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Rapid communication

Cannabinoid receptor antagonist reduces heroin self-administration only in dependent rats

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Abstract

Functionality of the endogenous cannabinoid system undergoes relevant changes in reward-related brain areas in animal models of opiate addiction. By using a limited access heroin self-administration paradigm we show that cannabinoid CB_1 receptor antagonist *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716A, 0.03–3.0 mg/kg) suppresses heroin self-administration only in opiate-dependent rats but not in non-dependent animals. These results further support the study of cannabinoid CB_1 receptor antagonists for the treatment of opiate addiction.

Keywords: Cannabinoid receptor antagonist; Heroin self-administration; (Rat)

Interactions between endogenous cannabinoid and opioid systems have important implications for addictive behaviors (Manzanares et al., 1999). Animal models have recently revealed that opioid-endocannabinoid interactions are relevant for opioid self-administration and dependence, as well as in ethanol and cocaine addiction (Maldonado and Rodriguez de Fonseca, 2002). Thus, chronic morphine exposure regulates both cannabinoid CB_1 receptor expression (Navarro et al., 2001) and endocannabinoid production (Vigano et al., 2003). Additionally, pharmacological administration of a cannabinoid CB_1 receptor antagonist reduces heroin self-administration in animals with a long history (3 months) of heroin access (Navarro et al., 2001) while the endocannabinoid uptake blocker *N*-(4-hydroxyphenyl) arachidonylethanolamide AM404 reduces spontaneous but not naloxone-precipitated opioid withdrawal (Del Arco et al., 2002). Interestingly, these findings indicate that the existence of drug-dependence is a crucial factor for endocannabinoid system regulation of reward processing on drug addiction, as also suggested in animal models of cocaine relapse (De Vries et al., 2001) as well as in animals exposed to cycles of alcohol dependence/withdrawal (Rodriguez de Fonseca et al., 1999) where an upregulation of cannabinoid CB_1 receptor gene expression has been described in reward-related brain areas (Rimondini et al., 2002).

Non-dependent and dependent opiate drug users appear to be driven by two distinct motivational factors: the primary reinforcing properties of the drug, and the negative reinforcing effects associated with relieving the negative affective component of opiate withdrawal in the dependent state. To clarify the contribution of the adaptive changes induced by opioids on cannabinoid CB_1 receptor modu-

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lation of heroin self-administration we investigated the significance of opioid dependence on the reduction of heroin self-administration induced by the cannabinoid receptor antagonist *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716 A) in rodents. Male Wistar rats obtained from Charles River Laboratory, Hollister, CA, were used in the present studies. Rats were trained to lever press for food (one 0.45-mg food pellet; Bio-Serve, Frenchtown, NJ) on a fixed ratio 1 (FR1) schedule of reinforcement, while food restricted to 20 g chow/rat/day. Once stable responding was achieved, animals were deeply anesthetized under halothane (1.0–1.5%), and implanted with chronic indwelling catheters in the jugular vein, as previously described Navarro et al., 2001). After a post-operative recovery period of 7 days, animals were trained to self-administer heroin on a limited access schedule (60 min sessions at a heroin dose of 0.03 mg/kg/infusion), as previously described (Carrera et al., 1999). The daily sessions for all the studies continued until the total number of heroin infusions per session stabilized to within ±10% for three consecutive days. Rats were then implanted with placebo pellets. Three days after pellet implantation animals resumed heroin self-administration training until baseline criteria were met again. Rats were then tested for the effects of SR 141716A (0, 0.03, 0.1, 0.3 and 3 mg/kg) in a Latin square-design. Each rat received one dose per day. Heroin self-administration sessions included a pretreatment of s.c.saline (1.0 ml/kg b.w.) 25 min into a session, and an i.p. dose of SR 141716A 55 min into a session. Immediately after each injection the lever was retracted for 5 min to avoid self-injections previous to the onset of drug effect. Somatic signs of withdrawal were rated for 10 min as described previously (Navarro et al., 2001). Once the dose response study was completed, the animals were re-operated, as described above, and implanted with two morphine pellets (s.c.; 75 mg morphine base, National Institute on Drug Abuse). This procedure allows the induction of physical dependence in the first 24 h after pellet implantation. Dependence status will remain for the following 12 days as revealed by both stable morphine plasma levels and behavioural responses to naloxone (Gold et al., 1994). Three days after pellet implantation, animals resumed heroin self-administration training until baseline criteria were met again. Rats were then tested again for the effects of SR 141716A, exactly as described after the implantation of the placebo pellets, and somatic signs of withdrawal were rated for 10 min. Data were analyzed by one-way analysis of variance (ANOVA) using a pure within subject, three factor design: pellet (placebo or morphine), interval (pre and post SR 141716A injection), and SR 141716A dose (0, 0.03, 0.1, 0.3, 3 mg/kg). Subsequent individual means comparisons were conducted with the Newman-Keuls a posteriori test.

In morphine dependent animals, but not in non-dependent ones, the acute administration of SR 141716A (3 mg/kg, 30 min within the 60 min session) almost suppressed heroin-self-administration (Fig. 1, pure within-subject design, condition×dose interaction $F[4,28]=3.6$, $P<0.02$, ANOVA; main effect of the 3 mg/kg dose, in dependent animals $F[1,7]=25.2$, $P<0.002$). A mild opiate withdrawal syndrome induced by SR 141716A could be observed in all the animals self-injecting heroin. However, as described previously, the severity of the syndrome was more intense in morphine-pellet-implanted animals than in placebo-pellet-implanted ones ($F[4,28]=11.2$, $P<0.01$, data not shown).

The present results extend to opioid self-administration the notion that the sensitivity to cannabinoid antagonist modulation of drug self-administration may be dependent on the existence of drug-dependence (Maldonado and Rodriguez de Fonseca, 2002). A similar effect was previously described in animals made ethanol-dependent (Rodriguez de Fonseca et al., 1999). The association between SR 141716A-induced somatic withdrawal, and the suppression of heroin self-administration resembles that observed for naloxone when the effects of this opioid antagonist were tested in non-dependent versus dependent conditions (Carrera et al., 1999). Cannabinoid receptor antagonist-induced withdrawal in opioid-dependent animals might result in a negative affective state that suppresses motivational responses for heroin. Supporting this notion, we have previously reported that SR 141716A adminis-

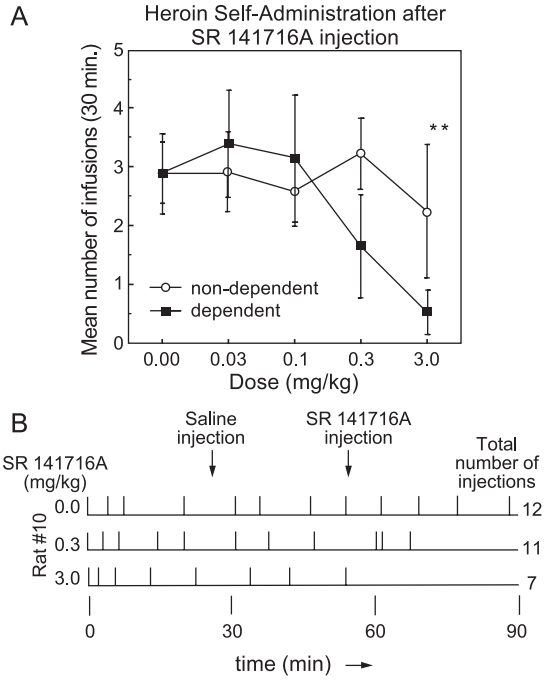

Fig. 1. (A) Acute administration of the cannabinoid CB1 receptor antagonist SR 141716A (3 mg/kg) supressed heroin self-administration (0.03 mg/injection) when injected 55 min into a 90-min session in animals bearing morphine pellet implantation, but not in placebo pellet-implanted animals (non-dependent condition). $n=8$. (**) $P<0.01$ versus vehicle-treated sessions, Newman-Keuls. (B) Reinforcement delivery record for a single morphine pellet-implanted animal on three different treatment days.

tration reduces food reinforcement in morphine-dependent, but not in placebo-implanted rats (Navarro et al., 2001). A similar finding was earlier reported with naloxone (Schulteis et al., 1994).

The differential response to cannabinoid CB_1 receptor antagonist in non-dependent and dependent conditions may have a neuropharmacological basis in the recently described changes in cannabinoid receptor expression after chronic opioid exposure. Morphine pellet implantation clearly upregulates CB_1 receptors in the ventral and dorsal striatum (Navarro et al., 2001). Whether this change is permanent throughout the opiate addiction cycle remains to be determined. However, because opioid addiction is a chronic relapsing disorder on which allostatic changes on behavior depends on the history/pattern of drug use, the identification of the specific contribution of the endocannabinoid system to the addictive cycle opens a much needed alternative for the treatment of drug abusers.

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