Effect of Chronic Delivery of the Toll-like Receptor 4 Antagonist (+)-Naltrexone on Incubation of Heroin Craving

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Background: Recent evidence implicates toll-like receptor 4 (TLR4) in opioid analgesia, tolerance, conditioned place preference, and self-administration. Here, we determined the effect of the TLR4 antagonist (+)-naltrexone (a μ-opioid receptor inactive isomer) on the time-dependent increases in cue-induced heroin seeking after withdrawal (incubation of heroin craving).

Methods: In an initial experiment, we trained rats for 9 hours per day to self-administer heroin (.1 mg/kg/infusion) for 9 days; lever presses were paired with a 5-second tone-light cue. We then assessed cue-induced heroin seeking in 30-minute extinction sessions on withdrawal day 1; immediately after testing, we surgically implanted rats with Alzet minipumps delivering (+)-naltrexone (0, 7.5, 15, 30 mg/kg/day, subcutaneous) for 14 days. We then tested the rats for incubated cue-induced heroin seeking in 3-hour extinction tests on withdrawal day 13.

Results: We found that chronic delivery of (+)-naltrexone via minipumps during the withdrawal phase decreased incubated cue-induced heroin seeking. In follow-up experiments, we found that acute injections of (+)-naltrexone immediately before withdrawal day 13 extinction tests had no effect on incubated cue-induced heroin seeking. Furthermore, chronic delivery of (+)-naltrexone (15 or 30 mg/kg/day) or acute systemic injections (15 or 30 mg/kg) had no effect on ongoing extended access heroin self-administration. Finally, in rats trained to self-administer methamphetamine (.1 mg/kg/infusion, 9 hours/day, 9 days), chronic delivery of (+)-naltrexone (30 mg/kg/day) during the withdrawal phase had no effect on incubated cue-induced methamphetamine seeking.

Conclusions: The present results suggest a critical role of TLR4 in the development of incubation of heroin, but not methamphetamine, craving.

Key Words: Craving, extinction, glia, heroin self-administration, opioid drugs, reinstatement, relapse, TLR4

A high rate of relapse to drug use is a main feature of heroin addiction (1,2). One factor thought to contribute to heroin relapse and craving in humans, even after prolonged abstinence, is exposure to environmental cues previously associated with drug use (3). In rat models of drug relapse and craving (4), response to cues previously associated with self-administration of heroin (5,6) and other abused drugs (7–11) progressively increases after withdrawal. We have termed this phenomenon incubation of drug craving (7,12). Over the last decade, we and others have identified several critical mechanisms of incubation of cocaine craving (13,14). In contrast, mechanisms underlying incubation of craving for heroin and other drugs are largely unknown (13). Here, we assessed the role of toll-like receptor 4 (TLR4) in incubation of heroin craving.

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Emerging evidence indicates that exposure to opioids and other abused drugs activates nonneuronal (glia, microglia, astrocytes) cells of the central immune system and that this activation plays a role in the behavioral effects of opioids and possibly other drugs (15–18). TLR4 is an innate immune system pattern recognition receptor and a member of the TLR family; this family includes 13 innate immune system receptors traditionally thought to primarily respond to pathogen-derived (pathogen associated molecular patterns) and tissue damage-related (damage associated molecular patterns) ligands (19,20). TLR4, the first discovered mammalian TLR, was initially found to recognize and to be activated by bacterial lipopolysaccharide (21). Subsequent studies have demonstrated that TLR4 is also activated by other foreign substances, such as small molecule xenobiotics (xenobiotic associated molecular patterns) (22) and several abused drugs (15,16).

TLR4 activation within the central nervous system causes the release of proinflammatory and neuroexcitatory cytokines, such as tumor necrosis factor-α and interleukin-1β (20,23). TLR4 and other TLRs are widely distributed in the brain, where they form an essential link between the innate immune system and the central nervous system (20,24). These innate immune receptors are expressed in different immunocompetent cells (20,24), including microglia (25), astrocytes (26), and oligodendrocytes (27). There is also evidence that TLR4 is expressed in cortical central nervous system neurons (28).

Recent studies indicate that morphine and other μ-opioid receptor (MOR) agonists, which stereoselectively activate MOR (29), induce nonstereoselective activation of TLR4 by binding to an accessory protein of TLR4, myeloid differentiation protein 2. Activation of TLR4 triggers oligomerization and subsequent

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glia-mediated proinflammatory responses (22,30). Conversely, the preferential MOR antagonists (−)-naloxone and (−)-naltrexone nonstereoselectively inhibit TLR4 activation by opioid agonists and other stimuli (e.g., stressors, pain manipulations) (16,24). Results from in vivo, in vitro, and in silico studies demonstrate that (+)-naloxone and (+)-naltrexone, the MOR inactive isomers of (−)-naloxone and (−)-naltrexone, are selective TLR4 antagonists (30–32). Importantly, blockade of TLR4 with (+)-naloxone or (+)-naltrexone attenuates neuropathic pain, morphine analgesic tolerance, and opioid withdrawal symptoms (16,32). Most recently, Hutchinson *et al.* (30) reported that blockade of TLR4 with (+)-naloxone decreased morphine conditioned place preference (CPP) and remifentanil (a short-acting MOR agonist) self-administration in rats.

The studies described above implicate TLR4 in the acute rewarding effects of opioid drugs, as assessed in CPP (33) and drug self-administration (34) procedures. The role of TLR4 in relapse to opioid seeking is unknown; additionally, mechanisms of drug reward, as assessed in these procedures, are often dissociable from those mediating relapse to drug seeking in rat models (35,36). Therefore, in the present study, we explored the role of TLR4 in relapse to heroin seeking using an incubation of heroin-craving procedure in which the response to heroin cues in extinction tests progressively increases after withdrawal from the drug (5,6). In the experiments described below, we used (+)-naltrexone as a long-acting TLR4 antagonist. After assessing its receptor selectivity, we determined the effect of acute and chronic (+)-naltrexone exposure on incubation of heroin craving. We also studied the effect of chronic delivery and acute injections of (+)-naltrexone on ongoing heroin self-administration and incubation of methamphetamine craving. To the degree that (+)-naltrexone is a selective TLR4 antagonist, our results demonstrate a novel role of TLR4 in the development of incubation of heroin but not methamphetamine craving.

Methods and Materials

Overview of the Behavioral Experiments

Using procedures similar to the ones described in the Supplemental Online Methods section in Supplement 1, we found that acute injections of the short-acting TLR4 antagonist (+)-naloxone (10 or 30 mg/kg, subcutaneous [SC]) had an inconsistent effect on cue-induced heroin seeking in extinction tests (3 hours) on withdrawal days 1 and 15 (F.R. Theberge, unpublished data). We also found in these pilot studies that twice daily repeated injections of (+)-naloxone (30 mg/kg) during the withdrawal period had no effect on incubated cue-induced heroin seeking on day 15.

Thus, in experiment 1 reported here, we employed an extended access heroin self-administration training procedure (9 hours of heroin access per day over 9 days) and used Alzet minipumps (Durect Corporation, Cupertino, California; 14-day delivery) to chronically deliver the long-acting TLR4 antagonist (+)-naltrexone during the 2 weeks of withdrawal from heroin. We tested the rats for incubated cue-induced heroin seeking in 3-hour extinction tests on withdrawal day 13. Before minipump implantation, we gave rats a 30-minute extinction session on day 1. This was done to verify that incubation of craving is reliably observed in each experiment in the minipump-vehicle condition and to allow us to match the different groups for baseline early withdrawal extinction responding.

In experiment 2, we determined whether the effect of chronic delivery of (+)-naltrexone on incubated cue-induced heroin seeking is mimicked by acute pretest injections of the TLR4 antagonist. We also used 12 rats that previously participated in experiment 2 to assess the effect of chronic delivery of (+)-naltrexone on operant responding maintained by palatable food pellets (37). In experiment 3, we surgically implanted rats with the minipumps containing (+)-naltrexone 2 days before the training phase to determine whether chronic delivery of the TLR4 antagonist would decrease ongoing extended-access heroin self-administration. We also assessed the effect of acute systemic injections of both (+)-naltrexone (both SC and intraperitoneal [IP]) and for comparison purposes (+)-naloxone (used in Hutchinson *et al.* [30] study) on ongoing extended-access heroin self-administration. Finally, in experiment 4, we used the same experimental conditions used in experiment 1, with the exception that lever presses during the training phase led to methamphetamine infusions, to determine whether chronic delivery of (+)-naltrexone would also decrease incubated cue-induced methamphetamine seeking. The details of the experimental procedures for these experiments are provided in the Supplemental Online Methods section in Supplement 1, which also provides a description of the initial in vitro experiments to assess potential non-TLR4 receptor binding sites or enzymatic activity of (+)-naltrexone.

Results

In Vitro Assays

Results from the target screening performed by Caliper Life Sciences showed that (+)-naltrexone displayed no significant activity at the 64 biological targets examined. The summary data in Table S1 in Supplement 1 show that (+)-naltrexone had greater than 10 μmol/L affinity for the receptors and ion channels tested and failed to exhibit significant inhibition of the enzymes tested. Figure 1 depicts the dose-response curves for (+) and (−) isomers of naltrexone in the binding assay for human MOR. K_i for (+)- and (−)-naltrexone were 1634 ± 146 nmol/L and .68 ± .04 nmol/L, respectively; the Ki for DAMGO was 11.1 ± .08 nmol/L. The binding data indicate that (+)-naltrexone is at least 2400-fold less potent than (−)-naltrexone in its binding affinity at MOR.

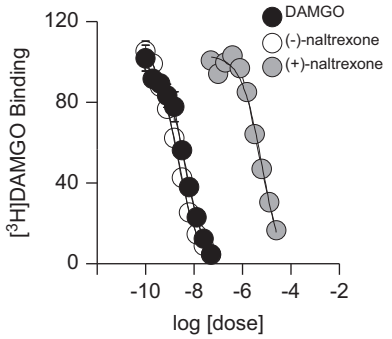

Figure 1. Dose-response curves for inhibition of [^{3}H]DAMGO binding for isomers of naltrexone: (−)-naltrexone and (+)-naltrexone. Membranes from Chinese hamster ovary cells expressing human μ opioid receptors were prepared as described in Methods and Materials. Ten concentrations of each test drug were incubated in the presence of 3 nmol/L [^{3}H]DAMGO to generate curves. Data are expressed as mean ± SD for three separate runs performed in triplicate.

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