

Nutrient control of hunger by extrinsic gastrointestinal neurons.

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1 NUTRIENT CONTROL OF HUNGER BY EXTRINSIC GASTROINTESTINAL
2 NEURONS

3

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12

13 ABSTRACT

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

23

24 **Keywords:**

25 Extrinsic gastrointestinal nerves, satiation, satiety, macronutrients

26

27

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

30 The worldwide increase in obesity and its associated disorders makes the efforts to
31 better understand the mechanisms that control food intake and energy homeostasis ever more
32 crucial. The sensations of hunger and fullness are key determinants in the control of appetite
33 and food intake. In normal individuals a precise balance exists between the sensation of
34 hunger that precedes a meal and the sensation of fullness occurring after nutrient
35 assimilation^{1, 2}. Human and animal studies have suggested that this balance is deregulated in
36 the context of obesity, whereby the sensation of fullness is inappropriately delayed or blunted,
37 including that following lipid ingestion that has previously been associated with suppression
38 of appetite and energy intake^{1, 2}. The mechanisms underlying the shift from the sensation of
39 hunger to the sensation of fullness after a meal encompass the modulation of gastric
40 distension, changes in gut motility and secretion of hunger stimulating or hunger suppressing
41 gastrointestinal hormones. These hormones include the hunger stimulating peptide ghrelin,
42 and peptides that reduce appetite such as cholecystinin (CCK), peptide YY₃₋₃₆ (PYY₃₋₃₆)
43 and glucagon-like peptide 1 (GLP1) (see^{3, 4} for recent reviews). However, our understanding
44 of the putative role of the gastrointestinal nervous system in the central or systemic effects of
45 these hormones is limited. It is noteworthy that the effect of these gut derived hormones is
46 blunted after surgical ablation of the vagal-brain stem neural communication⁵⁻⁸. Indeed,
47 increases in food intake and growth hormone (GH) secretion, both of which are promoted by
48 ghrelin, are blunted after vagotomy⁵, as are the satiety effects initiated by CCK⁶, GLP1⁷ or
49 PYY₃₋₃₆⁷. Furthermore, the well established antihyperglycemic action of GLP1, a
50 secretagogue that induces glucose stimulated insulin secretion (GSIS) and suppress glucagon
51 secretion, is mediated at least in part via GLP1 receptors located in the periportal neural
52 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 “satiating” 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 (see²⁵ 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

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

109

110 MOLECULAR MECHANISM OF PORTAL GLUCOSE SENSING

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

128 afferents innervating the portal vein may travel *via* both the common hepatic branch and the
129 celiac branch of the vagus nerve, but also *via* the dorsal root spinal way³². It is noteworthy
130 that the portal glucose signal was not ablated by surgical vagotomy of the common hepatic
131 branch¹¹. This suggests that the signal might also be conveyed either by the vagal celiac
132 branch or the spinal way, whereas a widely acceptable view is that it should be conveyed by
133 the ventral vagus¹¹. Therefore, SGLT3, and not Glut2 or taste receptors, is likely to be the
134 sensor initiating the portal glucose signal conveyed to the brain to suppress appetite.

135

136 ROLE OF PORTAL GLUCOSE SENSING IN THE SATIETY EFFECT OF FOOD 137 PROTEIN

138 The mechanism by which dietary proteins exert their satiety effect is not clear. An
139 interesting hypothesis was derived from the observation that diets deficient in one essential
140 amino acid, e.g. leucine, rapidly reduce food intake in animals due to an innate aversion to
141 diets with imbalanced amino acid composition (see^{33, 34} for recent reviews). The mechanism
142 underlying sensing of imbalanced amino acid diets was shown to involve phosphorylation of
143 the translation initiation factor 2 α (eIF2 α) by the ubiquitous kinase GCN2, in the anterior
144 pyriform cortex of the brain, in response to intracellular amino acid deficiency. Importantly,
145 inactivation of the kinase impaired this aversive response^{35, 36}. Therefore, this intracellular
146 signal transduction pathway activates a neuronal circuit that promotes rejection of imbalanced
147 food sources. Vagotomy experiments have also suggested a role for the autonomic efferent
148 nervous system in the reinforcement of the effect³⁷. However, a putative role for the extrinsic
149 gastrointestinal afferents in the primary sensing of imbalanced diets has not been established
150 yet (see “outstanding question” box).

151 It has been hypothesized that diets enriched in a given source of protein could initiate
152 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 diets³⁰ 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 diets¹¹. 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 environment³⁹.

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 diet²⁶. 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

278 notably centrally biased by the reward system^{42, 43}. To date, the impact of the portal glucose
279 signal has been characterized in the hypothalamus^{25, 26}. The hypothesis of an anatomical
280 and/or functional impact of portal glucose in brain regions implicated in the reward system,
281 e.g. the accumbens nucleus, deserves further investigation (see “Outstanding Questions”).
282 Recent progress has allowed us to understand better how macronutrients signal to the brain to
283 decrease appetite and food intake, and how important are the extrinsic nerves of the
284 gastrointestinal system in sensing and conveying these signals to the brain. Much remains to
285 be known relating to the specificities underlying the mechanisms initiated by lipids, proteins
286 or glucose, especially regarding to their routing and their brain targets. Continuing efforts is
287 warranted, since the future knowledge could offer novel paradigms of food intake control,
288 which may provide as much as novel approaches of treatment and/prevention of metabolic
289 diseases.

290

291 OUSTANDING QUESTIONS

- 292 • Does the extrinsic gastrointestinal nervous system have a role in the primary sensing
293 of amino-acid imbalanced diets?
- 294 • What are the mechanisms underlying the induction of gluconeogenic gene expression
295 after gastric bypass?
- 296 • Is there a specific role for μ -opioid receptors in the induction of intestinal
297 gluconeogenesis after bypass?
- 298 • How do jejunal lipid sensing and intestinal gluconeogenesis cooperate towards
299 improving glucose fluxes and and reducing food intake after gastric bypass?
- 300 • Do specific signals travel along the vagal or the spinal routes of the extrinsic
301 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: Satiating or satiety: a question of definition and time of occurrence**

306 There is often confusion in the use of the words “satiating” and “satiety”. “Satiating” 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 satiation¹⁵. 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, phenomenon¹⁶. It must be mentioned that it is
315 sometimes difficult to ascribe a role of “satiating” 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 emptying¹. 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 “satiating” 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).

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

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

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

366

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496 **FIGURE LEGEND:**

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

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

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

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

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