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COMMENTARY

Is cannabinoid transmission involved in rewarding properties of drugs of abuse?

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The endocannabinoid system is composed of at least the brain cannabinoid receptor (CB_1), the proposed endogenous ligands anandamide and 2-arachidonylglycerol, the biochemical pathways for their synthesis and degradation, and the anandamide uptake system. Pathophysiological circumstances in which this system might be active are beginning to become clear.

In their contribution to BJP, Braida & Sala (2002) provide a stimulating perspective on how the endogenous cannabinoid system is involved in the expression of the positive reinforcing properties of MDMA in rats, using intracerebroventricular (i.c.v.) drug administration in a free choice procedure. In this interesting manuscript the synthetic cannabinoid agonist CP55,940 reduced i.c.v. MDMA self-administration, while the cannabinoid CB_1 receptor antagonist SR141716 significantly increased it. At first glance, the data seem to suggest that the endocannabinoid system might have negative effects, rather than the positive ones shown in previous studies (Navarro *et al*., 2001; Cossu *et al*., 2001; Valjient *et al*., 2002; Colombo *et al*., 1998), on the reinforcing properties of a drug of abuse. The authors speculate that the stimulation of CB_1 receptors could result in a synergistic action with MDMA since it could mimic the effect of changes in the unit dose of reinforcer. Common neural mechanisms involved in brain reward substrates could account for this effect. In fact both drugs induce dopamine release in mesolimbic dopaminergic structures such as the nucleus accumbens, and thus CP55,940 co-infusion could potentially have effects besides its MDMA reinforcing properties by acting on the dopaminergic system. On the other hand, animals seem to display reduced sensitivity to the motivation when pretreated with SR141716A, which reduced the endocannabinoid tone, suggesting that MDMA's reinforcing effects are under an endogenous tonic control by the cannabinoid system.

Microdialysis studies in mesolimbic structures of these animals might further define this interaction, although some technical problems regarding the implantation of cannulas and microdialysis probes need first to be solved. This approach appears fundamental since other papers with different animal models reported opposite results. Cossu *et al*. (2001), using CB_1 receptor knockout mice, found that cocaine, d-amphetamine and nicotine were intravenously self-administered by both CB_1 knockout and CB_1 wild-type mice, without significant differences. These authors refer to their unpublished data (Cossu *et al*., 2001), where cocaine stimulated dopamine release to the same extent in the nucleus accumbens of CB_1 receptor knockout mice and the wild-type, thus providing an important neurochemical correlate to the behavioural studies.

Considering that the increase in dopamine levels in striatum and mesolimbic dopaminergic structures is believed to be of central importance to the rewarding properties of MDMA as well as of d-amphetamine and cocaine, other factors could account for the discrepancy. For example CB1 knockout mice are a different model from SR141716A pretreated animals, and the genetic manipulation could have led to the development of compensatory mechanisms absent in wild-type animals; then, too, differences in species and route of administration are also likely. However the same group, in a previous paper (Fattore *et al*., 1999), reported that pretreatment with WIN55,212-2, a CB_1 cannabinoid receptor agonist, significantly reduced cocaine intake, suggesting that activation of the CB_1 receptor produces reinforcing effects additional to those induced by cocaine.

In contrast with the variable data obtained with psychostimulants, the picture of the interaction between the cannabinoid and opioid systems is better defined. Morphine and heroin self-administration were significantly attenuated both in CB_1 receptor knockout mice (Cossu *et al*., 2001) and in SR141716 pretreated mice (Navarro *et al*., 2001). A possible mechanism for this interaction is provided by the finding that the dose-dependent increase in dopamine release from the nucleus accumbens by morphine, which has been linked to the rewarding properties of opiates, is absent in CB_1 knockout mice (Cossu *et al*., 2001). Thus the endocannabinoid system could play different roles depending on the drug of abuse under investigation: with psychostimulants (MDMA, cocaine and d-amphetamine) that directly raise dopamine levels, cannabinoids may (MDMA) or may not (cocaine and d-amphetamine) influence the reinforcing effects, whereas with psychodepressant drugs, such as morphine and heroin, these effects are likely to be under the tonic control of the endocannabinoid system. We can assume that endogenous cannabinoids serve to modulate dopamine neurotransmission and that these effects may differ depending upon the state of activation of the dopamine circuits. Therefore we need better knowledge of the dopamine-endocannabinoid connection.

One question regards the reciprocal regulation of the endocannabinoid and dopaminergic systems. How might it

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occur? Are the high dopamine levels induced by drugs of abuse associated with the release of endocannabinoids which participate in their reinforcing properties? Nothing is known about the changes in endocannabinoid levels and metabolism in brain areas after chronic treatment with drugs of abuse, except for the paper by Di Marzo *et al*. (2000) where chronic treatment with THC enhanced anandamideK formation in limbic structures. This response may be dopamine-mediated, as chronic THC stimulates dopamine release in the nucleus accumbens (Tanda *et al*., 1997) and dopamine in turn, acting through D_2-receptors, might selectively stimulate anandamide formation in this region, as proposed for the dorsal striatum (Giuffrida *et al*., 1999). Hence THC or other drugs of abuse might conceivably stimulate anandamide and/or endocannabinoid formation in the limbic forebrain and this in turn might increase the rewarding effects of these drugs. Extreme caution is needed when extending this assertion to all the different drugs of abuse, because of our limited knowledge.

Although these findings raise the possibility that endocannabinoids and CB_1 receptors may serve as a common pathway for the reinforcing properties of addictive drugs in general, most of experimental evidences support the interaction between the opiate and cannabinoid system. In contrast the potential cross-talk with psychostimulants still needs further investigation in view of the key role these interactions may have in the development of new drugs for the treatment of addiction.

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