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NUTRIENT CONTROL OF HUNGER BY EXTRINSIC GASTROINTESTINAL NEURONS

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ABSTRACT

The neural sensing of nutrients during food digestion plays a key role in the regulation of hunger. Recent data have emphasized that the extrinsic gastrointestinal nervous system is preponderant in this phenomenon and its translation in terms of control of food intake by the central nervous system (CNS). Nutrient sensing by the extrinsic gastrointestinal nervous system may account for the satiation induced by food lipids, the satiety initiated by food protein, and for the rapid benefits of gastric bypass surgeries on both glucose and energy homeostasis. Thus, this recent knowledge provides novel examples of the mechanisms that control food intake and body weight, which might pave the way to future approaches in the prevention and/or treatment of obesity.

Keywords:

Extrinsic gastrointestinal nerves, satiation, satiety, macronutrients

ROLE OF THE EXTRINSIC GASTROINTESTINAL NEURAL SYSTEM IN THE CONTROL OF HUNGER

The worldwide increase in obesity and its associated disorders makes the efforts to better understand the mechanisms that control food intake and energy homeostasis ever more crucial. The sensations of hunger and fullness are key determinants in the control of appetite and food intake. In normal individuals a precise balance exists between the sensation of hunger that precedes a meal and the sensation of fullness occurring after nutrient assimilation[1, 2]. Human and animal studies have suggested that this balance is deregulated in the context of obesity, whereby the sensation of fullness is inappropriately delayed or blunted, including that following lipid ingestion that has previously been associated with suppression of appetite and energy intake [1, 2]. The mechanisms underlying the shift from the sensation of hunger to the sensation of fullness after a meal encompass the modulation of gastric distension, changes in gut motility and secretion of hunger stimulating or hunger suppressing gastrointestinal hormones. These hormones include the hunger stimulating peptide ghrelin, and peptides that reduce appetite such as cholecystokinin (CCK), peptide YY_{3-36} (PYY_{3-36}) and glucagon-like peptide 1 (GLP1) (see [3, 4] for recent reviews). However, our understanding of the putative role of the gastrointestinal nervous system in the central or systemic effects of these hormones is limited. It is noteworthy that the effect of these gut derived hormones is blunted after surgical ablation of the vagal-brain stem neural communication [5-8]. Indeed, increases in food intake and growth hormone (GH) secretion, both of which are promoted by ghrelin, are blunted after vagotomy [5], as are the satiety effects initiated by CCK [6], GLP1 [7] or PYY_{3-36} [7]. Furthermore, the well established antihyperglycemic action of GLP1, a secretagogue that induces glucose stimulated insulin secretion (GSIS) and suppress glucagon secretion, is mediated at least in part via GLP1 receptors located in the periportal neural system. Accordingly, the improvement of glucose control by GLP1 is attenuated upon

53 inhibition of the GLP-1 receptor in the portal vein [8]. Along these lines, it is of interest that
54 recent data have highlighted the effect of macronutrients derived from food digestion in these
55 processes. A rise in lipids, protein and glucose derived from carbohydrates, shortly after
56 ingestion of a meal, activates the extrinsic gastrointestinal nervous system [9-12,] that alters
57 appetite and the rate of hepatic glucose production in order to reduce appetite and maintain
58 peripheral metabolic homeostasis. Such mechanisms may account for the rapid effects on
59 hunger sensations and glucose control observed after gastric bypass surgery in rodents[13,14]. In
60 this review, the mechanisms by which macronutrients are sensed by the extrinsic
61 gastrointestinal neural system in relation to their early (satiation) or delayed (satiety) (see box
62 1) effect on food intake are discussed. Discussing these mechanisms is timely, especially
63 because the knowledge of the nutrient effects on food intake has been updated recently.
64
65 JEJUNAL SENSING AND EFFECTS OF LIPIDS
66 It has long been accepted that lipids released from the digestion of fat-enriched meals
67 exert satiation effects [1, 2]. It was initially thought that the caloric load of lipids with regards to
68 other macronutrients was a likely explanation for this phenomenon. Implementing this
69 previous rationale, it was recently shown that the primary site of lipid sensing is restricted to
70 the upper intestine [17]. This seminal study showed that increased long-chain fatty acyl-CoAs
71 within the gut mucosa activate a gut-brain-liver neural axis that suppresses glucose
72 production, an effect that is abolished after hepatic vagotomy, thus revealing a previously
73 unrecognized regulatory pathway [17]. The mediator of this effect was shown to be the
74 biologically active form of CCK, CCK-8, in the duodenum, and an active gut CCK-A
75 receptor. It was subsequently deciphered that the downstream effector of the intestinal lipid
76 metabolism initiating CCK secretion and action to lower hepatic glucose production through a
77 neuronal network is duodenal protein kinase C delta (PKC δ) [18-20]. Although these latter

78 studies focused on the effects of jejunal lipid sensing (and/or CCK/ PKC δ) on glucose
79 production, and not on food intake, it is noteworthy to mention that unraveling the critical role
80 of CCK in the lipid mediated effects on glucose homeostasis has provided a mechanistic
81 rationale to the "satiation" action of lipids. It must be noted that a role for the membrane
82 protein CD36 has also been suggested in the satiation effect of lipids. CD36 may act either as
83 a transporter or a receptor of food lipids in the intestinal mucosa, thus serving as a molecular
84 sensor that links fat ingestion to satiety [21, 22].
85
86 PORTAL GLUCOSE ACTION ON FOOD INTAKE: SATIATION OR SATIETY?
87 The rate of glucose appearance in the portal vein during the digestion of a
88 carbohydrate-rich meal representative of current human nutrition (about 50 % of calories as
89 carbohydrates) is high. It may represent about one to two fold the equivalent of total
90 endogenous glucose production (EGP) [11] (Glossary). It has thus long been hypothesized that
91 glucose might induce satiation in the course of meal digestion. To document this hypothesis,
92 initial studies investigating the effect of glucose infusion into the portal vein on food intake
93 and meal size in previously fasting rats were performed at rates matching EGP [23, 24]. Glucose
94 infusion into the portal vein at these rates induced a wide array of physiological and
95 behavioral responses; a decrease in spontaneous food intake; an acquisition of food
96 preference; and an alteration of the electrical activity of hepato-portal vagal and spinal
97 afferents, and of hypothalamic neurons implicated in the control of appetite (see [25] for a
98 review). However, portal glucose infusion at much lower rates (one sixth to one third of EGP)
99 is sufficient to initiate both a limitation of food intake and the activation of hypothalamic
100 nuclei, as revealed by C-FOS labeling, in rats [11, 26]. Whilst either low or high rates of portal
101 glucose infusion might represent what occurs during the postprandial period, various
102 arguments have suggested that the portal delivery of glucose does not determine the

termination of an ongoing meal but, instead, drives the size of the following meal [27]. This has suggested that portal glucose sensing might be related to satiety, rather than to satiation. In agreement with the latter rationale, it is noteworthy that the portal region has also been demonstrated to be critical for the detection of slowly induced hypoglycemia [28], similar to the transition from a post-absorptive to a fasted state. Along these lines a question that arises is whether or not portal glucose appears under post-absorptive conditions.

MOLECULAR MECHANISM OF PORTAL GLUCOSE SENSING

Recently, molecular pathways involved in the sensing of glucose appearance at low rates in the portal vein were investigated, in rodents [11]. Three potential candidate mechanisms, which could account for different types of glucose sensing, were considered: (i) the low affinity glucose transporter Glut 2 which is coupled to glucokinase-induced glucose phosphorylation and may account for GSIS by pancreatic β cells in mice [29]; (ii) gut taste receptors. similar to those in the tongue, that respond to sweet, bitter, umami, and fatty acids and together with other chemosensory signals may coordinate the release of hormones that regulate glucose homeostasis [30]; and (iii) the sodium-coupled glucose co-transporter 3 (SGLT3), a member of the SGLT family of transport proteins that includes SGLT 1 and 2, a receptor (not a transporter) of glucose, which is responsible for glucose-stimulated secretions by enterochromaffin cells [31]. A body of evidence points to a critical role for SGLT3, rather than for Glut2-glucokinase or taste receptors, in the sensing of glucose appearance at low physiological rates in the portal vein walls which include the inhibition of portal glucose sensing by phloridzin (a specific inhibitor of SGLTs), the activation of portal glucose sensing by α-methyl-glucose (a non-phosphorylable analog of glucose), which is transported by SGLT 1 and 2 and binds to SGLT3, and the absence of activation by 3-0-methylglucose, which is transported by SGLT1 and 2, but does not bind to SGLT3 [11]. It must be noted that

afferents innervating the portal vein may travel *via* both the common hepatic branch and the celiac branch of the vagus nerve, but also *via* the dorsal root spinal way [32]. It is noteworthy that the portal glucose signal was not ablated by surgical vagotomy of the common hepatic branch [11]. This suggests that the signal might also be conveyed either by the vagal celiac branch or the spinal way, whereas a widely acceptable view is that it should be conveyed by the ventral vagus [11]. Therefore, SGLT3, and not Glut2 or taste receptors, is likely to be the sensor initiating the portal glucose signal conveyed to the brain to suppress appetite.

ROLE OF PORTAL GLUCOSE SENSING IN THE SATIETY EFFECT OF FOOD PROTEIN

The mechanism by which dietary proteins exert their satiety effect is not clear. An interesting hypothesis was derived from the observation that diets deficient in one essential amino acid, e.g. leucine, rapidly reduce food intake in animals due to an innate aversion to diets with imbalanced amino acid composition (see [33, 34] for recent reviews). The mechanism underlying sensing of imbalanced amino acid diets was shown to involve phosphorylation of the translation initiation factor 2α (eIF2alpha) by the ubiquitous kinase GCN2, in the anterior pyriform cortex of the brain, in response to intracellular amino acid deficiency. Importantly, inactivation of the kinase impaired this aversive response [35, 36]. Therefore, this intracellular signal transduction pathway activates a neuronal circuit that promotes rejection of imbalanced food sources. Vagotomy experiments have also suggested a role for the autonomic efferent nervous system in the reinforcement of the effect [37]. However, a putative role for the extrinsic gastrointestinal afferents in the primary sensing of imbalanced diets has not been established yet (see “outstanding question” box).

It has been hypothesized that diets enriched in a given source of protein could initiate a weak decrease in food intake because of the potential imbalance in their content in amino

153 acids. However, this hypothesis is not supported by experimental evidence. Two related
154 hypotheses with regards to the hunger-curbing effects of protein-enriched diets suggested that
155 the decreased food intake could be due to a conditioned taste aversion, driven by either
156 malaise or low palatability of the diet. However, both hypotheses have been ruled out [26, 38]. A
157 putative role of amino acid taste receptors in sensing imbalanced diets [30] has also been ruled
158 out. Indeed, mice null for the transient receptor potential melastin 5 (Trmp5), a protein
159 required for the transmission of the taste receptors signal, retained their sensitivity to the
160 satiety action of protein-enriched diets [11]. The role of the hypothalamic melanocortin system,
161 a collection of central nervous system circuits, which include orexigenic and anorexigenic
162 neuropeptides, has also been investigated. In this context, protein enriched diets had an
163 opposing effect and promoted an increase, rather than a decrease, in the orexigenic peptide
164 agouti-related protein (AGRP) and a decrease in the anorexigenic alpha melanocortin-
165 stimulating hormone (α-MSH). This suggests that the melanocortin system does not mediate
166 the hunger-curbing effects of protein enriched diet and instead, it might function to defend the
167 body against variations in food intake generated by the nutritional environment [39].

168 However, protein-enriched diets might initiate their satiety effects indirectly, via
169 glucose sensing. During their digestion, proteins induce the expression of gluconeogenic
170 genes in the gut, such as the genes encoding for glucose-6 phosphatase catalytic subunit
171 (G6PC), phosphoenolpyruvate carboxykinase-cytosolic form (PEPCK-C) and glutaminase
172 (see [25, 40] for recent reviews), thus resulting in the release of glucose into the portal vein, in the
173 post-absorptive period. Compared to the 5-10% of total EGP seen after a standard
174 carbohydrate-enriched meal, intestinal gluconeogenesis accounts for as much as 20-25% of
175 EGP after a protein-enriched diet [26]. This is enough to counterbalance the intestinal glucose
176 uptake, so that portal glycemia is equal to arterial glycemia in the post-absorptive state (portal
177 glycemia is lower than arterial glycemia in the post-absorptive state after carbohydrate diets)

178 [26]. This is sufficient to activate the portal glucose sensor and to curb hunger [25, 26, 40]. As
179 expected, portal innervation is essential in this phenomenon since a local peri-portal treatment
180 with capsaicin (a drug inactivating both vagal and spinal afferents) abolishes the satiety effect
181 induced by protein diets [26]. Mice with specific deletion of G6PC in the intestine are
182 insensitive to the satiety induced by protein-enriched diets, thus confirming a causal link in
183 the satiety effect of dietary protein [41].

184 Thus, proteins act indirectly by the means of intestinal gluconeogenesis and portal
185 glucose sensing to curb food intake.

186

187 SENSING OF PROTEIN DIGESTS AND INDUCTION OF GUT GLUCONEOGENESIS

188 Mu-opioid receptors (MORs) expressed in the brain can interfere with the control of
189 food intake, via their role in the "reward" system [42, 43]. It has long been known that proteolytic
190 moieties released from alimentary protein exhibit μ-opioid activity *in vitro* [44]. In line with
191 this, it is well established that oligopeptides of variable size that exhibit μ-opioid activity
192 require a minimal structure of a dipeptide [45-47]. Oligopeptides deriving from the digestion of
193 alimentary protein may be delivered in the portal blood [48]. However, it is unlikely that they
194 reach the brain, because they are metabolized in the liver. It has thus been proposed that these
195 oligopeptides might exert a signaling activity at a gastrointestinal or mesenteric site,
196 activating MORs present in the enteric neural system [49]. This has raised the attractive
197 hypothesis that sensing of oligopeptides deriving from protein digestion by MOR might be
198 involved in the control of food intake via intestinal gluconeogenesis [12]. In line with this,
199 MOR-agonists, such as the synthetic, high affinity opioid peptide DAMGO, suppress
200 intestinal gluconeogenesis genes expression and increase food intake when they are infused in
201 the portal vein of conscious rats. On the contrary, MOR-antagonists (such as naloxone) or
202 various protein derived oligopeptides induce intestinal gluconeogenesis and blunt food intake

203 [12]. The brain regions receiving inputs of both the ventral vagal afferents (i.e. the dorsal vagal
204 complex) or the spinal afferents (i.e. the parabrachial nucleus) are involved in the reflex arc
205 regulating gut gluconeogenesis. All these effects are dependent on the integrity of the
206 periportal nervous system [12]. That MOR-dependent induction of intestinal gluconeogenesis is
207 causal in the decreased hunger promoted by protein-diets was indicated by the observation
208 that: 1) MOR-knockout mice do not induce intestinal gluconeogenesis in response to
209 oligopeptides and are insensitive to protein-enriched diets; 2) mice with intestinal *G6pc* gene
210 deletion do not decrease food intake in response to portal infusions of MOR-antagonists or
211 oligopeptides [12].

212 It must be underlined that the induction of intestinal gluconeogenesis by dietary
213 protein is dependent on gene expression, that takes place over the postprandial period. After
214 that, portal glucose appearance may initiate portal glucose sensing and drive central satiety
215 (fig 1). This can last after the postprandial time, since it is dependent on enzyme induction [12,
216 26]. Hence, deciphering the role of intestinal gluconeogenesis in the decrease of food intake
217 induced by protein-enriched diets has provided both a mechanistic explanation for the satiety
218 (as opposed to satiation) effect of food protein and a physiological meaning to the hunger-
219 curbing effect of portal glucose-sensing.

220

221 WHICH MECHANISMS OPERATE IN OBESITY SURGERY?

222 Gastric bypass surgery has shown impressive outcomes in the control of overall
223 glucose homeostasis, even before the substantial weight loss following surgery of morbidly
224 obese diabetic patients [50-52]. It has been suggested that the decreased hunger sensation and the
225 rapid amelioration of diabetes after gastric surgery might be mediated by an increased
226 secretion of GLP-1 and consecutively insulin [50-52]. However, an alternative explanation, at
227 least in a model of gastric bypass in mice, is that induction of intestinal gluconeogenesis

228 relayed by portal glucose sensing is causal to these phenomena [13]. Along these lines, a
229 comparable increase in insulin sensitivity of EGP, with induction of gluconeogenic genes in
230 the kidney, was observed when intestinal gluconeogenesis was induced by protein-rich diets,
231 in rats [53]. On the other hand, a study by Hayes et al provided no direct evidence to support the
232 hypothesis that intestinal gluconeogenesis contributes to the resolution of T2D seen after
233 gastric bypass of obese and diabetic patients, when compared to obese non diabetic patients
234 [54]. The authors interpreted the net increase in portal glucose concentration observed in the
235 non-diabetic subjects as weak [54]. However, the role of intestinal blood flow, which is known
236 to be very high [55], was not taken into consideration, in this study. Taking into account
237 intestinal blood flow and the increase in portal glucose, a more careful interpretation might
238 suggest that intestinal glucose production after gastric bypass in the non-diabetics is no less
239 than 25% of the total glucose production of the body [55]. Moreover, in the diabetic subjects, the
240 portal glucose concentration was equal to that of the peripheral glucose concentration [55]. This
241 has been shown to be sufficient, at least in rodents, in activating portal glucose sensing and in
242 promoting its benefits on glucose and energy homeostasis [13, 26, 53]. Finally, it is noteworthy
243 that the beneficial effects of intestinal gluconeogenesis on insulin sensitivity, and of GLP 1
244 on insulin secretion, may act in synergy to account for the whole systemic effect of bypass on
245 glucose control [56]. A pending question in this area is why and how intestinal gluconeogenic
246 genes expression is induced after gastric bypass. Since MORs are widely expressed along the
247 gut [49], the possibility that they might be involved in this induction in relation with the protein
248 content of the diet is attractive and warrants careful testing (see "Outstanding Questions").
249 As outlined above, the benefits of portal glucose sensing may operate during the post-
250 absorptive period (time of occurrence of satiety) rather than during the postprandial period
251 (time of occurrence of satiation). Whether gastric bypass might also induce a process
252 compatible with the time of "satiation", i.e. deriving directly from the digestion of nutrients,

253 deserves further investigation. Indeed, it was recently shown that a jejunal lipid-sensing
254 mechanism might account for the effect of gastric bypass on glucose control in rats [14].
255 Interestingly, in the situation of gastric bypass, glucose absorption might concur to the effects
256 observed on glucose control [14]. Again, the mechanistic chain of events involves the extrinsic
257 gastrointestinal nervous afferents [14].

258 It is intuitive that the combination of mechanisms taking place during the postprandial
259 time (lipid sensing) [14], the satiety time (intestinal gluconeogenesis) [13], and of GLP1-driven
260 effects [56], might fully account for the dramatic amelioration of obesity and glucose control
261 after gastric bypass surgery. However, how jejunal lipid sensing and intestinal
262 gluconeogenesis cooperate to exert their effects is an open question.

263

264 CONCLUDING REMARKS AND FUTURE PERSPECTIVES

265 That the brain, especially the hypothalamus, plays a major role in integrating various
266 peripheral signals (e.g. hormones such as leptin or insulin) to influence food intake and
267 energy expenditure has been widely accepted for some time [57]. Now, peripheral sites such as
268 gastrointestinal neural system are also implicated as being crucial for the control of hunger
269 sensation or glucose homeostasis. Three major macronutrients derived from food digestion
270 (lipid, glucose, protein) may control hunger sensations via their intestinal sensing from the
271 gut, and working in harmony with the brain might integrate these signals to influence hunger
272 and endogenous glucose control [1, 2, 13, 14, 53]. The vagal way is often thought to play a major
273 role in conveying the signals from the extrinsic neural system to the brain [25, 32]. However, the
274 participation of the spinal way has been evidenced for the portal glucose signalling [11] or the
275 protein signalling [12]. It remains to be seen whether specific signals may travel along the one or
276 the other way, respectively. Another interesting point is that portal glucose has been
277 associated with the initiation of a food preference [23, 25]. The acquisition of food preference is

notably centrally biased by the reward system [42, 43]. To date, the impact of the portal glucose signal has been characterized in the hypothalamus [25, 26]. The hypothesis of an anatomical and/or functional impact of portal glucose in brain regions implicated in the reward system, e.g. the accumbens nucleus, deserves further investigation (see "Outstanding Questions").

Recent progress has allowed us to understand better how macronutrients signal to the brain to decrease appetite and food intake, and how important are the extrinsic nerves of the gastrointestinal system in sensing and conveying these signals to the brain. Much remains to be known relating to the specificities underlying the mechanisms initiated by lipids, proteins or glucose, especially regarding to their routing and their brain targets. Continuing efforts is warranted, since the future knowledge could offer novel paradigms of food intake control, which may provide as much as novel approaches of treatment and/prevention of metabolic diseases.

OUSTANDING QUESTIONS

- Does the extrinsic gastrointestinal nervous system have a role in the primary sensing of amino-acid imbalanced diets?
- What are the mechanisms underlying the induction of gluconeogenic gene expression after gastric bypass?
- Is there a specific role for μ-opioid receptors in the induction of intestinal gluconeogenesis after bypass?
- How do jejunal lipid sensing and intestinal gluconeogenesis cooperate towards improving glucose fluxes and and reducing food intake after gastric bypass?
- Do specific signals travel along the vagal or the spinal routes of the extrinsic gastrointestinal neural system, respectively?

302 • Does the portal glucose signal modulate the activity of the brain regions involved in
303 the reward system?
304
305 **TEXT BOX 1: <u>Satiation or satiety: a question of definition and time of occurrence</u>**
306 There is often confusion in the use of the words "satiation" and "satiety". "Satiation" is
307 defined as the sensation of fullness, which progressively takes place during the absorption and
308 digestion of the meal. In other words, satiation derives from the sum of the mechanisms,
309 which take place during the digestion of nutrients and concur to curb the sensation of hunger.
310 CCK, which is secreted early in the blood in response to the meal and decreases hunger, is a
311 typical hormone of satiation [15]. In contrast, "satiety" is defined as a state of no-hunger, taking
312 place sometime after the last meal. Thus, satiety operates to moderate the hunger sensation at
313 a time of initiation of the following meal. For instance, it has long been known that alimentary
314 protein induces a satiety, and not satiation, phenomenon [16]. It must be mentioned that it is
315 sometimes difficult to ascribe a role of "satiation" or "satiety" to a given mechanism. For
316 instance, CCK may have a delaying effect on the return of hunger sensations *via* its action of
317 inhibition of gastric emptying [1]. The notions of satiation and satiety are thus defined in a
318 context of physiology. Time constraints are often mandatory in certain experimental contexts,
319 e.g. hyperinsulinemic euglycemic clamp studies or brain C-FOS labeling determinations. The
320 data obtained from such experiments must therefore be reintegrated in the physiological
321 context with precautions, as far as their interpretation in terms of "satiation" or "satiety"
322 phenomenon is concerned.
323
324 **GLOSSARY**
325 *

326 **C-FOS labeling:** a method based on the immunohistochemical identification of the protein
327 C-FOS, an established marker of neuronal activation. The method is not specific and requires
328 that the analysis is performed in absence of any other signals capable of affecting the activity
329 of neurons in the same area.

330 **Endogenous glucose production (EGP):** a crucial physiological function, which allows the
331 body to maintain plasma glucose concentration around 1g/L in the absence of glucose supply
332 from food (post-absorptive and fasting periods). EGP may proceed from a pre-formed store of
333 glucose (glycogen) in the liver or from gluconeogenesis (see below) in the liver, kidney and
334 intestine. These three organs only can contribute to EGP, since they are the only organs
335 known to express glucose-6 phosphatase, the enzyme in the last step in the biochemical
336 reaction preceding glucose release [25].

337 Extrinsic gastrointestinal nervous system: refers to the nerves spreading in the abdomen,
338 which include the common hepatic and the celiac branches of the vagal nerve connected to the
339 CNS and the sympathetic nerves connected to the spinal cord [32].

340 **Gluconeogenesis:** refers to the synthesis of glucose from non-glucidic carbon compounds.
341 Gluconeogenesis becomes essential for EGP when liver glycogen stores are exhausted, such
342 as during fasting. The main glucose precursors are lactate and alanine in the case of liver
343 gluconeogenesis, whereas glutamine is an essential substrate for gluconeogenesis in the
344 kidney and intestine [25].

345 Glucose stimulated insulin secretion (GSIS): refers to the fraction of insulin, which is released
346 in response to an increase in blood glucose concentration and adds to the basal insulin release.

347 Intrinsic gastrointestinal nervous system: refers to the nerves closely surrounding the gut
348 mucosa (the so-called Meisner's plexus) and those of the gut muscular layer (the so-called
349 Auerbach's plexus).

Hyperinsulinemic euglycemic clamp: a method based on the use of metabolic tracers of glucose to quantify endogenous glucose fluxes (production and utilization) and/or the action of insulin to suppress glucose production and/or enhance glucose utilization. It must be carried out in the absence of glucose appearing from food origin.

Melanocortin system: a major system expressed in the hypothalamus that regulates hunger sensations. It notably comprises the melanocortin receptor type 4 (MC4R) and two main neuro-mediators able to control its activity: alpha-melanin stimulating hormone (α-MSH) is an MC4R agonist and allows MC4R to inhibit hunger, agouti-related protein (AgRP) is an antagonist and activates hunger. Insulin or leptin mediate their anorexigenic effect via the release of a-MSH, whereas ghrelin mediates its orexigenic effect via the activation of AgRP release. See [39] as a recent review.

μ-opioid receptor (MOR): receptors of opioids from exogenous (e.g. morphin) or endogenous (endorphins) origin. In the brain, MOR may participate to the control of food intake, especially *via* their implication in the so-called "reward" system [28, 29]. Agonists like morphine stimulate hunger, whereas antagonists like naloxone decrease hunger. In the gut, they were shown to control motility processes [31].

REFERENCES

1. Covasa M. (2010) Deficits in gastrointestinal responses controlling food intake and body weight. *Am J Physiol Regul Integr Comp Physiol* 299, R1423-R1439.
2. Little T.J. and Feinle-Bisset C. (2011) Effects of dietary fat on appetite and energy intake in health and obesity--oral and gastrointestinal sensory contributions. *Physiol Behav* 104, 613-620.
3. Yi C.X. *et al.* (2010) The role of the autonomic nervous liver innervation in the control of energy metabolism. *Biochim Biophys Acta* 1802, 416-431.
4. Janssen P. *et al.*, (2011) Review article: the role of gastric motility in the control of food intake. *Aliment Pharmacol Ther* 33, 880-894.
5. Date Y. *et al.* (2002) The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. *Gastroenterology* 123, 1120-1128.
6. Smith G.P. *et al.* (1981) Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat. *Science* 213, 1036-1037.

7. Abbott C.R. *et al.* (2005) The inhibitory effects of peripheral administration of peptide YY(3-36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway. *Brain Res* 1044, 127-131.
8. Vahl T.P *et al.* (2007) Glucagon-like peptide-1 (GLP-1) receptors expressed on nerve terminals in the portal vein mediate the effects of endogenous GLP-1 on glucose tolerance in rats. *Endocrinology* 148, 4965-4973.
9. Breen D.M. *et al.* (2011) Gut-brain signalling: how lipids can trigger the gut. *Diabetes Metab Res Rev* 27, 113-119.
10. Rasmussen B.A. *et al.* (2012) Lipid sensing in the gut, brain and liver. *Trends Endocrinol Metab* 23, 49-55
11. Delaere F. *et al.* (2012) The role of sodium-coupled glucose co-transporter 3 in the satiety effect of portal glucose sensing. *Mol Metab* doi: 10.1016/j.molmet.2012.11.003 http://www.elsevier.com/journals/molecular-metabolism/2212-8778
12. Duraffourd C. *et al.* (2012) Mu-opioid receptors and dietary protein stimulate a gut-brain neural circuitry limiting food intake. *Cell* 150, 377-388
13. Troy S. *et al.* (2008) Intestinal gluconeogenesis is a key factor for early metabolic changes after gastric bypass but not after gastric lap-band in mice. *Cell Metab* 8, 201-211.
14. Breen D.M. *et al.* (2012) Jejunal nutrient sensing is required for duodenal-jejunal bypass surgery to rapidly lower glucose concentrations in uncontrolled diabetes. *Nat Med* 18, 950-955.
15. Gibbs J. *et al.* (1976) Cholecystokinin-decreased food intake in rhesus monkeys. *Am J Physiol* 230, 15-18.
16. Rolls B.J. *et al.* (1988) The specificity of satiety: the influence of foods of different macronutrient content on the development of satiety. *Physiol Behav* 43, 145-153.
17. Wang P.Y. *et al.* (2008) Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production. *Nature* 452, 1012-1016.
18. Cheung G.W. *et al.* (2009) Intestinal cholecystokinin controls glucose production through a neuronal network. *Cell Metab* 10, 99-109.
19. Kokorovic A. *et al.* (2011) Duodenal mucosal protein kinase C-δ regulates glucose production in rats. *Gastroenterology* 141, 1720-1727.
20. Breen D.M. *et al.* (2011) Duodenal PKC-δ and cholecystokinin signaling axis regulates glucose production. *Diabetes* 60, 3148-3153.
21. Naville D. *et al.* (2012) Linik beetween intestinal CD36 ligand binding and satiety induced by a high protein diet in mice. *PlosONE* 7, e30686.
22. Schwartz G.J. *et al.* (2008) The lipid messenger OEA links dietary fat intake to satiety. *Cell Metab* 8, 281-288.
23. Tordoff M.G. and Friedman M.I. (1986) Hepatic portal glucose infusions decrease food intake and increase food preference. *Am J Physiol* 251(1 Pt 2), R192-R196.
24. Langhans W. et al. (2001) Intrameal hepatic-portal infusion of glucose reduces spontaneous meal size in rats. *Physiol Behav* 73, 499-507.
25. Delaere F. *et al.* (2010) Hypothalamic integration of portal glucose signals and control of food intake and insulin sensitivity. *Diabetes Metab* 36, 257-262.
26. Mithieux G. *et al.* (2005) Portal sensing of intestinal gluconeogenesis is a mechanistic link in the diminution of food intake induced by diet protein. *Cell Metab* 2, 321-329.
27. Baird J.P. *et al.* (1997) Intake suppression after hepatic portal glucose infusion: all-or-none effect and its temporal threshold. *Am J Physiol* 272(5 Pt 2), R1454-R1460.
28. Saberi M. *et al.* (2008) The locus for hypoglycemic detection shifts with the rate of fall in glycemia: the role of portal-superior mesenteric vein glucose sensing. *Diabetes* 57, 1380-1386.
29. Thorens B. and Larsen, P.J. (2004) Gut-derived signaling molecules and vagal afferents in the control of glucose and energy homeostasis. *Curr Opin Clin Nutr Metab Care* 7, 471-478.
30. Janssen S. and Depoortere, I. (2012) Nutrient sensing in the gut: new roads to therapeutics? *Trends Endocrinol Metab* doi: 10.1016/j.tem.2012.11.006 http://www.cell.com/trends/endocrinology-metabolism

31. Freeman S.L. *et al.* (2006) Luminal glucose sensing in the rat intestine has characteristics of a sodium-glucose cotransporter. *Am J Physiol Gastrointestinal and Liver Physiology* 8, 532-539.
32. Berthoud H.E. (2004) Anatomy and function of sensory hepatic nerves. *Anat Rec Discov Mol Cell Evol Biol* 280, 827-835.
33. Chaveroux C., *et al.* (2010) Molecular mechanisms involved in the adaptation to amino acid limitation in mammals. *Biochimie* 92, 736-745.
34. Anthony T.G. and Gietzen D.W. (2013) Detection of amino acid deprivation in the central nervous system. *Curr Opin Clin Nutr Metab Care* 16, 96-101.
35. Maurin A.C. *et al.* (2005) The GCN2 kinase biases feeding behavior to maintain amino acid homeostasis in omnivores. *Cell Metab* 1, 273-277.
36. Hao S. *et al.* (2005) Uncharged tRNA and sensing of amino acid deficiency in mammalian piriform cortex. *Science* 307, 1776-1778.
37. Bellinger L.L. *et al.* (2005) Autonomic efferents affect intake of imbalanced amino acid diets by rats. *Pharmacol Biochem Behav* 81, 24-31.
38. L'Heureux-Bouron D. *et al.* (2004) A very high 70%-protein diet does not induce conditioned taste aversion in rats. *J Nutr* 134, 1512-1515.
39. Pillot B. *et al.* (2011) Role of hypothalamic melanocortin system in adaptation of food intake to food protein increase in mice. *PlosONE* 6, 1-7.
40. Mithieux, G. *et al.* (2009) Intestinal gluconeogenesis : key signal of central control of energy and glucose homeostasis. *Curr Opin Clin Nutr Metab Care* 12, 419-423.
41. Penhoat, A. *et al.* (2011) Protein-induced satiety is abolished in the absence of intestinal gluconeogenesis. *Physiol Behav* 105, 89-93.
42. Berridge C.W. (2009) 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. *Physiol Behav* 97, 537-550.
43. Berridge C.W. *et al.* (2010) Hypocretin/orexin in arousal and stress. *Brain Res* 1314, 91-102.
44. Zioudrou C. et al. (1979) Opioid peptides derived from food proteins. The exorphins. *J Biol Chem* 254, 2446-1449.
45. Capasso A. et al. (1997) Design of mu selective opioid dipeptide antagonists. *FEBS Lett* 417, 141-144.
46. Moritoki H. *et al.* (1984) Tripeptides acting on opioid receptors in rat colon. *Eur J Pharmacol* 100, 29-39.
47. Schiller P. et al. (2002) Opioid dipeptide derivatives with a mixed μ antagonist/δ antagonist, partial μ agonist/δ antagonist or μ agonist/partial δ agonist profile. *American Peptide Symposia* 6, 229-270.
48. Lee V.H. (2000) Membrane transporters. *Eur J Pharm Sci.* Suppl 2, S41-S50.
49. Holzer P. (2009) Opioid receptors in the gastrointestinal tract. *Regul Pept* 155, 11-17.
50. Thaler J.P. and Cummings, D.E. (2009) Minireview: Hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. *Endocrinology* 150, 2518-2525.
51. Sala P.C. *et al.* (2012) Type 2 diabetes mellitus: a possible surgically reversible intestinal dysfunction. *Obes Surg* 22, 167-176.
52. Perez-Tilve D. *et al.* (2008) A sweet spot for the bariatric surgeon. *Cell Metab* 8, 177-179.
53. Pillot B. *et al.* (2009) Protein feeding promotes redistribution of endogenous glucose production to the kidney and potentiates its suppression by insulin. *Endocrinology* 150, 616-624.
54. Hayes M.T. *et al.* (2011) Is intestinal gluconeogenesis a key factor in the early changes in glucose homeostasis following gastric bypass ? *Obes Surg* 21, 759-762.
55. Mithieux G. (2011) Comment about intestinal gluconeogenesis after gastric bypass in human in relation with the paper by Hayes et al., Obes. Surg. 2011. *Obes Surg* 22, 1920-1922.
56. Mithieux G. (2012) A synergy between incretin effect and intestinal gluconeogenesis accounting for the rapid metabolic benefits of gastric bypass surgery. *Curr Diab Rep* 12, 167-171.
57. Warne, J.P. and Xu, A.W. (2012) Metabolic transceivers: in tune with the central melanocortin system. *Trends Endocrinol Metab* doi: 10.1016/j.tem.2012.10.005; http://www.cell.com/trends/endocrinology-metabolism

58. Croset M. *et al.* (2001) Rat small intestine is an insulin-sensitive gluconeogenic organ. *Diabetes* 50, 740-746.
59. Mithieux G. *et al.* (2004) A novel role for glucose 6-phosphatase in the small intestine in the control of glucose homeostasis. *J Biol Chem* 279, 44231-44234.

FIGURE LEGEND:

Figure 1: Sequential events controlled by food protein and glucose via the gastrointestinal neural network

A) During the postprandial period, peptides released in the portal vein from protein digestion binds to and antagonize MORs present in the peri-portal afferents. The MOR-controlled ascending nerves convey the message to the brain nuclei connecting the afferents from either the vagal or the spinal way. A reflex arc drives the induction of the intestinal regulatory gluconeogenesis genes.

B) The intestinal gluconeogenic pathway, stimulated in response to the induction of glutaminase, PEPCK-C and G6Pase activities, efficiently converts glutamine (the main intestinal glucose precursor) and glycerol (an accessory glucose precursor) into glucose. See ref [58, 59] for a comprehensive description of these pathways.

C) During the post-absorptive period, glucose is released in the portal vein and sensed by SGLT3, which sends a second message to the brain to decrease hunger at the hypothalamic site and increase insulin sensitivity of hepatic glucose production *via* a second reflex arc.