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An endocannabinoid hypothesis of drug reward

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Abstract

The dopamine hypothesis of drug reward remains a difficult area of research and perhaps a major problem and hindrance to progress in unraveling the biology of addiction. Pharmacological treatment of drug dependency has been disappointing and new therapeutic targets and hypotheses are needed. Since there is accumulating evidence indicating a central role of endocannabinoid physiological control system (EPCS) in the regulation of the rewarding effects of abused substances, an endocannabinoid hypothesis of drug reward is postulated. Endocannabinoids mediate retrograde signaling in neuronal tissues and suppress classical neurotransmitter release. This powerful modulatory action on synaptic transmission has significant functional implications and interactions with the effects of abused substances. Cannabinoids and endocannabinoids appear to be involved in adding to the rewarding effects of addictive substances including, nicotine, opiates, alcohol, cocaine and BDZs. Thus, the EPCS may be important natural regulatory mechanism for reward and a target for the treatment of addictive disorders.

Key words: Marijuana, endocannabinoids, CB1, CB2 receptors, dopamine, drug dependency, reward

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Introduction

In reviewing the history of human drug addictions, one finds misconceptions that people addicted to drugs lacked willpower and were morally weak. Now we know that drug addiction is a chronic relapsing brain disease characterized by the compulsive drug use despite adverse consequences. It has been demonstrated that abused drugs release dopamine in the brain's reward system to produce pleasure and euphoria, leading to addiction in vulnerable individuals [1, 2]. However, inhalants, barbiturates or benzodiazepines, do not activate midbrain dopamine consistently, yet these drugs have rewarding properties and are abused [1]. Hence dopamine is not a simple marker of reward and might no longer be tenable to suggest that drugs of abuse are simply activating the brains 'natural reward system' [2]. In this article I propose that the dopamine hypothesis is another misconception. Brain dopamine does not convey a "reward" signal since dopamine release occurs not only to drugs of abuse but also to stress, foot shock, aversive and salient stimuli [3, 4]. Mice that cannot make dopamine have been used to test dopamine hypothesis. The results show that dopamine is not required for natural and morphine reward [5, 6]. Thus, numerous problems are associated with dopamine hypothesis of reward (Table 1). For example, self-administration of opiates and alcohol occurs even when the meso-limbic dopamine system is lesioned [7]. Therefore, the activation of the 'natural reward system', mediated by the accumbens dopamine, cannot reasonably be used as a general explanation for drug addiction [2]. Although, we cannot underestimate the role of dopamine in the central nervous system, recent studies in schizophrenia where dopamine hypothesis had dominated the treatment approaches, new research shows that glutamate receptor offers promise for a new class of anti-psychotic agents (see new report in Nature Medicine, 2007, http://ealerts.nature.com/cgi-bin24/DM/y/ef6D0SoYzX0HjT0Bbiv0EH).

In drug addiction and reward research it is timely that there is accumulating evidence indicating a central role

of the endocannabinoid physiological control system (EPCS) in the regulation of the rewarding effects of abused substances. The studies show that the endocannabinoid system is involved in the common neurobiological mechanism underlying drug addiction [9-12] (Tables 2 and 3). Therefore, an endocannabinoid hypothesis of drug reward is postulated from data from our studies and those of others. A cautionary approach is important as those opposing this hypothesis have pointed out that the endocannabinoid hypothesis may fall in the same "trap" as the dopamine hypothesis. It is now recognized that drug addiction is dependent upon a convergence of genetic and environmental parameters that undoubtedly involves multiple neurotransmitters in multiple brain circuits. However, if one system can explain addiction, then it may be the endocannabinoid system. It is a complex system that we are beginning to tease out. This is because the cannabinoid receptors are the most abundant binding sites in the human brain. The cannabinoid system appears to exert a powerful modulatory action on retrograde signaling associated with cannabinoid inhibition of synaptic transmission to suppress neurotransmitter release by the presynaptic cannabinoid receptors (CB-Rs). This powerful modulatory action on synaptic transmission has significant functional implications and interactions with the effects of abused substances. CB-Rs are in most biological systems, it provides the cannabinoid system limitless signaling capabilities of cross talk within, and possible between, receptor families that may explain the numerous behavioral effects associated with smoking marijuana. In fact the vanilloid receptor 1 (VRI) had been proposed as a part of the cannabinoid system. Additional support for the endocannabinoid hypothesis of drug reward is derived from the action of cannabinoids or marijuana use on brain reward pathways that is similar to other abused substances. Further more administration of cannabinoids or the use of marijuana exerts numerous pharmacological effects through their interactions with various neurotransmitters and neuromodulators (Tables 2 and 3). In studies to test the endocannabinoid hypothesis, we investigated the interaction between vanilloid and cannabinoid agonist and antagonists in a mouse model of aversion. We also determined the effect of rimonabant on withdrawal aversions from chronic treatment with abused drugs. Our results suggest that the endocannabinoid system may be important natural regulatory mechanisms for drug reward.

Endocannabinoid physiological control system and reward, drug abuse and addictions

The endocannabinoid system [13, 14] is involved as a major player and most likely common neurobiological mechanism underlying drug reward. There is substantial evidence supporting a role for the endocannabinoid system as a modulator of dopaminergic activity in the basal ganglia [15]. The endocannabinoid system therefore participates in the primary rewarding effects of alcohol, opioids, nicotine, cocaine, amphetamine, cannabinoids, benzodiazepines through the release of endocannabinoids that act as retrograde messengers to inhibit classical transmitters including dopamine, serotonin, GABA, glutamate, acetylcholine, norepinephrine [13]. Furthermore the endocannabinoid system is intricately involved in the common mechanisms underlying relapse to drug-seeking behavior by mediating the motivational effects of drug-related environmental stimuli and drug re-exposure [11]. Thus a role exists for the endocannabinoid system in triggering and/or preventing reinstatement of drug seeking behavior [12]. It appears that the effects of perturbation of the endocannabinoid system by drugs of abuse can be ameliorated by restoring the perturbed system using cannabinoid ligands. It is not surprising that preliminary studies with cannabinoid antagonists are showing promise in the reduction of drug use, in smoking cessation and reduction in alcohol consumption and of course rimonabant has been approved in Europe for treating

Table 1: Problems associated with dopamine hypothesis of reward.

- Not all studies point to a unitary role for dopamine as the most relevant system in drug abuse.
- Dopamine may not be involved in brain reward mechanisms as previously thought.
- Dopamine independent mechanisms involving other neurotransmitters like glutamate, GABA, serotonin, endocannabinoids, stress hormones, dynorphin are potential substrates for the rewarding effects of abused substances.
- Reward centers in the brain consist of multiple systems and neuroanatomical sites other than the mesoaccumbens dopamine circuitry.
- In schizophrenics, dopamine excess causes heightened state of arousal and not pleasure.
- Smokers and cocaine addicts continue to take hits long after the cigarettes become distasteful or after the effects have worn off. http://dericbownds.net/bom99/Ch10/Ch10.html
- Addictions arise from a complex pattern of pathogenetic and environmental situations.
- Manipulation of dopamine circuitry as a pharmacology target does not provide medication for drug addiction.
- There is no causal relationship that dopamine is a pleasure or reward transmitter triggered by abused substances.
- Differential effects of abused substances on the complex network of genes, hormones, neurotransmitters, and modulators do not support the concept of a single reward transmitter.
- Activation of dopamine pathways is not involved in brain-stimulation reward of all brain sites relevant to addiction.
- Electrolytic lesions and 6-OH dopamine lesion studies of dopamine cell bodies in the ventral tegmental area and other brain sites did not attenuate brain-stimulation reward.

Table 2: Frame work for an endocannabinoid hypothesis of drug reward (I).

- The existence of an endocannabinoid physiological system control system (EPCS) with a central role in the regulation of the rewarding effects of abused substances.
- The EPCS is intricately involved in almost all the biological processes of the human body and brain.
- The EPCS appears to exert a powerful modulatory action on retrograde signaling associated with cannabinoid inhibition of synaptic transmission.
- The retrograde signaling appears to be involved in the modulation of neurotransmitter release by cannabinoids and endocannabinoids.
- The abundant distribution of the cannabinoid receptors in the brain provides the EPCS limitless signaling capabilities of cross talk within, and possibly between receptor families.
- A missense mutation in human fatty acid amide hydrolase may be associated with problem drug use in vulnerable individuals.
- Cannabinoids induce alterations in brain disposition and pharmacological actions of drugs of abuse.
- Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine.
- 'Runners high', the sense of euphoric well-being that comes with vigorous exercise running stimulates the release and elevated levels of endocannabinoids.

obesity. It is hoped that these encouraging positive results will lead to new therapeutic agents in the treatment of drug dependency. The EPCS therefore appears to play a central role in regulating the neural substrate underlying many aspects of drug addiction including craving and relapse [8]. The findings that the EPCS is involved in the reinstatement model provided evidence of the EPCS in the neural machinery underlying relapse. Relapse, the resumption of drug taking following a period of drug abstinence, is considered the main hurdle in treating drug addiction and pharmacological modulation of the endocannabinoid tone with rimonabant gave positive results in human trials. As the usefulness of the pharmacotherapy of substance abuse has been limited, there is sufficient pre-clinical evidence for clinical trials to evaluate the efficacy of cannabinoid based drugs in the treatment of drug dependency.

Interaction between CB1 and CB2 receptors in drug abuse and addiction

The expression of CB1 cannabinoid receptors (CB1-Rs) in the brain and periphery has been well studied but the brain neuronal expression of CB2-Rs had been ambiguous and controversial and its role in substance abuse is unknown. There is evidence for the functional presence of CB2-Rs in mammalian brain neurons [16-18]. We investigated the involvement of CB2-Rs in alcohol preference in mice and alcoholism in humans [19]. Our data revealed that CB2-Rs are functionally

Table 3: Frame work for an endocannabinoid hypothesis of drug reward (II).

- The mechanisms of dependence to different substances appear to be different in terms of their impact on the EPCS.
- The endocannabinoid transmission is a component of the brain reward system and appears to play a role in dependence/withdrawal to abused substances.
- Reduced sensitivity to reward in CB1 knockout mice. But mice that cannot make dopamine (mice lacking tyrosine hydroxylase) respond to rewarding stimuli, indicating reward without dopamine.
- Overeating, alcohol and sucrose consumption is decreased in CB1 receptor deleted mice.
- Involvement of endocannabinoid system in the neural circuitry regulating alcohol consumption and motivation to consume alcohol.
- Evidence for the existence of a functional link between the cannabinoid and opioid receptor systems in the control of alcohol intake and motivation to consume alcohol.
- Decreased alcohol self-administration and increased alcohol sensitivity and withdrawal in CB1 receptor knockout mice.
- Endocannabinoid system modulates opioid rewarding and addictive effects by crosstalk between endogenous opioid and endocannabinoid systems in drug reward.
- Involvement of endocannabinoid and glutamate neurotransmission in brain circuits linked to reward and mnemonic processes. Abolition of LTP in mice lacking mGluR5 receptors and enhanced LTP and memory in mice lacking cannabinoid CB1 receptors.
- Endocannabinoid system in memory related plasticity may be a common mechanism in the control of conditioned drug seeking by cannabinoids.

expressed in brain neurons and plays a role in substance abuse and dependency [17-19]. What are the nature of and the contribution of CB2-Rs to the effects of CB1-Rs in the rewarding effects of drug abuse? One possible explanation may be that CB2-Rs and CB1-Rs work independently and/or cooperatively in different neuronal populations to regulate a number of physiological activities influenced by drugs of abuse, cannabinoids, and marijuana use. Nevertheless brain CB-Rs may provide novel targets for the effects of cannabinoids in substance abuse disorders.

Experimental methods

The elevated plus-maze test is used to measure the performance of rodents to obtain an index of anxiety in animals that are exposed to the maze. The plus-maze consists of two open arms and two enclosed arms linked by a central platform and arranged in a plus Sign (+). The plus-maze test was used to study withdrawal anxiogenesis from selected drugs with abuse potential. Adult C57Bl/6 mice were evaluated in the plus-maze test following abrupt cessation from chronic twice

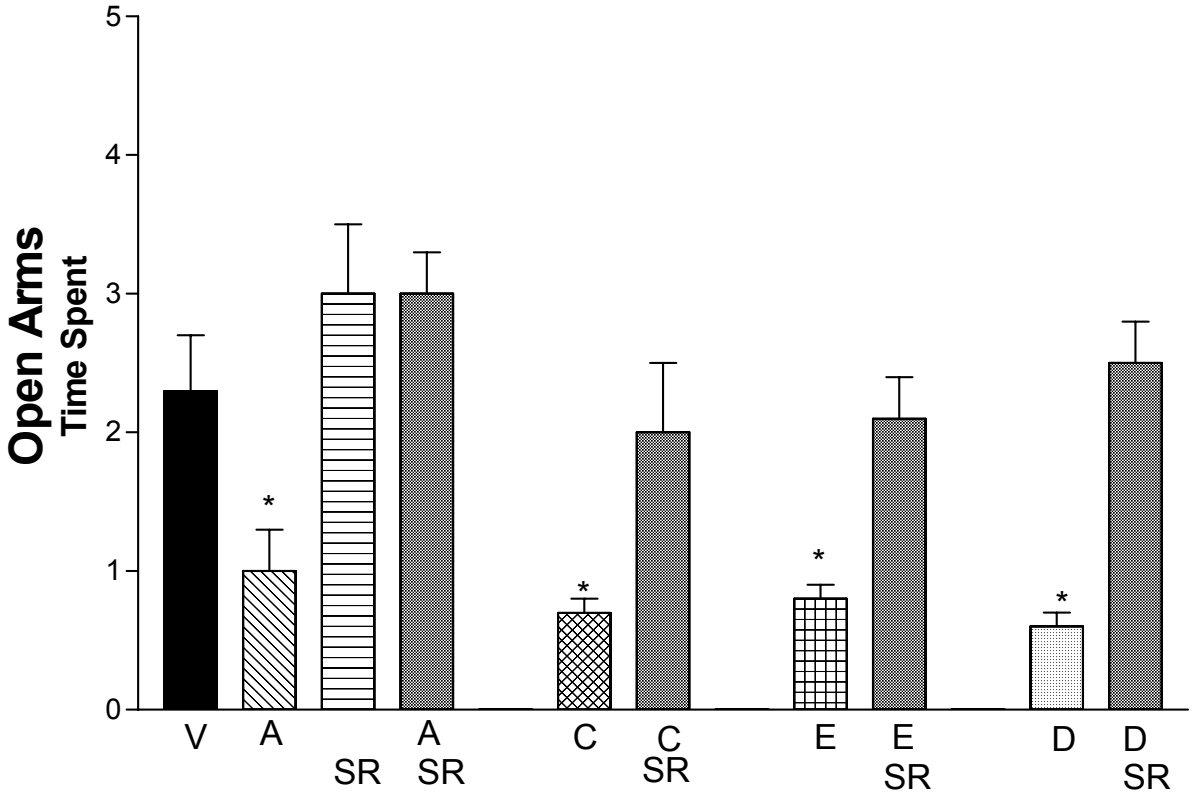

Figure 1: Antagonism of withdrawal aversions from drug abuse treatment by rimonabant in the plus-maze test. Modification of withdrawal aversions of mice from chronic cocaine (1.0 mg/kg) C, diazepam (1.0 mg/kg) D, ethanol (8% w/v) E, methanandamide (10 mg/kg) A, by rimonabant, (SR, 3 mg/kg). V is vehicle 1:1:18, Emulphor, ethanol (75%) and water.

daily treatment (ip) with selected doses of cocaine (1.0 mg/k), diazepam (1.0 mg/kg), ethanol (8% w/v) and methanandamide (10 mg/kg). In a separate group of mice the ability of rimonabant (3 mg/kg) 30 mins pretreatment, to block the withdrawal aversions of mice from the selected drugs with abuse potential was determined. Capsaicin known to activate CB-Rs and vanilloid receptors was used to study the involvement of the EPCS in its rewarding effects in mice. The interaction between vanilloid and cannabinoid systems was performed using their selected agonists and antagonists (data not shown). The data were analyzed by one-way analysis of variance followed by Dunnett's t-test for multiple comparisons. The acceptable level of significance was $p<0.05$.

Results and Discussion

The effects of rimonabant on the withdrawal aversions from cessation with chronic treatment of mice with the selected addictive drugs are shown (Figure 1). The reduced time the animal spent in the open arms of the plus-maze was reversed by pretreatment with rimonabant. Manipulating the EPCS could be exploited in reducing the behavioral consequences of withdrawal from abused drugs. Although the interaction between the EPCS and the vanilloid system is not well established the results on whether the interaction between endocannabinoid and endovanilloid systems induced by capsaicin, could be a basis of why some like hot chili peppers and others do not, is intriguing (data not shown). Rimonabant has been shown to counteract the CPP supported by classical reinforcers including food, cocaine, and morphine [20]. This is in agreement with data that demonstrates the antagonistic activity of rimonabant against disruption of cognition or reward-enhancing properties of morphine, amphetamine cocaine [21], that we have extended to ethanol and diazepam. The blockade of the behavioral aversions by cannabinoid antagonist following chronic administration with abused drugs is in agreement with data obtained during cannabinoid-induced alterations in brain dispositions of drugs of abuse that correlated with behavioral alterations in mice [22].

Conclusions

The association between activation of cannabinoid and vanilloid receptors shows that the interaction of abused substances with the endocannabinoid system is pivotal in habit formation and a neural basis of reward. Rimonabant blocked the behavioral aversions to the open arms of the plus-maze, which was precipitated from withdrawal from abused drugs. The results suggest that

the EPCS may be a directly important natural regulatory mechanism for reward in the brain and also contribute to reduction in aversive consequences of abused substances. It is a good thing that controversy is one of the fuels of scientific investigations. Thus, there is a lot more research to be done to better understand the nature, neurobiology of the endocannabinoid system in health and disease. In the end the eternal bliss may not be dopamine but endocannabinoids - the brain and body's marijuana and beyond [13].

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