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The role of NOP receptors in psychomotor stimulation and locomotor sensitization induced by cocaine and amphetamine in mice

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ABSTRACT

We have previously shown that orphanin FQ (also known as nociceptin; OFQ/N) attenuates the motor stimulatory effect of cocaine and blocks locomotor sensitization induced by cocaine. Furthermore, we have shown that cocaine treatment altered the level of endogenous OFQ/N, raising the possibility that endogenous OFQ/N and its receptor (NOP) may be crucial in these actions of cocaine. Accordingly, in the present study, we sought to determine the role of NOP receptors in psychomotor stimulation and locomotor sensitization induced by cocaine or amphetamine. Mice lacking the NOP receptor and their wild-type littermates were habituated to motor activity chambers for 1 h, injected with cocaine (0, 15 or 30 mg/kg) or amphetamine (0, 1 or 3 mg/kg), and motor activity was recorded for 1 h. For sensitization induced by these drugs, mice were treated with saline or the highest dose of each drug once daily for three consecutive days and tested on day 8. On this day, mice were habituated to the chambers for 1 h, then received a challenge dose of cocaine (15 mg/kg) or amphetamine (1 mg/kg), and motor activity was recorded for 1 h. Cocaine and amphetamine each induced hyperlocomotion but the extent of this response was not different between NOP receptor null mice and their controls. Sensitization developed to the motor stimulatory action of each drug, but the magnitude of cocaine-induced sensitization was only higher in null mice compared to their controls. Together, the present results suggest that the endogenous OFQ/N/NOP receptor system may modulate the development of cocaine-induced locomotor sensitization.

1. Introduction

Cocaine addiction is a serious public health issue which places a significant burden on society and economy. It is recognized as a chronic relapsing brain disorder characterized by compulsive drug seeking and drug taking behaviors with loss of control and associated negative consequences. The transition from occasional drug use to compulsive drug use involves instrumental, and classical conditioning processes (for reviews, see Hyman et al. (2006), Kelley (2004), Koob (2000), Nestler and Landsman (2001), Wolf (2002)). Thus, when administration of cocaine or another drug of abuse is often associated with a distinct environment, the context serves as a cue and this cue-drug association can induce subjective feelings even in the absence of the drug. Once this conditioned response develops and is consolidated, it can last for months and even years, due to its chronic nature (Hyman and Malenka, 2001). Importantly, subsequent exposure to the same surroundings, even in the absence of drugs, recalls old memories in abstinent addicts, thereby leading to craving and relapse (Foltin and Haney, 2000; Grant et al., 1996; Hyman et al., 2006; Kelley, 2004; Nestler and Landsman, 2001).

Locomotor sensitization is a long-lasting increase in locomotor activity that develops following repeated intermittent administration of cocaine and other psychoactive drugs (Kalivas and Weber, 1988; Post and Rose, 1976; Robinson and Becker, 1986; Stripling and Ellinwood, 1977a, b). This phenomenon which involves conditioned learning may play a role in the development and maintenance of drug addiction via enhanced motivational valence of cues associated with drug administration. Although there is little evidence for the development of this phenomenon in humans and that the disparity between animal and human data questions the clinical relevance of sensitization in rodents (for review, see (Narendran and Martinez (2008)), behavioral sensitization is thought to mimic at least some aspects of addiction, particularly craving (Robinson and Berridge, 1993, 2000). Despite decades of research in this area, the underpinning mechanism of this phenomenon is not fully characterized. Thus, further research is

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needed to assess the role of neurochemicals found in brain regions implicated in this process.

The opioid receptor-like (ORL1) receptor (also known as NOP receptor) and its endogenous ligand, orphanin FQ (Reinscheid et al., 1995) or nociceptin (Meunier et al., 1995), are expressed in the CNS and especially in brain regions implicated in motivated behaviors (Neal et al., 1999a; Neal et al., 1999b). Considering that neuronal adaptive changes that occur along the mesolimbic dopaminergic and corticolimbic glutamatergic neurons are the hallmarks of locomotor sensitization for review, see Thomas et al. (2008), and that OFQ/N negatively regulates dopaminergic and glutamatergic neurotransmission (for review, see (Murphy (2010)), drugs targeting NOP receptors could regulate the development of sensitization. Indeed, we have previously shown that intracerebroventricular OFQ/N administration reduced the motor stimulatory effect of cocaine and blocked the development of locomotor sensitization in rodents (Bebawy et al., 2010; Lutfy et al., 2001; Lutfy et al., 2002). Notably, we have previously demonstrated in rats that repeated intermittent cocaine treatment that led to locomotor sensitization increased the level of endogenous OFQ/N in the hippocampus (Lutfy et al., 2008). However, the role of the endogenous OFQ/N/NOP receptor system in cocaine sensitization largely remains unexplored. Thus, using mice lacking the NOP receptor and their wild-type littermates, we sought to assess the role of OFQ/N/NOP receptor system in cocaine-induced motor stimulation and locomotor sensitization. For comparison, we examined the role of this system in motor stimulation and locomotor sensitization induced by amphetamine.

2. Materials and methods

2.1. Subjects

Male mice lacking the NOP receptor (2–3 months old at the onset of experiments) bred in-house were the offspring of heterozygous breeding pairs crossed for 10–12 generations on C57BL/6 J mouse strain. Pups were weaned between the ages of 21–24 days and genotyped. Only knockout mice and their wild-type littermates were used for the experiments, whereas, heterozygous mice were used for future breeding pairs. Mice were housed 2–4 per cage with free access to water and food in temperature- and humidity-controlled room. All the experimental procedures were conducted according to the National Institute of Health (NIH) guideline for the proper use of animals in research and were approved by the Institutional Animal Care and Use Committee (IACUC) at Western University of Health Sciences (Pomona, California, USA).

2.2. Experimental protocols

2.2.1. The role of NOP receptors in motor stimulation and locomotor sensitization induced by cocaine

To determine the role of NOP in the acute motor stimulatory action of cocaine, male mice lacking the NOP receptor and their wild-type littermates/aged- and sex-matched wild-type controls were habituated to motor activity chambers (14 cm length × 14 cm width × 22 cm height) for 1 h, then injected with saline or cocaine (15 or 30 mg/kg, i.p.) and motor activity was recorded for an additional 1 h using the Videomex-V system (Columbus Instruments, Columbus, OH, USA). To determine the role of NOP receptors in sensitization developed to cocaine-induced motor stimulation, mice were treated with saline or cocaine (30 mg/kg, i.p.) for three consecutive days and mice were tested for locomotor sensitization on day 8. On this day, mice were habituated to the test chambers for 1 h, injected with cocaine (15 mg/kg) and motor activity was recorded for 1 h.

2.2.2. The role of NOP receptors in motor stimulation and locomotor sensitization induced by amphetamine

To assess the role of NOP receptors in amphetamine-induced motor stimulation, male mice lacking the NOP receptor and their wild-type littermates/controls were habituated to the test chambers for 1 h, then injected with saline or amphetamine (1 or 3 mg/kg), and motor activity was recorded for 1 h. To elucidate the role of NOP receptors in locomotor sensitization induced by amphetamine, mice were injected with saline or amphetamine (3 mg/kg, i.p.) once daily for three consecutive days and then tested for locomotor sensitization on day 8 following a challenge dose of amphetamine (1 mg/kg, i.p.).

2.3. Drugs

Cocaine hydrochloride and d-amphetamine sulfate were purchased from Sigma-Aldrich (St. Louis, MO, USA), and dissolved in normal saline on each test day. Drugs were injected intraperitoneally (i.p.) in a volume of 0.1 mL per 10 g of body weight.

2.4. Data analysis

Data represent mean (± S.E.M.) of distance traveled during 15-min epochs or the entire 1-h test period. Repeated measures analysis of variance (ANOVA) or two-factor ANOVA was used to analyze the data. The Newman-Keuls *post-hoc* test was used to reveal significant difference between groups. $P<0.05$ was considered statistically significant.

3. Results

3.1. The acute motor stimulatory action of cocaine was not altered in mice lacking the NOP receptor compared to their wild-type littermates/controls

Fig. 1 depicts the motor stimulatory action of cocaine (0, 15 or 30 mg/kg) in mice lacking the NOP receptor and their wild-type littermates on day 1. A two-factor ANOVA revealed a significant effect of cocaine's dose ($F2,45=36.96$; $P<0.0001$), but no significant effect of genotype ($F1,45=0.01$; $P>0.05$) and no significant interaction between the two factors ($F2,45=0.08$; $P>0.05$),

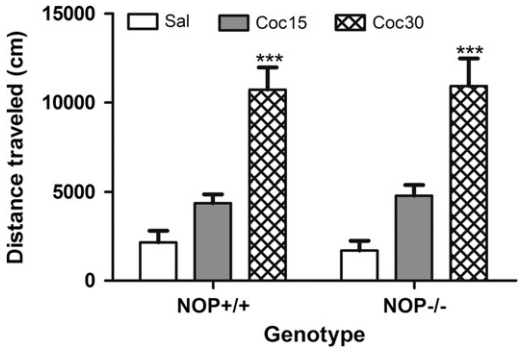

Fig. 1. Basal or cocaine-stimulated locomotor activity was not altered in mice lacking the NOP receptor compared to their wild-type controls. Mice were habituated to the motor activity chambers for 1 h, injected with saline or cocaine (15 or 30 mg/kg) and motor activity was recorded for 1 h. Data represent mean (± S.E.M.) of total distance traveled during the 1-h test period ($n=7$–11 mice per dose/genotype).$P<0.001$ vs. saline- or cocaine (15 mg/kg)-treated mice for each genotype.