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Intrinsic effects of AM4113, a putative neutral CB1 receptor selective antagonist, on open-field behaviors in rats

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ABSTRACT

We examined open-field effects in rats of the cannabinoid 1 receptor (CB1R) agonist WIN55,212-2 (WIN; 3 mg/kg) and its interaction with the CB1R putative neutral antagonist AM4113 (0.3 to 3 mg/kg). Separate studies examined AM4113 alone (0.3 to 5.6 mg/kg). Unlike the CB1R antagonist rimonabant, *in vitro* (e.g., [Sink K.S., McLaughlin P.J., Wood J.A., Brown C., Fan P., Vemuri V.K., Pang Y., Olzewska T., Thakur G.A., Makriyannis A., Parker L.A., Salamone J.D. 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. Neuropsychopharmacology 2008a; 33: 946–955.; Sink K.S., Vemuri V.K., Olszewska T., Makriyannis A., Salamone J.D. Cannabinoid CB1 antagonists and dopamine antagonists produce different effects on a task involving response allocation and effort-related choice in food-seeking behavior. Psychopharmacology (Berl) 2008b; 196: 565–574.]) AM4113 produced no change in cAMP accumulation (neutral antagonism vis-a-vis inverse agonism). Recorded behaviors were: ambulation, rearing, circling, latency, scratching, grooming, defecation, urination and vocalization/squeaking. WIN reduced ambulation and rearing; AM4113 completely (ambulation) or partially (rearing) antagonized these behaviors. WIN alone resulted in circling and an increased latency to leave the start area; effects blocked by AM4113. AM4113 increased scratching and grooming, effects attenuated but not abolished by WIN. AM4113 alone tended to reduce ambulation and rearing and had no effect on latency or circling. AM4113 alone increased scratching and grooming. Effects on defecation, urination and vocalization were non-significant. The open-field effects of AM4113 are similar to those reported for rimonabant in rats. Yet, unlike the inverse agonists rimonabant and AM251, the putative neutral CB1R antagonist AM4113 did not produce signs of nausea in ferrets and rats ([Chambers A.P., Vemuri V.K., Peng Y., Wood J.T., Olszewska T., Pittman Q.J., Makriyannis A., Sharkey K.A. A neutral CB1 receptor antagonist reduces weight gain in rat. Am J Physiol Regul Integr Comp Physiol 2007; 293: R2185–2193.; Sink K.S., McLaughlin P.J., Wood J.A., Brown C., Fan P., Vemuri V.K., Pang Y., Olzewska T., Thakur G.A., Makriyannis A., Parker L.A., Salamone J.D. 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. Neuropsychopharmacology 2008a; 33: 946–955.; Sink K.S., Vemuri V.K., Olszewska T., Makriyannis A., Salamone J.D. Cannabinoid CB1 antagonists and dopamine antagonists produce different effects on a task involving response allocation and effort-related choice in food-seeking behavior. Psychopharmacology (Berl) 2008b; 196: 565–574.]).

1. Introduction

The first selective cannabinoid 1 receptor (CB1R) antagonist developed was rimonabant (SR141716A; Rinaldi-Carmona et al., 1994). This discovery was followed by the synthesis of additional CB1R selective antagonists such as LY320135, SR147778, AM251, AM281, and AM1387 (Felder et al., 1998; Rinaldi-Carmona et al., 2004; Thakur et al., 2005). *In vitro* assays showed that higher concentrations of rimonabant decreased GTPγS binding and increased cAMP production, suggesting that this ligand has inverse agonist properties as do all of the other above CB1R antagonists by such definition (Howlett et al., 2004; Pertwee, 2005). In addition to its ability to antagonize the effects of CB1R agonists both *in vitro* and *in vivo*, rimonabant produces behavioral effects of its own. For example, increased locomotion has been described in mice (Bass et al., 2002; Compton et al., 1996; see also Cosenza et al., 2000) as well as an increased incidence of scratching (Darmani and Pandya, 2000; Janoyan et al., 2002). Likewise, increased levels of scratching and grooming have been observed for rats (Järbe et al., 2002, 2006; Navarro et al., 1997; Pavón et al., 2006; Rubino et al., 1998, 2000; Tallett et al., 2007a; Vickers et al., 2003). These characteristic rimonabant-induced intrinsic effects appear centrally mediated (Rodriguez de Fonseca et al., 1998; Pavón et al., 2006), and are attenuated to varying degrees by CB1R

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