International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 19s, 2025
https://theaspd.com/index.php

Central Serotonergic Transmission Modulates The Nicotine Induced Anxiolysis In Mice

Shalinee Soni[1], Lokesh Verma[2]
[1]Research Scholar, Department of Pharmacology, Sanjeev Agrawal Global Educational University, Bhopal 462022, Madhya Pradesh, India.
[2]Professor, Department of Pharmacology, Sanjeev Agrawal Global Educational University, Bhopal 462022, Madhya Pradesh, India.

Abstract: *Anxiety disorders are the most prevalent group of mental disorders globally, leading to considerable losses in health, functioning and increase of medical costs. Till now, the search for novel pharmacological treatments is driven by the growing medical need to improve on the effectiveness and the side effect profile of existing drugs. In central nervous system, the mitochondrially located translocator protein (18 kDa, TSPO) serves as the rate-limiting step for neurosteroidogenesis and influences GABAergic transmission. Since 5-HT is one of the most comprehensively studied neurotransmitter systems in the anxiety field. The aim of present study is to evaluate the role of seretonergic transmissions in the nicotine induced induced anxiolysis in mice. Our findings demonstrate that nicotine withdrawal markedly exacerbates anxiety and depressive-like behaviors by interfering with brain serotonin metabolism, inflammatory processes, neurotrophic factors, and oxidative balance.*

Keywords: *Anxiety, nicotine, serotonergic transmission, 5-Hydroxytryptamine*

INTRODUCTION

Anxiety disorders are the most prevalent group of mental disorders globally, which lead to considerable losses in health, functioning and increase of medical costs. Benzodiazepines (e.g. diazepam) represent effective treatment for anxiety disorders, which exert anxiolytic effects by activating type A GABA receptor (GABAA receptor). In the meanwhile, several selective serotonin reuptake inhibitors (SSRIs) (e.g. sertraline) are also among the first-line pharmacological approaches for patients with anxiety disorders [1]. However, long-term use of these drugs cause several side effects like memory disturbances, sedation, dependence liability and tolerance and selective serotonin reuptake inhibitors exhibit disadvantages including low efficiency, delayed onset of effect and sexual dysfunction. In addition, approximately half of anxiety patients do not respond to treatment with commonly used SSRIs. Thus, there is still urgent need to explore novel anxiolytics with improved efficacy and less side effects [2-3].

Nicotine, the primary psychoactive agent in tobacco leaves, has led to the widespread use of tobacco, with over one billion smokers globally. Nicotine induces various biological effects, such as neoangiogenesis, cell division, and proliferation, and it affects neural and non-neural cells through specific pathways downstream of nicotinic receptors (nAChRs). Specific effects mediated by α7 nAChRs are highlighted. Nicotine is highly addictive and hazardous. Public health initiatives should prioritize combating smoking and its associated risks. Understanding nicotine's complex biological effects is essential for comprehensive research and informed health policies [4-5].

Studies have demonstrated that nicotine alters the expression of microRNAs (miRNAs) in various smoking-related disorders and exerts its effects through miRNA-related pathways. This influence leads to subsequent changes in the expression of target genes. Importantly, alterations in miRNA expression can have both protective effects, such as the activation of anti-inflammatory processes, and detrimental effects, including those associated with conditions like atherosclerosis and Alzheimer's disease [6-7].

Most of the research on nicotine has focused on its effects on the dopaminergic system. However, because of the predominantly presynaptic localisation of the nicotinic receptors (nAChRs), nicotine induces the release of several other neurotransmitters, including acetylcholine (ACh), noradrenaline, serotonin [5-

hydroxytryptamine (5-HT)], GABA, and glutamate There is no direct evidence for presynaptic nicotinic receptors located on serotonergic nerve terminals, but as there is considerable evidence that nicotine does affect serotonergic neurotransmission. There are also several behavioural effects of nicotine that seem to be mediated by effects on the serotonergic system [8-10].

5-Hydroxytryptamine (5-HT), or serotonin, plays a crucial role as a neuromodulator and/or neurotransmitter of several nervous system functions. Its actions are complex, and depend on multiple factors, including the type of effector or receptor activated [11-12]. The aim of present study is to evaluate the role of seretonergic transmissions in the nicotine induced induced anxiolysis in mice.

MATERIALS AND METHODS

Drugs and Chemicals

Nicotine, 8-hydroxy-2 (-dipropylamino) tetralinhydro bromide (8-OH-DPAT), R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride, Ketanserin, WAY 100635 were procured from Sigma-Aldrich . All other chemical reagents used in the study were of analytical grade.

Subject

All procedures were carried out under strict compliance with ethical principles and guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Ministry of Environment and Forests, Government of India, New Delhi on adult male Swis mice (age 10–12 weeks). All the animals were maintained on a 12:12-h light/dark cycle (lights on at 06:00 h) in a temperature (24 ± 2◦C) and humidity controlled environment (65 ± 5%). Animals were group housed (n=5) except surgically cannulated mice, which were housed individually with free access to rodent chow and water ad libitum except during the experiments. All the behavioral assessments were conducted during the light cycle between 09:00 and 14:00 h to. The animals were naïve to drug treatment and for experimentation at the onset of all studies.

Effect of serotonergic antagonist/ agonist on nicotine induce anxiety

Open field test

The Open field test (OFT) is a commonly used behavioral assessment to assess fear- related emotional behaviors in rodents. In this test, the mice are placed in a large, enclosed arena that is typically divided into central and peripheral zones. In the OFT, the duration of time that rodents spend in the center of the arena is a commonly used indicator of anxiety levels, which means that a shorter time spent in the center is associated with higher anxiety. On the other hand, greater exploration of the central area indicates lower anxiety and a higher propensity for exploratory behavior. In this study, OFT was performed in a 100 ×100 ×40 cm square arena made of opaque material and divided into 25 equal quadrants of 20 ×20 cm each. Each rat was positioned in the center of the arena and had five minutes to explore this novel environment. Their locomotor activity, including the amount of time spent in central and peripheral zones was recorded and analyzed.

Forced swimming test

In FST, rodents are placed in a container filled with water from which they cannot escape. Time spent standing (swimming) is recorded along with active time (swimming or fighting). Greater immobility is considered a sign of behavioral despair, similar to depressive states observed in humans. In this study, animals were placed in glass cylinders filled with water maintained at a temperature of 24 ± 2 ◦C and a depth of 30 cm to promote swimming. Two swimming sessions were conducted: the first was a 15-minute pre-test to acclimate the animals to the environment, followed by a second session, a 5-minute test, conducted 24 hours later to assess their behavior. This 24-hour interval was designed to assess the consistency and reproducibility of observed behaviors over time. During the test, each animal was carefully placed in the water and allowed to swim freely in the tank. The duration of active swimming, struggling, and immobility was recorded for 5 minutes using a video camera. After each session, mice were removed, dried, and kept warm for 30 minutes before being returned to their cages for the remainder of the experiment.

Experimental design for effect of serotonergic agonist on nicotine withdrawn induce anxiety

Group 1: Animals received Solvent (5ml/kg) (sc)

Group 2: Animals received Nicotine 6 mg/kg (sc)

Group 3: Animals received 8-hydroxy-2 (-dipropylamino) tetralinhydro bromide (8-OH-DPAT) (5-HT1A agonist) (sc)

Group 4: Animals received R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride (DOI) (5-HT2A agonist) (sc)

Experimental design for effect of serotonergic antagonist on nicotine withdrawn induce anxiety

Group 1: Animals received Solvent (5ml/kg) (sc)

Group 2: Animals received Nicotine 6 mg/kg (sc)

Group 3: Animals received Ketanserin (5-HT2A/2C antagonist) (sc)

Group 4: Animals received WAY 100635 (5-HT1A antagonist) (sc)

Effect of chronic nicotine withdrawal induce anxiety

Nicotine dependence was induced by subcutaneous administration of nicotine solution at a dose of 6 mg·kg-1·d-1 at 7:00 h, 15:00 h and 23:00 h for 7 consecutive days. The control group was injected with sterile 0.9% sodium chloride solution at the same time course. To trigger nicotine withdrawal, mice were subcutaneously injected with 1 mg/kg of the nicotinic antagonist mecamyl amine hydrochloride (MEC) 60 min after the last injection of nicotine on the 7th day, and the following behavioural testing was performed during the next 7 d.

Effect of serotonergic agonist on nicotine induce anxiety

Effect of serotonergic agonist on nicotine induce anxiety were evaluated by Open field test and Forced swimming test. The Open field test (OFT) is a commonly used behavioral assessment to assess fear- related emotional behaviors in rodents. In the OFT, the duration of time that rodents spend in the center of the arena is a commonly used indicator of anxiety levels, which means that a shorter time spent in the center is associated with higher anxiety. On the other hand, greater exploration of the central area indicates lower anxiety and a higher propensity for exploratory behavior. Locomotor activity, including the amount of time spent in central and peripheral zones was recorded and analyzed.

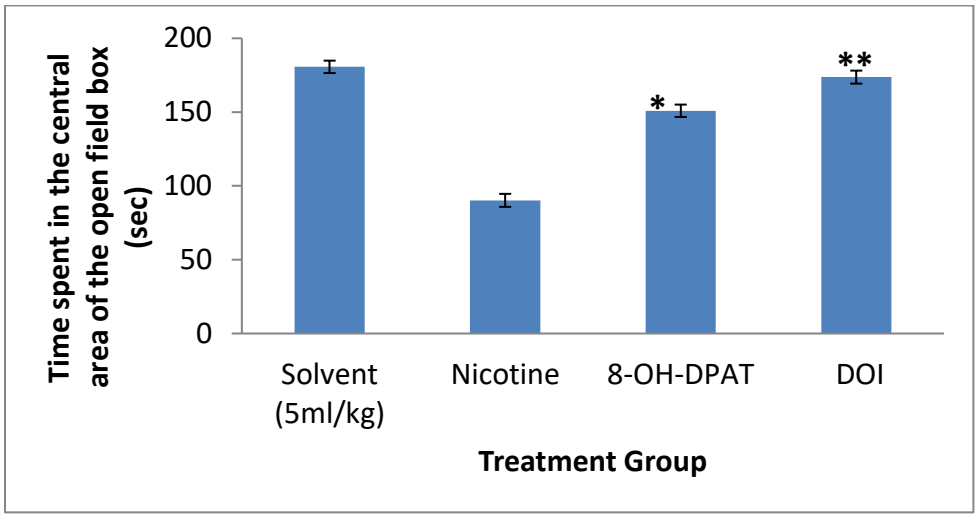
In Forced swimming test rodents are placed in a container filled with water from which they cannot escape. Time spent standing (swimming) is recorded along with active time (swimming or fighting). Greater immobility is considered a sign of behavioral despair, similar to depressive states observed in humans.

Table 1: Effect of serotonergic agonist on nicotine induce anxiety (open field test)

Treatment Group	Time spent in the central area of the open field box (sec)	Time spent in the peripheral sections of the open field box (sec)
Solvent (5ml/kg)	180.67 ± 0.5	95.13 ± 2.2
Nicotine	90.2 ± 1.2	170.2 ± 2.7
8-OH-DPAT	150.9 ± 1.7*	120.6 ± 1.9*
DOI	173.7 ± 1.4**	130.9 ± 1.2**

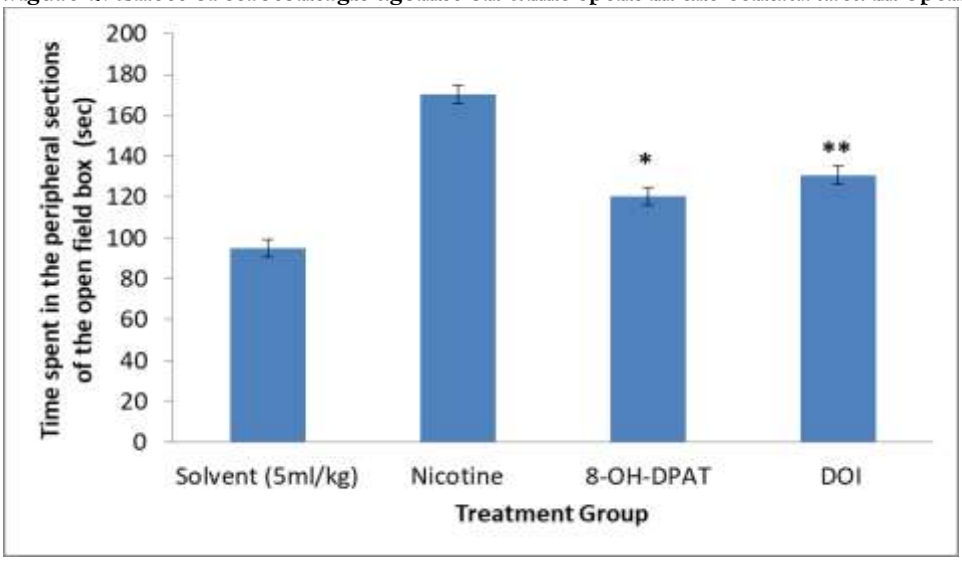
Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

(8-hydroxy-2 (-dipropylamino) tetralinhydro bromide (8-OH-DPAT) (5-HT_{1A} agonist; R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride (DOI) (5-HT_{2A} agonist)



*P <0.05, **P <0.01 compared to respective control group

Figure 1: Effect of serotonergic agonist on Time spent in the central area in open field test



*P <0.05, **P <0.01 compared to respective control group

Figure 2: Effect of serotonergic agonist on time spent in the peripheral sections in nicotine induce anxiety (open field test)

Table 2: Effect of serotonergic agonist on nicotine induce anxiety (Forced swimming test)

Treatment Group	Swimming time (sec)	Immobility time (sec)
Solvent (5ml/kg)	175.23 ± 0.8	62.03 ± 0.9
Nicotine	82.2 ± 0.9	140.2 ± 0.7
8-OH-DPAT	160.9 ± 0.9	115.6 ± 1.2
DOI	171.7 ± 0.8	110.9 ± 1.4

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group
(8-hydroxy-2 (-dipropylamino) tetralinhydro bromide (8-OH-DPAT) (5-HT_{1A} agonist; R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride (DOI) (5-HT_{2A} agonist)

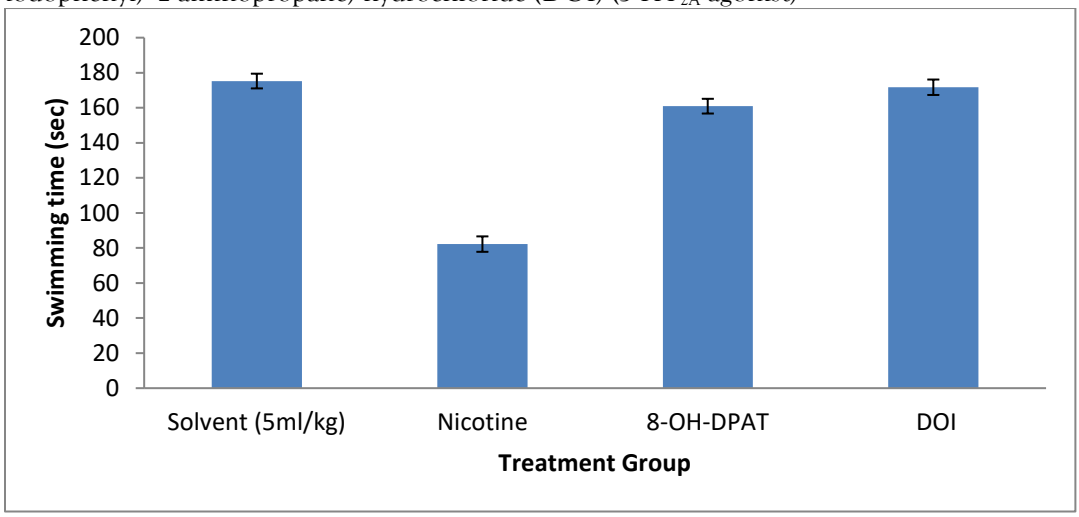


Figure 3: Effect of serotonergic agonist on nicotine induce anxiety (Forced swimming test)

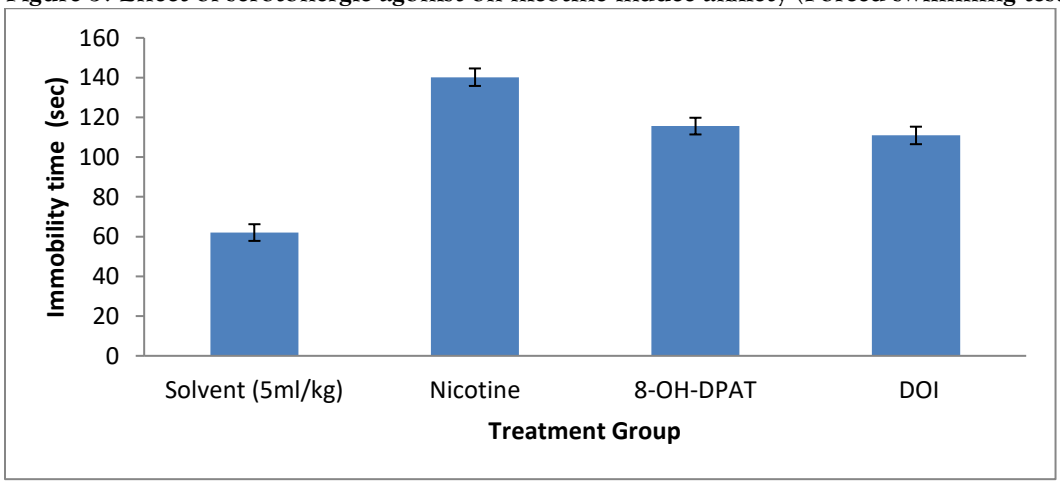


Figure 4: Effect of serotonergic agonist on nicotine induce anxiety (Forced swimming test)

Serotonergic agonist attenuates nicotine-withdrawal-induced anxiety-like behavior. Animals undergoing nicotine withdrawal exhibited pronounced anxiety-like behaviors, reflected in a significant decrease in central area exploration during OFT and an increase exploring the central area showed peripheral area compared to the vehicle group. Treatment with Serotonergic agonist significantly improved exploration of the central area, while exploration of the peripheral area was reduced relative to the nicotine group.

Treatment with Serotonergic agonist significantly improved exploration of the central area, while exploration of the peripheral area was reduced relative to the nicotine group. Treatment with serotonergic agonist (8-OH-DPAT) and R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride (DOI) significantly reduced immobility and increased swimming time compared to the nicotine group.

Effect of serotonergic antagonist on nicotine induce anxiety

Effect of serotonergic agonist on nicotine induce anxiety were evaluated by Open field test and Forced swimming test. The Open field test (OFT) is a commonly used behavioral assessment to assess fear- related emotional behaviors in rodents. In the OFT, the duration of time that rodents spend in the center of the arena is a commonly used indicator of anxiety levels, which means that a shorter time spent in the center is

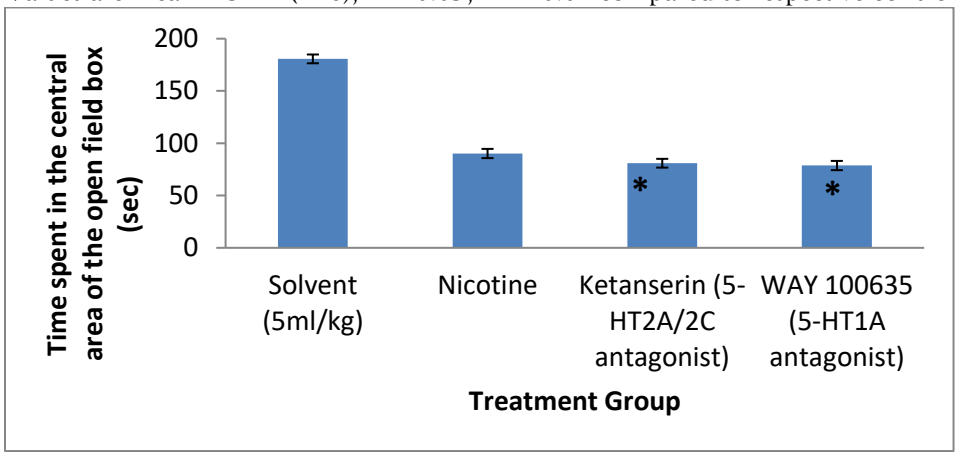
associated with higher anxiety. On the other hand, greater exploration of the central area indicates lower anxiety and a higher propensity for exploratory behavior. Locomotors activity, including the amount of time spent in central and peripheral zones was recorded and analyzed.

In forced swimming test rodents are placed in a container filled with water from which they cannot escape. Time spent standing (swimming) is recorded along with active time (swimming or fighting). Greater immobility is considered a sign of behavioral despair, similar to depressive states observed in humans.

Table 3: Effect of serotonergic antagonist on nicotine induce anxiety

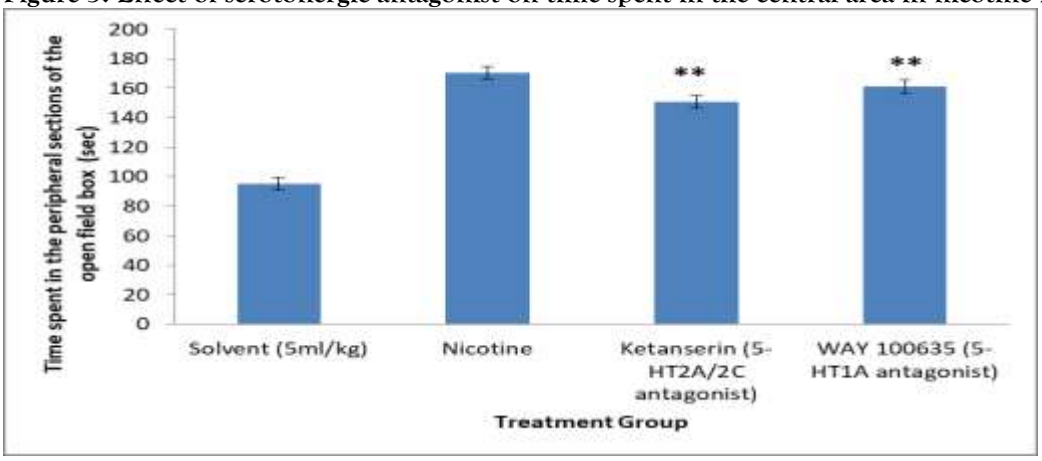
Treatment Group	time spent in the central area of the open field box (sec)	time spent in the peripheral sections of the open field box (sec)
Solvent (5ml/kg)	180.67 ± 0.5	95.13 ± 2.2
Nicotine	90.2 ± 1.2	170.2 ± 2.7
Ketanserin (5-$HT_{2A/2C}$ antagonist)	80.9 ± 1.3*	150.6 ± 1.4**
WAY 100635 (5-HT_{1A} antagonist)	78.7 ± 1.4*	160.9 ± 1.5**

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group group



P <0.05, **P <0.01 compared to respective control group

Figure 5: Effect of serotonergic antagonist on time spent in the central area in nicotine induce anxiety



*P <0.05, **P <0.01 compared to respective control group

Figure 6: Effect of serotonergic antagonist on time spent in the peripheral sections in nicotine induce anxiety

Serotonergic antagonist enhances nicotine-withdrawal-induced anxiety-like behavior. Animals undergoing nicotine withdrawal exhibited pronounced anxiety-like behaviors, reflected in a significant decrease in central area exploration during OFT and an increase exploring the central area showed peripheral area compared to the vehicle group. Treatment with Serotonergic antagonist significantly reduced exploration of the central area, while exploration of the peripheral area was increased relative to the nicotine group.

In the FST, nicotine withdrawal was linked to an increase in depressive-like behaviors, as demonstrated by a significant increase in immobility and a decrease in swimming time when compared to the vehicle group. Duration of immobility, which refers to the time when the animal does not actively swim to save itself; and treatment with serotonergic agonist Ketanserin and WAY 100635 significantly increase immobility time and reduce swimming time compared to the nicotine group.

Table 4: Effect of serotonergic antagonist on nicotine induce anxiety

Treatment Group	Swimming time (sec)	Immobility time (sec)
Solvent (5ml/kg)	175.23 ± 0.8	62.03 ± 0.9
Nicotine	82.2 ± 0.9	140.2 ± 0.7
Ketanserin	83.9 ± 0.3**	115.6 ± 0.4*
WAY 100635	76.7 ± 0.4*	155.9 ± 1.5**

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

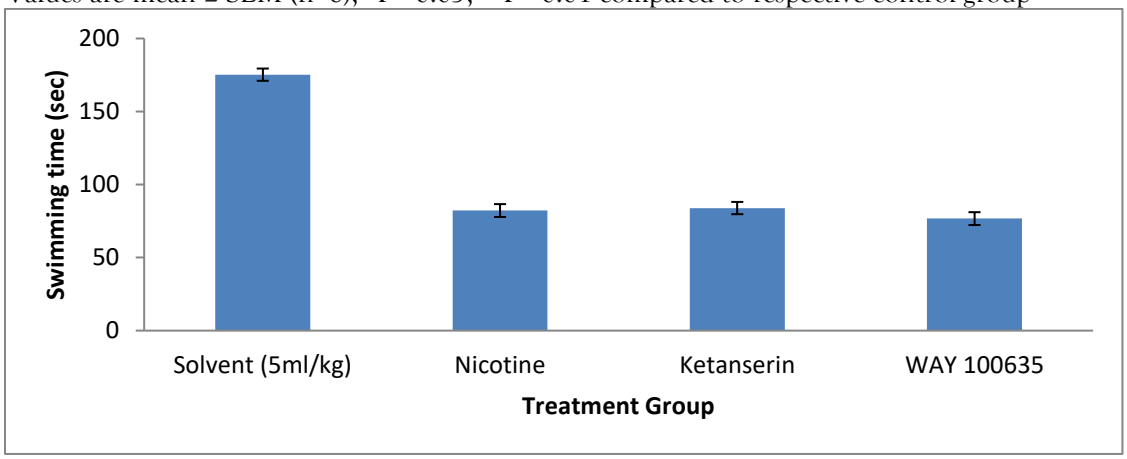


Figure 7: Effect of serotonergic antagonist on nicotine induce anxiety

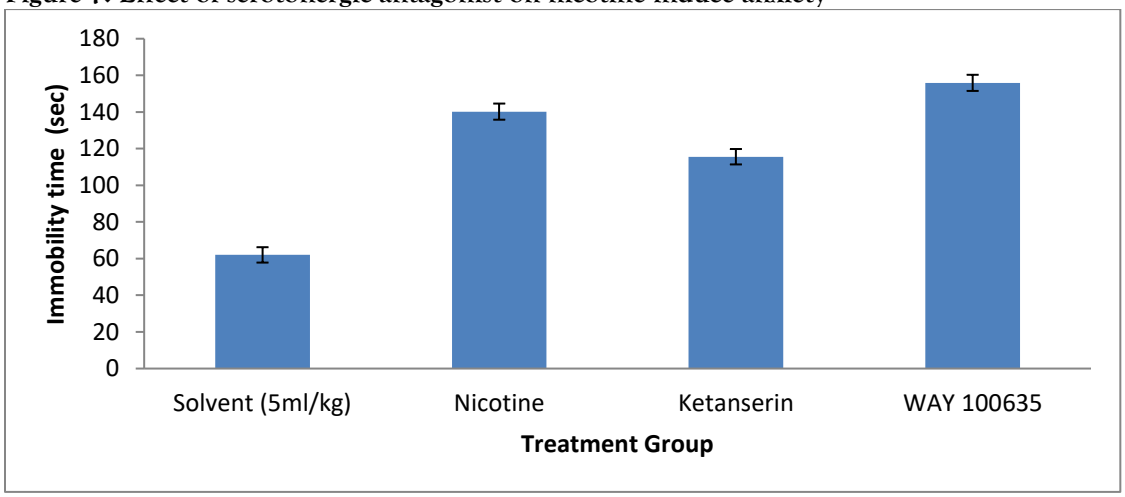


Figure 8: Effect of serotonergic antagonist on nicotine induce anxiety

Nicotine, can trigger oxidative stress and modulate neurotransmitter levels, which are linked to anxiety and depressive disorders. Furthermore, cessation of nicotine consumption correlates with increased anxiety-like behavior and the manifestation of depressive symptoms. Although numerous treatment protocols have effectively established models of nicotine withdrawal utilizing different doses and administration schedules, this study specifically induced nicotine withdrawal through a daily injection of 2 mg/kg of nicotine over 21-days. The results of the OFT showed that the animals spent significantly less time in the central area of the open field after nicotine withdrawal compared to the vehicle group. This indicates that the animal tends to spend more time in peripheral areas and avoids freely exploring open spaces, suggesting higher levels of anxiety and stress. This conclusion arises from the reduced exploration time of the animals in the open arms and their longer presence in the closed spaces

Nicotine withdrawal markedly exacerbates anxiety and depressive-like behaviors by interfering with brain serotonin metabolism, inflammatory processes, neurotrophic factors, and oxidative balance. Furthermore, we discovered that serratonergic agonist, given before nicotine exposure, effectively mitigated the development of depressive-like symptoms by normalizing serotonergic function in the brain.

Nicotine administered acutely modified the biosynthesis, release, and metabolism of the brain 5-HT, with the effects depending on its dose, route of administration, examined brain structure, and age of animals. Thus systemic administration of nicotine induced an increase of extracellular levels of 5-HT in the frontal cortex, the medial temporal cortex, the ventral tegmental area, the nucleus accumbens, and the dorsal hippocampus though no effect in the frontal cortex and a decrease in the dorsal hippocampus were also described.

In the FST, nicotine withdrawal was linked to an increase in depressive-like behaviors, as demonstrated by a significant increase in immobility and a decrease in swimming time when compared to the vehicle group. Treatment with serratonergic agonist (8-OH-DPAT) and R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride (DOI) significantly reduced immobility and increased swimming time compared to the nicotine group. Treatment with serratonergic agonist Ketanserin and WAY 100635 significantly increase immobility time and reduce swimming time compared to the nicotine group.

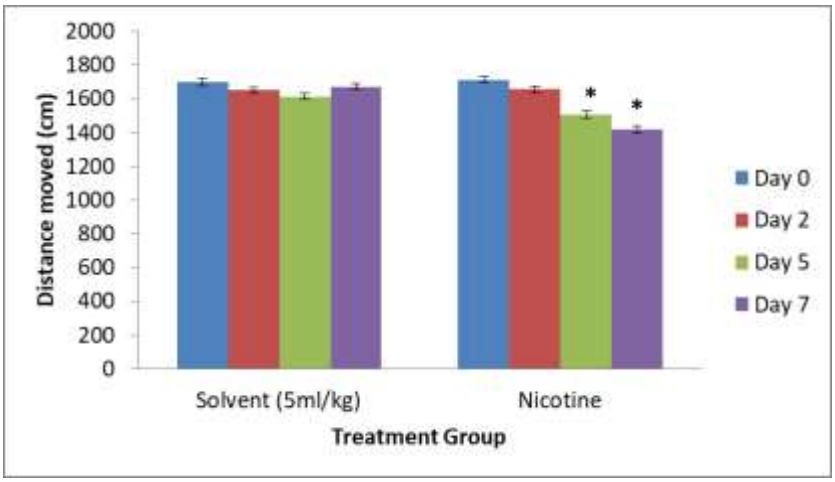
Effect of chronic nicotine withdrawal induce anxiety

Nicotine dependence was induced by subcutaneous administration of nicotine solution at a dose of 6 mg·kg-1·d-1 at 7 for 7 consecutive days. The control group was injected with sterile 0.9% sodium chloride solution at the same time course. To trigger nicotine withdrawal, mice were subcutaneously injected with 1 mg/kg of the nicotinic antagonist mecamyl amine hydrochloride (MEC) 60 min after the last injection of nicotine on the 7th day, and the following behavioural testing was performed during the next 7 d

Table 5: Effects of nicotine withdrawl on the locomotor activity in open-field test

Treatment Group	Distance moved (cm)			
	Days after nicotine withdrawal			
	Day 0	Day 2	Day 5	Day 7
Solvent (5ml/kg)	1700.02 ± 0.2	1650.5 ± 0.5	1613.50 ± 0.2	1673.20 ± 0.3
Nicotine	1714.05 ± 0.4	1656.6 ± 0.1	1508.2 ± 0.7*	1417.5 ± 0.7*

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group



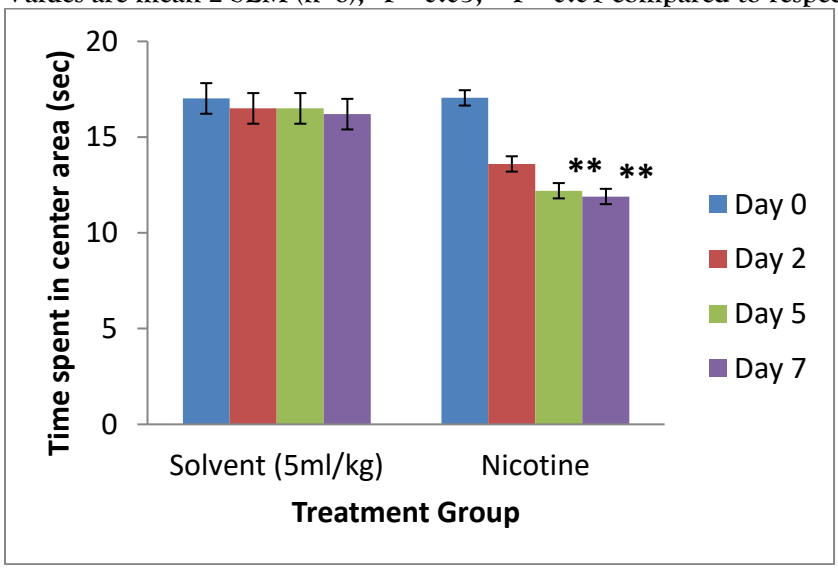
*P <0.05, **P <0.01 compared to respective control group

Figure 9: Effects of nicotine withdrawl on the locomotor activity in open-field test

Table 5.17: Effects of nicotine withdrawl on the time spent in center area in open-field test

Treatment Group	Time spent in center area (sec)			
	Days after nicotine withdrawal			
	Day 0	Day 2	Day 5	Day 7
Solvent (5ml/kg)	17.02 ± 0.2	16.5 ± 0.5	16.50 ± 0.2	16.20 ± 0.3
Nicotine	17.05 ± 0.4	13.6 ± 0.1	12.2 ± 0.7**	11.9 ± 0.7**

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group



*P <0.05, **P <0.01 compared to respective control group

Figure 10: Effects of nicotine withdrawl on the time spent in center area in open-field test

Twenty-four hours of last injection, mice were evaluated for anxiety-like behavior by subjecting to OFT. Anxiolytic activity increases time spent in open arms or in number of open arms entries in EPM, anxiogenic

effects was characterized by decreases in these measures. Separate group of animals received nicotine or saline as single injection and were tested 30 min after the last injection.

Administration of nicotine gradually increases locomotor activity in mice. Ambulations in the nicotine treated mice were significantly more as compared to saline group ($p<0.05$). This indicated the attenuation of nicotine induced development and expression of locomotor sensitization.

Spontaneous withdrawal from chronic nicotine administration significantly induced different measures of withdrawal signs after infusion of nicotine.

The effect on the time spent in the center area in open-field test decreased after withdrawal with no significant change in the number of crossings between arms. The increase in somatic signs and the time spent in open arms were reversed by pretreatment with nicotine. chronic exposure of nicotine produces both somatic and anxiety-like effect in the open-field test after terminating nicotine treatment. The nicotine withdrawal in was mild but prolonged. The signs peaked at about 24 to 48 h after spontaneous withdrawal and lasted for almost 4 days similar to the time course described in animals. Animals repeatedly exposed to nicotine showed increased anxiety like behavior and locomotor activity during withdrawal.

While acute nicotine treatment showed increased time spent by mice in open arm as compared to saline treated mice, Administration of Nicotine shows significant ($p<0.05$) increase in time spent and number of entries as compared to saline treated group representing the anxiolytic effect. 24 hrs following last injection of nicotine animals were tested for sign of anxiety by subjecting to OFT.

CONCLUSIONS

There is good evidence that nicotine increases 5-HT release in several brain regions, although there is as yet little evidence that this is the result of a direct effect of nicotine on presynaptic heteroreceptors on 5-HT terminals. However, it is clear that the 5-HT tone plays a crucial permissive role in the expression of nicotine's effects and this can be seen at the level of 5-HT release and on nicotine's effects on cognition. This is important because it means that results from in vitro preparations or electrophysiological recordings from anaesthetised animals may not provide results that are pertinent to the in vivo conditions pertaining in animal tests.

The strongest evidence is for nicotinic effects mediated by 5-HT1A receptors and it is interesting that both nicotine and 5-HT1A receptor agonists can have anxiolytic actions. However, the antidepressant actions of both compounds may be importantly linked to their anxiogenic effects that are evident at higher doses, rather than to their low-dose anxiolytic actions.

Administration of nicotine gradually increases locomotor activity in mice. This indicated the attenuation of nicotine induced development and expression of locomotor sensitization. acute nicotine treatment showed increased time spent by mice in open arm as compared to saline treated mice, Administration of Nicotine shows significant ($p<0.05$) increase in time spent and number of entries as compared to saline treated group representing the anxiolytic effect.

CONCLUSION

Nicotine, a major alkaloid in tobacco, can trigger oxidative stress and modulate neurotransmitter levels, which are linked to anxiety and depressive disorders. Furthermore, cessation of nicotine consumption correlates with increased anxiety-like behavior and the manifestation of depressive symptoms. Although numerous treatment protocols have effectively established models of nicotine withdrawal. The results of the OFT showed that the animals spent significantly less time in the central area of the open field after nicotine withdrawal compared to the vehicle group. This indicates that the animal tends to spend more time in peripheral areas and avoids freely exploring open spaces, suggesting higher levels of anxiety and stress. Animals showed higher levels of anxiety in subjects undergoing nicotine withdrawal. This conclusion arises from the reduced exploration time of the animals in the open arms and their longer presence in the closed

spaces. FST findings suggest that nicotine withdrawal reduces animals' efforts to avoid drowning in the pool. This was evidenced by a reduction in time spent struggling in the water, indicating psychological distress. So far, our results are consistent with previous research suggesting that withdrawal from chronic nicotine exposure leads to neuroadaptations that increase anxiety and depressive-like behavior in rodents

In conclusion, our findings demonstrate that nicotine withdrawal markedly exacerbates anxiety and depressive-like behaviors by interfering with brain serotonin metabolism, inflammatory processes, neurotrophic factors, and oxidative balance. The strongest evidence is for nicotinic effects mediated by 5-HT1A receptors and it is interesting that both nicotine and 5-HT1A receptor agonists can have anxiolytic actions. However, the antidepressant actions of both compounds may be importantly linked to their anxiogenic effects that are evident at higher doses, rather than to their low-dose anxiolytic actions.

REFERENCES

1. Soni S, Verma L. Nicotine and Neurotransmitters an Update. Research Journal of Pharmacy and Technology. 2024; 17(6):2605-2. doi: 10.52711/0974-360X.2024.00407
2. Alkondon M, Albuquerque EX. Diversity of nicotinic acetylcholine receptors in rat hippocampal neurons: I. Pharmacological and functional evidence for distinct structural subtypes. J Pharmacol Exp Ther 1993; 265:1455 – 73.
3. Decker MW, McGaugh JL. The role of interactions between the cholinergic system and other neuromodulatory systems in learning and memory. Synapse 1991;7:151 – 68.
4. Hodges H, Sowinski P, Sinden JD, Netto CA, Fletcher A. The selective 5-HT3 receptor antagonist, WAY100289, enhances spatial memory in mice with ibotenate lesions of the forebrain cholinergic projection system. Psychopharmacology 1995;117:318 – 32.
5. Miyata G, Meguid MM, Fetissov SO, Torelli GF, Kim HJ. Nicotine's effect on hypothalamic neurotransmitters and appetite regulation. Surgery 1999;126:255 – 63.
6. Riekkinen P, Riekkinen M, Sirvio J, Riekkinen P. Effects of concurrent nicotinic antagonist and pCPA treatments on spatial and passive avoidance learning. Brain Res 1992;575:247 – 50.
7. Arnold B, Allison K, Ivanova S, Paetsch PR, Paslawski T, Greenshaw AJ. 5HT3 receptor antagonists do not block nicotine-induced hyperactivity in mice. Psychopharmacology 1995;119:213 – 21.
8. Barnes NM, Costall B, Kelly ME, Onaivi ES, Naylor RJ. Ketotifen and its analogues reduce aversive responding in the rodent. Pharmacol, Biochem Behav 1990;37:785 – 93.
9. Benwell ME, Balfour DJ. The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol 1992;105:849 – 56.
10. Hogg S, Andrews N, File SE. Contrasting behavioural effects of 8-OH DPAT in the dorsal raphe´ nucleus and ventral hippocampus. Neuropharmacology 1994;33:343 – 8.
11. Mitchell SN, Brazell MP, Joseph MH, Alavijeh MS, Gray JA. Regionally specific effects of acute and chronic nicotine on rates of catecholamine and 5-hydroxytryptamine synthesis in rat brain. Eur J Pharmacol 1989; 167:311 – 22.
12. Benwell ME, Balfour DJ. Effects of nicotine administration and its withdrawal on plasma corticosterone and brain 5-hydroxyindoles. Psychopharmacology 1979;63:7 – 11.