**J**D**-5037, a** N**on-Brain-**P**enetrant** C**B1** R**eceptor** I**nverse Agonist** I**mproves Glycemic** C**ontrol in** M**ouse** M**odels of** I**nsulin** R**esistance**

JOSEPH TAM, RESAT CINAR, ROBERT J. CHORVAT, JOHN F. MCELROY, GEORGE KUNOS, Bethesda, MD, West Chester, PA

Overactivity of the endocannabinoid system has been associated with insulin resistance, a prominent feature of the metabolic syndrome and type-2 diabetes. Cannabinoid 1 receptor (CB1R) antagonists improve insulin sensitivity in obese humans and rodents, but their value as anti-obesity/anti-diabetic agents is limited by side effects mediated at CB1R in the CNS. CB1R are also present in peripheral tissues including liver, skeletal muscle, pancreatic beta cells and fat, where their activation contributes to obesity-related metabolic/hormonal abnormalities. Here, we describe a novel, peripherally restricted and orally bioavailable CB1R inverse agonist, JD-5037, and its effects in genetically obese (*ob/ob*) and high fat diet-induced obese (DIO) mice. JD-5037, an analog of the brain-penetrant CB1R inverse agonist SLV-319, has high CB1R affinity (Ki 0.3 nM) and 700-fold CB1/CB2 selectivity, with minimal brain penetrance as evidenced by 1) brain/plasma ratio <2% after acute or ∼7% after 28-day oral dosing at the maximally effective dose of 3 mg/kg, 2) lack of brain CB1R occupancy, verified by CB1R positron emission tomography as well as *ex vivo* ligand binding, and 3) no behavioral effects, as tested for catalepsy, ambulatory activity and anxiety. Oral JD-5037 treatment for 28 days at 3 mg/kg/day normalizes the hyperinsulinemia and hyperglycemia as well as improves glucose tolerance and insulin sensitivity in DIO mice. A shorter (7-day) treatment has similar effects in both DIO and *ob/ob* mice, even though weight and food intake are unaffected in *ob/ob* but reduced in DIO mice, indicating that the glycemic effects are weight- and food intake independent. At doses equieffective for reducing hepatic steatosis, JD-5037 causes significantly greater insulin sensitization than does the peripherally restricted CB1R neutral antagonist, AM6545, indicating the importance of CB1R inverse agonism in improving glycemic control. We conclude that peripherally restricted CB1R inverse agonists have therapeutic value in the management of obesity-related insulin resistance/type-2 diabetes.