Our natural stress response system stimulates the release and circulation of glucocorticoids (GCs) that in the short-term act on the tissues to help mobilize fuel substrates needed to meet metabolic demands of the body. If GCs remain elevated for a chronic period of time, such as those with Cushing's syndrome, they can present major physiological consequences to the body such as increased visceral adiposity, peripheral insulin resistance, non-alcoholic fatty liver, and abnormal pancreatic islet function, all of which can increase an individual's risk for developing type 2 diabetes (T2DM). Some treatment to reduce the adverse effects of elevated GCs is the administration of a GC receptor II (GRII) antagonist to eliminate the binding of GCs, but due to their non-selective nature they bind to other receptors besides the GRII and treatment usually results in undesirable side effects (i.e. termination of pregnancy). Therefore, it is now an important issue in this area of research to study alternative agents that will reduce the devastating effects of elevated GCs without harmful side effects.

Our lab has established a rodent model that induces rapid-onset diabetes (ROD) in young rats via slow-releasing corticosterone (active GC in rodents) pellets. In this present study we used our ROD model to show that the administration of the non-selective GRII antagonist, RU486 is a very effective agent that reverses the ROD phenotype. In comparison, we also tested two other GRII antagonists (C113176 and C108297) that specifically target the GRII and showed that C108297 demonstrated little impact to reverse the pathophysiological effects of ROD. C113176 proved to be a more effective agent in the ROD model as it attenuates elevated fasting glucose, reinstates β-cell function, and improves insulin resistance.We concluded from this study that selective GRII antagonist C113176 might provide an alternative treatment to the effective but controversial non-selective GRII antagonist RU486. Therefore, this study is the first to show that the agent C113176 might be a considerable candidate for future therapeutic use towards diabetes prevention in patients with elevated GCs.

Reference: Beaudry JL, Dunford EC, Teich T, Zaharieva D, Hunt H, Belanoff JK, Riddell MC. Effects of selective and non-selective glucocorticoid receptor II antagonists on rapid-onset diabetes in young rats. PLoS One, 2014 Mar 18;9(3):e91248

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