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Varenicline and mecamylamine attenuate locomotor sensitization and cross-sensitization induced by nicotine and morphine in mice

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ABSTRACT

The present study focused on the evaluation of behavioural sensitization and cross-sensitization induced by nicotine and morphine in mice. First, we revealed that after 9 days of nicotine administration (0.175 mg/kg, free base), every other day and following its 7-day withdrawal, challenge doses of nicotine (0.175 mg/kg) and morphine (5 mg/kg) induced locomotor sensitization in mice. When we examined the influence of varenicline, a partial alpha4beta2 nicotinic receptor agonist (0.5, 1 and 2 mg/kg) and mecamylamine (0.5, 1 and 2 mg/kg), a non-selective nicotinic receptor antagonist, we found that both agents attenuated the acquisition and expression of nicotine sensitization as well as locomotor cross-sensitization between nicotine and morphine. Our results indicate similar cholinergic mechanisms involved in the locomotor stimulant effects of nicotine and morphine in mice, and as such these data may suggest that nicotinic neurotransmission could be a potential target for developing pharmacotherapeutic strategies to treat and prevent nicotine and/or opioid addiction.

1. Introduction

Drug addiction, including polydrug use, is a chronic relapsing brain disease characterized by the compulsive use of addictive substances despite adverse consequences. Dual concomitant drug dependence is becoming increasingly more common, with nicotine and morphine being two of the co-abused psychoactive drugs. Some epidemiological studies revealed that tobacco dependence is more frequent in the opioid-dependent individuals (Frosch et al., 2000; Elkader et al., 2009; Epstein et al., 2010). Despite these epidemiological findings, there have been relatively few animal studies on the neurobiological substrates that may underlie this combined nicotine and morphine exposure.

The dependence-producing effects of nicotine, an alkaloid present in tobacco, are believed to be mediated through the activation of multiple subtypes of neuronal nicotinic acetylcholine receptors (nAChRs), among which the mesolimbic alpha4beta2 subtypes has a pivotal role. Activation of these receptors by nicotine, indirectly increases the release of dopamine in the nucleus accumbens (NAC) and the prefrontal cortex, an effect shared by most substances of abuse with distinct neurochemical targets (Picciotto et al., 2000; Di Chiara, 2000; Dani and De Biasi, 2001). Recent data confirm that the alpha4beta2, but not homomeric alpha7 nAChR subtype plays an important role in modulating the hyperlocomotor (acute and sensitized) or rewarding effects of nicotine, as their antagonists abolish these effects (Grottick et al., 2000; Rahmann et al., 2007). Moreover, nicotine self-administration is reduced in animals given the competitive, and relatively selective (beta2-preferring nAChR) antagonist, dihydro-ß-erythroidine (Watkins et al., 1999). Accordingly, preclinical studies in transgenic mice have shown that elimination of either the alpha4 or beta2 subunit attenuates the pharmacological and behavioural effects of nicotine, including reinforcement (Picciotto et al., 1998; Marubio et al., 2003; Pons et al., 2008).

Given the important role of alpha4beta2 nAChRs in the reinforcement and maintenance of nicotine dependence, modulating the activity of these receptors would be expected to have therapeutic benefits. Specifically, selective partial agonists of alpha4beta2 nAChRs that enhance the activity of these receptors sufficiently to blunt craving and withdrawal, but without abuse potential, have been already proposed as efficacious smoking cessation agents (Buchhalter et al., 2008). Recently, a partial agonist at the alpha4beta2 varenicline (Chantix, Champix, Pfizer) derived from the cytisine compound (Mihalak et al., 2006), was approved as a smoking cessation aid. Varenicline is a partial nAChR agonist that binds to alpha4beta2 nAChRs with greater affinity, but fewer efficacies than nicotine (Coe et al., 2005; Mihalak et al., 2006; Carroll et al., 2008). If such, biochemical studies show that, in the presence of nicotine, varenicline reduces nicotine intake and nicotine-evoked dopamine release in the rat NAC by its antagonist activity, while mimicking the stimulatory effect of nicotine on accumbal dopamine release through its agonist activity (Coe et al., 2005; Rollema et al., 2007a, 2007b). It can be hypothesized that an effective alpha4beta2 partial agonist would, through its intrinsic partial activation, elicit a moderate and sustained increase in mesolimbic dopamine levels, counteracting

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the low dopamine levels encountered in the absence of nicotine during smoking cessation attempts.

Behavioural responses related to drug addiction can be measured in various animal models e.g., in the conditioned place preference (CPP) paradigm (Carr et al., 1989). An alternative characteristic is a phenomenon termed sensitization or reverse tolerance (Robinson and Becker, 1986). Using this paradigm it has been shown that after intermittent chronic exposure to a drug (e.g., psychostimulants and nicotine), animals began to develop addiction-like symptoms including continued drug seeking and an escalation of drug intake, increased motivation to obtain drugs, and a greater propensity to relapse after enforced abstinence (Robinson and Berridge, 1993). Considering that functional interactions between nicotine and morphine within the central nervous system have been already documented (Zarrindast et al., 1999; Berrendero et al., 2002; Biala and Weglinska, 2006), the present studies were undertaken to further investigate behavioural cross-over locomotor effects of both drugs. We used the nicotine-induced locomotor sensitization procedure evaluated in our previous studies (Biala, 2003; Biala and Weglinska, 2004) to examine if nicotine-experienced mice develop sensitization to locomotor stimulating effect of morphine. Additionally, we investigated and compared the influence of varenicline, a partial alpha4beta2 agonist and mecamylamine, a non-selective nicotinic receptor antagonist, on the acquisition and expression of nicotine sensitization and the expression of cross-over effects between nicotine and morphine. Even though varenicline is recently approved medication for the treatment of tobacco dependence, yet very little preclinical research on this drug has been published. It is also plausible that the ability of varenicline to elevate dopamine can provide relief also from withdrawal symptoms and craving related to other drugs of abuse, including morphine, at least in a certain dose range. The antismoking agent varenicline may exhibit properties with respect to its interaction with morphine and nicotine in the brain reward system that may be beneficial for treating patients with nicotine dependence with or without concomitant opioid dependence.

2. Material and methods

2.1. Animals

The experiments were carried out on naive male Swiss mice weighing 20–25 g (Farm of Laboratory Animals, Warszawa, Poland) at the beginning of the experiments. The animals were kept under standard laboratory conditions (12/12-h light/dark cycle, temperature 21 ± 1 °C, humidity 40–50%) with free access to tap water and lab chow (Bacutil, Motycz, Poland), and adapted to the laboratory conditions for at least 1 week. Additionally, all efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data. Each experimental group consisted of 8–12 animals. The experiments were performed between 9:00 a.m. and 3:00 p.m. All experiments were carried out according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and the European Community Council Directive of 24 November 1986 for Care and Use of Laboratory Animals (86/609/EEC), and approved by the local ethics committee at the Medical University of Lublin.

2.2. Drugs

The compounds tested were: morphine hydrochloride (Polfa, Kutno, Poland), (-)-nicotine hydrogen tartrate (Sigma, St. Louis, MO, USA), mecamylamine hydrochloride (Sigma, St. Louis, MO, USA), and varenicline (CP-526555, gift of Pfizer Inc, Groton, USA). All compounds were dissolved in saline (0.9% NaCl). The pH of the nicotine solution was adjusted to 7.0**.** Fresh drug solutions were prepared on each day of experimentation. Agents were administered subcutaneously (s.c.) or intraperitoneally (i.p.) in a volume of 10 ml/kg, and, except for nicotine, drug doses refer to the salt form. Control groups received saline injections at the same volume and by the same route. Doses of the nAChR ligands have been chosen accordingly to publish data indicating their influence on drug-induced effects (Liu et al., 2007; Zaniewska et al., 2008; LeSage et al., 2009).

2.3. Apparatus

Locomotion was recorded individually in round actometer cages (Multiserv, Lublin, Poland; 32 cm in diameter) kept in a sound-attenuated experimental room. Two photocell beams located across the axis measured the animal's movements automatically.

2.4. Experimental procedure and treatment

In order to measure locomotor effects of both nAChR ligands, the animals, naive for any drug treatment, were injected with varenicline (0.5, 1 and 2 mg/kg, i.p.), mecamylamine (0.5, 1 and 2 mg/kg, i.p.) or saline for the control group, and immediately placed in the activity chamber. Locomotor activity, i.e., the number of photocell beam breaks was automatically recorded for 60 min.

2.4.1. Influence of varenicline and mecamylamine on the acquisition of nicotine-induced locomotor sensitization

During the pairing phase (days 1–9), mice received the following injections: saline (i.p.) + saline (s.c.) or saline (i.p.) + nicotine (0.175 mg/kg, s.c.) every other day for five sessions. This method was similar to that used in our previous experiments accordingly to the data indicating that this dose of nicotine produces robust locomotor sensitization in mice under our laboratory conditions (Biala and Weglinska, 2004). The mice remained drug free for 1 week and, on day 16, the same groups of mice were further challenged with nicotine (0.175 mg/kg, s.c.), morphine (5 mg/kg, s.c.) or saline, respectively. Locomotor activity was recorded for 60 min during the pairing phase (days 1–9) and on the 16th day, immediately after injections. Next, during the pairing phase (day 1–9) the mice received the following injections: saline + saline, saline + nicotine (0.175 mg/kg), varenicline (0.5, 1 and 2 mg/kg) + nicotine or mecamylamine (0.5, 1 and 2 mg/kg) + nicotine. Both nAChR ligands were administered 30 min before each nicotine injection and locomotor activity of animals was measured for 60 min. After 1 week of withdrawal (day 16), all groups were given a challenge dose of nicotine equal to that previously used to induce behavioural sensitization.

2.4.2. Influence of varenicline and mecamylamine on the expression of nicotine-induced locomotor sensitization

In the next experiment, on the challenge day (day 16) the mice pretreated with saline or nicotine (as mentioned above) were injected with saline + nicotine (0.175 mg/kg), or varenicline (1 and 2 mg/kg, i.p.) and mecamylamine (1 and 2 mg/kg, i.p.) 30 min before nicotine challenge injection. Locomotor activity of mice was also recorded for 60 min. We have chosen the doses of both agents effective in blocking the acquisition of nicotine sensitization.

2.4.3. Influence of varenicline and mecamylamine on the expression of cross-sensitization between nicotine and morphine

In this experiment, on the challenge day (day 16) the mice pretreated with saline or nicotine were injected with saline + morphine (5 mg/kg), or varenicline (1 and 2 mg/kg, i.p.) and mecamylamine (1 and 2 mg/kg, i.p.) 30 min before morphine challenge injection. Locomotor activity of mice was also recorded for 60 min.

2.5. Statistical analysis

The data are expressed as means ± S.E.M. For locomotor sensitization, data were analyzed using repeated measure analysis of variance (ANOVA) with treatment as independent factor and days as repeated measures. The response to drugs on the challenge day was compared using one-way ANOVA. Post-hoc comparison of means was carried out