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Short communication

Effects of the histamine $(H)_3$ receptor antagonist ABT-239 on acute and repeated nicotine locomotor responses in rats

Joanna Miszkiel[1], Marta Kruk[2], Andrew C. McCreary[3], Edmund Przegaliński[1], Grażyna Biała[2], Małgorzata Filip[1,4]

[1]Laboratory of Drug Addiction Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

[2]Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, Staszica 4, PL 20-081 Lublin, Poland

[3]Abbott Healthcare Products B.V., Weesp, The Netherlands

[4]Department of Toxicology, Faculty of Pharmacy, Jagiellonian University, College of Medicine, Medyczna 9, PL 30-688 Kraków, Poland

Correspondence: Małgorzata Filip, e-mail: filip@if-pan.krakow.pl

Abstract:
The addictive potential of nicotine is linked to psychomotor and cognition-enhancing effects. Histamine $(H)_3$ receptor antagonism has similarly received attention for a role in cognition, however, the role of H_3 receptors are far less studied for affects on nicotine-induced locomotor responses. In the present study we tested whether the H_3 receptor antagonist 4-(2-{2-[(2R)-2methylpyrrolidinyl]ethyl}-benzofuran-5-yl) benzonitrile (ABT-239) influenced the psychomotor responses to acute and repeated nicotine, including sensitization and conditioned locomotion. ABT-239 (0.3–3 mg/kg) did not alter basal, nicotine-evoked (0.4 mg/kg) locomotor responses, the expression of sensitization, or cue-conditioned locomotion. However, in combination studies rats pretreated with a separate dose of ABT-239 (1 mg/kg) prior to nicotine (0.4 mg/kg) for 5 days and then challenged with nicotine (0.4 mg/kg) after a 5-day withdrawal period, showed significantly higher locomotor hyperactivity in comparison with the effect observed in nicotine-pretreated and challenged rats. Our findings implicate a limited role for H_3 receptors in locomotor responses to nicotine.

Key words:
conditioned locomotion activity, histamine3 receptor, locomotor activity, nicotine, sensitization

Introduction

Nicotine, the predominant addictive component of tobacco, is arguably the most widely consumed legal stimulant and accounts for the largest cause of avoidable deaths and disease in developed countries (for review see [41]). The drug is responsible for the development of physical and psychological addiction including drug seeking and relapse. Additionally, in humans, nicotine withdrawal syndrome, including irritability, anxiety, depressed mood, concentration difficulties and craving, limits abstinence and increases relapse (for brief review see [40]). In laboratory ani-

mals nicotine also affects many aspects of behavior, such as reward, discrimination, psychomotor activation and behavioral sensitization [2, 39, 40].

Interestingly, some human and animal studies demonstrate that nicotine administration improves cognitive functions, especially memory and attentional function [23, 25]. This fact is especially important in the scope of addiction as a link between drug addiction and learning and memory formation processes was suggested together with similarities in the molecular signaling mechanisms associated with long-term adaptations [24, 26, 35]. It is therefore critically important to understand the pharmacology of the cognitive effects of nicotine.

Nicotine exerts its behavioral effects acting at the nicotinic acetylocholine (ACh) receptors (nAChRs) (for review see [41]). Among all central nAChR subtypes, both the $\alpha4\alpha2$ heterodimeric combination and $\alpha7$ homodimeric receptors seem to play a crucial role in the reinforcing and locomotor effects [1, 6, 17, 20, 22, 38, 39] and the mnemonic responses [7] of nicotine. By the stimulation of $\alpha4\alpha2$ and $\alpha7$ receptors located presynaptically nicotine facilitates the release of a variety of neurotransmitters including Ach, catecholoamines, serotonin, γ-aminobutyric acid, glutamate and histamine [37] that may all be responsible for or modulate the nicotine-evoked addiction and/or cognition processes.

Histaminergic (H) neurotransmission is also an important candidate for the interactions with nicotinic systems and has been implicated in many functions of the central nervous system [18]. Distinct H receptor subtypes have been characterized, including H_1, H_2, H_3 and the recently discovered the H_4 receptor subtype [25, 29]. Of interested here, H_3 receptors are constitutively active and highly expressed in the central nervous system as autoreceptors on H neurons and also as heteroreceptors on non-H neurons. Research suggests that H_3 receptors regulate Ach, dopamine, γ-aminobutyric acid, glutamine, noradrenaline and serotonin neurotransmission [16, 33] and influence cognition, memory, sleep, food intake and many other processes [16, 18]. Specifically blockade of H_3 receptors promotes attention, wakefulness and adjusts short term and social memory in rodents [16, 28, 30, 33]. Moreover, limited studies on H_3 receptor antagonists plus nicotine indicated reversal of nicotine choice accuracy impairment in the radial-arm maze repeated acquisition task [21]. However, the role of H_3 receptors is much less – if any – studied in the nicotine-induced locomotor and sensitizing responses and other forms of memory-related behaviors.

For this reason we focused on separate and combined effects of an H_3 receptor antagonist in models of locomotor activity and sensitization to shed light on this question. In the present study we tested whether the H_3 receptor antagonist 4-(2-{2-[(2*R*)-2-methylpyrrolidinyl]ethyl}-benzofuran-5-yl (ABT-239) [8] influenced the psychomotor response to acute and repeated nicotine treatment in rats using locomotor activity measurements as the readout. The experimental design included several animal models to develop nicotine sensitization or nicotine-evoked the conditioned locomotor activation. Locomotor stimulation and the development of psychomotor sensitization have been suggested to predict the additive property of a drug [31, 36; but see also 32], while a drug of abuse-induced conditioned locomotion activity may be considered as a valid animal model of craving [9]. Moreover, the sensitized state, which parallels the addictive process, more than certainly involves mnemonic processes [35].

Materials and Methods

Animals

Male Wistar rats (220–250 g; derived from Charles River Laboratories, Germany) housed under standard laboratory condition (12 h light/dark cycle, room temperature 21 ± 1°C, 40–50% humidity) were used. Food and water were available *ad libitum*. Animals were habituated to the laboratory conditions for at least one week prior to use. All behavioral experiments were performed between 8:00 and 14:00, and were conducted according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and to the European Community Council Directive for the Care and Use of Laboratory Animals of 24 November 1986 (86/609/EEC), and approved by the Local Ethics Committee. Each experimental group consisted of 7–8 rats. The animals were drug naive at the start of the studies.

Drugs

Nicotine bitartrate, reported as free base nicotine weight (Sigma-Aldrich, St. Louis, USA) was diluted in saline (0.9% NaCl) with the pH (5–7) adjusted and

given *sc* immediately before behavioral recording. ABT-239 (Solvay Pharmaceuticals Research Laboratories, Weesp, The Netherlands) was suspended in one drop of 1% solution of Tween 80 (Sigma, St. Louis, USA) and dissolved in saline (0.9% NaCl). ABT-239 was administered *ip* 60 min before behavioral recording. Fresh drug solutions were prepared on each day of experimentation. The doses of nicotine and ABT-239 used were selected according to those previously reported [2, 11, 14, 15, 39, 41].

Locomotor activity measurements

Apparatus

Locomotor activity in rats was recorded individually for each animal in Opto-Varimex cages (Columbus Instruments, Columbus, USA) linked on-line to a compatible IBM-PC. Each cage (43 × 44 × 25 cm) was surrounded with an 15 × 15 array of photocell beams located 3 cm above the floor surface as reported previously [15, 41]. Interruptions of the photobeams resulted in the recording of horizontal locomotor activity, defined as a distance traveled and expressed in cm.

Basal and acute nicotine-evoked hyperactivation

Locomotor activity was recorded in non-habituated rats which received either ABT-239 (0.3, 1 and 3 mg/kg) or vehicle (1 ml/kg) combined with saline or nicotine (0.4 mg/kg). Measurements of locomotor activity in Opto-Varimex cages (see above) began immediately after the second injection (saline or nicotine) and lasted 60 min.

Development of nicotine-evoked sensitization

Rats received either ABT-239 (0.3, 1 and 3 mg/kg) or vehicle combined with saline or nicotine (0.4 mg/kg) repeatedly for 5 days in the experimental chambers in order to develop sensitization. Animals remained in their home cages during days 6–9 of the experiment. On the 10th day, rats were challenged with nicotine (0.4 mg/kg) before the locomotor measurements. Measurements of locomotor activity began immediately after nicotine injection and lasted 60 min.

Expression of nicotine-evoked sensitization

Rats were given repeated pairings of a distinct test environment (experimental chamber, above) with either nicotine (0.4 mg/kg) or vehicle (1 ml/kg) for 5 days. Rats remained in their home cages during days 6–9 of the experiment. Animals were then challenged on day 10, with nicotine (0.4 mg/kg), in experimental chambers. ABT-239 (0.3, 1 and 3 mg/kg) was given on day 10 of the experimentation before injection of the nicotine. Measurements of locomotor activity began immediately after nicotine injection and lasted 60 min.

Expression of nicotine-evoked conditioned locomotor hyperactivity

Rats were given repeated pairings of a distinct test environment (an experimental chamber) with either nicotine (0.4 mg/kg) or saline (1 ml/kg) for 5 successive days. Animals remained in their home cages during next 6–9 days of the experiment. On the day 10, they were challenged with saline in experimental chambers. ABT-239 (0.3, 1 and 3 mg/kg) or vehicle was given on day 10 of the experimentation before injection of saline. Measurements of locomotor activity began immediately after saline injection and lasted 60 min.

Statistical analyses

The data were expressed as the means ± SEM. The locomotor activity data were analyzed using a one (nicotine repeated treatment)- or two (acute treatment)-way analysis of variance (ANOVA), followed by *post-hoc* Dunnett's or Newman-Keuls tests applied to evaluate the treatment group effect. All comparisons were made with an experiment wise type I error rate (α) set at 0.05.

Results

Basal locomotor activation

ABT-239 at each of the doses tested (0.3, 1 and 3 mg/kg) caused no statistically significant changes ($p > 0.5$) in basal locomotor activity as compared with vehicle treated controls (Tab. 1).

Tab. 1. Effects of ABT-239 on basal locomotor activity in rodents

Drug and dose (mg/kg)	Distance traveled [cm]/60 min the mean ± SEM
Vehicle	1947 ± 389
ABT-239, 0.3 mg/kg	1879 ± 357
ABT-239, 1 mg/kg	2014 ± 403
ABT-239, 3 mg/kg	2104 ± 378

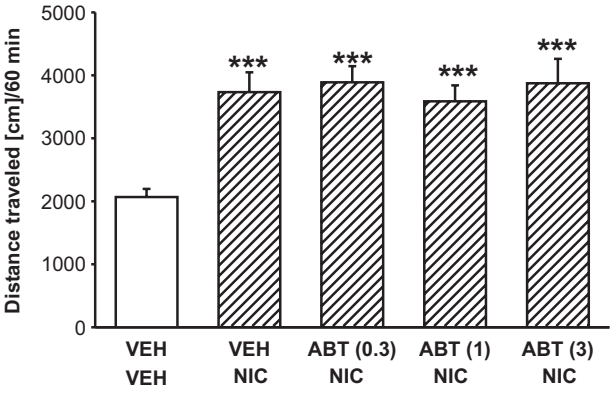

Fig. 1. Effects of ABT-239 on the acute nicotine-stimulated locomotor activity in rats. Total (60-min) horizontal activity mean after administration of vehicle (VEH) or ABT-239 (0.3–3 mg/kg) followed by injection of vehicle or nicotine (NIC; 0.4 mg/kg) are presented. N = 7–8/group. Each bar represents the horizontal locomotor activity means ± SEM; *** $p < 0.001$ compared to VEH

Acute nicotine-evoked hyperactivation

A main overall effect of treatment ($F(1,55) = 5.6$, $p < 0.001$) was observed. In rats, nicotine (0.4 mg/kg) significantly (ca. 88%) augmented basal locomotor activity compared with the effect of saline treated rats (Fig. 1), yet pretreatment with ABT-239 (0.3–3 mg/kg) did not affect nicotine hyperactivation.

Nicotine-evoked sensitization

On day 10, administration of a challenge dose of nicotine (0.4 mg/kg) to animals that received nicotine (0.4 mg/kg) repeatedly (days: 1–5) resulted in a significant (ca. 89–97%) increase in the locomotor activity compared to the effect of acute nicotine injection to vehicle-treated (days: 1–5) rats (Fig. 2).

ABT-239 at a dose of 1 mg/kg (but not 0.3 or 3 mg/kg) administered repeatedly (days: 1–5) in combination with nicotine enhanced the locomotor hyperactivity induced by nicotine challenge on day 10 ($F(4,32) = 6.23$, $p < 0.01$) (Fig. 2A).

On day 10, pretreatment with ABT-239 (0.3–3 mg/kg) did not change the locomotor activity stimulated by nicotine in rats exposed to repeated (days: 1–5)-nicotine treatment ($F(4,31) = 5.98$, $p < 0.01$) (Fig. 2B).

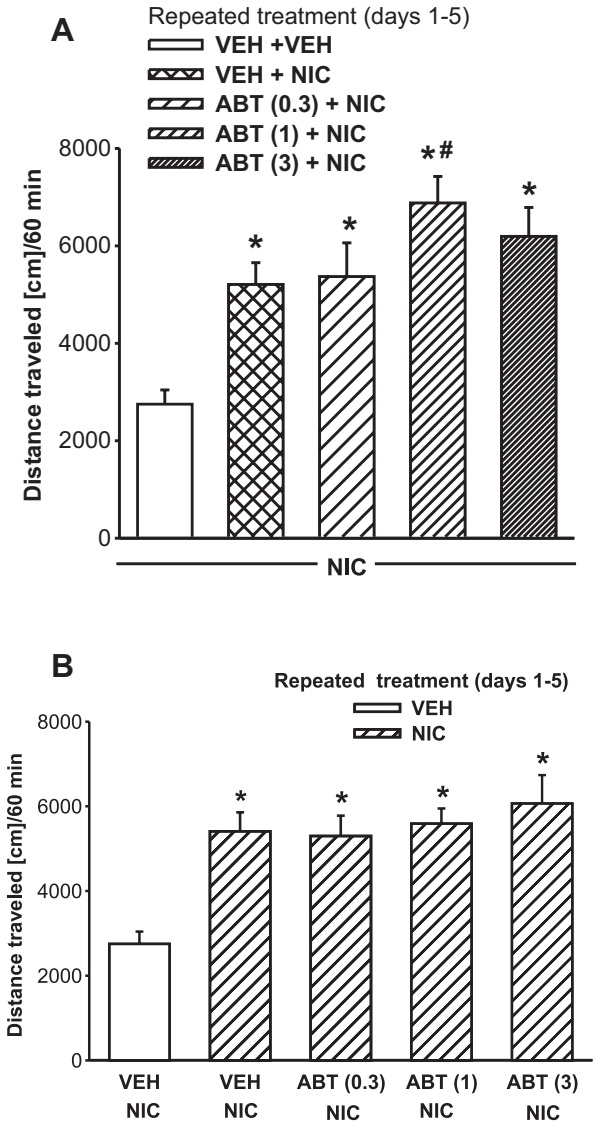

Fig. 2. Effects of ABT-239 on the development (**A**) and expression (**B**) of nicotine-evoked sensitization in rats. (**A**) Rats were treated repeatedly (days 1–5) with vehicle (VEH) or ABT-239 (ABT; 0.3–3 mg/kg) before nicotine (NIC; 0.4 mg/kg). On day 10, the animals were given a challenge dose of nicotine (0.4 mg/kg). N = 7–8/group. Each bar represents the horizontal locomotor activity means ± SEM; * $p < 0.01$ compared to VEH, # $p < 0.05$ compared to NIC. (**B**) Rats were treated repeatedly (days 1–5) with vehicle (VEH) or nicotine (NIC; 0.4 mg/kg). On day 10, the animals were given ABT-239 (ABT; 0.3–3 mg/kg) before a challenge dose of nicotine (0.4 mg/kg). N = 7–8/group. Each bar represents the horizontal locomotor activity means ± SEM; * $p < 0.01$ compared to VEH

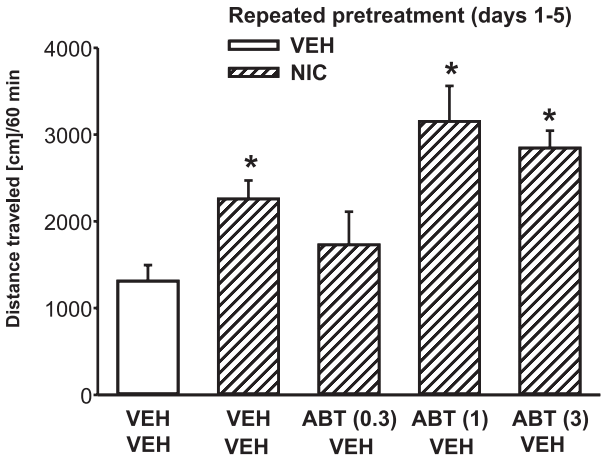

Fig. 3. Effects of ABT-239 on the expression of nicotine (NIC)-evoked conditioned locomotor activity. Rats were treated repeatedly (days 1–5) with vehicle (VEH) or nicotine (NIC; 0.4 mg/kg) On day 10, the animals were given a challenge dose of vehicle (VEH) or ABT-239 (ABT; 0.3–3 mg/kg). N = 6–8/group. Each bar represents the horizontal locomotor activity means ± SEM; * $p < 0.05$ compared to VEH

Expression of nicotine-evoked conditioned locomotor hyperactivity

Intermittent nicotine treatment paired with the environment (experimental chambers) for 5 days significantly enhanced (at least by 72%) locomotor activity on day 10 compared with the effect of saline-treated (days: 1–5) exposed to the same conditions (conditioned locomotor activity; Fig. 3).

On day 10, when ABT-239 (0.3 mg/kg) was given in combination with vehicle, no alterations in locomotor responses were observed in comparison to nicotine-treated (days: 1–5) and vehicle-challenged rats (Fig. 3).

Discussion

Locomotor activation and behavioral sensitization following chronic intermittent administration of nicotine are the commonly used screening methods to assess the neuropsychopharmacological effects of novel chemical entities on drugs of abuse [10, 31]. Some authors have also suggested that sensitization and drug-associated cue-induced conditioned locomotion may additionally represent relevant paradigms modeling relapse and drug seeking behavior, respectively [cf. 9]. Recently, it was underlined that during the development of drug addiction modulation of the associative learning processes (drug and environment) might impact the addictive process [35] and the mechanisms influencing the learning and memory processes might impact the addictive properties of nicotine. In this context, the H_3 receptor seems to be valid target to modulate the neurobiology of memory as H_3 receptor antagonists act as cognitive enhancers [11, 28, 30].

In the present study, we observed that the H_3 receptor antagonist ABT-239 with Ki = 0.45 and 1.4 nM at human and rat H_3 receptors, respectively, and with some off-target action (Ki = 400 nM activity at the human ERK channel) [8] given acutely at 0.3–3 mg/kg to rats did not alter basal, acute nicotine-evoked locomotor responses, the expression of nicotine sensitization, or cue-conditioned locomotion in rats. There is some limited evidence that ABT-239 can enhance the development of nicotine sensitization but an inverted U-shape response and spurious effects moves this hypothesis for further verification. The data presented in this paper indicate that tonic activation of H_3 receptors does not play an important role in the locomotor responses to nicotine in rats.

Our findings extend existing studies concerning the multifunctional influence of H_3 receptor inactivation on the behavioral actions of abused drugs that appears very dependant on their pharmacology and on the aspects of reinforcement measured. Thus, more recent results have demonstrated that ABT-239 ameliorated ethanol-induced deficits on hippocampal long-term potentiation, leading to the conclusion that H_3 receptor antagonists may have the utility for reverse changes in synaptic plasticity and learning deficits related to ethanol [34]. On the other hand, behavioral reports evidence that H_3 receptor antagonism enhanced cocaine-induced hyperactivity [3, 4] or ethanol-induced conditioned place preference [27], diminished methamphetamine- or alcohol-induced locomotor stimulation [5, 14]. To support our behavioral findings, microdialysis studies have reported no change in extracellular dopamine in the striatum following systemic administration of ABT-239 [14] while nicotine – acting *via* nACh receptors – evokes a variety of behavioral effects due to facilitation of the release of dopamine in the striatal pathways [37]. Despite the findings showing the existence of behaviorally and biochemically significant negative modulation between striatal H_3 and dopamine D_1 and of D_2

receptors [12, 13, 19], the above-cited neurochemical results [14] could partly explained the lack of effect of ABT-239 on dopamine efflux.

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