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GDF15-INDUCED ANOREXIA IN RATS AND SHREWS IS DRIVEN BY MALAISE

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Poster

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Background

Growth differentiation factor-15 (GDF15) is an inflammatory cytokine implicated in a variety of biological processes. The potential use of GDF15-based approaches for the treatments of energy-balance disorders, including obesity and anorexia, is an area of intense investigation. In 2017 its receptor, GFRAL, exclusively localized in the dorsal medulla, was discovered. While GDF15-induced weight loss is driven by reduced food intake, there is limited understanding of the underlying neuronal mechanisms.

Methods

Given its association with cancer, chemotherapy, and morning sickness we asked whether GDF15-induced anorexia/weight loss is malaise-associated (i.e., stimulates kaolin intake, or pica), and if GDF15 effects on feeding behavior require central glucagon-like peptide-1 (GLP-1) or/and serotonin signaling in rats.In addition, we tested the emetogenic and anorectic properties of GDF15 in the musk shrew (Suncus murinus), a mammalian model capable of emesis.

Results

GDF15 delivered centrally into the 4th ventricle (4th ICV, 30pmol) induced acute pica and anorexia in rats. Interestingly, GDF15-induced pica preceded the onset of anorexia. The observed malaise responses seem to be independent of central serotonin and hindbrain GLP-1 signaling as GDF15 effects were not prevented by either Ondansetron (1mg/kg IP and 25ug 4th ICV; respectively) or Exendin-9 (10ug 4th ICV) pre-treatment. Furthermore, the highest dose of GDF15 tested (1mg/kg, IP) in shrews induced a strong emetic response within our observed 2 hr time window post-injection, while food intake and body weight reductions were only evident after 48 hr.

Conclusions

Our results suggest that GDF15 causes anorexia and body weight loss by inducing nausea and/or emesis in our model animals of malaise. Further study is required to decipher the neuronal mechanisms engaged by GDF15 to cause animal distress in light of the field’s focus on GDF15 as a target for obesity treatment.Support: DK112812, DK097675, DK115762, DK097675 and SNF P2ZHP3_178114