Abstract

The introduction of glucagon-like peptide-1 (GLP-1) receptor agonists changed the treatment strategies of type 2 diabetes mellitus (T2DM) as GLP-1 receptor agonists not only provide Glycaemic Control but have additional body weight control and cardiovascular benefits. However, the use of GLP-1 based therapy can be associated with gastrointestinal side effects, including nausea and emesis, limiting the doses that can be used. The mechanisms controlling emesis and the sensation of nausea and those involved in appetite are subtly different and is less well understood. Research strategies elucidating emesis and anti-emetic drugs have focused on the brainstem vomiting centre. The potential involvement of the hypothalamus, which is integral to autonomic control, has been overlooked. This project is based on our own original findings that intracerebral paraventricular hypothalamic (iPVH) administration of exendin-4 inhibited significantly food and water intake and induced emesis in a dose-dependent manner in *Suncus murinus*. Exendin-4 appeared more potent in inducing emesis following iPVH compared to intracerebroventricular administrations. We also showed that subcutaneous administration of exendin-4 induced emesis but not the associated inhibition of feeding was antagonized by iPVH administration of the GLP-1 receptor antagonist, exendin (9-39). In addition, the emetic effect of exendin-4 was dissociated from its anorectic effect. These findings suggest that hypothalamic GLP-1 receptors may be at least partially involved in the mechanism of nausea and emesis. The parabrachial nucleus receives reciprocal inputs from the hypothalamus, amygdala and limbic system and sends projections to the nucleus tractus solitaries. We hypothesize that GLP-1 receptor activation in the PVH may modulate local release of GABA and/or glutamate and other transmitters which act as key modulators in these brain areas and are involved in mechanism of emesis control as well as nausea which is a subjective feeling involving higher brain functions.

In the present project, we aim to determine the role of the hypothalamic GLP-1 receptor system in feeding and emesis and the possible underlying mechanism of the signaling pathway. Animal experiments will be performed using standard behavioural testing and established radiotelemetric techniques to evaluate physiological changes indicative of nausea (PCIN) coupled with c-Fos immunohistochemistry analysis of brain function. Changes in brain neurotransmitters will be monitored using brain microdialysis. Our studies will uncover a novel mechanism of nausea and emesis. Data obtained from studying the emetic mechanisms of GLP-1 receptor system may not only enable a more improved management of diabetes and obesity but may also lead to the discovery of new target for anti-emetic development and improve the quality of life of cancer patients receiving chemotherapy.