Abstract

Cocaine- and ampheamine-regulated transcript (CART) peptides are important modulators that act in the brain and contribute to a range of physiological and behavioural processes including feeding, stress, energy expenditure and body weight control. In rodents, CART peptides and their mRNAs are found in many brain regions and in peripheral tissues that are involved in reward/ enforcement, feeding and emesis, and there is strong anatomical association between CART and various orexigenic and anorexigenic neuropeptides. Acute administration of d-amphetamine, which upregulates CART mRNA in rat striatum, is anti-emetic against apomorphine-induced emesis and motion sickness. Central administration of CART peptides in rodents inhibits food intake and induces c-Fos expression in the hypothalamic neuroendocrine neurons, nucleus of the solitary tract (NTS) and area postrema (AP). Recent evidence indicates that alternations in *CART* have been associated with reduced metabolic rate, obesity and increased risk of type 2 diabetes, making it a potential target for anti-obesity drug development. Nevertheless, the potential involvement of CART system in emesis control is poorly understood because common laboratory animals (e.g. rat and mouse) are incapable of emesis. In this proposal, we will use *Suncus murinus*, a species with proven translational value in anti-emetic research in our studies. Our recent data identified that the CART protein in *S. murinus* exists in the short form of 117 amino acids. In the C-terminal region of the protein, the region that shows physiological activity, there are only two amino-acid differences between human, rat, mouse and *S. murinus* form. In conscious animals, central administration of CART (55-102) produced a complete blockade of emesis in 83% and 67% animals in the first 60 and 90 min, resulting in an overall reduction in vomits by 89% and 79%, respectively. CART (55-102) also produced a complete inhibition of cyclophosphamide-induced emesis in 5 out of 6 animals tested over a 4-h observation period, without effect on food intake and spontaneous activities. In the current proposal, therefore, we will identify the anatomical distribution of CART peptide and CART mRNA in *Suncus murinus* using immunohistochemistry and in situ hybridization, respectively. We will elucidate the mechanism of action of CART system in emesis control. Experiments will be performed using standard behavioural testing and established surgical and radiotelemetric techniques to track a cluster of physiological changes indicative of nausea (PCIN). c-Fos immunohistochemistry will be performed to gain more insight into the neuro-anatomical signaling following various nauseagenic treatments. Our findings will unlock the role of CART peptides in the mechanism of emesis and also provide insight on whether targeting CART system could be a potential therapeutic strategy for anti-emetic development.