Pharmacology Biochemistry and Behavior, Vol. 64, No. 2, pp. 257–260, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00059-3

Cannabis: Discrimination of "Internal Bliss"?

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WILEY, J. L. *Cannabis: Discrimination of "internal bliss"?* PHARMACOL BIOCHEM BEHAV. **64**(2) 257–260, 1999.— The recent discovery of arachidonylethanolamide (anandamide), an endogenous ligand for cannabinoid receptors, and the synthesis of SR141716A, a cannabinoid antagonist selective for brain cannabinoid (CB1) receptors, have provided new tools to explore the mechanisms underlying cannabis abuse and dependence. Drug discrimination is the animal model with the most predictive validity and specificity for investigation of the psychoactive effects of cannabinoids related to their abuse potential, because, unlike many other drugs of abuse, Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive ingredient of marijuana, is not self-administered by animals. Results of Δ^9-THC discrimination studies have revealed that the subjective effects of cannabis intoxication are pharmacologically selective for centrally active cannabinoid compounds, and that cannabis action at CB1 receptors is involved in medication of these effects. Less clear is the role of endogenous cannabinoid system(s) in cannabis intoxication. Anandamide, named for a Sanskrit word for "internal bliss," unreliably substitutes for Δ^9-THC. Further, substitution, when it is observed, occurs only at doses that also significantly decrease response rates. In contrast, Δ^9-THC and other structurally diverse cannabinoids fully substitute for Δ^9-THC at doses that do not substantially affect response rates. Attempts to train animals to discriminate anandamide (or SR141716A) have so far been unsuccessful. Preliminary evidence from drug discrimination studies with more metabolically stable anandamide analogs have suggested that these differences in the discriminative stimulus effects of Δ^9- THC and anandamide-like cannabinoids are not entirely due to pharmacokinetic factors, but the exact role of "internal bliss" in cannabis intoxication and dependence is still not completely understood. © 1999 Elsevier Science Inc.

Anandamide Cannabinoid Discrimination SR141716A Tetrahydrocannabinol

MARIJUANA (*Cannabis sativa*) is the most commonly used illicit drug of abuse in the United States. Although its primary psychoactive ingredient, Δ^9-tetrahydrocannabinol (Δ^9-THC), is largely responsible for the subjective "high" experienced by users, the marijuana plant contains many other psychoactive and inactive cannabinoid substances, including cannabinol, cannabidiol, and Δ^8-THC (16). The influence of interaction(s) of these constituents on the pharmacological effects of Δ^9-THC has not been completely determined. To a large extent, preclinical research on marijuana abuse and dependence has focused on the effects of Δ^9-THC in isolation. Hence, this review will concentrate on research with Δ^9- THC, with the caveat that interactions among substances within the marijuana plant, as well as the different typical method of administration in humans vs. animals (smoked and injection, respectively), may alter the magnitude or quality of observed pharmacological effects.

Early hypotheses concerning the mechanism of action of Δ^9-THC posited that this substance perturbed neuronal cell membranes, resulting in relatively nonselective disruption of neurotransmission (19); however, a series of new advances in the field within the last decade have cast doubt upon earlier ideas and have suggested that a more specific, receptor-mediated response may be responsible for the pharmacological effects of cannabinoids. One of the first advances was synthesis and radiolabeling of a selective and potent cannabinoid ligand, CP 55,940, which was suitable for use in binding assays (14). The synthesis of CP 55,490 not only offered further support for the hypothesis that cannabinoid effects were receptor mediated, but allowed identification of the possible distribution of these receptors in the brain (18). A second advance was the cloning of a brain cannabinoid (CB1) receptor (25). Investigation of receptor activation/G-protein coupling soon followed [for a review, see (9)]. In 1992, an endogenous ligand for this receptor was isolated and identified in the porcine brain (15). This substance, arachidonyl ethanolamide, was named anandamide after the Sanskrit word for "internal bliss." The discovery of anandamide led to the identification of other endocannabinoids (26), although research on these substances is minimal compared to that on anandamide. The most recent major advance in the cannabinoid field occurred with synthesis of the first, specific CB1 receptor antagonist, SR141716A, reported in 1994 (29). A peripheral (CB2) cannabinoid receptor antagonist, SR144528, was synthesized a few years later (30). Together, these advances (and others mentioned below) have provided strong support for the hypothesis that interaction of Δ^9-THC with CB1 receptors is responsible for its centrally mediated pharmacological effects and, probably, for the abuse of potential of marijuana. This latter hypothesis has been further evaluated in a number of preclinical behavioral studies in our and other laboratories.

Preclinical behavioral methods for investigation of abused drugs include self-administration, drug discrimination, assessment of pharmacological similarity to other abused drugs, and

evaluation of physical dependence liability (3). Cannabinoids, unlike many other abused drugs, are not self- administered by rhesus monkeys in an intravenous self-administration procedure (23); hence, self- administration results for cannabinoids represent a false negative (i.e., marijuana is abused in humans, but its primary psychoactive constituent is not self-administered by nonhuman primates). In contrast, animals can discriminate Δ^9-THC and other psychoactive cannabinoids in two-lever drug discrimination procedures. Consequently, drug discrimination may be one of the most pharmacologically selective preclinical behavioral methods for inves tigation of mechanism(s) of action of cannabinoids related to the intoxicating effects. The purpose of the article is to review and evaluate ways in which results of recent drug discrimination research with cannabinoids may aid in understanding the mechanism through which Δ^9-THC produces cannabimimetic intoxication. Previous reviews have summarized the results of Δ^9-THC discrimination studies that occurred before most of the recent scientific advances in the cannabinoid field (4,20,21). Our current working hypothesis concerning the mechanism of action mediating the intoxicating effects of cannabinoids is that the psychoactive substances contained in marijuana interact with CB1 receptors in an endocannabinoid system in a manner that is similar to that with which substances derived from the poppy plant interact with certain receptors of endogenous opioid systems.

PHARMACOLOGICAL SPECIFICITY OF CANNABINOID DISCRIMINATION

As might be expected, the most commonly used training drug in cannabinoid drug discrimination is Δ^9-THC. The discriminative stimulus effects of Δ^9-THC are pharmacologically selective for naturally occurring psychoactive cannabinoids with a potency in this procedure that is highly correlated with potency for subjective effects in humans (5). Further, the discriminative stimulus effects of classical cannabinoids show stereoselectivity with activity residing in the (−)-isomer (4,12). Plant-derived cannabinoids that do not bind to CB1 receptors fail to substitute fully for Δ^9-THC in two-lever drug discrimination procedures, as do noncannabinoid compounds of many classes (6,7,40). Consistent partial substitution is obtained with the benzodiazepine diazepam in rats (27); however, this effect appears to be mediated via diazepam's action at GABA receptors, as it is blocked by the benzodiazepine-site antagonist flumazenil but is not blocked by SR141716A (27,33). In contrast to partial substitution obtained at high doses of diazepam, full substitution of other cannabinoids for Δ^9-THC is predicted by good affinity for CB1 receptors, at least among cannabinoids with classical tricyclic structures similar to that of Δ^9-THC itself (12). Although most cannabinoid discrimination studies have used rats as subjects, others have trained monkeys, pigeons, or gerbils. Pharamacological specificity of Δ^9-THC discriminative stimulus effects is observed cross-species in rats and rhesus monkeys (6,40).

Although most of the earlier studies examined the discriminative stimulus effects of classical tricyclic cannabinoids, synthetic cannabinoids with quite different chemical structures have been tested in more recent studies. These new classes of psychoactive cannabinoids include bicyclic compounds (e.g., CP 55,940), aminoakylindoles (e.g., WIN 55,212-2), other indole- and pyrrole-derived cannabinoids [see (37)], and, of course, the anandamides. With the exception of the anandamides (to be discussed later in this article), cannabinoids from each of these novel classes substitute fully Δ^9-THC in both rats and rhesus monkeys with a rank order potency that corresponds with their affinity for CB1 receptors (11,17,37,40). Results of drug discrimination studies that used CP 55,490 or WIN 55,212-2 as training drugs have not revealed systematic differences in characteristics of the discriminative stimulus effects of these compounds (other than obvious potency differences) compared with those of Δ^9-THC and other classical cannabinoids (28,36). Δ^9-THC, CP 55,940, and WIN 55,212-2 substitute and cross-substitute for each other. Further, the discriminative stimulus effects of CP 55,940 are pharmacologically selective for psychoactive cannabinoids, although diazepam partially substitutes for CP 55,940 as it does for Δ^9-THC (36). Thus far, lack of substitution for Δ^9-THC has not been reported for any cannabinoid with a novel tricyclic, bicyclic, aminoakylindole, indole- or pyrrole-derived chemical structure that exhibited high binding affinity at CB1 receptors.

ANTAGONIST STUDIES

Drugs from a number of different pharmacological classes that do not bind to CB1 receptors have been tested in combination with Δ^9-THC and failed to block its discriminative stimulus effects (7). In addition, several cannabinoid compounds have been tested as antagonists in Δ^9-THC discrimination procedures. These compounds, $\Delta^{9,11}$-THC and cyano and nitrogen mustard derivatives of Δ^9-THC, failed to attenuate the discriminative stimulus effects of Δ^9-THC and, in fact, substituted for Δ^9-THC, albeit with different time courses and/or potencies (35,38). Not until SR141716A was synthesized in 1994 did we have a pharmacological tool to block the discriminative stimulus effects of cannabinoids. SR141716A dose dependently blocks discriminative stimulus effects of three major classes of cannabinoids, as represented by prototypic drugs, Δ^9-THC, CP 55,940, and WIN 55,212-2 (24,28,36,41). Further, this antagonism has been observed in rats, pigeons, and rhesus monkeys. An attempt to train animals to discriminate SR141716A from vehicle was unsuccessful, suggesting that it does not have discriminative stimulus effects of its own (24,28). The results of these studies provide additional support for the hypothesis that the discriminative stimulus effects of Δ^9-THC are mediated via interaction with CB1 cannabinoid receptors.

ANANDAMIDE AND ANANDAMIDE ANALOGS

The role of the endogenous cannabinoid system in cannabis intoxication is still unclear. Anandamide is a partial agonist at CB1 receptors, as is Δ^9-THC. Whereas Δ^9-THC is metabolized mainly through the P450 enzyme system in the liver, anandamide is metabolized into arachidonic acid via the enzyme fatty acid amide hydrolase, a process that proceeds more quickly (13). Because of the fast metabolism of anandamide, an amidase inhibitor such as phenylmethylsulfonyl fluoride (PMSF) must be added to the medium in binding assays to gauge the true affinity of anandamide analogs for CB1 receptors (10,13). Because the protocols for drug discrimination and most other in vivo studies with anandamide have not included coadministration of an amidase inhibitor, the relationship between binding affinity at CB1 receptors (with PMSF) and in vivo potency has been less strong for anandamides than for other classes of cannabinoids (1,2). The rapid metabolism of anandamide adds to the difficulty of separating any potential pharmacodynamic differences between anandamides and Δ^9-THC from pharmacokinetic differences. Nevertheless, anandamide has been tested in drug discrimination paradigms.

In rats, anandamide itself substitute for Δ^9-THC and CP 55,940, but does so only at doses that severely decrease response rates (34). The fact that Δ^9-THC and other structurally diverse cannabinoids fully substitute for Δ^9-THC at doses that do not substantially affect response rates suggests that there are differences as well as similarities between anandamide and other cannabinoids in this procedure. In rhesus monkeys, anandamide does not substitute for Δ^9-THC (39). In addition, contradictory results in rats have been reported (8,42). Indeed, although our initial tests showed that anandamide substituted in Δ^9-THC- and CP 55,940-trained rats, these results were not replicated in a follow-up study in which anandamide was tested twice under conditions identical to those of our first study in a different group of Δ^9-THC–trained rats (42). Manipulation of the route of administration and presession injection time as part of this study did not alter the degree of anandamide substitution. Hence, anandamide substitution for Δ^9-THC is, at best, unreliable.

In an attempt to increase metabolic stability, a variety of anandamide analogs have been synthesized. These anandamide analogs have exhibited less correspondence between measures of in vitro and in vivo potency than have classical cannabinoids (1,2). Some of these analogs have been tested in drug discrimination in rats, including compounds with the following structural manipulations: saturation of the arachidonyl constituent, substitution for the ethanolamide constituent or C2′ hydroxyl, and addition of a methyl group (8,22,42). The nonmethylated compounds had little or no affinity for cannabinoid CB_1 receptors in the absence of PMSF and, as predicted, they did not substitute for Δ^9-THC. In contrast, the methylated anandamide analogs produced the greatest degree of substitution for Δ^9-THC, albeit substitution was usually accompanied by suppression of response rates in rats. In rhesus monkeys, 2-methylarachidonyl-2′-fluoroethylamide (O-875) fully substituted for Δ^9-THC in the absence of response rate effects (39). Interestingly, affinities of these methylated compounds measured with and without enzyme inhibitor PMSF added to binding medium are more similar to each other than they are for analogs with other types of manipulations (1,2,42). Unfortunately, direct measurement of metabolic stability of these analogs has not been performed; however, this step has been taken with anandamide itself. Willoughby et al. (43) have reported that some of the in vivo cannabimimetic pharmacological effects of anandamide in mice persisted even though brain levels of anandamide showed drastic decreases. One explanation is that anandamide stimulates the release of an endogenous cannabimimetic substance. Metabolic stability of anandamide or its analogs has not been evaluated within the context of a drug discrimination study nor in rats.

Although initial attempts in our lab to train rats to discriminate anandamide from vehicle were unsuccessful, Järbe and his colleagues presented a preliminary report of a study at the 1998 annual meeting of the College on Problems of Drug Dependence in Scottsdale, AZ, in which they had trained rats to discriminate methanandamide from vehicle. Differences in the patterns of substitution, cross-substitution, and antagonism between discriminations based upon Δ^9-THC and (R)-methanandamide were noted. Additional research in this area is especially needed.

SUMMARY AND CONCLUSIONS

In summary, drug discrimination with cannabinoids is pharmacologically selective: naturally occurring psychoactive cannabinoids fully substitute for Δ^9-THC and CP 55,940, whereas inactive cannabinoids and drugs from other classes do not. The results of drug discrimination studies have revealed remarkable similarities among the discriminative stimulus effects of classical and bicyclic cannabinoids and the aminoalkylindoles. In contrast, compounds with anandamide-like structures exhibit differences from classical cannabinoids with respect to their discriminative stimulus effects, in that some of these drugs bind to CB1 receptors but fail to substitute for Δ^9-THC, whereas others fully substitute only at response-rate decreasing doses. In conclusion, preliminary evidence from drug discrimination studies with more metabolically stable anandamide analogs have suggested that these differences in the discriminative stimulus effects of Δ^9-THC and anandamide-like cannabinoids are not entirely due to pharmacokinetic factors, but the exact role of "internal bliss" in cannabis intoxication and dependence is still not completely understood.

ACKNOWLEDGEMENTS

This article is a compilation of talks presented at the fifth international meeting of the Society for the Stimulus Properties of Drugs, Beerse, Belgium, and at the seventh biennial meeting of the European Behaviourial Pharmacology Society, Brno, Czech Republic. Abstracts for these presentations have been published as part of the proceedings of each meeting (31,32). I would like to thank Dr. Billy Martin for his helpful comments on an earlier draft of this article. Preparation of this review was supported by National Institute on Drug Abuse Grants DA-03672 and 09789.

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