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Research report

Chronic nicotine and dizocilpine effects on regionally specific nicotinic and NMDA glutamate receptor binding

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Abstract

Chronic nicotine administration has long been known to increase the number of high-affinity α4β2 nicotinic receptors with lesser effects on low-affinity α7 nicotinic receptors. Nicotine has been shown to promote the release of a variety of neurotransmitters including glutamate. Nicotine may also interact directly with the glutamatergic receptors. Nicotinic–glutamate interactions may be critical to the long-term effects of nicotine. Conversely, glutamatergic drugs may interact with the nicotinic system. Such interactions have important implications in interpretation of the mechanism of drug actions, especially when the drugs are given together. The current study examined the effects of chronic administration of nicotine (5 mg of the nicotine base/kg/day for 28 days), dizocilpine (MK-801) (0.3 mg/kg/day for 28 days), an NMDA receptor antagonist, as well as the combination of the two drugs on nicotinic and NMDA receptor densities in discrete brain regions. The chronic dose of dizocilpine used was behaviorally active causing a dramatic reduction in prepulse inhibition (PPI) of acoustic startle response. The nicotine dose used did not significantly affect PPI but previously we have found it to be behaviorally active in improving working memory function. High-affinity nicotinic receptor binding, as has been seen previously, was significantly increased by chronic nicotine in most areas. Chronic dizocilpine alone did not affect high-affinity nicotinic receptor binding, but it did modify the effects of chronic nicotine, attenuating nicotine-induced increases in the frontal cortex and striatum. Low-affinity nicotinic binding was significantly increased by chronic nicotine in only one area, the cerebellum. Chronic dizocilpine significantly increased low-affinity nicotinic binding in several brain areas, the colliculi, hippocampus, and the hypothalamus. The combination of nicotine and dizocilpine attenuated the effects of each with diminished nicotine-induced increased nicotinic low-affinity binding in the cerebellum and diminished dizocilpine-induced increased nicotinic low-affinity binding in the hippocampus and hypothalamus. In contrast, chronic nicotine and dizocilpine had a mutually potentiating effect of increasing nicotinic low-affinity binding in the frontal cortex. NMDA receptor binding was affected only in the hippocampus, where both dizocilpine and nicotine significantly increased binding. Chronic nicotine effects on receptor regulation are significantly affected by concurrent blockade of NMDA glutamate receptors.

Theme: Receptor regulation
Topic: Nicotinic alpha7 and alpha4-beta2 receptors and glutamate NMDA receptors

Keywords: Nicotine; Dizocilpine; MK-801; Nicotinic receptors; NMDA receptors; Hippocampus; Frontal cortex; Striatum; Rats

1. Introduction

Whereas chronic nicotine administration has been long known to cause a significant increase in the binding of high-affinity nicotinic binding sites [25,38], its long-term effects on low-affinity sites are less well characterized. In addition, there appears to be some regional heterogeneity of these responses. Chronic nicotine may also have effects on the glutamatergic NMDA receptors. These effects may be due to a direct interaction of nicotine with the NMDA receptors [2,12] or indirectly through the release of glutamate [46].

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Dizocilpine, also known as MK-801, is a glutamate NMDA antagonist, which has been found to have psychotomimetic effects [4]. Thus, administration of dizocilpine results in memory impairments in the radial-arm maze [23]. It also produces a robust reduction in prepulse inhibition (PPI) [17]. PPI reduction, reflecting sensorimotor gating impairment, is commonly observed in schizophrenic patients. Interestingly, dizocilpine-induced jumping behavior in mice, which has been developed as a model of psychotomimetic activity, is attenuated by nicotine pretreatment [41]. Moreover, it has been reported that nicotine may normalize sensory gating impairment in schizophrenic patients as well as enhancing cognitive functions in various paradigms [3,19,24,34–37]. Recently, it was found that acute administration of dizocilpine reduced sustained attention as measured by choice accuracy on a visual signal detection task. Nicotine co-treatment was found to be effective in reversing the dizocilpine-induced deficit [35]. Critical nicotinic–NMDA interactions are also seen in terms of receptor binding. Shoaib et al. [39] showed that repeated injections of nicotine (0.4 mg/kg, SC for 7 days) caused high-affinity nicotinic receptor upregulation and that this nicotinic upregulation was significantly reduced by pretreatment with the NMDA antagonist dizocilpine (0.3 mg/kg, IP).

Therefore, nicotinic interactions with NMDA glutamate systems may have important implications in cognitive functions. In vitro studies have shown that nicotine can reduce the binding of dizocilpine to NMDA receptors [2,12]. Interestingly, it has been demonstrated that systemic administration of MK-801 prevents behavioral sensitization to nicotine via the prevention of the nicotinic receptor upregulation [39], suggesting a functional interaction between nicotine and glutamate systems. Shoaib et al. showed significant interactions with repeated injections of nicotine and dizocilpine over a period of 1 week. The current study extended this to include effects of chronic continuous infusions over a period of 4 weeks. Chronic nicotine and dizocilpine effects on high- and low-affinity nicotinic receptor binding and NMDA glutamate receptor binding were studied in a region-specific manner. Moreover, the effects of nicotine, dizocilpine, and their combination on PPI was also evaluated.

2. Methods

2.1. Animals

Adult female Sprague–Dawley rats were used for the experiment. The animals were allowed to acclimate to the housing facility for 1 week after arrival. The rats in the experiment were housed in groups of three with ad lib access to both food and water and kept on a 12:12 reversed light:dark cycle. As a part of the experimental protocol, the animals were further acclimated to the test room and test chambers before the experiment started. The same rats were used in the PPI and receptor binding portions of the study.

2.2. Prepulse inhibition

PPI was assessed weekly to determine the behavioral impact of the dizocilpine and nicotine treatments. Acoustic startle reflex amplitude and PPI were measured using a Med Associates Startle Reflex System (St. Albans, VT, USA). The equipment included response platforms that were placed in sound-attenuated chambers. Each platform was calibrated with a spinner type calibrator (Med Associates Startle Calibrator). A speaker was placed within the chamber midway on the long axis of the platform. The sound intensity of the speaker in each chamber was calibrated (Digital Sound Level Meter, Extech Instruments). Plexiglas cylinders (7.5 cm diameter), large enough to allow animals to turn around, were mounted on the platforms. The background noise was 65 dB white noise.

The PPI experiment was designed in 3 blocks. After the animals were placed in the chambers, there was a 5-min acclimation period before the testing began. Block 1 consisted of 6 startle alone trials with a 110-dB white noise stimulus. Block 2 had a total of 48 trials: 12 startle alone trials and 36 prepulse plus startle trials. Within the prepulse trials, there were 3 prepulse levels: 68, 71, and 77 dB pure tone. The trials were presented in random order with the inter-trial duration ranging from 10 to 20 s. Block 3 was an additional 5 trials of startle alone. Each stimulus had a 2-ms rise/fall time. The null period was 100 ms and the prepulse/startle delay was 100 ms. The entire test period lasted approximately 34 min.

Data from preliminary experiments using a startle alone design revealed that the initial trials in any session could be variable. The amplitude in the first and second trials was quite low and in subsequent trials increased and reached a plateau within 6 trials. Block 1, with 6 trials of startle alone, was included in the experimental design to control for these variations; however, the data was not used. The startle alone data from Block 2 was used for comparison with data from Block 3 to assess whether habituation had occurred.

2.3. Drug administration

Nicotine ditartrate (5 mg/kg/day of the base weight) and dizocilpine (0.3 mg/kg/day) or both were infused SC via osmotic minipumps (Alzet Model 2004) for 4 weeks. The nicotine dose is the same as what we have previously found to significantly improve memory performance in the radial-arm maze [20]. The dizocilpine dose has previously found to significantly attenuate nicotine-induced receptor upregulation and locomotor sensitization [39]. The saline vehicle served as control. There were 6–8 rats per group for each of the four treatment groups: control, nicotine,