Getting Stoned Without Inhaling: Anandamide Is the Brain's Natural Marijuana

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Issue: *The brain has at least 2 receptors for marijuana and at least 1 naturally occurring ligand, which may be the brain's own marijuana.*

The brain makes its own morphine, so why not its own marijuana? Marijuana has been in use for over 4000 years as both a therapeutic agent and a recreational drug. Until 10 years ago, however, the exact mechanism of marijuana's psychoactive properties was relatively obscure, even though the psychoactive ingredient has long been known to be delta-9-tetrahydrocannabinol (THC).[1–3] Analogous to how the endogenous opiates were discovered, isolation and characterization of cannabinoid (CB) receptors provided the key for their use as a tool in isolating an endogenous ligand for marijuana receptors in the brain.[1–3] This endogenous ligand is called *anandamide*.[1–3]

Marijuana Receptors

So far, 2 CB receptors have been identified, 1 in brain and the other in the immune system.[1–4] THC binds to at least 2 distinct receptors: CB1 (and another possible subtype called CB1A) and CB2.[1–3] CB1 receptors are found in highest concentration in brain neurons, are coupled via G proteins, and modulate adenylate cyclase and ion channels.[5,6] CB2 receptors are found in cells of the immune system, are also coupled via G proteins, but inhibit adenylate cyclase.[1–3]

Brain Cannabinoid Receptors

Not surprisingly, brain CB1 receptors are thought to mediate reinforcement and reward.[1–3] They may not only be involved in the mediation of marijuana's reinforcing properties, but also may impact ethanol's reinforcing properties, since the CB1 selective antagonist SR141716A reduces ethanol intake in rats.[7]

The pharmacologic activity of cannabinoids may be partially mediated through 5-HT receptors.[8] Cannabinoids also regulate mesolimbic dopamine transmission, which affects the dopamine "pleasure pathway" and may help to explain the reinforcing properties of marijuana,[9] especially since this mechanism seems to serve as a final common pathway for nearly all drugs of abuse, including nicotine, alcohol, stimulants, and marijuana.[10–12]

Studies of CB1 receptors in experimental animals exposed to chronic cannabinoids are beginning to explore issues of tolerance, dependence, and withdrawal. Although it is clear that acute administration of marijuana to humans produces intoxication with euphoria, there is a relative absence of acute withdrawal signs typical for other drugs of abuse. This lack of withdrawal symptoms may occur because cannabinoids are stored in body lipids and slowly released into the blood after self-administration has ceased.[1–3] Presumably, the CB1 receptors that undergo adaptation during acute drug administration have time to readapt by the time the residual drug leaking out of body lipids is all gone.

In terms of chronic administration of marijuana in humans, tolerance to cannabinoids has been well established, but the question of cannabinoid dependence has always been very controversial. The discovery of the CB1 antagonist SR141716A has settled this controversy because it precipitates a withdrawal syndrome in mice chronically exposed to THC.[13] It is therefore likely, but not yet proved, that dependence also occurs in humans, presumably due to the same types of adaptive changes in cannabinoid receptors that occur in other neurotransmitter receptors after

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Take-Home Points

- The active component of marijuana is delta-9-tetrahydrocannabinol, and 2 receptors for this psychoactive substance, called cannabinoid (CB) 1 and CB receptors, have been identified
- An endogenous ligand for the CB1 receptors in the brain has been identified. It is a naturally occurring lipid called anandamide and acts as an agonist at CNS CB1 receptors
- A synthetic antagonist (SR141716A) for the CB1 receptor has also been discovered and is in clinical testing for psychoactive substance abuse, schizophrenia, and other disorders

chronic administration of other drugs of abuse.[10–12]

Peripheral Cannabinoid Receptors

Actions of cannabinoids at peripheral cannabinoid receptors may explain altered immune function after long-term cannabinoid administration. Cannabinoids acting at CB2 receptors in the immune system cause inhibition of T-cell-dependent humoral immune responses through direct inhibition of accessory T-cell function.[4] These and other types of signaling events observed in leukocytes responding to cannabinoids that bind to leukocyte CB2 receptors provide interesting insights into how genes may be modulated in cell types other than neurons.

Anandamide, The Brain's Own Marijuana

Anandamide is a member of a family of fatty acid ethanolamides that may represent a novel class of naturally occurring lipid neurotransmitters.[1–3,14] Anandamide shares most but not all of the pharmacologic properties of THC. For instance, anandamide's actions at CB1 receptors are mimicked not only by THC, but also by a recently discovered synthetic agonist, CP55-940,[15] and its activities at CB1 receptors are antagonized in part by the selective CB1 antagonist SR141716A.[1,14]

The discovery of SR141716A opens the door to using this drug as a tool for determining the biological function of CB1 receptors in the human CNS. It may certainly lead to a role in preventing various types of drug abuse, in treating various types of drug dependence, and in reducing symptoms in various disorders hypothesized to be the result of a defect in the mesolimbic dopamine system, such as schizophrenia.[12] ◆

REFERENCES

1. Axelrod J, Felder CC. Cannabinoid receptors and their endogenous agonist anandamide. Neurochem Res 1998;23:575–581
2. Yamamoto I, Kimura T, Kamei A, et al. Competitive inhibition of delta-8-tetrahydrocannabinol and its active metabolites for cannabinoid receptor binding. Biol Pharm Bull 1998;21: 408–410
3. Felder CC, Glass M. Cannabinoid receptors and their endogenous agonists. Ann Rev Pharmacol Toxicol 1998;38:179–200
4. Kaminski NE. Regulation of the cAMP cascade, gene expression and immune function by cannabinoid receptors. J Neuroimmunol 1998;83: 124–132
5. Rubino T, Patrini G, Massi P, et al. Cannabinoid-precipitated withdrawal: a time-course study of the behavioral aspect and its correlation with cannabinoid receptors and G protein expression. J Pharmacol Exp Ther 1998;285: 813–819
6. Tao Q, Abood ME. Mutation of a highly conserved aspartate residue in the second transmembrane domain of the cannabinoid receptors, CB1 and CB2, disrupts G-protein coupling. J Pharmacol Exp Ther 1998;285: 651–658
7. Colombo G, Agabio R, Fa M, et al. Reduction of voluntary ethanol intake in ethanol-preferring sP rats by the cannabinoid antagonist SR-141716. Alcohol Alcohol 1998;33:126–130
8. Kimura, Ohta T, Watanabe K, et al. Anandamide, an endogenous cannabinoid receptor ligand, also interacts with 5-hydroxytryptamine (5HT) receptors. Biol Pharm Bull 1998;21: 224–226
9. Gessa GL, Melis M, Muntoni AL, et al. Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB1 receptors. Eur J Pharmacol 1998;341:39–44
10. Nestler EJ. Molecular neurobiology of drug addiction. Neuropsychopharmacology 1994;11: 77–87
11. Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology 1998;18:135–174
12. Stahl SM. Essential Psychopharmacology. New York, NY: Cambridge University Press; 1996
13. Cook SA, Lowe JA, Martin BR. CB1 receptor antagonist precipitates withdrawal in mice exposed to delta-9-tetrahydrocannabinol. J Pharmacol Exp Ther 1998;285:1150–1156
14. Adams IB, Compton DR, Martin BR. Assessment of anandamide interaction with the cannabinoid brain receptor: SR141716A antagonism studies in mice and autoradiographic analysis of receptor binding in rat brain. J Pharmacol Exp Ther 1998;284:1209–1217
15. Qureshi J, Saady M, Cardounel A, et al. Identification and characterization of a novel synthetic cannabinoid CP55-940 binder in rat brain cytosol. Mol Cell Biochem 1998;181:21–27