Peripheral selective CB1-antagonists as metabolic disorder therapeutics devoid of psychiatric liabilities

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Systemic cannabinoid 1 (CB1) receptor blockade produces weight loss and improves a variety of parameters associated with diabetes/metabolic disorders including triglyceride, insulin and glucose levels. Rimonabant and other CB1 inverse agonists (e.g., SLV-319) that have undergone clinical development have high brain penetrance, and their ability to cause weight loss is associated with reduced appetite due to CB1 receptor blockade in the hypothalamus. However, there appears to be little if any separation between doses that affect appetite/weight loss, and those that cause neuropsychiatric liabilities such as depression, anxiety and suicidality. Since the anti-diabetic efficacy of these globally acting CB1 antagonists may in part be mediated via direct CB1 receptor blockade in peripheral tissues including liver, muscle and fat, we have attempted to capture the beneficial activity exclusively associated with this type of action. A number of chemically distinct compounds, based on the most clinically advanced agents of this class, were synthesized with functionality to limit brain exposure. JD-5006 with high affinity (IC50 14 nM, single enantiomer) and selectivity (> 400x vs. CB2 receptor) is representative of these peripherally selective, non brain penetrating CB1 antagonists. This agent shows low brain to plasma levels after oral dosing: 3 days (3 mg/kg) to chow fed mice; 21 days (3, 10 and 30 mg/kg) to DIO mice; 7 days (30 and 100 mg/kg) to chow fed mice. Negligible brain receptor occupancy was also seen in chow fed mice dosed at 30 mg/kg (10x efficacious dose) of JD-5006 for 3 days; Rimonabant and SLV-319 showed 87% and 100% occupancy, respectively, at this dose. Glucose intolerance in mice maintained on a high fat diet for 14 weeks after an oral glucose challenge was significantly improved and insulin sensitivity was enhanced by both JD-5006 and Rimonabant. Body weights were significantly reduced from 51.3g to 41.3g by Rimonabant after 7 days of dosing (20% decrease; $p<0.001$), whereas JD-5006 produced only 5% weight loss (p = NS) with no effect on food intake. Liver mass and triglycerides were also normalized with JD-5006 to the same degree as SLV-319 at 3, 10 and 30 mg/kg doses. These results demonstrate that: 1) JD-5006 is a compound with low brain exposure compared to previously developed CB1 receptor blockers; 2) blockade of peripheral CB1 receptors is sufficient to ameliorate abnormalities in glucose metabolism, elevated triglyceride levels and increased liver weights associated with diet-induced obesity; 3) significant weight loss is not required for CB1-mediated anti-diabetic efficacy. JD-5006 may represent a safer alternative to highly brain-penetrant CB1 inverse agonists for the treatment of liver disease, diabetes and related metabolic disorders.