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The appropriateness of GPR119 agonism as a treatment modality for metabolic diseases

Lauren M. Cornall
Victoria University, Australia

Abstract

Agonism of GPR119, a novel G-protein coupled receptor, is being rapidly developed as a pharmaceutical means of treating metabolic diseases. Research to-date has shown that GPR119 activation improves systemic glycaemia in rodents and in some instances exerts an anorectic effect. These findings are consistent with GPR119 activation being targeted for the treatment of type 2 diabetes mellitus (T2DM) and obesity. Interestingly, the molecular mechanisms behind the beneficial effects of GPR119 agonism remain largely unknown. Furthermore, not all studies utilizing GPR119 agonists have yielded positive metabolic effects. Further research is therefore needed if GPR119 agonists are to be developed with confidence for the treatment of metabolic diseases. Our research focuses on the effect of activating GPR119 on the molecular signaling pathways which regulate skeletal and cardiac muscle nutrient metabolism and oxidation. These muscles contribute largely to the maintenance of overall systemic metabolic health through regulation of systemic adiposity, insulin sensitivity/resistance and cardiovascular health. These processes are known to be perturbed in obesity, T2DM and cardiovascular disease which leads to an increase in associated morbidity and premature mortality. Surprisingly, our results suggest that in both skeletal and cardiac muscle cells, GPR119 activation impairs key signaling pathways which promotes metabolism of glucose and fatty acids. This implies GPR119 agonists are unlikely to have large beneficial effects at the level of the muscle and may increase risk factors for metabolic disease. Thus, we suggest that caution is currently required if GPR119 agonists are to be further developed for the treatment of metabolic disease states.

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Biography

Lauren is a scholar of the National Heart Foundation of Australia undertaking research at Victoria University. With a background in nutrition, Lauren's research investigates the role of G-protein coupled receptors in the treatment of obesity, type 2 diabetes mellitus and cardiovascular disease. Lauren has presented her research at a number of national and international conferences and has published her research in leading journals within the field.