Physiology & Behavior 104 (2011) 613–620

Contents lists available at ScienceDirect

Physiology & Behavior

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

Effects of dietary fat on appetite and energy intake in health and obesity — Oral and gastrointestinal sensory contributions

Tanya J. Little *, Christine Feinle-Bisset

University of Adelaide Discipline of Medicine, Royal Adelaide Hospital, Australia
NHMRC Centre of Clinical Research Excellence in Nutritional Physiology, Interactions and Outcomes, University of Adelaide, Adelaide, Australia

ARTICLE INFO

Article history:
Received 17 January 2011
Received in revised form 15 April 2011
Accepted 26 April 2011

Keywords:
Fatty acids
Gastrointestinal function
Taste
Fat sensing

ABSTRACT

While epidemiological studies have revealed a strong positive relationship between the intake of dietary fat with total energy intake and body weight, laboratory-based studies investigating physiological effects of fat have demonstrated that the direct exposure of receptors in the oral cavity and small intestine to fat, specifically fatty acids (FAs), induces potent effects on gastrointestinal (GI) motility and gut peptide secretion that favor the suppression of appetite and energy intake. Recent studies in humans have demonstrated an association between a decreased ability to detect the presence of FAs in the oral cavity with increased energy intake and body mass index suggesting that impairment of oral fat sensing mechanisms may contribute to overeating and obesity. Furthermore, while sensing of the presence of FAs in the small intestine results in the modulation of GI motility, stimulation of GI hormone release, including cholecystokinin (CCK) and peptide YY (PYY), and suppression of subsequent energy intake, recent data indicate that these effects of fat are attenuated in individuals with reduced oral sensitivity to fat, and following consumption of a high-fat diet. This review will focus on emerging knowledge about the physiological mechanisms that sense the presence of fat in both the oral cavity and the small intestine, and environmental factors, such as high-fat diet exposure and energy restriction, that may modulate sensitivity to nutrients, and thereby contribute to the regulation of appetite and body weight.

1. Introduction

The presence of fat (triacylglyceride (TAG)), and specifically the digestion products, free fatty acids (FAs), in the small intestine potently suppresses appetite and energy intake, effects that are mediated, at least in part, by changes in gastrointestinal (GI) function [1–5]. Recently, evidence has also emerged for a sensory ("taste") system that detects the presence of FAs in the oral cavity [6–8], and may contribute to the regulation of GI function [8–10], fat preference [11], and fat and energy intake [12]. This review will discuss current knowledge regarding the mechanisms underlying both oral and GI fat sensing, and emerging evidence that reduced oral and small intestinal sensitivity to fat following acute consumption of a high-fat diet, or in obesity, may contribute to overeating and, ultimately, weight gain.

2. Oral fatty acid sensing

While it is well established that the gustatory system can detect the taste qualities of sweet, sour, bitter, salty and umami, more recently it has become apparent that both rodents and humans can detect (or "taste") the presence of FAs in the oral cavity [13–17]. In contrast, oral exposure to undigested TAG does not appear to be an effective stimulus [14]. Humans are able to detect a range of FAs, including polyunsaturated (linoleic acid (C18:2)), monounsaturated (oleic acid (C18:1)), and saturated (stearic (C18:0), lauric (C12:0), and caproic (C6:0)), even when olfaction is blocked using nose clips, and texture is masked using gum acacia and mineral oil [16–18], suggesting a true "taste" component to FA detection. FAs are detected in the millimolar range (0.02–6.4 mM) of concentration [12]. While the presence of lingual lipase in humans has been debated, recent evidence indicates that lipolytic activity in saliva is sufficient to elicit amounts of fatty acids within this range [12]. Furthermore, the thresholds reported for FA detection in humans are consistent with the concentrations of FAs naturally present in foods (~0.5% FA) [19].

2.1. Physiological effects of oral fat exposure

Oral stimulation with fat(triacylglyceride)-containing meals, using modified sham-feeding techniques, has been reported in humans to induce a number of physiological cephalic-phase responses, including the stimulation of gastric lipase [20] and insulin [10] secretion, elevation of serum triglycerides [21,22], the stimulation of pancreatic polypeptide (indicating vagal efferent activity) [23], and the suppression of ghrelin [9]. Modified sham-feeding with a high-fat food for 1 h before ingestion of a 50 g fat test meal has been reported to accelerate

* Corresponding author at: University of Adelaide Discipline of Medicine, Level 6, Eleanor Harrald Building, Royal Adelaide Hospital, North Terrace, Adelaide, SA, Australia, 5000. Tel.: +61 8 8222 0724; fax: +61 8 8223 3870.
E-mail address: tanya.little@adelaide.edu.au (T.J. Little).

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doi:10.1016/j.physbeh.2011.04.038

gastric emptying (as assessed using a breath test) [9]. In contrast, gastric emptying (assessed using the gold standard method of scintigraphy) of a high-fat meal was shown to be much slower when the meal was ingested orally compared with direct intragastric infusion [24], suggesting that orosensory stimulation by fat plays an important role in the regulation of gastrointestinal motor function. Modified sham-feeding with high-fat meals also appears to reduce appetite (i.e. enhances satiety) [9,10,25]. As all of these studies evaluated the effects of meals containing TAGs (e.g. high-fat cream cheese or cake vs. low-fat versions), rather than FAs, it is currently not possible to discriminate FA responses from those that may be elicited by other sensory factors, such as texture, or viscosity. It will, therefore, be important to perform detailed evaluations of the effects of oral FA exposure on GI function, appetite and energy intake.

2.2. Role of oral fatty acid sensitivity in determining fat preference and intake

There is evidence that oral FA exposure may play an important role in mediating dietary fat preference and intake. In both animal and human studies, substantial inter-individual differences in the ability to detect FAs in the oral cavity have been reported and associated with marked differences in fat preference and intake. For example, in rodents, FA sensitivity varies significantly between diet-induced obesity-prone (DIO-P) (Osborne–Mendel) and diet-induced obesity-resistant (DIO-R) (S5B/PL) rats, such that DIO-P rats, when maintained on normal rat chow, have lower oral FA acid sensitivity, as determined by a lower responsiveness of delayed rectifying potassium channels (DRK) to polyunsaturated FA (i.e. activation of taste receptor cells (TRCs)), than DIO-R rats [26]. DIO-P rats also have a significantly higher fat intake and an increased preference for fat when exposed to a high-fat diet, associated with greater predisposition for obesity when compared with DIO-R rats [6]. More recently, studies in humans have also identified large inter-individual differences in the ability to detect oral FAs, with detection thresholds ranging from 0.02 to 12 mM, although all participants were able to detect FAs within this range [12,27]. Moreover, positive relationships were observed between the ability to detect oral FAs with habitual dietary intakes and body mass index (BMI) [12], such that individuals who reported higher habitual dietary energy and fat intakes (as assessed by a 2-day diet diary) and with a higher BMI were unable to detect C18:1 at a concentration of 1.4 mM [12]. Taken together, these studies provide persuasive evidence that differences in oral FA sensitivity may play an important role in determining dietary fat preference and intake, and consequently, this may have implications for body weight regulation and obesity. However, it remains to be determined whether individuals are predisposed to obesity on the basis of being relatively insensitive to oral FAs, or whether oral FA sensitivity is influenced by environmental, or behavioral factors, such as previous patterns of nutrient exposure, or preference for high-fat foods.

2.3. Mechanisms underlying oral fatty acid detection

It is well established that oral detection of sweet, bitter and umami tastants occurs as a result of the interaction of nutrients with specific receptors/molecules on the apical surface of TRCs. Understanding of the mechanisms underlying oral FA detection is more limited, however, recently a number of receptors/molecules that interact with FAs across a range of chain lengths and saturations, including CD36, DRKs and a series of G-protein coupled receptors (GPRs), including GPR40, GPR 41, GPR43 and GPR120, have been reported to be expressed on TRCs [14], and have, therefore, been implicated in mediating the gustatory response to FAs. The detection of FAs by these molecules induces a signaling cascade activating gustatory nerves (chorda tympani, glossopharyngeal) that transmit sensory information to the nucleus tractus solitarius (NTS) of the brainstem [15], and from there to higher brain centers, such as the lateral hypothalamus and the nucleus accumbens, which play an important role in the regulation of food intake and reward [28].

The receptor-like glycoprotein, CD36, appears to play a key role in oral fat detection. CD36 has been reported to be expressed on the apical surface of human and porcine TRCs from the circumvallate and foliate papillae [29,30], and in TRCs of the circumvallate papillae in rats [31]. Linoleic acid has been shown to bind to mouse gustatory cells expressing CD36, triggering calcium signaling, and the release of neurotransmitters, including 5-hydroxytryptamine and noradrenaline [32], which may mediate the transmission of the FA signal from the oral cavity to the CNS. In vivo, in wild type mice oral exposure to long-chain FAs increases c-fos expression in the NTS, an effect that is not apparent in $CD36^{-/-}$ knockout mice [15]. $CD36^{-/-}$ mice also display a reduced preference for linoleic acid and soybean oil [11,33], supporting an important role for CD36 in mediating fat taste and preference.

GPR120 and GPR40 are also expressed in TRCs [34,35]. Furthermore, GPR120 has been reported to be co-localized with molecules known to be involved in mediating the transduction of other taste modalities, such as sweet and bitter, including phospholipase Cβ2 and α-gustducin. GPR120 and GPR40 knockout mice have attenuated glossopharyngeal and chorda tympani nerve responses to FAs, and a reduced preference for oleic and linoleic acid [35], demonstrating that GPR120 and GPR40 also play an important role in mediating the gustatory response to FAs.

Much further work is required to determine the mechanisms underlying oral responsiveness to different FAs, to explain the large inter-individual differences in oral FA sensitivity, and to define the mechanisms by which oral FA detection modulate appetite, energy intake and the preference for dietary fat. It may then be possible to specifically target oral fat sensing mechanisms, by diet or pharmacological agents, to modulate fat preference and energy intake, and thereby, body weight.

3. Intestinal fat sensing: effects on upper GI function, appetite and energy intake

In humans it is currently not possible to directly assess GI fat sensing, however, by determining changes in physiological parameters, such as GI motility and gut peptide secretion, the downstream effects of GI fat sensing have been characterized. It is now well established that the presence of fat in the small intestinal lumen induces a number of changes in GI function, including stimulation of GI hormones, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), as well as the suppression of ghrelin [4,36], and feedback inhibition of gastric emptying [37,38]. The slowing of gastric emptying by fat occurs as a result of the relaxation of the proximal stomach [39,40], suppression of antral and duodenal pressures [1] and stimulation of tonic and phasic pyloric pressures [41], as well as the action of GI hormones [42–44]. These effects of fat on gastric emptying and GI hormone release mediate, at least in part, the inhibitory effects of fat on appetite and energy intake [45–47]. For example, in a recent pooled analysis of data from all the published studies in our laboratory, in which antropyloroduodenal pressures, GI hormones and appetite perceptions were measured during intraduodenal nutrient, or intravenous hormone, infusions, we identified that the magnitude of the stimulation of pyloric pressures and CCK are independent predictors of subsequent energy intake [5].

Furthermore, it is now well established that, similar to oral sensing, it is the digestive products of fat, FAs, rather than intact TAGs, that are sensed in the small intestine and are responsible for generating the GI, and appetite-suppressant, responses outlined above [4,48,49]. For example, administration of the lipase inhibitor, tetrahydrolipstatin (THL), which prevents the digestion of TAG, and thus the liberation of FAs, accelerates gastric emptying of a mixed nutrient meal [50], and attenuates the effects of intraduodenal fat on