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Role of Central 5 HT Receptor in Nicotine Mediated Behavioral Neurochemical Outcomes

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KEYWORDS

Nicotine, Central 5 HT receptor, neurochemical outcomes

ABSTRACT:

Nicotine is the principal neuroactive component in tobacco, but, despite ongoing research efforts, the cellular basis of its effects on behavior remains unclear. Efforts to resolve this conundrum have focused on the dopamine system, which contributes to the rewarding effects of many addictive drugs, including nicotine. Sensitization occurs with repeated or prolonged drug treatment and results in enhanced responsiveness to subsequent drug exposure, even after long withdrawal times. The phenomenon can be assayed as an increase in locomotor response to drug administration or as enhanced extracellular dopamine (DA) levels at the projection areas of the midbrain reward pathway, as measured by microdialysis. It may also reflect a drug-induced change in motivation. The aim of present study is to evaluate the role of central 5 HT receptor in nicotine mediated behavioral neurochemical outcomes

Introduction

Nicotine exerts its effects on behaviour by modulating the release of various neurotransmitters in the brain, particularly dopamine. This leads to a range of outcomes, including reinforcing effects, improved learning and memory, and modulation of anxiety. The complex behavioral phenomenon of drug addiction is ultimately a biological process, where repeated exposure to a drug alters the activity and metabolism of neurons that are sensitive to that drug [1-3].

Over time, this alters the properties of individual neurons and the circuits to which they contribute, leading to complex behaviors such as dependence, tolerance, sensitization, and craving. Considerable research effort is now focused on identifying the cellular mechanisms underlying each of these behaviors. Sensitization occurs with repeated or prolonged drug treatment and results in enhanced responsiveness to subsequent drug exposure, even after long withdrawal times. The phenomenon can be assayed as an increase in locomotor response to drug administration or as enhanced extracellular dopamine (DA) levels at the projection areas of the midbrain reward pathway, as measured by microdialysis [4-6].

Behavioral sensitization has been implicated in the development of drug addiction with its potential relevance to continuous self-administration in animals and drug craving and abuse in human addicts. It may also reflect a drug-induced change in motivation. Although it is important to note that sensitization is not equivalent to drug dependence, several behavioral and neurochemical consequences of repeated noncontingent drug exposure are also associated with drug addiction [7-8].

Nicotine primarily acts on nicotinic acetylcholine receptors (nAChRs), which are found throughout the brain. Activation of these receptors triggers the release of several neurotransmitters. Nicotine increases dopamine release in the mesolimbic pathway, a key area for reward and motivation. Nicotine also stimulates

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norepinephrine release, which plays a role in arousal and attention. Nicotine enhances acetylcholine release, influencing various cognitive functions. Nicotine increases glutamate release, which is crucial for synaptic plasticity and learning. Nicotine can also modulate GABA release, affecting anxiety and other behaviors. Nicotine can influence serotonin release, potentially impacting mood and impulsivity [9-10].

Nicotine influences neuronal activity, and ultimately behavior, through its effects on nicotinic acetylcholine receptors (nAChRs). These receptors are pentameric membrane proteins that include two or more agonist binding sites and a central aqueous pore that opens to allow ion flux following agonist binding. Three properties of these receptors that contribute to their physiological effects include activation, desensitization, and upregulation following nicotine exposure. Each of these phenomena is likely to contribute to the behavioral sensitization to nicotine, but the relative importance of each is not known [11-14]. The aim of present study is to evaluate the role of central 5 HT receptor in nicotine mediated behavioral neurochemical outcomes.

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.

Nicotine treatment and withdrawal

Nicotine dependence was induced by subcutaneous administration of nicotine solution at a dose of 6 mg/kg/day for 7 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 mecamylamine 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 days.

Behavioural testing

To assess thermal hyperalgesia, mice were placed in the testing equipment and allowed to acclimate to the environment for at least 60 min/d for 3 d. Thermal hyperalgesia was assessed by measuring the paw withdrawal latency in response to a radiant heat stimulus using a plantar test apparatus (Ugo Basile, Comerio, Italy). On test days, mice were placed in a Plexiglass box on a piece of 3-mm-thick glass plate and allowed to adapt to the environment for 30 min. Then, a radiant heat source was placed underneath the glass and focused directly onto the hind paw. The nociceptive endpoint in the radiant heat test was lifting or licking of the hind paw. A maximum cut-off of 20 s was set to prevent tissue damage. A thermal stimulus was delivered three times to each hind paw at 5-min intervals.

Effect of serotonergic agonist on nicotine induce sensitization

Locomotor activity was monitored and quantified using a photocell beam break system - “Photobeam Activity System” for home cages. Measurements were performed in 24 Perspex test cages (21 X36 X18 cm), placed between 7 photobeams, and arranged 4 cm above the chamber floor. The activity of each animal was recorded over twenty-four consecutive 5 min intervals for a total of 120 min, 60 min habituation and 60 min recording after drug injection. During experimentation, counts of ambulatory movement were integrated by the

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control software (Photobeam Activity Software) and stored for subsequent off-line (statistical) analyses.

The effect of Serotonin antagonist Ketanserin and WAY 100635 on the development and subsequent expression of nicotine-induced behavioural sensitization. Animals were habituated to the test apparatus one day prior to the experiment (day 0) and locomotor activity was recorded. On days 1 and 5, animals were placed in the test apparatus and after 30 min injected with Serotonin antagonist Ketanserin and WAY 100635 or vehicle. Thirty minutes later, nicotine (0.4 mg/kg SC) or saline was administered and locomotor activity was recorded for 60 min in 5 time epochs. On days 2, 3 and 4 the same treatments were performed but animals were administered in the home cage. Following a withdrawal period of 16 days, mice were habituated to the testing apparatus to test for conditioning effects and to serve to habituate the animals for subsequent pharmacology testing. After 17 days of withdrawal, on day 23, a challenge test was performed. Mice received either nicotine (0.4 mg/kg SC) or saline.

The effect of Serotonin antagonist on the expression of nicotine-induced sensitization

The methods were essentially similar to those above. However, on days 1 to 5 mice received either nicotine (0.4 mg/kg SC) or vehicle. Following a withdrawal period of 16 days, mice were habituated to the testing apparatus for 1 h and received injection of vehicle to test for conditioning effects and to serve to habituate the animals for subsequent pharmacological testing. On the following day (17 days after withdrawal) the hypothesis that Serotonin antagonist Ketanserin and WAY 100635 attenuated nicotine-induced sensitisation (vehicle) was tested in mice previously administered nicotine or vehicle. Thus, mice were placed in the locomotor activity activity chambers and 30 min later received Serotonin antagonist Ketanserin and WAY 100635 or vehicle followed 30 min later by either nicotine (0.4 mg/kg SC) or vehicle (SC) However, in order to verify this we tested the effects of Serotonin antagonist Ketanserin and WAY 100635 or its vehicle on locomotor activity

Table 1: Experimental design to assess the effects of Serotonin antagonist on nicotine-induced sensitization

Group	Day (1-5) Development of nicotine sensitization	Day 23 expression of nicotine sensitization
Group I	saline	saline
Group II	saline	Nicotine (0.4 mg/kg sc)
Group II	Nicotine (0.4 mg/kg sc)	Nicotine (0.4 mg/kg sc)
Group III	Nicotine (0.4 mg/kg sc)	Nicotine (0.4 mg/kg sc) + Ketanserin
Group IV	Nicotine (0.4 mg/kg sc)	Nicotine (0.4 mg/kg sc) + WAY 100635

Effect of serotonergic agonist on nicotine induce sensitization

The effect of Serotonin agonist 8-OH-DPAT (8-hydroxy-2 (-dipropylamino) tetralinhydro bromide) and DOI (R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride) on the development and subsequent expression of nicotine-induced behavioural sensitization. Animals were habituated to the test apparatus one day prior to the experiment (day 0) and locomotor activity was recorded. On days 1 and 5, animals were placed in the test apparatus and after 30 min injected with Serotonin agonist or vehicle. Thirty minutes later, nicotine (0.4 mg/kg SC) or saline was administered and locomotor activity was recorded for 60 min in 5 time epochs. On days 2, 3 and 4 the same treatments were performed but animals were administered in the home cage. Following a withdrawal period of 16 days, mice were habituated to the testing

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apparatus to test for conditioning effects and to serve to habituate the animals for subsequent pharmacology testing. After 17 days of withdrawal, on day 23, a challenge test was performed. Mice received either nicotine (0.4 mg/kg SC) or saline.

The effect of Serotonin agonist on the expression of nicotine-induced behavioural sensitization. However, on days 1 to 5 mice received either nicotine (0.4 mg/kg SC) or vehicle. Following a withdrawal period of 16 days, mice were habituated to the testing apparatus for 1 h and received injection of vehicle to test for conditioning effects and to serve to habituate the animals for subsequent pharmacological testing. Mice were placed in the locomotor activity activity chambers and 30 min later received Serotonin agonist OH-DPAT (8-hydroxy-2 (-dipropylamino) tetralinhydro bromide) and DOI (R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride) or vehicle followed 30 min later by either nicotine or vehicle.

Table 2: Experimental design for effect of serotonergic agonist on nicotine induce sensitization

Group	**Day (1-5)** **Development of nicotine sensitization**	**Day 23 expression of nicotine sensitization**
Group I	saline	saline
Group II	saline	Nicotine (0.4 mg/kg sc)
Group II	Nicotine (0.4 mg/kg sc)	Nicotine (0.4 mg/kg sc)
Group III	Nicotine (0.4 mg/kg sc)	Nicotine (0.4 mg/kg sc) + 8-OH-DPAT
Group IV	Nicotine (0.4 mg/kg sc)	Nicotine (0.4 mg/kg sc) + DOI

8-OH-DPAT (8-hydroxy-2 (-dipropylamino) tetralinhydro bromide)

DOI (R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride)

Effect of nicotine on elevated plus maze

Nicotine (0.1, 0.5, or 1.0 mg/kg) or physiologic saline was administered via subcutaneous injections between the shoulder blades. These dosages were selected to span those commonly used in the literature. Physiological saline also was used as a vehicle for the nicotine solution. Solutions were pH adjusted to physiologic saline pH using Na2PO4

The elevated plus maze is a plus shaped apparatus with four arms at right angles to each other. The two open arms lie across from each other measuring 25 x 5 x5 cm and perpendicular to two closed arms measuring 25 x 5 x 16 cm with a centre platform (5 x 5 x 0.5 cm). The closed arms have a high wall (16 cm) to enclose the arms whereas the open arms have no side wall. Animals (25-30 g) were divided into groups and each group containing six animals. The animals of Group- I served as control, remaining groups of animals were administered nicotine at different dose level, orally.

Following administration vehicle, standard drugs and test samples, mice were placed in the central platform facing the closed arm and their behaviour recorded for 5 min. The criterion for arm visit was considered only when the animal decisively moved all its four limbs into an arm. The elevated plus maze relies upon rodents proclivity toward dark, enclosed spaces (approach) and an unconditioned fear of heights/open spaces (avoidance).The percentage of time spent in the arms was calculated as time in open arms or closed arm/total time x100, the number of entries into the arms was calculated using number of entries into open or closed arms/total number of entries.

Experimental design for effect of nicotine on elevated plus maze

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

Group 2: Animals received Nicotine 0.1 mg/kg (sc)

Group 3: Animals received Nicotine 0.5 mg/kg (sc)

Group 4: Animals received Nicotine 1 mg/kg (sc)

Result and discussion

Effect of serotonergic antagonist on nicotine induce sensitization

Effect of serotonergic antagonist on nicotine induce sensitization were evaluated by Locomotor activity

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monitored and quantified using a photocell beam break system - "Photobeam Activity System" for home cages.

Table 3: Effects of serotonergic antagonist on nicotine induce sensitization

Group	No of beam break (in 60 min)		
	Day 1	Day 5	Day 23
Group I	200	205	200
Group II	190	180	460
Group III	540	570	875
Group IV	542	580	510
Group V	531	569	320

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

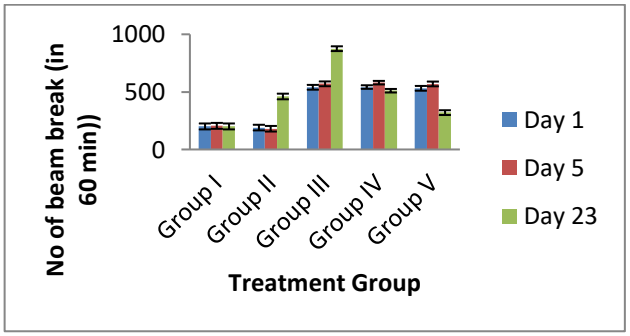

Figure 1: Effects of serotonergic antagonist on nicotine induce sensitization

The effect of Serotonin antagonist Ketanserin and WAY 100635 on the development of nicotine-induced locomotor activity

Group I animals received saline on day 1 to 5 and 23, Group II animals received saline on day 1 to 5 and 23 and nicotine only on day 23. Group III animals received nicotine on day 1 to 5 and 23. Group IV and V animals received nicotine on day 1 to 5 and 23 and Serotonin antagonist Ketanserin and WAY 100635 on day 23 respectively. These data demonstrate that animals treated with nicotine developed and expressed behavioural sensitisation. On the habituation day prior to experimental initiation (day 0), no significant difference in locomotion was found between the experimental groups.

Nicotine sensization occurred, since animals in group III showed a higher nicotine-induced locomotor activity response on day 5 versus day 1. Expression of nicotine sensization occurred, since on day 23, animals in group III showed significantly higher

Animals were re-assessed on day 23 while there was a reduction in the expression sensitization. Locomotor activity is expressed as number of beam breaks across a 60 min period after the nicotine or saline injection.

On day 1, there was a significant treatment effect and a modest effect of nicotine to augment locomotor activity. Extended 5 days of nicotine or saline administration significant treatment effects on locomotor activity were seen that nicotine increased locomotor activity ($P < 0.05$,). Comparison of day 1 vs day 5 data demonstrated that extended (5 day) treatment with nicotine did result in the development of locomotor sensitization in each of the groups tested.

A serotonergic antagonist, by blocking serotonin receptors in the brain, is likely to attenuate or reduce the development of nicotine-induced sensitization; meaning it could lessen the increased behavioral response to repeated nicotine exposure, potentially by impacting the neurocircuitry involved in reward and reinforcement pathways that are influenced by serotonin activity.

Nicotine is known to directly stimulate serotonin release in certain brain regions, contributing to its rewarding effects. Repeated nicotine exposure can lead to changes in brain circuitry, including increased sensitivity to dopamine release in the reward pathway, which is partially modulated by serotonin. By blocking serotonin receptors, a serotonergic antagonist could disrupt this sensitization process, potentially reducing the enhanced response to subsequent nicotine administration.

Serotonin antagonist Ketanserin and WAY 100635 attenuated the expression of nicotine sensitisation. Nicotine pretreated mice (days 1 to 5) displayed the expression of nicotine sensitisation following withdrawal. These effects were doses dependently and significantly blocked by treatment with the Serotonin antagonist Ketanserin and WAY 100635

Locomotor activity (mean S.E.M.) is expressed as number of beam breaks across a 60-min period after the

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nicotine injection. *P < 0.05 indicates the difference from the nicotine pretreated mice group on each day.

Serotonin receptor antagonism with Ketanserin and WAY 100635 attenuated the development and expression of nicotine-induced locomotor sensitisation. These data suggest the potential utility of Serotonin antagonist for the treatment of nicotine abuse. The mechanisms underlying the modulatory role of 5-HT6 receptor antagonists on the behavioural effects of nicotine warrant further exploration, but it is interesting to speculate whether associative learning changes are linked to this phenomenon.

Effect of serotonergic agonist on nicotine induce sensitization

Effect of serotonergic agonist on nicotine induce sensitization were evaluated by Locomotor activity monitored and quantified using a photocell beam break system - "Photobeam Activity System" for home cages.

Table 4: Effects of serotonergic agonist on nicotine induce sensitization

Group	No of beam break (in 60 min)		
	Day 1	Day 5	Day 23
Group I	210	210	200
Group II	195	190	460
Group III	548	578	875
Group IV	547	585	870
Group V	532	570	895

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

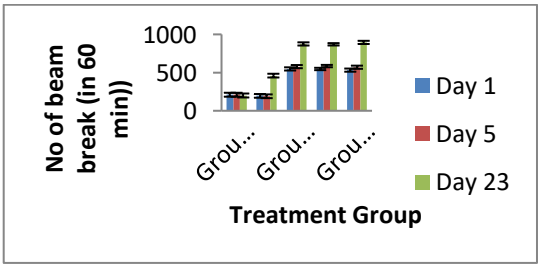

Figure 2: Effects of serotonergic agonist on nicotine induce sensitization

The effect of Serotonin agonist 8-OH-DPAT (8-hydroxy-2 (-dipropylamino) tetralinhydro bromide) and DOI (R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride) on the development and subsequent expression of nicotine-induced behavioural sensitization. Animals were habituated to the test apparatus one day prior to the experiment (day 0) and locomotor activity was recorded. On days 1 and 5, animals were placed in the test apparatus and after 30 min injected with Serotonin agonist or vehicle. Thirty minutes later, nicotine (0.4 mg/kg SC) or saline was administered and locomotor activity was recorded for 60 min in 5 time epochs. On days 2, 3 and 4 the same treatments were performed but animals were administered in the home cage. Following a withdrawal period of 16 days, mice were habituated to the testing apparatus to test for conditioning effects and to serve to habituate the animals for subsequent pharmacology testing. After 17 days of withdrawal, on day 23, a challenge test was performed. Mice received either nicotine (0.4 mg/kg SC) or saline.

The effect of Serotonin antagonist on the expression of nicotine-induced behavioural sensitisation, on days 1 to 5 mice received either nicotine or saline. Following a withdrawal period of 16 days, mice were habituated to the testing apparatus for 1 h and received injection of vehicle to test for conditioning effects and to serve to habituate the animals for subsequent pharmacological testing. Mice were placed in the locomotor activity activity chambers and 30 min later received Serotonin agonist OH-DPAT (8-hydroxy-2 (-dipropylamino) tetralinhydro bromide) and DOI (R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride) or saline followed 30 min later by either nicotine or vehicle.

A serotonergic agonist, by cooperative serotonin receptors in the brain, is likely to enhance the development of nicotine-induced sensitization; meaning it could increase behavioral response to repeated nicotine exposure that is influenced by serotonin activity.

Nicotine is known to directly stimulate serotonin release in certain brain regions, contributing to its rewarding effects. Repeated nicotine exposure can lead to changes in brain circuitry, including increased sensitivity to dopamine release in the reward pathway, which is

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partially modulated by serotonin. By increase serotonin receptors, a serotonergic agonist could increase sensitization process, potentially enhanced response to subsequent nicotine administration.

Serotonin agonist 8-OH-DPAT and DOI (R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride) enhance the expression of nicotine sensitisation. Nicotine pretreated mice (days 1e5) displayed the expression of nicotine sensitisation following withdrawal. These effects were doses dependently and significantly enhance by treatment with the Serotonin agonist.

Locomotor activity is expressed as number of beam breaks across a 60-min period after the nicotine injection. *P < 0.05 indicates the difference from the nicotine pretreated mice group on each day. Serotonin receptor agonism enhances the development and expression of nicotine-induced locomotor sensitisation.

Effect of nicotine on elevated plus maze

Nicotine (0.1, 0.5, or 1.0 mg/kg) or physiologic saline was administered via subcutaneous injections between the shoulder blades. These dosages were selected to span those commonly used in the literature. Physiological saline also was used as a vehicle for the nicotine solution. Solutions were pH adjusted to physiologic saline pH using Na2PO4. The elevated plus maze is a plus shaped apparatus with four arms at right angles to each other. The animals of Group- I served as control, remaining groups of animals were administered nicotine at different dose level, orally.

Following administration vehicle, standard drugs and test samples, mice were placed in the central platform facing the closed arm and their behavior recorded for 5 min. The criterion for arm visit was considered only when the animal decisively moved all its four limbs into an arm. The elevated plus maze relies upon rodents proclivity toward dark, enclosed spaces (approach) and an unconditioned fear of heights/open spaces (avoidance).The percentage of time spent in the arms was calculated as time in open arms or closed arm/total time x100, the number of entries into the arms was calculated using number of entries into open or closed arms/total number of entries.

Table 5: Effect of nicotine on elevated plus maze

Treatment	No of entries in open arm in 5 min	Time spent in open arm (sec)
Solvent (5ml/kg)	4.67 ± 0.5	37.13 ± 2.2
Nicotine 0.1 mg/kg	10.2 ± 1.2	51.2 ± 2.7
Nicotine 0.5 mg/kg	11.9 ± 1.7	79.6 ± 1.9
Nicotine 1 mg/kg	13.7 ± 1.4	99.9 ± 1.2

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

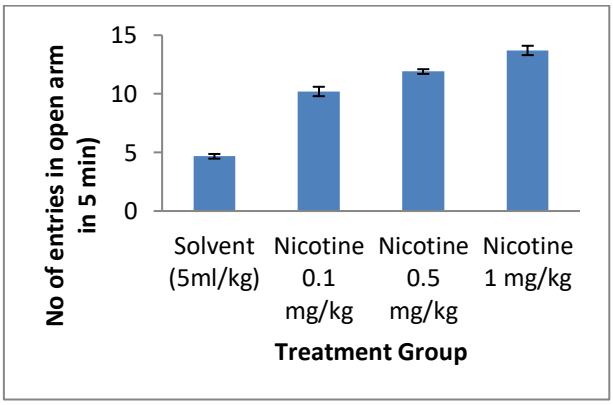

Figure 3: Effect of nicotine on elevated plus maze (No of entries in open arm in 5 min)

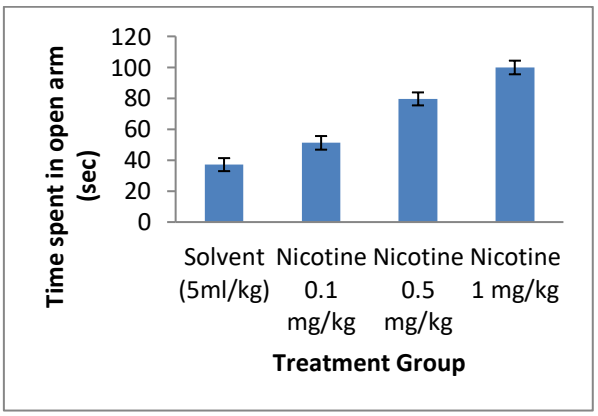

Figure 4: Effect of nicotine on elevated plus maze (Time spent in open arm (sec)

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Elevated plus maze (EPM) behavior was observed for 5 min, 10 min following an injection of nicotine (0.1, 0.5, or 1.0 mg/kg) or saline. Increases in percentage time in open arms are interpreted as evidence of anxiolysis. When all animals were considered Nicotine-treated animals generally spent more time in the open arms than did saline-treated controls.

Increases in percentage of open arm entries can be interpreted as evidence of anxiolysis but also may reflect exploration because this measure depends on the number of times an animal moves back and forth between the closed and open arms. Nicotine increased percentage of open arm entries in the 1.0-mg/kg group exhibited greater percentage open arm entries than did the saline group. Percent closed arm entries is interpreted as evidence of general activity when animals were analyzed.

Nicotine generally decreased the percentage of closed arm entries. Nicotine did not significantly affect closed arm entries. This experiment examined the effects of repeated –acute nicotine administration (saline, 0.1, 0.5, or 1.0 mg/kg daily) on EPM. Nicotine exerted anxiolytic effects (increased percentage of time in the open arms). Nicotine decreased percentage of time in the close arms

Increases in percentage time in open arms are interpreted as evidence of anxiolysis Nicotine-treated animals generally spent less time in the open arms than did saline-treated controls nicotine reduced percentage of time spent in the open arms. Percentage of open arm entries Increases in percentage of open arm entries can be interpreted as evidence of anxiolysis but also may reflect exploration because this measure depends on the number of times an animal moves back and forth between the closed and open arms. Nicotine increased percentage of open arm entries. Within adults, nicotine reduced the percentage of open arm entries with all groups differing significantly from saline

Percent closed arm entries is interpreted as evidence of general activity. When all animals were analyzed together, nicotine generally decreased the percentage of closed arm entries. nicotine decreased the total number of closed arm entries at the 1.0-mg/kg dose only. Nicotine exerted anxiolytic effects (increased percentage of time in the open arms) in adolescent males. nicotine's effects on percentage of entries into closed arms (a measure of activity) for each group did not parallel effects on percentage of time in the open arms.

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 utilizing different doses and administration schedules, The acute and persistent effects of nicotine exposure are the focus of ongoing investigations by many different research groups. The extent to which specific receptor functions and cellular consequences contribute to the behavioral effects of the drug remains to be determined. Nicotine generally decreased the percentage of closed arm entries. Nicotine decreased the total number of closed arm entries at the 1.0-mg/kg dose only. Nicotine is known to directly stimulate serotonin release in certain brain regions, contributing to its rewarding effects. Repeated nicotine exposure can lead to changes in brain circuitry, including increased sensitivity to dopamine release in the reward pathway, which is partially modulated by serotonin. By increase serotonin receptors, a serotonergic agonist could increase sensitization process, potentially enhanced response to subsequent nicotine administration. Serotonin agonist 8-OH-DPAT and DOI (R-1-(2, 5-dimethoxyl-4-iodophenyl) -2-aminopropane) hydrochloride) enhance the expression of nicotine sensitisation. Nicotine pretreated mice (days 1e5) displayed the expression of nicotine sensitisation following withdrawal. These effects were doses dependently and significantly enhance by treatment with the Serotonin agonist.

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