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New Perspectives in the Studies on Endocannabinoid and Cannabis: A Role for the Endocannabinoid-Arachidonic Acid Pathway in Drug Reward and Long-Lasting Relapse to Drug Taking

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Abstract. Growing evidence on the involvement of cannabinoids in the rewarding effects of various kinds of drugs of abuse has suggested that not only the classical dopaminergic and opioidergic, but also the most recently established endocannabinoid system is implicated in the brain reward system. Furthermore, the interplay between the three systems has been shown to be an essential neural substrate underlying many aspects of drug addiction including craving and relapse. Relapse, the resumption of drug taking following a period of drug abstinence, is considered the main hurdle in treating drug addiction. Yet, little is known about its underlying mechanisms. The link between the endocannabinoid system and the arachidonic cascade is currently being clarified. While several findings have, indeed, shown the essential role of the endocannabinoid system in the reinstatement model, the endocannabinoid-arachidonic acid pathway may also be an important part in the neural machinery underlying relapse. This evidence may provide an alternative approach that will open a novel strategy in combating drug addiction.

Keywords: drug seeking behavior, relapse, addiction, endocannabinoid system, arachidonic acid cascade

Cannabinoid and reward

The brain substrates believed to mediate the rewarding/reinforcing effects of various kinds of drugs of abuse are a set of forebrain structures known as the brain reward system; these include the nucleus accumbens (the major part of ventral striatum), the basal forebrain (components of which have been termed the extended amygdala), and regions of the medial prefrontal cortex. These structures receive rich dopaminergic innervation from the ventral tegmental area of the midbrain.

Within the last few years, cannabinoids research has progressed in leaps and bounds due primarily to the development of potent cannabinoid compounds and demonstration of the presence of cannabinoid receptors in the brain.

Cannabis was long considered by some to not interact with the brain reward mechanisms, and to constitute an atypical habit-forming drug. However, given that marijuana is the most widely used illicit recreational drug, with well-described and well-characterized euphorigenic properties, it may be hypothesized that there is an interaction between cannabinoids and the brain reward mechanism.

Recently, growing evidence has indicated the involvement of the endocannabinoid system in the reward circuits in the brain (for review, see 1, 2). Early studies have shown that the psychoactive ingredient of marihuana, Δ^9-tetrahydrocannabinol (Δ^9-THC), enhanced brain reward, as indicated by its effect of reducing electrical brain stimulation threshold levels in the medial forebrain bundle (3). Furthermore, like other well-known habit-forming drugs, Δ^9-THC was demonstrated to enhance the extracellular dopamine efflux in reward-relevant brain loci such as the striatum, nucleus accumbens, and medial prefrontal cortex (4, 5). The manifestation of the withdrawal syndrome has been clearly demonstrated following cessation of repeated intake of natural (6) and synthetic (7) cannabinoids as

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well as endogenous cannabinoid ligands (8) in dependent animals. On the other hand, the rewarding properties of cannabinoids were blocked by the opioid receptor antagonist naloxone (9). Furthermore, in preclinical drug dependence studies, withdrawal signs were induced by naloxone in rats chronically treated with Δ^9-THC (10). Conversely, withdrawal signs were precipitated by the CB_1-receptor antagonist SR141716A in morphine-dependent rats (11). A psychoactive ingredient of *Cannabis sativa* Δ^8-THC, the synthetic cannabinoid CB_1-receptor agonist HU-210, and the endogenous ligand 2-arachidonoylglycerol (2-AG) significantly inhibited withdrawal signs following naloxone challenge in morphine dependent animals (12). Therefore, it is suggested that inactivation of the endocannabinoid system is related to the induction of withdrawal syndrome in morphine-dependent mice. Taken together, these findings strongly suggest that in the brain, the cannnabinoid system and opioid system modulate each other.

Judging from the aforementioned evidence, it may be suggested that not only the classical dopaminergic, as well as the opioid, but also the recently established endocannabinoid system plays an essential role in the rewarding effects of drugs of abuse. The interaction between the dopamine, opioid and endocannabinoid system are represented simply in Fig. 1.

Relationship between the endocannabinoid system and arachidonic acid cascade

The existence of putative cannabinoid receptors has advanced the understanding of signal transduction by these canabinoids at cellular levels. Therefore, the issue of the possible involvement of second messengers in the actions of cannabinoids gains considerable importance. In this regard, the CB_1 receptors belong to the seven-transmembrane domain family of G-protein-coupled receptors are linked to the Gi/o protein and inhibit adenylate cyclase (13). Other cannabinoid-receptor-mediated intracellular actions have also been reported for cannabinoids. THC and anandamide stimulate arachidonic acid mobilization (14 – 16) and induce activation of phospholipase (17, 18). THC increased the amount of prostaglandin E_2 (PGE_2) in the brain (19, 20). PGE_2, one of the final products of the arachidonic acid cascade, is widely distributed in tissues and exerts a variety of physiological actions in its role as a lipid

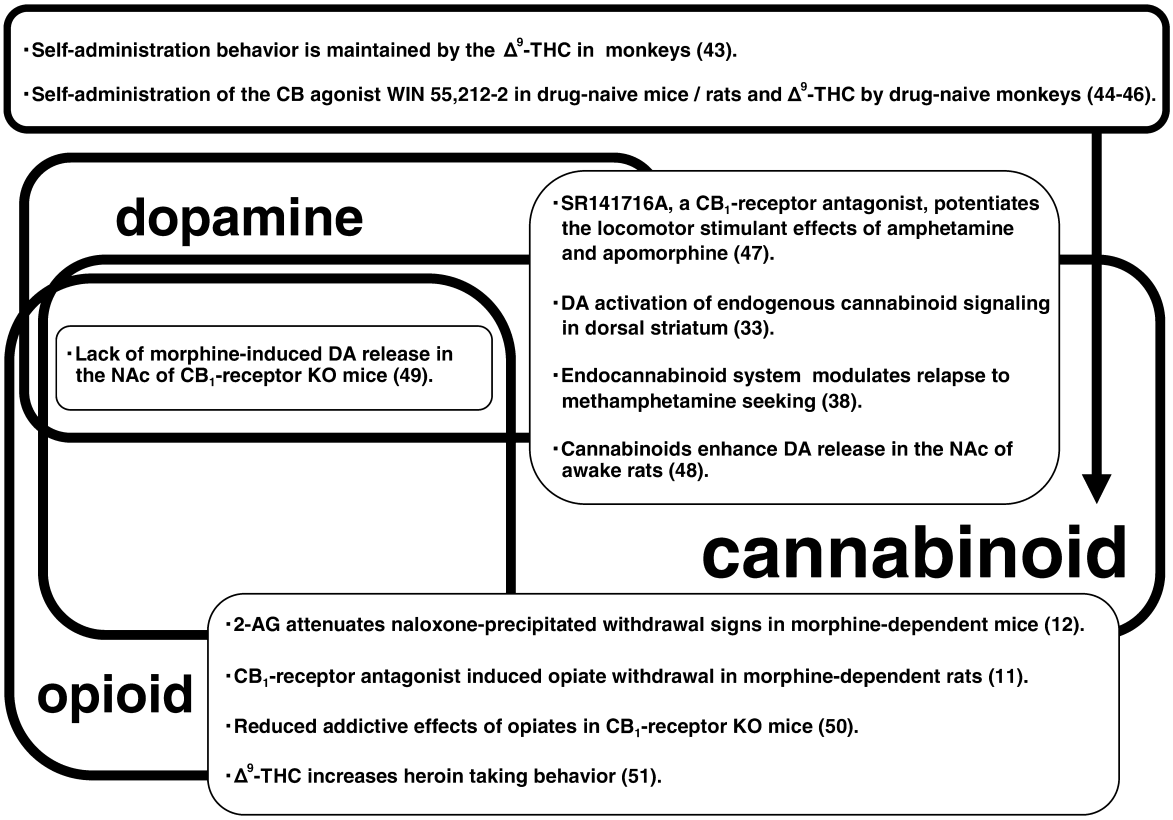

Fig. 1. Diagrammatic representation of interaction between cannabinoid, opioid, and dopamine in the brain reward system. Representative supporting evidence is shown at each point of interaction. NAc, nucleus accumbens.

mediator. These functions of PGE_2 are exerted by a variety of prostanoid EP receptors, which are classified into four types, EP1, EP2, EP3, and EP4 (21). In the brain, prostanoid EP3 receptors are abundant and widely distributed (22, 23). In the brain, PGE_2 exerts several neurophysiological functions through the EP3 receptor, that is, pain modulation (24) and fever induction (25).

The early studies suggesting a role for prostaglandins in the actions of cannabinoids were prompted by a consideration of some of their pharmacological effects. It was already known that arachidonic acid and its metabolites were abundant constituents of the central nervous system and therefore may be involved in regulating mood and perception, which are part of the spectrum of activities affected by cannabinoids.

Previously, our group has demonstrated that behavioral suppression induced by Δ^8-THC and the potent synthetic CB_1-receptor agonist HU-210 were antagonized by the cyclooxygenase inhibitor (26). Furthermore, intracerebroventricular administration of PGE_2 significantly inhibited the lever-pressing behavior performance similar to Δ^8-THC. Prostanoid EP3 receptor antisense-oligodeoxynucleotide (AS-ODN) significantly decreased prostanoid EP3 receptor mRNA levels, as determined by the RT-PCR analysis in the cerebral cortex, hippocampus, and midbrain. AS-ODN also antagonized the PGE_2-induced suppression of the lever pressing behavior (27). In the same way, the suppression of lever-pressing behavior by Δ^8-THC was significantly improved by AS-ODN (27). It is concluded that the suppression of lever-pressing behavior caused by cannabinoids is due to activation of the prostanoid EP3 receptor through an elevation of PGE_2 in the brain. In another study, we have also demonstrated that PGE_2 attenuated the expression of SR141716A-precipitated withdrawal signs in Δ^8-THC-dependent mice (28). Altogether, these findings suggest that the arachidonic acid cascade regulates the intracellular action of cannabinoids and consequently, takes the role of the endocannabinoid in the brain reward system.

Relapse and reinstatement model: the modulating role of the endocannabinoid system and possible mediation by the arachidonic acid cascade

Treatment of addiction to drugs of abuse becomes problematic due to the propensity of addicts for the resumption of drug taking, even after prolonged withdrawal periods. This relapse may be induced by exposure to the abused drugs, environmental stimuli that previously accompanied active drug taking, and stress. However, it appears that relapse to drug taking is maintained by contingencies established between the drug and environmental stimuli during drug use.

The reinforcing effects of drugs can be demonstrated in experiments in which drug acquisition is contingent upon a specific behavioral response; for example, an animal may learn that it will receive an injection of drug every time it presses a particular lever in its cage. For modeling relapse, in the reinstatement procedure in animals, the establishment of responding is maintained by drug reinforcer and then followed by its extinction. Once the behavior has decreased in frequency, experimental manipulations are imposed and the frequency of the previously reinforced behavior is then reassessed.

Along with the advancing knowledge of the role of the endocannabinoid system in the brain reward system, the functioning of the endocannabinoid system in reinstating effects of drugs of abuse is starting to gain more attention. Hungund and Basavarajappa (29) have indicated a cannabinoid mechanism in alcohol abuse. Recently, it has been demonstrated that a synthetic cannabinoid agonist could also reinstate cocaine seeking and a CB_1-receptor antagonist attenuated cocaine-induced reinstatement (30). It is likely that some of the above pharmacological manipulations attenuate cocaine-induced reinstatement via inhibition of drug priming-induced mesocorticolimbic dopamine (DA) release (31, 32). Based on evidence for a cannabinoid-dopamine interaction in the striatum (33), however, de Vries et al. (30) suggested that the activation of endogenous endocannabinoid systems downstream of the DA synapse may contribute to cocaine seeking. Furthermore, these authors showed a similar role of the system in the reinstating effects of heroin (34). On the other hand, NMDA-receptor antagonists, injected systemically, also prevented the reinstatement of cocaine-seeking behavior produced by cocaine-associated cues (35). These findings point to a potential role of glutamate and endocannabinoids in discrete cue-induced reinstatement of cocaine seeking. Recent studies have demonstrated that activation of postsynaptic metabotropic glutamate receptors suppressed presynaptic functions via the endocannabinoid system in a retrograde manner (36, 37); that is, endocannabinoids may function as a retrograde messenger from depolarized postsynaptic neurons to presynaptic terminals, suppressing the release of glutamate, probably by inhibiting presynaptic Ca^{2+} channels. Judging from these results, the attenuating effect of CB_1-receptor antagonist on the appearance of drug seeking behavior may be due to inhibition of glutamate release.

More recently, we demonstrated the importance of this system in the reinstatement of methamphetamine seeking behavior (38). In this preliminary report, not only the endocannabinoid system, but also the arachi-

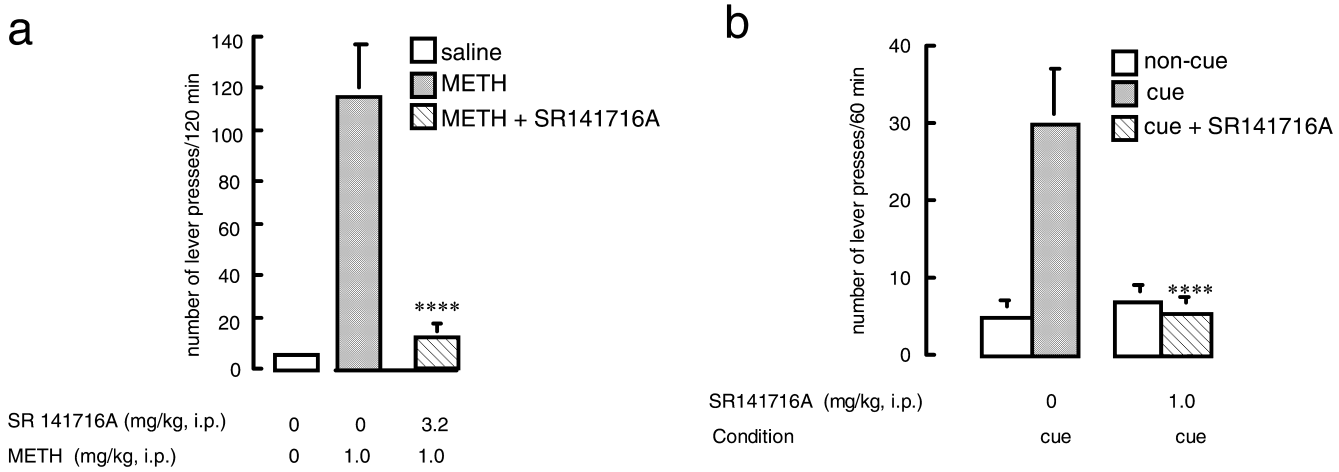

Fig. 2. Effects of the selective CB1 receptor antagonist SR141716A on reinstatement of methamphetamine (METH)-seeking behavior in rats. (a) Co-administered with METH 30 min before the test session, 3.2 mg/kg SR141716A produced a decreased number of lever press responses, which were significantly different from those produced by METH alone. Data represent the average ± S.E. number of lever presses, with 5 – 8 rats per group; ****P<0.0001 compared with the METH only treated group. (b) This antagonist at 1.0 mg/kg also suppressed the reinstatement of METH-seeking behavior when administered 30 min prior to the second hour (cue phase) of the test session. Data represent the average ± S.E. number of lever presses, with 5 – 8 rats per group; ****P<0.0001 compared with the cue session in only saline-treated rats. Data are from Ref. 38.

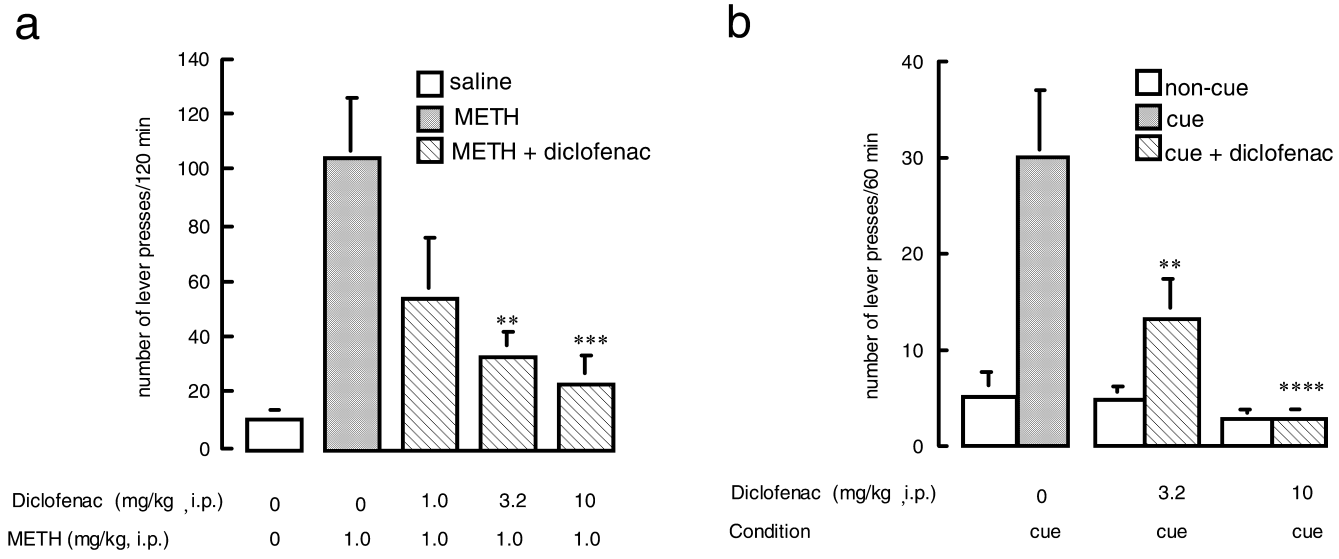

Fig. 3. Effects of the cyclooxygenase inhibitor diclofenac on reinstatement of METH-seeking behavior. (a) Given along with METH-priming 30 min prior to test session, diclofenac suppressed the reinstatement of METH-seeking behavior. Data represent the average ± S.E. number of lever presses, with 5 – 8 rats per group; **P<0.01, ***P<0.001 compared with the METH only treated group. (b) Pretreatment with diclofenac 30 min before the second hour (cue phase) of the test session attenuated the reinstatement induced by METH-associated cues. Data represent the average ± S.E. of number of lever presses. Five to 8 rats were in each group; **P<0.01, ****P<0.0001 compared with only cue-treated group. Data are from Ref. 38.

donic acid cascade was indicated to be an essential factor in the relapse of methamphetamine seeking, further supporting the importance of the endo-cannabinoid-arachidonic acid cascade interaction in the brain reward system (see Figs. 2 and 3). As shown in Fig. 4, in this study, in addition to the observation that cannabinoid antagonist suppressed the reinstatement of methamphetamine-maintained responses, we have found that the administration of a cannabinoid agonist 24 h before the induction of reinstatement blocks the reinstatement. This evidence leads us to propose that some sort of modulation occurs following the cessation

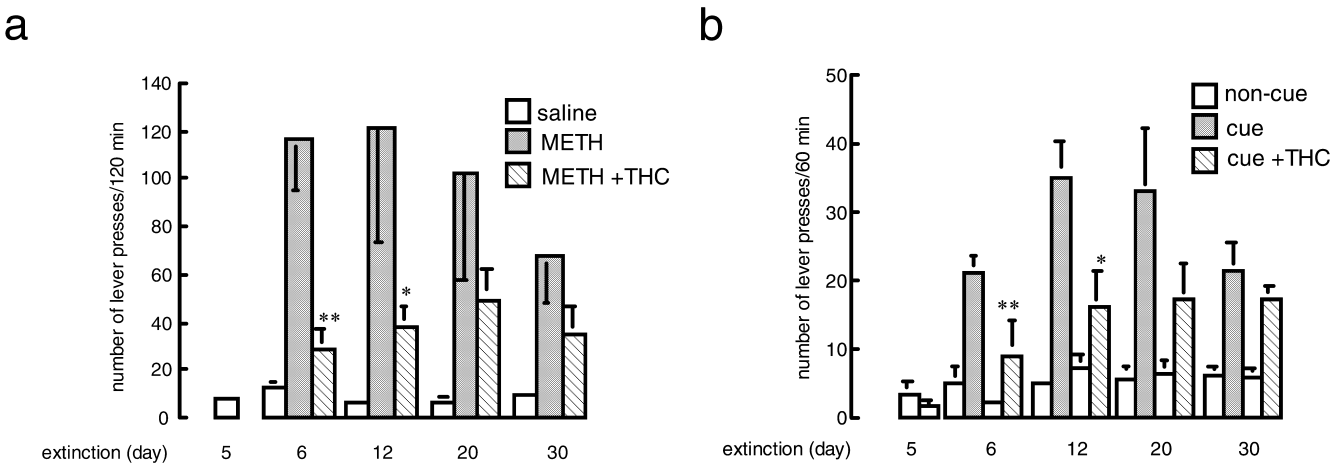

Fig. 4. Effects of THC administered during the extinction phase on reinstatement of METH-seeking behavior. (a) Single THC pretreatment after the session on day 5 of extinction, 24 h prior to METH-priming, blocked METH-seeking behavior. Data represent the average ± S.E. number of lever presses, with 5 – 8 rats per group; $^{**}P<0.01$ compared with the METH only treated group. (b) Similar results were found in the group challenged with METH-associated cues. Single THC pretreatment after the session on day 5 of extinction produced decreased number of lever press responses. Data represent the average ± S.E. number of lever presses, with 4 – 7 rats per group; $^{**}P<0.01$ compared with the cue only-treated group. Data are from Ref. 38.

of active drug taking in terms of the endocannabinoid system. The system is hyposensitized before the appearance of reinstatement; conversely, it is hypersensitized when reinstatement is expressed. It is likely that the downstream arachidonic acid cascade is regulated in this way.

A further question that may be addressed is how might the endocannabinoid system (and the downstream arachidonic acid cascade) play its role in the relapse of drug taking. Recently, the convergence of the molecular and cellular pathway of learning and memory, on the one hand, and drug addiction, on the other, has been clarified. It is now known that environmental stimuli produce stable changes in the brain that underlie the stable behavioral changes that define addiction and memory (39). In particular, the limbic-striatal memory systems are believed to play an essential role in drug addiction (40). Meanwhile, it has been demonstrated that amphetamine-induced long-term synaptic depression in the amygdala, which appears to be important in memory consolidation leading to amphetamine-induced conditioned place preference, is blocked by the cannabinoid CB_1-receptor antagonist AM251 (41). Taking these data into consideration, one may suggest that the endocannabinoid system serves as a common neural pathway for addiction and the memory system; in other words, the endocannabinoid system is the common facet of the addiction and memory system. Furthermore, the arachidonic acid cascade, downstream of the endocannabinoid system, may also be expected to take part in this function considering the recent ample evidence suggesting a potential role of phospholipase in long-term consolidation (42).

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