UGCS/FDS11/M03/25

Title of Project:

(English) Roles of the amygdala in GLP-1 receptor agonist-induced nausea and emesis

(Chinese) 杏仁核在GLP-1受體激動劑誘導的噁心和嘔吐中的作用

Obesity and diabetes have become critical public health problems affecting 8 – 10% population globally. Glucagon-like peptide-1 (GLP-1) receptor agonists represent a novel class of medications to treat type 2 diabetes and obesity. However, 40 – 70% patients may develop adverse gastrointestinal side effects, including nausea and emesis, limiting the dose that can be used. Understanding the mechanism of the side effects associated with GLP-1 receptor agonists is important for developing new treatments with improved tolerability. However, most studies have focused on the brainstem, and this limits our understanding of mechanisms involved in nausea.

There is evidence that nausea and emesis induced by GLP-1 receptor agonists involves an activation of emesis pathways in the brain. We previously found that GLP-1 receptors in the brainstem and hypothalamus may be involved in exendin-4- and GLP-1 (7-36) amide-induced emesis in *Suncus murinus*. Central administration of these drugs also increases c-Fos expression in the central nucleus of the amygdala (CeA) where GLP-1 receptors are located. By using radiotelemetry techniques, we found that exendin-4 induces behaviour indicative of nausea. Recently, we showed that peripherally administered exendin-4 induces emesis and increases c-Fos expression in the CeA, nucleus tractus solitarius, and area postrema. Intracerebral paraventricular hypothalamic (PVH) administration of baclofen antagonizes emesis induced by peripherally administered exendin-4, without modulating its actions to inhibit food intake, suggesting a role of hypothalamic γ-aminobutyric acid B ($GABA_B$) receptors in exendin-4-induced emesis. Furthermore, continuous infusion of ghrelin into the CeA antagonizes cisplatin-induced emesis while des-acyl-ghrelin enhances the cardiovascular and respiratory changes caused by cisplatin. The CeA receives projections from the parabrachial nucleus and PVH and sends descending projections to the brainstem to modulate emotions and mediate the perception of nausea. We hypothesize that the CeA may be involved in the mechanism of nausea and emesis of GLP-1 receptor agonists. Activation of the inhibitory $GABA_B$ neurons in the CeA may attenuate signal transduction pathway of GLP-1 receptors, ultimately alleviating nausea and/or emesis induced by GLP-1 receptor agonists.

In this project, animal experiments will be conducted using a combination of behavioral testing and established radiotelemetry recording techniques to assess physiological changes indicative of nausea, coupled with c-Fos immunohistochemical and western blot analysis of brain functions. Overall, these studies will provide biological and molecular insights pertaining to GLP-1 receptor agonists-induced side effects which may ultimately help guiding developing of improved anti-diabetic and anti-obesity therapies. Our new knowledge may also uncover novel mechanisms of nausea and emesis leading to advanced therapeutics for anti-emetic that would have a major public health impact.