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The Novel Cannabinoid CB_1 Receptor Neutral Antagonist AM4113 Suppresses Food Intake and Food-Reinforced Behavior but Does not Induce Signs of Nausea in Rats

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Drugs that interfere with cannabinoid CB1 transmission suppress various food-motivated behaviors, and it has been suggested that such drugs could be useful as appetite suppressants. Biochemical studies indicate that most of these drugs assessed thus far have been CB1 inverse agonists, and although they have been shown to suppress food intake, they also appear to induce nausea and malaise. The present studies were undertaken to characterize the behavioral effects of AM4113, which is a CB1 neutral antagonist, and to examine whether this drug can reduce food-reinforced behaviors and feeding on diets with varying macronutrient compositions. Biochemical data demonstrated that AM4113 binds to CB1 receptors, but does not show inverse agonist properties (ie no effects on cyclic-AMP production). In tests of spontaneous locomotion and analgesia, AM4113 reversed the effects of the CB1 agonist AM411. AM4113 suppressed food-reinforced operant responding with rats responding on fixed ratio (FR) 1 and 5 schedules of reinforcement in a dose-dependent manner, and also suppressed feeding on high-fat, high-carbohydrate, and lab chow diets. However, in the same dose range that suppressed feeding, AM4113 did not induce conditioned gaping, which is a sign of nausea and food-related malaise in rats. These results suggest that AM4113 may decrease appetite by blocking endogenous cannabinoid tone, and that this drug may be less associated with nausea than CB1 inverse agonists.
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INTRODUCTION

CB1 antagonist/inverse agonists such as SR141716 have been shown repeatedly to suppress feeding and food-motivated behavior. SR141716 attenuated the hyperphagia induced by CB1 agonists (Jamshidi and Taylor, 2001; Kirkham *et al*, 2002; Williams and Kirkham, 1999), and when administered alone it reduced food intake in a number of different animal models (Arnone *et al*, 1997; Colombo *et al*, 1998; Simiand *et al*, 1998; Williams and Kirkham, 1999). Feeding suppression induced by CB1 antagonists/inverse agonists has been demonstrated in both satiated and food-deprived animals following systemic or central administration, and after either acute or chronic treatment (Chen *et al*, 2004; Colombo *et al*, 1998; Shearman *et al*, 2003; Wiley *et al*, 2005). Although it is clear that drugs that interfere with CB1 transmission can suppress food intake, the mechanisms by which they accomplish this are less well understood. Biochemical studies indicate that many of these drugs, including SR141716, AM251, and AM1387, act as inverse agonists and exert actions on signal transduction mechanisms when administered in the absence of CB1 receptor stimulation (ie they inhibit GTPγS and increase cAMP production; Landsman *et al*, 1997; Mato *et al*, 2002; McLaughlin *et al*, 2006). In one recent study, CB1-knockout and wild-type mice responded comparably on a progressive ratio schedule reinforced with corn oil, while wild-type mice treated with SR141716 decreased responding, suggesting that SR141716 may exert inverse agonist effects in addition to simply blocking CB1 receptors (Ward and Dykstra, 2005).

There is evidence to suggest that some of the feeding-related effects produced by drugs that act on CB1 receptors may be due to actions such as food avoidance, food aversion, nausea, or malaise. Several studies have shown that CB1 agonists have anti-emetic actions (Gonzalez-Rosales and Walsh, 1997; Simoneau *et al*, 2001; Darmani and Johnson, 2004). CB1 receptors are present in the brain stem dorsal vagal complex, and CB1 receptors in this area are associated with triggering emetic responses (Van Sickle *et al*, 2003). Conditioned taste avoidance can be produced

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