TrePsy

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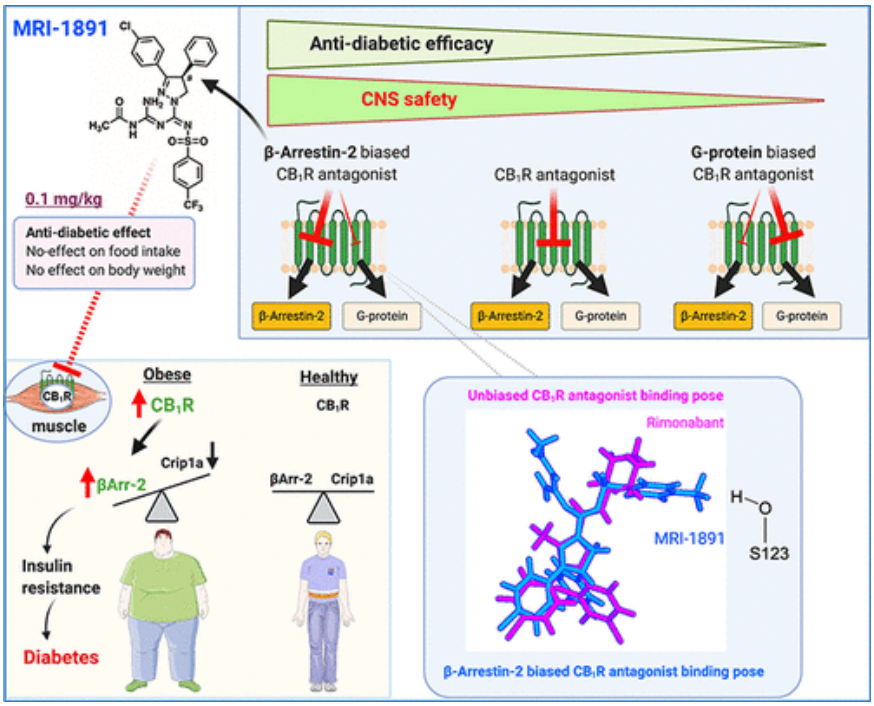
A leading global healthcare company to acquire a privately owned, clinical stage company to develop new therapies for people living with obesity, diabetes and other serious metabolic diseases

Endocannabinoids interact with G-protein-coupled receptors (GPCRs) via G-protein and β-arrestin-dependent pathways. The endocannabinoid system regulates metabolism, with CB1 receptor activation impacting energy balance and contributing to conditions like visceral obesity and metabolic syndrome (1,2). Rimonabant, the first selective CB1 receptor antagonist to be approved and used in the clinical practice, initially demonstrated highly promising in treating obesity-related issues was not approved by the FDA due to undesirable neuropsychiatric effects (3). Recently, MRI-1891, a peripheral CB1R antagonist, exhibits a strong bias towards inhibiting CB1R-triggered β-arrestin-2 (βArr2) recruitment compared to G-protein activation. Biased antagonism of CB1R signaling via βArr2 improves obesity-related insulin resistance without eliciting central nervous system-mediated adverse behavioral effects.

Liu et al. proved, that treatment with MRI-1891 leads to reduced food intake and body weight, without inducing anxiety even at high doses that partially occupy brain CB1Rs, in both obese wild-type and βArr2-knockout (KO) mice. Conversely, rimonabant elicited long-lasting hyperambulatory activity and caused strong anxiogenic responses, suggesting altered βArr2 signaling is not involved in these behavioral responses to central CB1R blockade. In high-fat-diet-induced obesity/metabolic syndrome mouse model (DIO), MRI-1891 reduced food intake, body weight and hyperleptinemia in wild type and βArr2-KO mice, however improved obesity-related hyperinsulinemia and muscle insulin resistance in wild-type, but not in βArr2-KO mice. In C2C12 myoblasts, CB1R activation reduced insulin-induced akt-2 phosphorylation, which was prevented by MRI-1891, βArr2 knockdown, or CB1R-interacting protein overexpression. MRI-1891, unlike rimonabant, interacts with specific residues, enabling βArr2 bias, showing that CB1R induces muscle insulin resistance through βArr2 signaling, effectively alleviated by a selective CB1R antagonist with lowered potential for central nervous system side effects (4).



Liu Z, Iyer MR, Godlewski G, Jourdan T, Liu J, Coffey NJ, Zawatsky CN, Puhl HL, Wess J, Meister J, Liow JS, Innis RB, Hassan SA, Lee YS, Kunos G, Cinar R. Functional Selectivity of a Biased Cannabinoid-1 Receptor (CB1R) Antagonist. ACS Pharmacol Transl Sci. 2021 Apr 8;4(3):1175-1187. doi: 10.1021/acsptsci.1c00048. PMID: 34151207; PMCID: PMC8204328.

The groundbreaking results mentioned above in using cannabinoids to treat obesity and type II diabetes have laid the foundation for its commercial implementation. Clinical trials for the drug INV-202 were initiated by a privately owned clinical-stage company, yielding promising outcomes that caught the attention of a prominent global healthcare entity. On August 10, 2023, it was announced that the leading global healthcare company, will acquire the privately owned, clinical stage company for a potential $1.075 billion, contingent upon achieving specific developmental and commercial milestones. The company specializes in CB1 receptor-based therapies targeting obesity, diabetes, and metabolic disorders, with INV-202, an oral CB1 inverse agonist, as its primary asset. INV-202 selectively inhibits the CB1 receptor in peripheral tissues crucial for metabolism and appetite control. INV-202 shows promise in reducing weight and currently undergoing a phase 2 trial for diabetic kidney disease. This collaboration is set to augment the leading global healthcare company's clinical development in obesity and related matters, unlocking CB1 blocker potential and expanding metabolic syndrome treatments.

Cannabinoid-based medications offer a promising alternative to current treatments. Since recently, the European Medicines Agency (EMA) is investigating the potential risk of suicidal thoughts and self-harm linked to glucagon-like peptide-1 receptor (GLP-1) agonist medications used for weight loss and type 2 diabetes treatment. This review, prompted by reported issues with liraglutide and semaglutide use, is studying around 150 cases. It's uncertain if these

problems directly stem from the drugs or underlying conditions. The signal procedure will conclude in November 2023, encompassing other GLP-1 receptor agonists. While not currently listed as a side effect, patients and professionals are urged to follow approved guidelines and report any side effects.

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