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**Results:** Cannabinoid 1 (CB1) receptor antagonists produce weight loss and improve associated risk factors, including diabetes. Rimonabant and other developed CB1 antagonists were primarily intended to block CB1 receptors in hypothalamus to reduce appetite and thus have been optimized for high brain penetrance. However, there is little if any separation between doses that produce weight loss and doses that produce depression, anxiety and suicidality. Evidence suggests that the anti-diabetic efficacy of these globally acting CB1 antagonists may be mediated via direct CB1 receptor blockade in peripheral tissues including liver, muscle and fat. JD-5006 is a peripherally selective, non brain penetrating CB1 antagonist with high affinity (14 nM) and selectivity (> 400x vs. CB2 receptor). The effect of JD-5006 on glucose metabolism was assessed by the glycemic and insulin responses to an oral glucose challenge (2g/kg body weight) in mice maintained on a high fat diet for 14 weeks. JD-5006 (20 mg/kg, PO) and the brain-penetrant CB1 antagonist rimonabant (20 mg/kg, PO) were dosed for 7 days. Glucose intolerance in these diet-induced obese (DIO) mice (AUCg = 44,686) was significantly improved by both JD-5006 (AUCg = 35,569; p=.006) and rimonabant (AUCg = 35,373; p=.005). Both compounds enhanced insulin sensitivity as indicated by reduced insulin levels during the oral glucose tolerance testing (p=.001). Body weights were significantly reduced from 51.3g to 41.3g by rimonabant after 7 days of dosing (20% decrease; p<.001), whereas JD-5006 produced only 5% weight loss (p = NS). These results demonstrate that blockade of peripheral CB1 receptors is sufficient to ameliorate abnormalities in glucose metabolism associated with diet-induced obesity and are consistent with a recent report that liver-specific CB1knock outs were protected from dietary fat induced glycemic dysregulation. Our results also demonstrate that significant weight loss is not required for CB1-mediated anti-diabetic efficacy. Therefore, JD-5006 may represent a safer alternative to highly brain-penetrant CB1 antagonists for the treatment of diabetes and related metabolic disorders.