NeuroImage 144 (2017) 101–112

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Differential brain responses to gradual intragastric nutrient infusion and gastric balloon distension: A role for gut peptides?

Huynh Giao Ly [a,*], Patrick Dupont [b], Koen Van Laere [c], Inge Depoortere [a], Jan Tack [a], Lukas Van Oudenhove [a,d]

[a] Laboratory for Brain-Gut Axis Studies (LABGAS), Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine, University of Leuven, Leuven, Belgium
[b] Laboratory for Cognitive Neurology, Division of Experimental Neurology, Department of Neurosciences, University of Leuven, Leuven, Belgium
[c] Division of Nuclear Medicine and Molecular Imaging, University Hospitals Leuven, Leuven, Belgium
[d] Consultation-Liaison Psychiatry, University Psychiatric Centre KU Leuven, Campus Gasthuisberg, University of Leuven, Leuven, Belgium

ARTICLE INFO

Article history:
Received 8 February 2016
Accepted 13 September 2016
Available online 14 September 2016

Keywords:
Gut-brain axis
Ghrelin
Midbrain
Nutrient tolerance
Pain neuromatrix

ABSTRACT

Background: Rapid gastric balloon distension to discomfort threshold activates the "pain neuromatrix" and deactivates exteroceptive sensory and "default mode network" regions. However, little is known about brain mechanisms underlying tolerance of meal-induced gastric distension. We aimed to directly compare brain responses to gradual balloon distension and intragastric nutrient infusion and to explore the role of differential gut peptide release in these responses.

Materials and methods: Brain responses to balloon- and nutrient-induced distension (to individually titrated pain or maximal satiation threshold) were measured in 15 healthy volunteers using $H_2{}^{15}O$-PET on 2 separate days in counterbalanced order. The effects of increasing gastric distension and plasma levels of ghrelin and peptide $YY_{3\text{-}36}$ ($PYY_{3\text{-}36}$) on neural activity were assessed.

Results: Balloon distension progressively activated pain-responsive regions and deactivated exteroceptive sensory and "default mode network" areas. During nutrient infusion, "pain neuromatrix" regions and the orbitofrontal cortex were progressively deactivated, while the midbrain was activated. Plasma levels of $PYY_{3\text{-}36}$ and ghrelin increased and decreased, respectively, during nutrient infusion only; decreasing ghrelin levels correlated with increasing midbrain activity.

Conclusion: Different brain responses to gastric balloon distension and intragastric nutrient infusion are associated with nutrient-induced gut-brain signals, particularly to the midbrain, where these signals may interfere with both descending pain modulatory and mesolimbic reward processes. Deactivation of the "pain neuromatrix" during nutrient infusion may constitute the neurophysiological mechanism underlying the tolerance of normal meal volumes in health without induction of (painful) symptoms. Nutrient-induced deactivation of the orbitofrontal cortex may represent a key interoceptive meal termination signal.

1. Introduction

The gastrointestinal tract and the brain communicate in a bidirectional fashion through a neuro-humoral signalling system. This system, which is generally referred to as the "gut-brain axis", constitutes a core part of the integrated interoceptive system through which homeostatic information about the body's physiological condition is continuously transmitted to the brain by means of immune mediators, endocrine signals (including gut hormones), and vagal and spinal afferents. These interoceptive signals are integrated with and modulated by exteroceptive sensory input as well as affective and cognitive processes in the brain. The gut-brain axis plays a key role in the regulation of appetite and food intake, as well as in perception of (painful) visceral stimuli (Mayer, 2011).

Abbreviations: 3D-MPRAGE, 3-dimensional T_1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo; aMCC, anterior midcingulate cortex; CCK, cholecystokinin; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; FD, Functional Dyspepsia; FWE, family-wise error; FWHM, Full Width at Half Maximum; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; IPL, inferior parietal lobule; k_E, cluster size extent; MBq, megabecquerel; MCC, midcingulate cortex; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; OP, rolandic operculum; pACC, perigenual anterior cingulate cortex; PAG, periaqueductal gray; PET, positron emission tomography; PYY, peptide tyrosine tyrosine; RIA, radioimmunoassay; SII, secondary somatosensory cortex; SPM, Statistical Parametric Mapping; VAS, visual analogue scale; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

* Correspondence to: Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Herestraat 49 bus 701, B-3000 Leuven, Belgium.
E-mail address: huynhgiao.ly@med.kuleuven.be (H.G. Ly).

http://dx.doi.org/10.1016/j.neuroimage.2016.09.032
1053-8119/

Nutrients in the GI tract trigger changes in the secretion of peptide hormones by entero-endocrine cells (Field et al., 2010). The main anorexigenic "gut peptides", secreted in response to the presence of nutrients to trigger satiety, are peptide tyrosine tyrosine (PYY), glucagon-like peptide 1 (GLP-1) and cholecystokinin (CCK). Ghrelin, the secretion of which peaks before meals to induce hunger, is the main orexigenic gut peptide. Together with neural signals reflecting the gastric distension level, these hormones act as gut-brain signals to regulate initiation and termination of food intake by signalling to homeostatic, but also hedonic (reward-related) brain circuits (Berthoud, 2011).

Healthy subjects can ingest normal-sized meals without experiencing bothersome/painful symptoms. However, the gut-brain signalling mechanisms underlying normal meal volume tolerance in health are poorly understood. Functional Dyspepsia (FD), defined by epigastric pain or burning, postprandial fullness and/or early satiation in the absence of organic disease, is a prevalent condition (5–15% of the general population) with major health economic impact (Tack et al., 2013). In FD, normal-sized meals often induce epigastric symptoms (Vanheel et al., 2013). This impaired meal volume tolerance constitutes a hallmark of the disorder (Mimidis, 2007) and may lead to unexplained weight loss, another common feature of FD (Tack et al., 2010). Obese subjects, on the contrary, are characterized by increased meal volume tolerance (Delgado-Aros et al., 2004). Therefore, understanding the gut-brain signalling mechanisms underlying normal meal volume tolerance is a crucial step towards unravelling the pathophysiology of these difficult-to-treat disorders of meal volume tolerance.

The subjective experience of epigastric pain results from conscious perception of noxious gut-brain signals which are processed in a "homeostatic-afferent" brain network and subsequently integrated with and modulated by exteroceptive sensory input as well as affective and cognitive processes (Mayer, 2011). This set of networks and its connections involved in (visceral) pain processing is often collectively and descriptively referred to as "the pain neuromatrix", although it is important to note that none of these abovementioned networks is pain-specific (Hayes et al., 2012; Iannetti et al., 2010). "Top-down" projections from cognitive and affective circuits to the midbrain periaqueductal gray (PAG), which in turn sends efferent projections to the dorsal horn of the spinal cord, constitute the core mechanisms underlying *endogenous pain modulation*. Dysfunctional responses of this endogenous pain modulation system to painful GI balloon distensions have been demonstrated in FD and contribute to visceral hypersensitivity, a hallmark of the disorder (Wilder-Smith, 2011). However, these studies have used rapid gastric balloon distension to induce epigastric pain (Van Oudenhove et al., 2010). This stimulus is not representative of normal meal ingestion, in terms of timing (rapid versus gradual) nor modality of gastric distension (inert balloon versus nutrients).

Using $H_2{}^{15}O$-positron emission tomography (PET) in healthy volunteers, we previously demonstrated that rapid gastric balloon distension activated key regions of the "pain neuromatrix" (Vandenberghe et al., 2005) and deactivated exteroceptive sensory brain areas as well as regions of the 'default mode' network, the neural substrate of a coherent set of brain processes that are active during rest, when attention is not directed to a particular stimulus (Van Oudenhove et al., 2009). In contrast, slow gradual intragastric liquid meal infusion to individual maximal satiation threshold induced progressive deactivation of homeostatic-afferent pain-processing regions (Geeraerts et al., 2011). However, the different timing of gastric distension (rapid balloon distension versus gradual nutrient-driven volume increase), between-subject design and post-hoc comparison hampered interpretation of these results.

The present study aimed to unravel the neurophysiological mechanisms underlying meal volume tolerance in healthy subjects by comparing brain responses to similarly timed (i.e. gradual) balloon distension and intragastric nutrient infusion. We hypothesized that nutrient-driven distension would be associated with lower perceptual responses paralleled by deactivation of pain-responsive brain regions. Further, we hypothesized that differential gut peptide release (decrease in orexigenic and increase in anorexigenic hormones during nutrient infusion, no changes during balloon distension) would account for the differences in brain responses between both conditions.

2. Materials and methods

2.1. Subjects

Eighteen healthy volunteers, free of psychiatric or gastrointestinal disorders, substance abuse and medication use, were included. This study was approved by the medical ethics committee of the University Hospitals Leuven and was performed according to the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all subjects prior to inclusion.

2.2. 'Offline' threshold determination

Prior to scanning, the individual threshold for pain or maximal satiation in the 2 gastric distension conditions – gradual balloon distension (BALLOON) and gradual nutrient infusion (NUTRIENT) – was determined on 2 separate days in counterbalanced order. The nutrient drink (Nutridrink™) and the gradual nature of the nutrient infusion condition were adapted from the slow caloric drinking test, previously validated as a non-invasive method to assess meal volume tolerance (Tack et al., 2003). A constant inflation/infusion rate of 20 ml min^{-1} was used (see below), based on a pilot study showing that with this rate, which was well tolerated, maximal satiation could be reached within the time frame of the PET scanning sessions.

2.2.1. Gradual balloon distension procedure

After an overnight fast of at least 12 h, a double-lumen polyvinyl tube (Salem sump tube 14 Ch; Sherwood Medical, Petit Rechain, Belgium) with a finely folded adherent polyethylene bag (maximal volume 1200 ml) was intubated through the mouth. The tube was then secured to the subject's chin with adhesive tape and connected to a barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). The subject was then positioned in the same position as later in the PET scanner, i.e. lying down in supine position. In order to unfold the bag, it was inflated with a fixed volume of 300 mL of air for 5 min and then deflated completely. Gastric sensitivity to gradual balloon distension was then assessed by distending the balloon at a constant rate of 20 ml min^{-1}, while recording the intra-gastric pressure. Each six minutes, subjects were instructed to rate their perception of gastric sensation ("how much sensation in the upper abdomen due to gastric distension do you feel right now?") and satiation ("how satiated are you right now?") using Likert scales combining verbal descriptors on a graded scale [range: 0–6 for gastric sensation (0=no sensation, 5=discomfort, 6=pain) and 0–5 for satiation (0=no satiation, 5=maximal satiation)] (Notivol et al., 1995). Balloon distension stopped as soon as the subjects scored maximally on either of both scales (6 for gastric sensation, corresponds to pain; or 5 for satiation, corresponds to maximal satiation).

2.2.2. Gradual nutrient infusion procedure

For intragastric nutrient drink infusion, a feeding catheter (Flowcare, Nutricia, Bornem, Belgium) was positioned in the