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Influence of bupropion and calcium channel antagonists on the nicotine-induced memory-related response of mice in the elevated plus maze

Grażyna Biała, Marta Kruk

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

Correspondence: Grażyna Biała, e-mail: grazyna.biala@am.lublin.pl

Abstract:
In this study, we investigated the effects of acute administration of nicotine on memory-related behavior in mice using the elevated plus maze test. In this test, the time necessary for mice to move from the open arm to the enclosed arm (i.e., transfer latency) was used as an index of memory. Our results revealed that nicotine (0.035 and 0.175 mg/kg, base, *sc*) shortened the transfer latency relative to the saline-treated group. Moreover, we investigated the effects of bupropion (10, 20 and 40 mg/kg, *ip*) and L-type voltage-dependent calcium channel antagonists (nimodipine, flunarizine, verapamil, diltiazem – 5, 10 and 20 mg/kg, *ip*) on memory-related behavior**.** At all tested doses, bupropion, did not significantly affect transfer latency. However, flunarizine and verapamil (both at 10 mg/kg) resulted in a slight decrease in transfer latency, whereas nimodipine (10 mg/kg) increased transfer latency. Interestingly, both bupropion (20 mg/kg) and calcium channel blockers (5 mg/kg) attenuated the improvement of memory induced by nicotine.
Our findings indicate that the cholinergic nicotinic system may play an important role in memory consolidation, and that neural calcium-dependent mechanisms can be involved in the modulation of memory-related responses induced by nicotine. The results of these studies have revealed neuronal mechanisms that are important for nicotinic modulation of cognition and will be useful for the treatments of human disorders in which cholinergic pathways have been implicated, such as psychiatric disorders and addiction.

Key words:
memory and learning, elevated plus maze, bupropion, nicotine, calcium channel antagonists

Abbreviations: EPM – elevated plus maze, GABA – gamma-aminobutyric acid, LTP – long-term potentiation, nAChRs – nicotinic acetylcholine receptors, TL – transfer latency, VDCCs – voltage-dependent calcium channels

Introduction

Nicotine, the primary psychoactive component in tobacco smoke, is responsible for the development of dependence leading to harmful consequences. Successful smoking cessation is difficult to achieve because nicotine causes both physical and psychological addiction. The nicotine abstinence syndrome in humans is generally unpleasant and includes irritability, anxiety, depressed mood, restlessness, concentration difficulties and nicotine craving [29]. The pharmacological properties of nicotine are complex and poorly understood and the effects of this drug have been extensively investigated, not only in humans, but also in animals. It has been reported that nicotine can affect

many aspects of animal behavior including reward and dependence, aggression, anxiety, antinociception, locomotor activity or memory and learning processes [3, 5, 8, 12, 21, 44, 58]. It is well known that nicotine exerts its behavioral effects through a direct action on the neuronal nicotinic acetylcholine receptors (nAChRs) [57]. Nicotine, which functions through the activation of presynaptic nAChRs, causes the release of a number of neurotransmitters including acetylcholine, catecholamines, gamma-aminobutyric acid (GABA), serotonin and glutamate, which are involved in the modulation of various neural functions, e.g., memory-related responses [27, 40]. The strong correlation between central cholinergic pathways and learning and memory, and influence of the nicotinic cholinergic system on memory-related behavior has been described in the literature [27, 35, 36, 38].

With respect to the influence of nicotine on memory functions, experimental studies in animals and humans have yielded contradictory results. In humans, many studies have described deficits, or the improved efficiency of cognitive processing after nicotine administration [29, 37]. In animals, some researchers have argued that nicotine improved memory function, while others have reported non-contributory or negative effects [38, 40].

Based on the results previously mentioned, our experiments were designed to further investigate the possible mechanisms of nicotine-induced memory-related behavior in mice using the elevated plus maze (EPM) test. Recently, this test, originally developed to estimate anxiety in rodents, was modified to evaluate spatial learning and memory [20, 31, 33, 34, 47, 53]. Briefly, this simple method consists of measuring of the time necessary for the animal to move from the open to the enclosed arm, i.e., the transfer latency (TL). A reduction in TL using the retention trial represents an improvement in learning and memory and has been interpreted as the ability for animals to remember the location of the enclosed arms, and escape from the unsafe open and high space faster on the second retention trial. On the contrary, increases in TL during retention testing could be used to indicate impairments in memory induced by drugs that possess amnesic properties. This method has been successfully used in studies investigating the involvement of different neurotransmitter systems, including cholinergic pathways, on learning and memory processes. For instance, amnesic properties of scopolamine, a muscarinic receptor antagonist, were evaluated. Indeed, scopolamine increased the TL time, while physostigmine decreased the TL values on the second retention trial and reversed the effects of scopolamine [30, 31, 33, 34, 47, 53].

Additionally, we compared the influence of bupropion, a drug currently used as first-line pharmacotherapy for smoking cessation in humans, with calcium channels blockers specific for the L-type voltage-dependent calcium channels (VDCCs) on nicotine's effects. Bupropion has been established as an antidepressant, which alleviates the symptoms of nicotine withdrawal in rodents as well as in humans, e.g., depression, irritation and difficulty with concentration [13, 44, 54]**.** However, the actions underlying the therapeutic efficacy of bupropion as a smoking cessation agent are still unknown. It has been proposed that its pharmacological characteristics are mediated by two different mechanisms. One proposed mechanism suggests that bupropion inhibits monoamine uptake [41], but this antidepressant may also act as a non-competitive antagonist of nAChRs [54]. Additionally, based on previous findings implicating a role for calcium ions and L-type VDCCs on numerous cell functions, including several aspects of drug reward, addiction, anxiety and memory [3, 4, 6, 7, 16], we investigated the influence of VDCC antagonists on acute memory-related effects of nicotine. VDCC antagonists of various classes including dihydropyridines (e.g., nimodipine), diphenylalkylamines (e.g., flunarizine), phenylalkylamines (e.g., verapamil), and benzothiazepines (e.g., diltiazem) were used. These compounds are specific for L-type VDCC, although they bind to three distinct binding sites [56, for review]. Dihydropyridine derivatives interact directly with the dihydropyridine binding site on the calcium channel, while other antagonists induce allosteric changes. 1,4-Dihydropyridines have also shown activity on N-type channels, which is less pronounced than that exhibited at L-type VDCC. Overall, results from this study demonstrate a potential role for calcium homeostasis on nicotine-induced cognitive processing.

Materials and Methods

Animals

The experiments were conducted using adult naive Swiss mice (Farm of Laboratory Animals, Warszawa, Poland) weighing 20–30 g. The animals were main-