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Antagonism of Opioid μ Receptors for Smoking Cessation

Xiu Liu

Abstract

Opioid neurotransmission plays a role in rewarding process including the reinforcing actions of nicotine. In the past four decades, a great effort has been exercised to test the effectiveness of nonselective opioid antagonists (mainly naloxone and naltrexone) for smoking cessation. However, both clinical and animal researches have yielded equivocal results. That may be attributable to the fact that opioid receptors have three distinctive subtypes (μ, δ, and κ), functions of which are from complimentary to opposite. Our laboratory studies have used animal models of nicotine self-administration to examine involvement of individual opioid receptor subtypes in the reinforcement of nicotine. Specifically, rats were trained in daily 1-h sessions to press a lever to intravenously self-administer nicotine, and antagonists selective for the three subtypes of opioid receptors were administered prior to the test sessions. Results showed that selective blockade of the μ, but not δ or κ, opioid receptors effectively reduced nicotine self-administration, whereas it produced no effect on food self-administration. These results indicate that activation of the opioid μ, but not δ or κ, receptors is specifically involved in nicotine reinforcement. It is suggested that opioid μ receptor-mediated neurotransmission would be a promising target for developing smoking cessation medication.

Keywords: nicotine self-administration, opioid receptors, smoking cessation

1. Introduction

Tobacco-related diseases are a major problem in many perspectives from human health to social economics [1]. For example, in the United States, tobacco smoking becomes a leading cause of death, accounting for the loss of 480,000 lives each year. Alarmingly, every day more than 3200 youth aged 18 years or younger smoke their first cigarette, and 2100 young people become daily cigarette smokers. The prevalence rates of smoking are 7.2% in middle and 20.2% in high school, accounting for a total young smokers being about 4 million [2]. Although almost all smokers want to quit smoking and make attempts, up to 97% of them relapse to tobacco smoking [3–6]. Unfortunately, the currently available medications, i.e., nicotine replacement, bupropion, and varenicline, show low clinical effectiveness [7–11].

Opioid neurotransmission has been implicated in mediating rewarding actions and dependence of drugs of abuse including nicotine [12–16]. For instance, nicotine

administration has been found to increase expression and release of opioid peptides in mesolimbic regions [17–22]. Opioid receptor antagonists have been reported to decrease nicotine-induced dopamine release in the nucleus accumbens, an important terminal region of the mesolimbic dopamine circuitry [23], reduce nicotine reward [24, 25], and precipitate withdrawal symptoms in rats treated chronically with nicotine [26].

Over the past four decades or so, however, clinical effort to test the potential of opioid antagonists (mainly naloxone and naltrexone) for smoking cessation has yielded equivocal results: some trials reported that these antagonists reduced consumption of cigarettes, while others failed to find any benefit [27–37]. Similarly, laboratory animal research has also produced mixed findings. In our own studies, neither acute nor chronic pretreatment with naltrexone across seven daily nicotine self-administration test sessions altered nicotine intake in the rats trained to steadily self-administer nicotine [38]. That is consistent with previous reports showing that naloxone and naltrexone did not produce an effect on nicotine self-administration [39, 40]. However, intracranial manipulation studies have found that a μ-opioid agonist, DAMGO, microinjected into the ventral tegmental area [41] or the pedunculopontine tegmental nucleus [42] effectively reduced nicotine self-administration in rats. Studies using knockout mice showed that deletion of the μ-opioid receptors or their endogenous ligand β-endorphin resulted in decreased rewarding properties of nicotine as measured by the conditioned place preference paradigm [43, 44]. Moreover, a recent rat study reported that naloxone reduced nicotine self-administration [45].

These inconsistent results in both clinical and animal research may be attributable to the existence of different subtypes of the opioid receptors. There are three main subtypes of the opioid receptors: μ, δ, and κ [46–48]. These receptors have quite divergent and in some cases even opposite actions. In the drug rewarding processes, for instance, activation of the μ and κ receptors may have opposite actions with the κ receptors opposing rewarding actions and/or enhancing aversive effects of drugs [49–52]. In knockout mice, animals deficient in μ receptors showed decreased level of anxiety, whereas the δ receptor knockout mice had higher anxiety [53], suggesting these two subtypes have an opposite role in regulating anxiety states. In the tests measuring the anxiety states induced by nicotine, the μ and δ receptor antagonism produced opposite effects, whereas the κ receptor antagonist showed no effect [54]. Therefore, due to their broad spectrum of actions, the nonselective receptor antagonists such as naloxone and naltrexone can block different opioid receptors, and unfortunately the effects of blocking individual types of receptors might have offset one another.

2. Research purposes

In light of the facts that nonselective antagonism of opioid receptors produced inconclusive results for smoking cessation, that three subtypes of opioid receptors exist with distinct and even opposing functions, and that effects of antagonizing these individual receptor subtypes have received little experimental attention, it is imperative to elucidate the involvement of the opioid receptor subtypes in mediating nicotine reinforcement. Thus, our laboratory used animal models of tobacco smoking and the currently available antagonists that are highly selective for the different subtypes of the opioid receptors to examine the roles of the μ, δ, and κ receptors in nicotine consumption behavior [55].

3. Experimental procedures

Male Sprague-Dawley rats (n = 26) were trained in daily 1-h sessions to intravenously self-administer nicotine (0.03 mg/kg/infusion, free base) after implantation of an indwelling intravenous catheter under isoflurane anesthesia. In each session, animals were placed in the standard operant conditioning chambers and connected to the drug delivery system. The sessions were initiated by introduction of two levers. Once responses on the active lever met a fixed-ratio 5 requirement, an infusion of nicotine was dispensed with a presentation of an auditory/visual stimulus consisting of a 5 s tone and 20 s turn-on of the lever light. All rats received 25 daily self-administration training sessions before any pharmacological tests because our work showed that rats readily developed stable nicotine self-administration behavior within 25 sessions [56].

4. Main research findings

Blockade of the μ opioid receptors by a selective antagonist naloxonazine dose-dependently reduced lever-press responses and correspondingly the number of nicotine infusions rats willingly self-administered. However, naloxonazine did not alter food self-administering responses, which was tested in the same set of rats that were retrained for food self-administration after completion of nicotine test. In contrast, neither did blockade of the δ receptors via administration of the selective antagonist naltrindole nor the κ-selective antagonist 5′-guanidinonaltrindole (GNTI) change nicotine self-administration behavior (**Figure 1**).
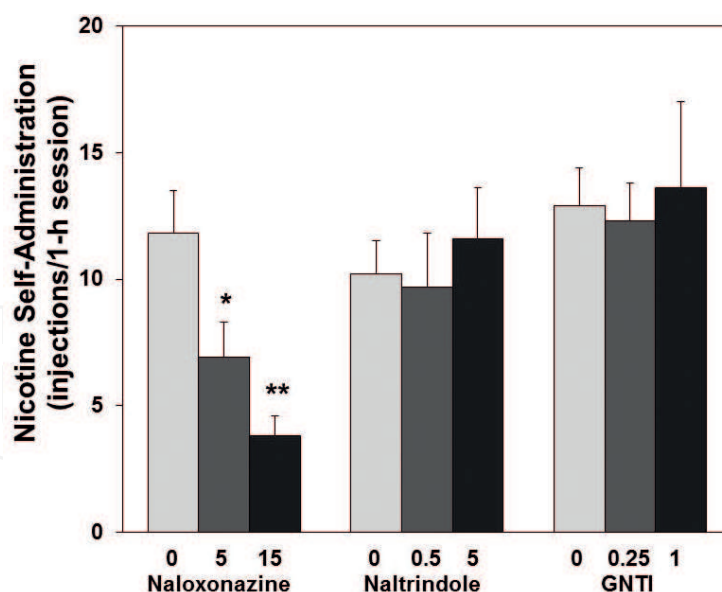
Figure 1.
*Effects of antagonists selective for μ (naloxonazine), δ (naltrindole), and κ (GNTI) receptors on nicotine self-administration in rats. The doses of these antagonists are in mg/kg. Nicotine self-administration data are expressed as mean (±SEM). *p < 0.05, **P < 0.01 significant difference from respective 0 (vehicle) condition.*

5. Discussion

The significant finding is that naloxonazine produced a specific suppressant effect on the lever-press responses maintained by nicotine self-administration, i.e.,

the primary reinforcement of nicotine. Given that naloxonazine did not change food self-administering responses, indicating no nonspecific interference with operant behavior directed to get natural reward, the results indicate the critical involvement of opioid neurotransmission via the μ receptors in the nicotine rewarding process. The underlying mechanism may involve the μ modulation of dopamine neurons in the mesolimbic circuitry, which mediates the rewarding properties of drug of abuse including nicotine. For example, in the ventral tegmental area, opioid peptides modulate dopamine neurotransmission predominantly via activation of the μ receptors [23], and in the nucleus accumbens, μ agonist inhibited dopamine overflow, and this effect was reversed by naloxonazine [57]. The suppressant effect of naloxonazine on nicotine intake is in line with previous research suggesting a role of the μ receptors in mediating the reinforcement of nicotine and tobacco smoking [27, 31, 35, 43–45]. Of significance is that our results further pinpoint the μ subtype of the opioid receptors in mediating reinforcement of nicotine. Therefore, these findings lend support for the continued clinical effort to test the effectiveness of opioid antagonists for smoking cessation and further instructively suggest that the effort focus should be shifted to targeting at the μ receptors.

The finding that naltrindole produced no effect on nicotine intake indicates that opioid neurotransmission via the δ receptors may not mediate the reinforcing actions of nicotine as measured by the operant nicotine self-administration paradigm. It is in line with evidence showing that this agent produced no change in nicotine-induced sensitization [58] and consistent with another report showing unaltered nicotine intake after naltrindole pretreatment using similar nicotine self-administration procedures [45]. However, these negative results seem to be at odds with a previous study using knockout mice that were deficient of preproenkephalin gene (producing enkephalin, the endogenous agonist for the δ receptors). These knockout mice showed a significant decrease in nicotine-induced conditioned place preference, indicating a reduction of the rewarding effects of nicotine [59]. This discrepancy regarding involvement of the δ receptors in nicotine reward may be attributable to the significant differences in subjects (rats versus gene knockout mice) and the methods of measuring nicotine reward (self-administration versus conditioned place preference). Besides, it is interesting to note the evidence showing that the δ receptors have been implicated in other actions of nicotine. For instance, the δ receptor antagonists were reported to change nicotine-induced antinociception [60] and anxiogenic response [54]. Nevertheless, an alternative explanation of the knockout mouse data exists. Due to the fact that in addition to preferentially activating the δ receptors enkephalin also acts at the μ receptors [61], it is argued that the reduced rewarding actions of nicotine in these knockout mice may result at least to some extent from the diminished μ receptor activities. Thus, the results obtained from these knockout mice in fact reconcile with the suppression of nicotine self-administration by naloxonazine observed in our study.

There was no effect of κ-selective antagonist 5′-guanidinonaltrindole (GNTI) on nicotine self-administration. This finding is consistent with results obtained from gene knockout mice. In the mice deficient of prodynorphin genes, which produce dynorphin, the endogenous agonist for k receptors, the conditioned place preference induced by nicotine (and ethanol and cocaine as well) was comparable to that observed in their wild-type counterparts [51, 62, 63]. In another report [45], however, the elevated activation of the κ receptors by experimenter administered agonist seemed to interfere with operant behavior for nicotine intake. In that study [45], the selective κ receptor agonist U50,488 changed nicotine self-administering behavior in opposing directions depending on the doses administered. An increase of nicotine self-administration was observed after pretreatment with a low dose of 0.3 mg/kg, whereas rats decreased their nicotine self-administration after

administration of higher doses (1 and 3 mg/kg). It should be noted that U50,488 was found to produce "abnormal" behaviors (such as biting the edge of behavioral testing arena) at doses above 0.9 mg/kg [64] and that the κ agonists may bind to other opioid receptors and thereby to produce opposing actions [65]. Furthermore, it is interesting to note that activation of the κ receptors may play a role in the increased drug self-administration in drug-dependent but not non-dependent subjects [66, 67]. For instance, nor-BNI (a κ receptor antagonist) has been found to effectively reduce the escalated cocaine self-administration in rats with a prolonged access to cocaine and the increased ethanol intake in rats that became ethanol dependent by an ethanol vapor inhalation procedure [67, 68].

6. Conclusions

These research results demonstrate that nicotine self-administration behavior is sensitive to pharmacological antagonism of the μ, but not the δ or the κ, opioid receptors. Together with the evidence showing that nicotine administration enhances release of the endogenous μ receptor ligand endorphin [19, 69–71], these data indicate a critical role of opioid neurotransmission via the μ receptors in the rewarding properties of nicotine. On one hand, these results help understand the inconsistent outcomes obtained from bot clinical trials and animal tests using the nonselective antagonists naloxone and naltrexone. On the other hand, the findings suggest that focusing on manipulation of the μ receptor-mediated pathways within the opioid system might prove to be a fruitful strategy for the development of medication for nicotine addiction and smoking cessation.

Acknowledgements

Author details

Xiu Liu
Department of Pathology, University of Mississippi Medical Center,
Jackson, MS, USA

*Address all correspondence to: xliu@umc.edu

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