The Role of Hindbrain GABA-ergic Signaling in the Modulation of Anorexia and Malaise Induced by GLP-1R Agonists

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Introduction

Nausea and vomiting are two of the most distressing side effects in treatments for diseases such as diabetes and obesity which often leads to poor quality of life and treatment discontinuation.

Emesis and nausea are largely controlled by the central nervous system (CNS), specifically by the area postrema (AP) and the nucleus of the solitary tract (NTS), two adjacent hindbrain nuclei. Recent work from our lab has shown that glucose-dependent insulinotrophic polypeptide receptor (GIPR) agonism reduces the occurrence of nausea and emesis induced by Glucagon-like peptide 1 (GLP-1) based therapeutics.

A high percentage of the GIPR expressing neurons co-express the inhibitory neurotransmitter GABA (Gad2) in the AP/NTS, suggesting that GIPR agonism may exert its anti-emetic effects by indirectly inhibiting emetic AP/NTS neurons, through increasing local GABA release.

Methods

• Bilateral AP/NTS injections of adeno-associated viruses (AAVs) which cre-dependently encode for excitatory (Gq coupled) designer receptors exclusively activated by designer drugs (DREADDS) were performed in the Gad-cre rats.
• Fourth intracerebroventricular cannula implantation surgery was conducted on Sprague Dawley rats for central infusion of muscimol.
• Food consumption, kaolin intake, and body weight were measured in the Gad-cre rats and the Sprague Dawley rats.
• GIP-532-induced c-Fos expression on AP/NTS GABAergic neurons was analyzed through immunohistochemistry assay.

Results

Activation of AP/NTS GABA-ergic neurons enhances semaglutide-induced hypophagia while reducing malaise

Figure 1: Working model. GIPR activation may counteract GLP-1/retrograde-induced malaise via direct modulation of the AP/NTS circuitry. Given the inhibitory nature of the GIPR-expressing neurons, one can speculate the existence of a local inhibitory network within the caudal hindbrain that could be exploited via GIPR activation to reduce hindbrain GLP-1R-mediated emesis and nausea.

Systemic and Central GABA-A Receptor Agonism by Muscimol has Minor Effects on Ex4 induced Anorexia, Pica and Body Weight Loss in Rats

Figure 2: GABA-A receptor agonism by muscimol has little effects on Ex4 induced hypophagia and malaise.

(A) Compared to control rats, there is no significant change in food intake following systemic muscimol injection (1 mg/kg). Muscimol pre-treatment alleviated hypophagia induced by systemic Ex4 (10 µg/kg) in rats (n = 12 per group). (B) Ex4 significantly induced kaolin consumption but muscimol pre-treatment was ineffective in reducing pica behavior. (C) No significant changes in body weights have been observed 24h post injection across all conditions. (D) Muscimol iv pre- treatment (0.05 µg/kg) infused into the 4° ventricle failed to prevent Ex4 induced anorexia (D), pica (E), and body weight loss (F) (n = 12 per group). Data in (A,B,D,E) analyzed with RM 2-Way ANOVA followed by Tukey post hoc test. Data in (C,F) analyzed with One-Way ANOVA followed by Tukey post hoc test. All data expressed as mean ± SEM. Means with different letters are significantly different from each other (P < 0.05). Scale bar, 100 µm.

Conclusions and Future Directions

Our results point to a key role of GABA-ergic neurons as understudied modulators of feeding and illness-like behaviors and provide a neuroanatomical and mechanistic explanation for the anti-emetic effects of GIPR agonists.

• Chemogentic activation of AP/NTS GABA-ergic neurons attenuated semaglutide-induced malaise and enhanced the hypogaphic effects.
• The potent and selective GIP analogs GIP-532 induced neuronal activation across the whole AP/NTS. Importantly, 25% of the activated neurons are GABA-ergic neurons.
• The selected doses of muscimol were largely ineffective in counteracting Ex4-induced effects. On going studies aim at adjusting the dosage of muscimol and evaluate the effects of other types of GABA-R analogs on GLP-1-based therapeutics side effects.

Acknowledgement

This work was supported by the Ernest M. Brown, Jr. College Alumni Society Undergraduate Research Grant.