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Cannabinoid CB_1 receptor inverse agonists and neutral antagonists: Effects on food intake, food-reinforced behavior and food aversions

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Abstract

Drugs that interfere with cannabinoid CB1 receptor transmission suppress a number of food-related behaviors, and these compounds are currently being assessed for their potential utility as appetite suppressants. In addition to rimonabant (SR141716A), several other compounds have been evaluated, including AM251 and AM1387. Biochemical studies indicate that most of the drugs assessed thus far have been CB1 inverse agonists, and these drugs all act to suppress food intake and disrupt food-reinforced behavior. Behavioral tests involving intake of different diets (i.e., high fat, high carbohydrate, laboratory chow) indicate that consumption of all three food types is disrupted by CB1 inverse agonists, and that, expressed as a percent of baseline intake, the effect is roughly comparable across different diets. Although CB1 inverse agonists do not appear to produce severe motor impairments that disrupt feeding behavior, there is evidence that they can induce nausea and malaise. Recent studies have been undertaken to characterize the behavioral effects of CB1 receptor neutral antagonists such as AM4113 to determine if these drugs can reduce feeding and food-reinforced behaviors. Across a variety of different tests, AM4113 produces effects on food-motivated behavior that are very similar to those produced by CB1 inverse agonists. Moreover, this drug did not induce conditioned gaping in rats or vomiting in ferrets. These results suggest that CB1 receptor neutral antagonists may decrease appetite by blocking endogenous cannabinoid tone, and that these drugs may be less associated with nausea than is the case for CB1 inverse agonists.

Keywords: Appetite; Motivation; Operant; Feeding; THC; Rimonabant

1. Introduction

Cannabinoid CB1 receptor agonists, including delta-9-tetrahydrocannabinol (THC), have a wide variety of behavioral effects, including actions on motor control [1–3], pain [1,3], and cognitive function [4–7]. These drugs also have been reported to exert effects upon processes related to food intake. Early reports suggested that consumption of marijuana could be accompanied by feelings of increased hunger and decreased satiety, as well as increases in food intake [8]. Initial laboratory experiments showed that CB1 agonists could increase eating [9,10] and enhance body weight gain [11]. Furthermore, CB1 agonists have been investigated for their potential as treatments for anorexia and wasting syndrome associated with chemotherapy and AIDS [12]. In animals, the effects of cannabinoid CB1 agonists on food intake depend greatly upon the dose [13]. Although some papers have reported that CB1 agonist administration decreases feeding, these studies have generally used higher doses that also produced catalepsy and suppressed locomotion (e.g., [14]). Several papers that employed moderate-to-low doses have shown that CB1 agonists can increase food intake [13,15–19].

Consistent with these observations that moderate doses of CB1 agonists could enhance food intake, it was suggested that CB1 antagonists such as SR 141716A (rimonabant; [20]) should have suppressive effects on food intake. Arnone et al. [21] observed that rimonabant decreased intake of high-sucrose food pellets.

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Rimonabant also was shown to decrease food intake, but not water intake, over the first few days of repeated administration in rats that had ad libitum access to lab chow and water [22]. Tolerance developed rapidly to the appetite suppression effect, although body weight was significantly decreased during the entire injection series, even at the lowest dose (2.5 mg/kg). In addition to these studies with food intake, food-reinforced operant responding also was demonstrated to be sensitive to rimonabant; this drug suppressed fixed ratio 15 responding in a dose-related manner, an effect that was partially reversed by coadministration of the CB1 agonist WIN55,212-2 [23]. These initial studies instigated a period of rapid development in this area, with a wide variety of methods being used for assessment of a growing number of compounds that interfered with cannabinoid CB1 transmission [18,22,24–28,55]. The present review is intended to provide a brief overview of some of the recent studies that have focused upon newly developed compounds, including AM251, AM1387, and AM4113 [29–33].

2. Effects of AM251 and AM1387 on food intake and food-reinforced behavior

Like rimonabant, AM251 and AM1387 can bind with relatively high affinity to CB1 receptors, and they have a modest degree of CB1 selectivity relative to CB2 receptors. Moreover, biochemical studies indicate that rimonabant, AM251, and AM1387 all act as inverse agonists, and exert actions on signal transduction mechanisms when administered in the absence of CB1 receptor stimulation (i.e., they inhibit GTPγS binding and increase cAMP production [31,34,35]). All three drugs have been assessed under comparable conditions in a series of studies measuring food-reinforced behavior and food intake. Several experiments examined the effects of rimonabant, AM 251 and AM1387 on food-reinforced responding using fixed ratio schedules with two different ratio requirements (i.e., fixed ratio 1(FR1) and 5 (FR5)). These particular ratio values were used because previous studies have indicated that FR1 and FR5 schedules can show differential sensitivity to various neurochemical or pharmacological conditions [36–38]. In fact, all three CB1 antagonists/inverse agonists suppressed performance on both schedules of reinforcement [29,31]. These effects occurred over roughly the same dose range for each schedule employed. In addition, the suppression of FR5 lever pressing was used to assess the duration of action for each compound. Both rimonabant and AM251 had a relatively long duration of action ($t_{1/2}$: rimonabant—15.6 h; AM251—22.0 h [29]), while the half-life AM1387 was considerably shorter ($t_{1/2}$=4.87 h [31]). These studies showed that AM251 and AM1387, like rimonabant, could suppress food reinforced behavior, and also demonstrated the utility of the operant procedures for assessing features of drug effects such as duration of action.

Additional studies were conducted to characterize the effects of rimonabant, AM251 and AM1387 on intake of diets with differing macronutrient compositions. For several years, there has been intense interest in identifying the role that different types of food may play in modulating the appetite-related effects of drugs that act on CB1 receptors. In studies of cannabinoid-induced hyperphagia in humans, snacking on sweets between meals was reported to increase, but size of meals did not change [9]. In rats, stimulation of food intake with Δ9-THC was significantly greater for intake of a high-fat diet as compared to standard laboratory chow [17]. Although some researchers have reported that interference with CB1 transmission suppressed intake of sweet foods such as sucrose to a greater extent than intake of laboratory chow [21,24], other researchers have observed a substantial suppression of intake of standard diets such as laboratory chow [39,40]. For these reasons, rimonabant, AM251 and AM1387 were assessed for their effects on intake of three different foods [29,31]: a high-fat diet (HF; Diet # D12451, Research Diets, New Brunswick, New Jersey, 45% kcal from fat), a high-carbohydrate diet (HC; Diet # D12450B, Research Diets, New Brunswick, New Jersey, 67% kcal from carbohydrate) and standard laboratory chow (LC, 5P00 Prolab RMH 3000, PMI Nutrition International, St. Louis, Missouri). Food-deprived rats were trained to eat their assigned diet in test cages for three days a week, and after several weeks of training the drug treatment period began (1 drug treatment per week following two baseline days). Administration of all three drugs (rimonabant, AM251, AM1387) produced a dose-related suppression of intake of all three types of food. In the case of rimonabant and AM251, analysis of variance indicated that there was no drug treatment × diet interaction [29]. This suggests that the suppressive effects of these drugs on laboratory chow intake were not different from the suppressive effects of these drugs on intake of the other two foods. With AM1387, there was a significant interaction in terms of the raw gram quantity of food consumed [31]. Nevertheless, separate analyses indicated that all three drugs, including AM1387, significantly suppressed intake of laboratory chow, an effect similar to that reported in other studies [39,40].

One of the features of these studies was that the baseline or control level of intake differed substantially for the three different foods; intake was highest for the high carbohydrate and high fat diets, and lowest for the laboratory chow [29,31]. In order to correct for these baseline differences, data were re-analyzed with food intake being expressed as a percent of the two previous baseline days. When the data were analyzed in this way, there were significant dose-related decreases in food intake with all three drugs, but no significant interactions; in fact, the dose–response curves for consumption of each food overlapped considerably [29,30] (see Fig. 1). Taken together, these results suggest that rimonabant, AM251 and AM1387 are not selectively suppressing feeding upon diets that are high in carbohydrates or fat. Rather, it seems that apparent differences in the effects of these drugs on intake of different foods may be due to differences in baseline consumption or scaling. Provided that the testing conditions generate substantial levels of chow intake, interference with CB1 transmission appears to suppress consumption of this particular food. Nevertheless, in considering the potential use of these drugs as appetite suppressants, it is worth emphasizing that the substantial feeding suppression seen in rats consuming calorically dense foods at high baseline rates suggests that CB1 inverse agonists could substantially reduce caloric intake in patients who consume large quantities of these foods. Moreover, it is possible that