Modulation of neuropeptide W on gastric vagal afferents

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ABSTRACT

Background: Gastric vagal afferents play an important role in the regulation of food intake in response to mechanical stimuli. In the stomach neuropeptide W (NPW) is secreted from G-cells. It is known that NPW is involved in central regulation of food intake and energy homeostasis, however, whether NPW can modulate gastric vagal afferents mechanosensitivity and how this role changes in different nutritional states, such as obesity, is not known. Furthermore, the role of different macronutrients in NPW expression and secretion in the stomach is not clear.

Aims: This thesis aims to determine:

1) The modulatory effect of NPW on gastric vagal afferent mechanosensitivity under different states of nutrition including food restriction and high-fat diet-induced obese mice.
2) The modulatory effect of NPW on gastric vagal afferent mechanosensitivity in mice of different age and gender.
3) The macronutrients responsible for regulation of gastric NPW.

Methods: An *in vitro* electrophysiology preparation was used to determine the effect of NPW on the mechanosensitivity of gastric mucosal and tension receptors in C57BL/6 mice fed *ad libitum*, fasted overnight, or fed with a high-fat diet. Expression of NPW in the gastric mucosa and GPR7 in the whole nodose ganglia was determined by quantitative RT-PCR (QRT-PCR). Expression of GPR7 in gastric vagal afferent neurons was determined by retrograde tracing and QRT-PCR. Plasma NPW levels were determined in healthy lean subjects after nutrient intake. Plasma and gastric NPW levels were determined in mice after feeding with different nutrients. Primary cell cultures of

mouse gastric antral mucosal cells were used to investigate the signalling pathway of NPW expression.

Results: In 20-week-old adult mice NPW selectively inhibited the responses of gastric vagal tension receptors to stretch. The inhibitory effect of NPW on gastric vagal tension receptors was gender consistent, but not observed in younger mice, high-fat diet-fed mice or food restricted mice. Protein and glucose intake increased gastric NPW transcript and protein levels in mice but had no effect on plasma NPW levels in human and mice. Protein and glucose are stimulants of gastric NPW expression, via distinct mechanisms.

Conclusion: NPW modulates mechanosensitivity of gastric vagal afferents; an effect related to feeding status, age and gender. Gastric NPW is regulated by specific nutrients.

STATEMENT

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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CONFERENCE PROCEEDINGS

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AgRP	agouti-related peptide
α-MSH	α-melanocyte stimulating hormone
ARC	arcuate nucleus
BMI	body mass index
CART	cocaine and amphetamine regulated transcript
CaSR	calcium sensing receptor
CB1 receptor	cannabinoid receptor type 1
CCK	cholecystokinin
CNS	central nervous system
CRH	corticotropin-releasing hormone
DH	dorsal hypothalamus
DMN	dorsomedial nucleus
DMV	dorsal motor nucleus of vagus
DRN	dorsal raphe nucleus
EW	Edinger-Westphal nucleus
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GPCRs	G-protein-coupled receptors
GPR7	G-protein-coupled receptor 7
GPR8	G-protein-coupled receptor 8
GHRH	growth-hormone-releasing hormone
GHSR	growth hormone secretagogue receptor
HFD	high-fat diet
HPA axis	hypothalamus-pituitary-adrenal axis

HPT axis	hypothalamus-pituitary-thyroid axis
I.c.v.	intracerebroventricular
I.p.	intraperitoneal
IGLEs	intraganglionic laminar endings
IMAs	intramuscular arrays
LHA	lateral hypothalamic area
MCH	melanin-concentrating hormone
MCH1R	melanin-concentrating hormone-1 receptor
NPB	neuropeptide B
NPW	neuropeptide W
NPY	neuropeptide Y
NTS	nucleus tractus solitaries
PAG	periaqueductal gray
POMC	pro-opiomelanocortin
PVN	paraventricular nucleus
PYY	peptide YY
SON	supraoptic nucleus
SCN	suprachiasmatic nucleus
TRH	thyrotropin-releasing hormone
VMN	ventral medial nucleus
VTA	ventral tegmental area