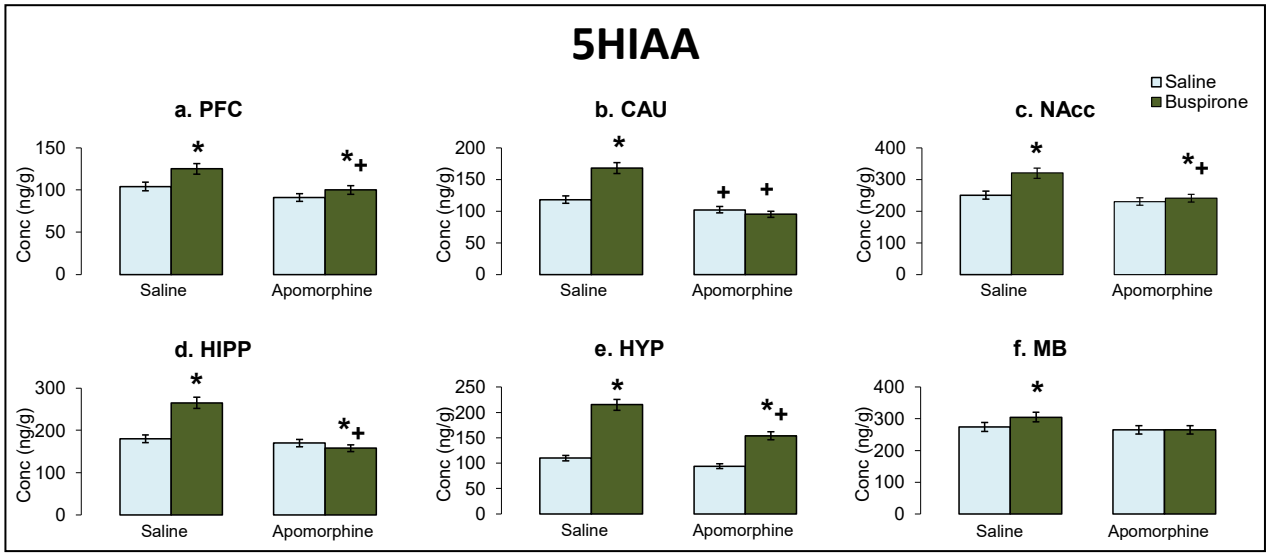

Fig. 6: Effects of repeated apomorphine-buspirone coadministration on 5HIAA levels in: PFC= prefrontal cortex, DS= dorsal striatum, VS= ventral striatum, HIPP= hippocampus, HYP= hypothalamus and MB= mid brain. Values are means±SD (n=6). Significant differences by Tukey's test: *p<0.01 from respective saline injected rats following two-way ANOVA.

administration. Decreased activity of dopaminergic neurons following its withdrawal, can be a probable reason for the compulsive use of apomorphine (Kassubek *et al*., 2024). In the present study apomorphine altered metabolism of dopamine and serotonin specially in dorsal striatum, ventral striatum and mid brain. Dopamine and HVA levels had been accelerated (p= 0.001) in dorsal striatum (Fig. 2 and 4). This suggests that apomorphine can be effectively used for the pharmacotherapy of Parkinson's and associated issues. During past few years, new options for on demand therapies in Parkinson-associated 'off' episodes have been developed, including new formulations of levodopa and apomorphine to provide fast and readily accessible sublingual apomorphine administration. However, there are few challenges associated with the treatment of PD-associated fluctuations and off states (Kassubek *et al*., 2024).

Results from the present study exhibited drastically reduced levels of DOPAC and HVA within the ventral

Table 1: Effects of repeated apomorphine-buspirone coadministration on neurotransmitter levels in various brain regions as assessed by two-way ANOVA (df= 1,20; *p= 0.001). PFC= prefrontal cortex, DS= dorsal striatum, VS= ventral striatum, HIPP= hippocampus, HYP= hypothalamus and MB= mid brain

Treatment	PFC	CAU	NAcc	HIPP	HYP	MB
Dopamine						
Apomorphine	F= 65.32*	F= 83.25*	F= 51.25*	F= 23.26*	F= 26.15*	F= 36.82*
Buspirone	F= 52.36*	F= 62.36*	F= 53.26*	F= 95.32*	F= 21.54*	F= 85.23*
Apomorphine*Buspirone	F= 41.63*	F= 26.32*	F= 45.32*	F= 56.16*	F= 26.13*	F= 61.29*
DOPAC						
Apomorphine	F= 62.35*	F= 25.11*	F= 52.14*	F= 26.31*	F= 52.13*	F= 31.26*
Buspirone	F= 58.21*	F= 32.11*	F= 85.16*	F= 36.25*	F= 52.17*	F= 74.16*
Apomorphine*Buspirone	F= 65.78*	F= 26.32*	F= 48.16*	F= 38.59*	F= 41.23*	F= 84.13*
HVA						
Apomorphine	F= 31.28*	F= 58.16*	F= 62.13*	F= 68.12*	F= 94.78*	F= 61.45*
Buspirone	F= 61.54*	F= 64.13*	F= 74.16*	F= 45.13*	F= 69.13*	F= 95.31*
Apomorphine*Buspirone	F= 45.29*	F= 95.36*	F= 61.25*	F= 35.26*	F= 91.45*	F= 46.32*
5HT						
Apomorphine	F= 23.12*	F= 65.21*	F=71.23*	F= 23.52*	F= 45.23*	F= 38.23*
Buspirone	F= 26.15*	F= 74.16*	F= 83.24*	F= 65.25*	F= 95.36*	F=65.21*
Apomorphine*Buspirone	F= 56.25*	F= 46.13*	F= 35.89*	F= 68.95*	F= 45.23*	F=72.91*
5HIAA						
Apomorphine	F= 78.16*	F=64.58*	F= 45.13*	F= 56.10*	F= 46.23*	F= 65.25*
Buspirone	F= 59.13*	F= 91.25*	F= 66.25*	F= 98.16*	F= 62.13*	F= 85.74*
Apomorphine*Buspirone	F= 45.26*	F= 75.23*	F= 56.23*	F= 56.32*	F= 31.53*	F= 69.25*

striatum (Fig. 3 and 4) suggesting that reduced release of dopamine in the ventral striatum is probably involved within the reinforcing consequences of drugs of abuse after withdrawal. Other studies have reported that dopamine holds a pivotal position within the establishment of reinforcement. Drugs of abuse have unique initial goals and mechanisms, but the resultant reinforcing impact shares several key capabilities (Ferron *et al*., 2024) such as elevation in extracellular Dopamine (DA) ranges, mainly in Nucleus Accumbens (NAcc) (Diepenbroek *et al*., 2024). Self-administration of various drugs of abuse is reported to be related with dopamine transporters (Hur *et al*., 2024; Estav *et al*., 2024). Substantial extracellular dopamine release is pronounced to be related to reinforcing consequences of drugs of abuse (Lauretani *et al*., 2024).

Although final effect of drug of abuse is hooked up with elevation of dopaminergic release within the nucleus accumbens, exclusive components of limbic system seem to be the targets of addictive substances which include ventral tegmental region, prefrontal cortex, hippocampus and pedunculopontine nucleus. Drugs of abuse exposed in adolescence may predispose to mental illness in adult life by altering dopamine axon growth in these regions (Avramescu *et al*., 2024). In the present study, ranges of dopamine and HVA (Fig. 2 and 4) were reduced in the mid brain suggesting its crucial function in mediating the reinforcing effects of apomorphine. Any huge alteration within the dopamine metabolism was not found in different regions like prefrontal cortex, hippocampus and hypothalamus. This may be because of the reason that apomorphine in this study was administered sub-chronically which would not have been sufficient for substantial changes in the dopamine metabolism in these brain regions.

Results from present study display that 5-HT levels were decreased (p= 0.001) within the dorsal and ventral striatum of apomorphine injected rats compared to saline injected controls (Fig. 5). Whereas levels of 5-HIAA had also been

reduced within the mid brain (Fig. 6). This shows that withdrawal from repeated apomorphine-buspirone coadministration induces a decrease in the serotonergic neurotransmission which could be a probable predisposing and precipitating agent in drug yearning and dependency (Haleem *et al*., 2014).

Studies have recommended that 5HT-2C receptor agonist RO60-0175, WAY 161503 and WAY 161503 coadministration could reduce cocaine self-administration and cocaine-seeking as induced by stressor and drug-associated cues (Jastrzębska *et al*., 2023). Previously we have mentioned that coadministration of buspirone on the dose of 1mg/kg; mediating its outcomes via 5HT-1A receptors, could attenuate apomorphine-triggered motor sensitization. It supports the speculation that an increase within the inhibitory serotonergic influence at the pastime of dopaminergic neurons may be the mechanisms via which 5HT-1A receptor agonists should attenuate apomorphine-prompted motor sensitization. As repeated management of apomorphine will increase the responsiveness of somatodendritic 5HT-1A receptors and repeated administration of buspirone decreases it, the present consequences recommend that an increase the sensitivity of somatodendritic 5HT-1A receptors. This decline in serotonin metabolism could also be due to the supersensitization of the somatodendritic 5HT-1A receptors and strategies concerning desensitization of these receptors should assist in attenuating the reinforcing effects of apomorphine and CNS stimulants. Results from the present study could help recognize the outcomes of apomorphine on dopamine and serotonin in special brain areas and assist in extending therapeutic usage of apomorphine for treatment-resistant patients.

CONCLUSION

The present results concluded that coadministration of apomorphine and buspirone induces massive neurochemical changes in unique brain areas. These findings highlight the complicated interaction among dopamine and serotonin structures in the pathophysiology of addiction and advocate that buspirone may additionally mitigate some of the reinforcing results of apomorphine. The determined changes in neurotransmitter levels and receptor activities underscore the capability of therapeutic focus on a couple of neurochemical pathways in treating dependency. Our study is limited due to the use of single dose of buspirone, which might restrict expertise of long-term results and functional outcomes. Additionally, there could be gender-related differences that could be directly applicability to human drug addiction treatment. Future research should consider chronic administration studies to assess long-term effects and should include rats of both genders/ different species to link neurochemical modifications with gender differences, and ultimately transition to clinical trials to evaluate healing potential in people.

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Authors' contributions
Ikram H-manuscript writing, data curation, data analysis, writing; Haleem DJ-supervision, validation, review and editing.

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Data availability statement
All data generated or analyzed during this study are included in this published article.

Ethical approval
All animal experiments were carried out according to the NIH guidelines and accredited through the Institutional Ethics Committee (approval number: IBC KU-340/2023).

Conflict of interest statement
Authors have no conflict of interest.

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