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Nicotine-induced Nicotinic receptor upregulation and the involvement of the role of central serotonergic transmission

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Abstract

Nicotine, the psychoactive component of tobacco, is commonly used by humans due to its addictive propensity. Nociception (sometimes nocioception or nociperception) is the nervous system's encoding and processing of noxious stimuli. For a long time, central serotonergic pathways have been linked to antinociception mechanisms. Locomotor activity will be represented as the total number of locomotor counts for each light beam disrupted in the past six minutes of testing. After each test, the arena will be cleaned with damp cotton soaked in alcohol before exposing the next treated animal. In behavioral and electrophysiological paradigms, there is evidence for both pronociceptive and antinociceptive effects of 5-HT, which are mediated by different 5-HT receptor subtypes. In this research, we will explore the effect of a serotonergic analogue on nicotine tolerance, antinociceptive effect, and withdrawal-induced hyperalgesia. The current study aims to elucidate the function of seretonergic transmission in nicotine's diverse reinforcing effects. As a result, we will be attempting to shed new light on the probable mechanisms of nicotine-induced effects such as antinociception and hyperalgesia.

Keywords: Nicotine, Antinociceptive effect, Hyperalgesia, Nociception, Nocioception.

Introduction

Nicotine is largely metabolised by CYP2A6, and variations in metabolic rate relates to tobacco dependence, responsiveness to smoking cessation treatment, and lung cancer risk[1]. Nicotine causes a variety of behavioural reactions in mice, such as alterations in locomotion, nociception, anxiety, learning, and memory, and these rewarding effects lead to physical dependency and/or are responsible for its reinforcing qualities [2,3]. When nicotine is delivered, it increases tolerance to its antinociceptive action [4,5]. Chronic nicotine

abstinence/withdrawal causes hyperalgesia. Nicotine and other cholinergic agonists have long been known to inhibit nociception. The heteromeric α 4 β 2 and homomeric a 7 receptors appear to play a crucial role in these reinforcing and discriminative nicotine-induced stimuli[6,7].

Nociception (sometimes nocioception or nociperception) is the encoding and processing of noxious stimuli in the nervous system. It is the stimulation of specialised free nerve endings called "nociceptors" or "pain receptors" that only respond to tissue injury or other strong chemical (e.g., chilli powder in the eyes), mechanical (e.g., pinching, crushing), or thermal (hot and cold) stimulation. When triggered, a nociceptor delivers a signal to the brain via a series of nerve fibres in the spinal cord.

Nociception causes a number of autonomic responses as well as the subjective sensation of pain in sentient beings. In response to severe stimuli, nociceptive neurons fire trains of action potentials, and the frequency of firing determines the intensity of the pain.

Effect of serotonin on nociception:

For some years, central serotonergic pathways have been linked to antinociception mechanisms. While both supraspinally and spinally projecting pathways are involved in nociceptive transmission regulation, pathways originating in the brainstem and projecting to the dorsal horn of the spinal cord have received the most attention due to the proposal of an endogenous pain-suppressing system utilising 5 hydroxytryptamine (5-HT). The actions of 5-HT in the spinal cord are complex, and can be influenced by: (1) the receptor subtype being activated; (2) the relative contributions of pre- versus postsynaptic receptor actions; (terms of stimulus quality and intensity); and (4) potential contributory effects of temperature changes. Autoradiographic studies have demonstrated the presence and location of numerous 5-HT receptor populations inside the spinal cord. The activation of spinal 5-HT1A receptors causes pronociception, whereas the activation of 5-HT1B and 5-HT3 receptors causes antinociception. Antinociception is produced by activating 5-HT2 receptors, which can be preceded by pronociceptive responses [8,9].

Interactions with other brainstem projection routes, such as those containing noradrenaline (NA), transmission neurons, and excitatory and/or inhibitory interneurons expressing -aminobutyric acid or enkephalin, have been implicated in 5-HT's nociceptive spinal action[10].

Nicotine Effects on Brain and Human body

Significant evidence suggests that nicotine, like other addictive chemicals, affects behaviour by stimulating the mesocorticolimbic dopamine (DA) system, a route that begins in the ventral tegmental area (VTA) and extends to the nucleus accumbens (NAcc) and other forebrain regions[11-13]. This system's activation has also been

proven to be crucial for the drug's rewarding qualities. Nicotine stimulates the firing of midbrain DA neurons and increases DA overflow in the NAcc in experimental animals [14-16]. Nicotine's locomotor activating effects and ability to support self-administration are likely mediated by these actions, as both are prevented by DA receptor blockade and lesions of the mesoaccumbens DA system, and all nicotine effects are blocked by nicotine receptor antagonists [17-21]. Nicotine receptors in the VTA are especially significant since inhibiting these receptors but not those in other places such as the NAcc reduces nicotine-induced NAcc DA release, motility, and nicotine self-administration [22-26]. When nicotine injections are repeated, the drug's locomotor activating effects become sensitised, like with other stimulants such as amphetamine and cocaine [27-29]. There is also evidence that repeated nicotine injections sensitise this drug's potential to boost NAcc DA release. Interestingly, like with other stimulants, prolonged withdrawal durations may augment the hypersensitive NAcc DA response to nicotine [30, 31].

When nicotine injections are repeated, the drug's locomotor activating effects become sensitised, like with other stimulants such as amphetamine and cocaine. There is also evidence that repeated nicotine injections sensitise this drug's potential to boost NAcc DA release. Interestingly, like with other stimulants, prolonged withdrawal durations may augment the hypersensitive NAcc DA response to nicotine [32-35].

Nicotine from cigarettes is absorbed into the bloodstream through the lungs. It binds to nicotinic cholinergic receptors in the central nervous system (CNS) and peripheral nervous system (PNS) as a tertiary amine (PNS). Binding of these receptors causes the release of a neurotransmitter, dopamine, and activates the rewards circuit, among other things. If nicotine usage is reduced or discontinued, it can cause neuroadaptation, dependence, mood/arousal modulation, and withdrawal symptoms. Over the last decade, investigations on nicotine's effects on cognitive performance have yielded inconclusive results. Some research found nicotine to be harmful, while others found nicotine to improve cognitive function [36-42].

Nicotine's carcinogenicity and implications on cancer therapy response

Nicotine works by stimulating nicotinic acetylcholine receptors (nAChRs), which are found in the CNS, at autonomic nervous system interganglionic junctions, and on target organs throughout the body as part of the parasympathetic autonomic nervous system. nAChRs are ligand-gated ion channels made up of five membrane-spanning subunits that work together to produce a functioning receptor.

Although the homomeric 7-nAChR has been identified as the major receptor promoting nicotine-mediated cell proliferation, additional receptor subunits may also be involved. Nicotine has a stronger affinity for nAChRs than acetylcholine (Ach). Tobacco-specific N-nitrosamines (TSNA) and cotinine have been shown to bind to nAChRs.

Nicotine binding to nAChR in the brain is implicated in nicotine's rewarding effects as well as the modifications that occur in response to chronic exposure, which give rise to dependence and withdrawal

symptoms. The release of dopamine is principally responsible for the positive reinforcing elements of nicotine addiction [43-45].

N-nitrosation of tobacco alkaloids produces tobacco-specific N-nitrosamines. The carcinogens NNN (N′-nitrosonornicotine) and NNK (4-(metylnitrosamino)-1-(3-pyridyl)-1-butanon) are among the most important and potent in tobacco and tobacco smoke. NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) is a metabolite of NNK, and total NNAL (NNAL and its glucuronides) measurement in urine is frequently used to analyse the possible function of TSNA in tumour growth. Total NNAL levels in smokers' serum were found to have a substantial connection with lung cancer risk. The International Agency for Cancer Research (IARC) has designated NNN and NNK as human carcinogens [46-47].

Nicotine can activate cholinergic receptors because it has a similar structure to acetylcholine. Unlike acetylcholine, nicotine penetrates the brain and affects normal brain function. Cigarette smoking causes an increase in the number of cholinergic receptors as well as changes in the sensitivity of these receptors, which may lead to nicotine tolerance. A smoker must therefore maintain a consistent supply of nicotine in order to maintain normal brain function, and the behaviour becomes addicted [48].

Nicotine also increases the release of neurotransmitters such norepinephrine, epinephrine, vasopressin, dopamine, arginine, and beta-endorphin. Pain, anxiety, and other unpleasant symptoms are alleviated, while positive pleasure sensations are enhanced[49-50].

Nicotine consumption raises blood glucose levels, which is assumed to be due to the elevated adrenalin levels caused by nicotine consumption activating the liver to release glucose. The increased availability of glucose, in conjunction with adrenalin, is assumed to be responsible for the improved learning ability, memory, and alertness associated with smoking. An increase in blood glucose levels reduces appetite, which raises metabolic rate and, in the long run, leads to weight loss [51-53].

Literature Survey

1. Carstens Earl *et al.,2022* examining the current understanding of nicotine's activities on nAChRs and emphasise considerations surrounding nAChR subtype localisation and pharmacodynamics. Following that, we will go over the seminal findings generated from genetically modified mouse models, which have considerably aided our knowledge of nicotine's effects on the reward-related mesolimbic pathway and the aversion-related habenulo-interpeduncular network. It is assumed that antinociception is mediated by descending suppression of spinal nociceptive transmission. Menthol reduces harshness by cross-desensitizing nicotine-evoked oral irritation, which may account for its popularity as a taste addition in tobacco products[54].

2. Sherafat Yasmine *et al.,2021* In addition to nicotine's immediate activities in binding to and activating nAChRs, the following activation of circuits and downstream signalling cascades causes a wide range of alterations in gene expression, which can then influence behavioural expression. In this review, we present an overview of nicotine's effects that lead to changes in gene expression, as well as evidence indicating how these changes can frequently be bidirectional, prompting subsequent changes in behaviours associated with additional drug intake[55].
3. Cristiano Bombardi *et al.,2020* In this context, the 5-HT2A receptors (5-HT2ARs) and the lateral habenula (LHb), a crucial location in nicotine addiction that we demonstrated to be under intense 5-HT2AR-modulation, are particularly intriguing. The strong agonist TCB-2 was administered intravenously to evaluate the 5-HT2AR function using single-cell extracellular recording of LHb neurons. Acute nicotine (2 mg/kg intraperitoneal, i.p.) and chronic nicotine (6 mg/kg/day for 14 days) had varied effects on the number of 5-HT2AR-immuno reactive (IR) neurons and the area of 5-HT2AR immunostaining in the various brain locations investigated. These findings suggest that acute and chronic nicotine affect 5-HT2AR function differently in different brain areas, which could be useful in the treatment of nicotine addiction[56].

4. Philippe De Deurwaerdère *et al., 2020* 5-HT is a central nervous system (CNS) neurotransmitter, blood factor, and neurohormone that regulates the operation of various peripheral organs. Aside from its vast role in physiology, the 5-HT system is implicated in a variety of CNS and peripheral organ diseases (e.g., depression, anxiety, schizophrenia, obsessive-compulsive disorders, addiction, Parkinson's disease) (e.g., gastrointestinal disorders, cardiac arrhythmia, hypertension). The current advancements made on the function and malfunction of the 5-HT system will undoubtedly boost comprehension of 5-HT's extensive involvement, eventually leading to a better understanding of its targeting in human disorders[57].
5. Anand Ramalingam *et al.,2019.* In a rat model, researchers looked at the effects of resveratrol supplementation on nicotine-induced kidney damage and oxidative stress. Following treatment, kidneys were examined for structural alterations, renal damage indicators, and oxidative stress. Nicotine administration alone for 28 days caused severe renal damage, as evidenced by a rise in plasma creatinine, blood urea nitrogen (BUN), and oxidative stress. Co-administration with resveratrol, on the other hand, successfully reduced these alterations, with a simultaneous increase in renal antioxidants such as glutathione comparable to the commonly used angiotensin II receptor blocker, irbesartan. These findings imply that addressing renal oxidative stress with resveratrol may help to mitigate nicotine-induced kidney damage. Antioxidants may be clinically significant in the control of renal function in heavy smokers[58].

6. Martin Lea M. *et al.,2018* In this research, thirteen studies that experimentally altered nicotine and assessed social functioning were identified, with twelve of them finding support for nicotine's increase of social functioning. Despite the fact that few studies have been conducted on social functioning, they provide persuasive evidence that nicotine improves social functioning in smokers and that nicotine deprivation may impair social functioning in individuals who are nicotine dependent. Future directions for studying social effects and context in nicotine product users are reviewed, with an emphasis on utilising breakthroughs in social and developmental psychology, animal studies, sociology, and neuroimaging to better understand smoking behavior[59].

7. Chang Seong Kim *et al.,2016* The levels of reactive oxygen species (ROS) within cells, as well as the expression of mitogen-activated protein kinase (MAPK) and nuclear factor-B (NF-B) proteins, were measured. HK-2 cells were shown to have nAChRs. Nicotine therapy decreased cell viability in a dose-dependent manner, increased ROS levels, and enhanced the expression of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. Nicotine induced apoptosis in HK-2 cells by producing ROS, which activated the NF-B signalling pathway via the MAPK pathway and stopped the cell cycle during the G2/M phase. The nAChRs are involved in nicotine-induced apoptosis in HK-2 cells[60].

8. Tore Sanner *et al.*,2015 They discovered that nicotine can alter multiple crucial phases in the formation of cancer, and that it may promote disease aggravation and recurrence. In the body, nicotine can be converted into TSNA. Nicotine's significance as the primary addictive component of tobacco products may have diverted our attention away from toxicological effects on cell proliferation, angiogenesis, and tumour aggressiveness. Cancer disease impacts are key considerations in assessing the potential long-term consequences of nicotine sources such as e-cigarettes and nicotine replacement treatment products, both of which have the potential for life-long usage[61].

9. Massimo Pierucci B.Sc.,*et al,2014* They discuss the role of 5-HT and its numerous receptors, with a focus on 5-HT2 subtypes and their significance in the neurobiology of nicotine addiction. We also investigate novel pharmacological techniques based on 5-HT drugs for the treatment of nicotine addiction. Although further research is needed, compelling evidence suggests that 5-HT2C receptor agonists could be potential therapeutic targets for smoking cessation[62].

10. Shanmugavelu Muthukumaran *et al.,2013* contrasted N-acetylcysteine (NAC), a well-known antioxidant, to the protective impact of quercetin, a polyphenolic flavonoid, on lipid peroxidation, endogenous antioxidant status, and DNA damage during nicotine-induced toxicity in cultured rat peripheral blood cells. Reduced lipid peroxidation was observed to be beneficial with a 75 M dosage of quercetin. We used comet and micronucleus assays, which are credible measures for assessing genetic damage, to investigate quercetin's preventive ability against nicotine's genotoxic effects[63].

11. Gabriel Rezonzew *et al.*,2011 Nicotine has been demonstrated to stimulate mesangial cell proliferation and hypertrophy via nonneuronal nicotinic acetylcholine receptors (nAChRs). The 7-nAChR is one of the most essential nAChR subunits. The tail-cuff method was used to measure blood pressure, and urine was collected to test for proteinuria. Nicotine delivery to sham rats increased overall proteinuria but not albuminuria, indicating that nicotine has a direct effect on tubular protein reabsorption. MLA blocked these effects, revealing a key function for the 7-nAChR as a mediator of nicotine effects in the pathogenesis of CKD[64].

12. Benowitz Neal L. et al .,2009 The release of dopamine, glutamate, and gamma aminobutyric acid is especially crucial in the development of nicotine dependence, and corticotropin-releasing factor appears to contribute to nicotine withdrawal. Nicotine addiction is strongly heritable. Genetic studies suggest that nicotinic receptor subtypes, as well as genes involved in neuroplasticity and learning, play important roles in the development of dependence. Nicotine is largely metabolised by CYP2A6, and variations in metabolic rate relates to tobacco dependence, responsiveness to smoking cessation treatment, and lung cancer risk. Tobacco addiction is far more likely in those suffering from mental illnesses and substance abuse disorders, who account for a large proportion of current smokers. Nicotine replacement therapy, bupropion, and varenicline, a selective nicotine receptor partial agonist, are all pharmacotherapeutic treatments to tobacco addiction[65].

13. Sharma Geeta *et al.,2008* Nicotinic receptors have been linked to psychiatric disorders such as schizophrenia, as well as being neuroprotective and potentially useful for neurodegenerative diseases. These nicotine effects highlight the drug's diverse roles, as it acts on many nicotinic acetylcholine receptor subtypes. The findings also highlight the complexities of signalling processes and the possibilities of unexpected outcomes of nicotine addiction medicines[66].

14. Sala F. *et al.2007* Acetylcholine generated by sympathetic splanchnic nerves stimulates neuronal-type nicotinic acetylcholine receptors (nAChRs) on the membrane of chromaffin cells, releasing catecholamines into the bloodstream in preparation for fight or flight reactions. Chromaffin cell nAChRs activate and desensitise fast, with complete recovery after washout. Dynamic control of nAChR activity occurs in a variety of ways. It is allosterically controlled by the endogenous neuropeptide substance P, which stabilises desensitised receptors, lowering their reactivity. These findings highlight the plastic features of cholinergic neurotransmission in the adrenal medulla, which provide powerful mechanisms for adjusting catecholamine release to variations in sympathetic activity, both acute and chronic[67].

15. Brody L. Arthur *et al.,2006* The effect of cigarette smoking on 42* nAChR occupancy in tobacco-dependent smokers was studied. For 3.1 hours after smoking, 0.13 (1 to 2 puffs) of a cigarette resulted in 50% occupancy of 42* nAChRs. Smoking a complete cigarette (or more) resulted in over 88% receptor occupancy and a decrease in cigarette appetite. A venous plasma nicotine concentration of 0.87 ng/mL (about 1/25th of what average daily smokers attain) was linked to 50% occupancy of 42* nAChRs[68].

Material and Method

The studies would be carried out in strict conformity with the rules approved by the Institutional Animal Ethics Committee established under the Ministry of Environment and Forests, Government of India, New Delhi, India, for the purpose of controlling and supervising experimental animals. Adult male Sprague-Dawley rats (180-200 g) and albino Swiss mice (20-25 g) will be housed in groups of three or four for several days to adjust to the animal facility circumstances (light:dark cycle of 12:12, with lights on between 09:00 and 21:00). They will be kept in a calm, temperature- and humidity-controlled environment (22 3 C and 65 5%, respectively).

Drugs and solutions

The nicotine, 5-HT receptor ligands such as 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), Ketanserin (5-HT 2A/2C antagonist), WAY (5-HT neuronal synthesis inhibitor). Nicotine in the concentration of 8% w/v will be diluted with 0.9% saline and administered intraperitonially (i.p.). Except for p-CPA, all 5-HT medications will be delivered intracerebroventricularly (i.c.v.). p-CPA will be dissolved in 0.1 N NaOH, (pH 7) with 0.1N HCl, and diluted in 0.9% saline before being given intravenously. The medications will be dissolved and diluted with artificial cerebrospinal fluid (aCSF) with the following composition: 0.2 M NaCl, 0.02 M NaHCO 3, 2 mM KCl, 0.5mM KH 2 PO 4 ,1.2 mM CaCl 2 , 1.8 mM MgCl 2 , 0.5 mM Na2SO4 and 5.8 mM D-glucose (Dissolved in double distilled water). The remaining medications will be dissolved and diluted in 0.9% saline.

Table 1 Patents in Nicotine Induced effects

S.no	**Inventors**	**Formulations**	**File No.**	**Country**	**Status**
1.	Jie Wu.,2005	Iptakalim hydrochloride for decreasing nicotine use	US20060293393A1	USA	Active
2.	James E. Audia *et al.,1996*	Compounds having effects on serotonin-related systems	WO1996022290A1	USA	Active
3.	J. Richard *et al.*,1995	Compositions for treating tobacco withdrawel symptoms	EP0440704B1	EU	Expired Lifetime
4.	Henri Hansson *et al.*, 2005	Physically and chemically stable nicotine-containing particulate material	US9629832B2	US	Active
5.	Sanberg Paul Ronald *et al.*1998	Nicotine antagonists for nicotine-responsive neuropsychiatric disorders.	WO1999007378A1	US	-

Administration route

i.c.v.(intra cerebro ventricular) (intra cerebro ventricular). If icv is not an option, i.p. or alternative routes will be preferred.

METHOD

Hot Plate Test

The hot plate test, like the tail flick test, assesses an animal's pain reaction. It is used in basic pain research and to test the efficacy of analgesics by examining the response to pain generated by heat.

Tail Flicking

Mice are placed in cages with their tails exposed. A light beam is directed on the tail's proximal third. Within a few seconds, the animal either flicks its tail away or attempts to flee. The time it takes for this reaction to occur is monitored. The time limit is 6 seconds.

Test of tail immersion

The tail immersion experiment is a heat test used to assess a compound's analgesic properties. A number of therapeutically licenced pharmacological drugs, including opioids like morphine and alpha adrenergic medications, have been shown to postpone the onset of heat sensitivity after tail exposure to heat.

Cataleptic test procedure

The bar test, which involves placing a rat's forepaws on an elevated bar while the rear paws stay on the floor, is a common method for evaluating catalepsy. The time it takes the rat to correct its posture is an indicator of the severity of the catalepsy.

Maze Plus Elevated

The Elevated Plus Maze (EPM) test is used in mouse models of CNS diseases to detect anxiety-related behaviour. The EPM device is made up of a shaped maze raised above the floor with two oppositely positioned closed arms, two oppositely positioned open arms, and a middle region.

Swim test under duress (FST)

The FST(forced swim test) is founded on the concept that when an animal is placed in a container filled with water, it will first try to escape but will gradually demonstrate immobility, which may be interpreted as a sign of behavioural despair.

Designing of Experiments

TFT response to acute nicotine treatment

Different groups of mice (n=6) will be injected i.p. with varying dosages of nicotine (0.1-1.5 g/kg) or saline (10 ml/kg). Following that, each mouse will be exposed to a "test session" 50 minutes after nicotine administration, with the length of TFT assessed over the last four minutes of a six-minute test session as described above. Because nicotine has the greatest effect on immobility time around 50 minutes after treatment (Hirani et al. 2002). As a result, this time period will be chosen for further investigation.

Tolerance to nicotine's antinociceptive action develops in TIT and HPT

Tolerance to nicotine will be developed utilising the Pauly et al., 1992 technique. Separate groups of rats (n=6) will be administered i.p. for 12 days with saline (10 ml/kg) or nicotine (2 mg/kg; 3 injections per day at 08:00, 13:00, and 18:00 h). These chronically nicotine-treated animals will be challenged with saline (10 ml/kg, i.p.) or nicotine (2 mg/kg, i.p.) 30 minutes before being subjected to Hot plate, TFT, TIT, or HPT models, and nociception parameters will be recorded.

The influence of 5-HT 1A receptor stimulation on nicotine-induced effects in TFT

To assess the modulatory effect of 5-HT 1A receptor stimulation on nicotine-induced effects, a separate group of mice (n=6) will be injected with aCSF (5 l/mouse, i.c.v.) or the 5-HT 1A receptor agonist, 8-OH-DPAT (0.1 g/mouse, i.c.v.) 15 minutes before the administration of nicotine (1.5 g/kg, i.p.) or saline (10 After 50 minutes, each animal will be put to FST for 6 minutes and TFT time will be measured during the last four minutes as indicated above.

The effect of a 5-HT 1A receptor antagonist on nicotine-induced effects in TFT

Separate groups of mice (n=6) will be injected with CSF (5 l/mouse, i.c.v.) or WAY 100635 (0.1 g/mouse, i.c.v.) 15 minutes before receiving a sub-effective dosage of nicotine (1.5 g/kg, i.p.) or saline (10 ml/kg, i.p.). After 50 minutes, each animal will be given to the TFT test mentioned above for 6 minutes.

The influence of 5-HT 2A receptor activation on nicotine-induced behavioural consequences in TFT

To investigate the role of 5-HT 2A receptor stimulation in the nicotine-induced effect, a CSF (5 l/mouse, i.c.v.) or 5-HT 2A receptor agonist, DOI (10 g/mouse, i.c.v.) will be injected to a separate group of mice (n=6) 15 minutes before an injection of nicotine (1.5 g/kg, i.p.) or saline (10 ml/kg). After 50 minutes, the animals will be subjected to TFT to determine the TFT time for the last four minutes as described above in a 6-minute test session.

The influence of a 5-HT 2A/2C receptor antagonist on nicotine-induced behavioural consequences in TFT

Separate groups of mice (n=6) will be injected with either aCSF (5 l/mouse, i.c.v.) or ketanserin (1.5 g/mouse, i.c.v.). After 15 minutes, mice will be treated with either a sub-effective dose of nicotine (2.5 g/kg, i.p.) or saline (10 ml/kg, i.p.). Individual animals will be treated to TFT in the test-session outlined earlier for 6 minutes fifty minutes after the last dose.

The influence of a 5-HT 2A/2C receptor antagonist on nicotine-induced behavioural consequences in TFT

Separate groups of mice (n=6) will be injected with either aCSF (5 l/mouse, i.c.v.) or ketanserin (1.5 g/mouse, i.c.v.). After 15 minutes, mice will be treated with either a sub-effective dose of nicotine (2.5 g/kg, i.p.) or saline (10 ml/kg, i.p.). Individual animals will be treated to TFT in the test-session outlined earlier for 6 minutes fifty minutes after the last dose.

The effect of a 5-HT neural production inhibitor on nicotine's action in TFT

To determine the role of central 5-HT transmission in nicotine effects, we tested the effect of p-CPA, a 5-HT neuronal production inhibitor, on nicotine-induced effects on TFT time in FST. 5-HT neuronal synthesis inhibitor, p-CPA (300 mg/kg, i.p.) or saline (10 ml/kg, i.p.) will be injected for 3 days (Chenu et al. 2008; Page et al. 1999), and 24 hours after a third day dose of p-CPA, a dose of nicotine (2.5 g/kg, i.p.) or Vehicle (10 ml/kg, i.p.) will be administered, and the animals will be subjected to TFT for 50 minutes to record the TFT time.

All medications had an effect on locomotor activity.

Locomotor activity will be measured using an actophotometer (INCO LABS, Umbala, India), which consists of a 40-cm-diameter circular chamber outfitted with three infrared beams and photo-cells linked to a digital counter that records the number of beam interruptions with a lid on it. Individual animals will be placed in the centre of the actophotometer arena for 6 minutes with the lid closed. Locomotor activity will be expressed as the total number of locomotor counts for each light beam interrupted during the previous six minutes of testing.

Conclusion

The current study aims to elucidate the function of seretonergic transmission in nicotine's diverse reinforcing effects. As a result, we will be attempting to shed new light on the probable mechanisms of nicotine-induced effects such as antinociception and hyperalgesia. All of nicotine's effects contribute to its misuse potential and subsequent relapse. As a result, we expected that the findings of this study will throw fresh light on the 5-HT receptor as a novel target for managing and controlling nicotine addiction.

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