

Nutrient control of hunger by extrinsic gastrointestinal neurons.

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1	NUTRIENT CONTROL OF HUNGER BY EXTRINSIC GASTROINTESTINAL
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13 ABSTRACT

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

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24 Keywords:

25 Extrinsic gastrointestinal nerves, satiation, satiety, macronutrients

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28 ROLE OF THE EXTRINSIC GASTROINTESTINAL NEURAL SYSTEM IN THE29 CONTROL OF HUNGER

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

inhibition of the GLP-1 receptor in the portal vein⁸. Along these lines, it is of interest that 53 recent data have highlighted the effect of macronutrients derived from food digestion in these 54 processes. A rise in lipids, protein and glucose derived from carbohydrates, shortly after 55 ingestion of a meal, activates the extrinsic gastrointestinal nervous system ⁹⁻¹², that alters 56 appetite and the rate of hepatic glucose production in order to reduce appetite and maintain 57 peripheral metabolic homeostasis. Such mechanisms may account for the rapid effects on 58 hunger sensations and glucose control observed after gastric bypass surgery in rodents^{13,14}. In 59 this review, the mechanisms by which macronutrients are sensed by the extrinsic 60 gastrointestinal neural system in relation to their early (satiation) or delayed (satiety) (see box 61 1) effect on food intake are discussed. Discussing these mechanisms is timely, especially 62 because the knowledge of the nutrient effects on food intake has been updated recently. 63

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5 JEJUNAL SENSING AND EFFECTS OF LIPIDS

It has long been accepted that lipids released from the digestion of fat-enriched meals 66 exert satiation effects ^{1, 2}. It was initially thought that the caloric load of lipids with regards to 67 other macronutrients was a likely explanation for this phenomenon. Implementing this 68 previous rationale, it was recently shown that the primary site of lipid sensing is restricted to 69 the upper intestine ¹⁷. This seminal study showed that increased long-chain fatty acyl-CoAs 70 within the gut mucosa activate a gut-brain-liver neural axis that suppresses glucose 71 production, an effect that is abolished after hepatic vagotomy, thus revealing a previously 72 unrecognized regulatory pathway¹⁷. The mediator of this effect was shown to be the 73 biologically active form of CCK, CCK-8, in the duodenum, and an active gut CCK-A 74 receptor. It was subsequently deciphered that the downstream effector of the intestinal lipid 75 metabolism initiating CCK secretion and action to lower hepatic glucose production through a 76 neuronal network is duodenal protein kinase C delta (PKC δ)¹⁸⁻²⁰. Although these latter 77

studies focused on the effects of jejunal lipid sensing (and/or CCK/ PKC δ) on glucose production, and not on food intake, it is noteworthy to mention that unraveling the critical role of CCK in the lipid mediated effects on glucose homeostasis has provided a mechanistic rationale to the "satiation" action of lipids. It must be noted that a role for the membrane protein CD36 has also been suggested in the satiation effect of lipids. CD36 may act either as a transporter or a receptor of food lipids in the intestinal mucosa, thus serving as a molecular sensor that links fat ingestion to satiety ^{21, 22}.

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86 PORTAL GLUCOSE ACTION ON FOOD INTAKE: SATIATION OR SATIETY?

The rate of glucose appearance in the portal vein during the digestion of a 87 carbohydrate-rich meal representative of current human nutrition (about 50 % of calories as 88 carbohydrates) is high. It may represent about one to two fold the equivalent of total 89 endogenous glucose production (EGP)¹¹ (Glossary). It has thus long been hypothesized that 90 glucose might induce satiation in the course of meal digestion. To document this hypothesis, 91 initial studies investigating the effect of glucose infusion into the portal vein on food intake 92 and meal size in previously fasting rats were performed at rates matching EGP^{23, 24}. Glucose 93 infusion into the portal vein at these rates induced a wide array of physiological and 94 behavioral responses; a decrease in spontaneous food intake; an acquisition of food 95 preference; and an alteration of the electrical activity of hepato-portal vagal and spinal 96 afferents, and of hypothalamic neurons implicated in the control of appetite (see ²⁵ for a 97 review). However, portal glucose infusion at much lower rates (one sixth to one third of EGP) 98 is sufficient to initiate both a limitation of food intake and the activation of hypothalamic 99 nuclei, as revealed by C-FOS labeling, in rats ^{11, 26}. Whilst either low or high rates of portal 100 glucose infusion might represent what occurs during the postprandial period, various 101 102 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 103 suggested that portal glucose sensing might be related to satiety, rather than to satiation. In 104 agreement with the latter rationale, it is noteworthy that the portal region has also been 105 demonstrated to be critical for the detection of slowly induced hypoglycemia²⁸, similar to the 106 transition from a post-absorptive to a fasted state. Along these lines a question that arises is 107 whether or not portal glucose appears under post-absorptive conditions. 108

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MOLECULAR MECHANISM OF PORTAL GLUCOSE SENSING

Recently, molecular pathways involved in the sensing of glucose appearance at low 111 rates in the portal vein were investigated, in rodents ¹¹. Three potential candidate mechanisms, 112 which could account for different types of glucose sensing, were considered: (i) the low 113 affinity glucose transporter Glut 2 which is coupled to glucokinase-induced glucose 114 phosphorylation and may account for GSIS by pancreatic β cells in mice²⁹; (ii) gut taste 115 receptors. similar to those in the tongue, that respond to sweet, bitter, umami, and fatty acids 116 and together with other chemosensory signals may coordinate the release of hormones that 117 regulate glucose homeostasis ³⁰; and (iii) the sodium-coupled glucose co-transporter 3 118 (SGLT3), a member of the SGLT family of transport proteins that includes SGLT 1 and 2, a 119 receptor (not a transporter) of glucose, which is responsible for glucose-stimulated secretions 120 by enterochromaffin cells³¹. A body of evidence points to a critical role for SGLT3, rather 121 than for Glut2-glucokinase or taste receptors, in the sensing of glucose appearance at low 122 physiological rates in the portal vein walls which include the inhibition of portal glucose 123 sensing by phloridzin (a specific inhibitor of SGLTs), the activation of portal glucose sensing 124 by α -methyl-glucose (a non-phosphorylable analog of glucose), which is transported by 125 SGLT 1 and 2 and binds to SGLT3, and the absence of activation by 3-0-methylglucose, 126 which is transported by SGLT1 and 2, but does not bind to SGLT3¹¹. It must be noted that 127

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.

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136 ROLE OF PORTAL GLUCOSE SENSING IN THE SATIETY EFFECT OF FOOD137 PROTEIN

The mechanism by which dietary proteins exert their satiety effect is not clear. An 138 interesting hypothesis was derived from the observation that diets deficient in one essential 139 amino acid, e.g. leucine, rapidly reduce food intake in animals due to an innate aversion to 140 diets with imbalanced amino acid composition (see ^{33, 34} for recent reviews). The mechanism 141 underlying sensing of imbalanced amino acid diets was shown to involve phosphorylation of 142 the translation initiation factor 2α (eIF2alpha) by the ubiquitous kinase GCN2, in the anterior 143 pyriform cortex of the brain, in response to intracellular amino acid deficiency. Importantly, 144 inactivation of the kinase impaired this aversive response ^{35, 36}. Therefore, this intracellular 145 signal transduction pathway activates a neuronal circuit that promotes rejection of imbalanced 146 food sources. Vagotomy experiments have also suggested a role for the autonomic efferent 147 nervous system in the reinforcement of the effect ³⁷. However, a putative role for the extrinsic 148 gastrointestinal afferents in the primary sensing of imbalanced diets has not been established 149 yet (see "outstanding question" box). 150

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

acids. However, this hypothesis is not supported by experimental evidence. Two related 153 hypotheses with regards to the hunger-curbing effects of protein-enriched diets suggested that 154 the decreased food intake could be due to a conditioned taste aversion, driven by either 155 malaise or low palatability of the diet. However, both hypotheses have been ruled out ^{26, 38}. A 156 putative role of amino acid taste receptors in sensing imbalanced diets ³⁰ has also been ruled 157 out. Indeed, mice null for the transient receptor potential melastin 5 (Trmp5), a protein 158 required for the transmission of the taste receptors signal, retained their sensitivity to the 159 satiety action of protein-enriched diets¹¹. The role of the hypothalamic melanocortin system, 160 a collection of central nervous system circuits, which include orexigenic and anorexigenic 161 neuropeptides, has also been investigated. In this context, protein enriched diets had an 162 opposing effect and promoted an increase, rather than a decrease, in the orexigenic peptide 163 agouti-related protein (AGRP) and a decrease in the anorexigenic alpha melanocortin-164 stimulating hormone (α -MSH). This suggests that the melanocortin system does not mediate 165 the hunger-curbing effects of protein enriched diet and instead, it might function to defend the 166 body against variations in food intake generated by the nutritional environment ³⁹. 167

However, protein-enriched diets might initiate their satiety effects indirectly, via 168 glucose sensing. During their digestion, proteins induce the expression of gluconeogenic 169 genes in the gut, such as the genes encoding for glucose-6 phosphatase catalytic subunit 170 (G6PC), phosphoenolpyruvate carboxykinase-cytosolic form (PEPCK-C) and glutaminase 171 (see ^{25, 40} for recent reviews), thus resulting in the release of glucose into the portal vein, in the 172 post-absorptive period. Compared to the 5-10% of total EGP seen after a standard 173 carbohydrate-enriched meal, intestinal gluconeogenesis accounts for as much as 20-25% of 174 EGP after a protein-enriched diet ²⁶. This is enough to counterbalance the intestinal glucose 175 uptake, so that portal glycemia is equal to arterial glycemia in the post-absorptive state (portal 176 177 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 portal185 glucose sensing to curb food intake.

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187 SENSING OF PROTEIN DIGESTS AND INDUCTION OF GUT GLUCONEOGENESIS

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

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

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

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221 WHICH MECHANISMS OPERATE IN OBESITY SURGERY?

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

relayed by portal glucose sensing is causal to these phenomena¹³. Along these lines, a 228 comparable increase in insulin sensitivity of EGP, with induction of gluconeogenic genes in 229 the kidney, was observed when intestinal gluconeogenesis was induced by protein-rich diets, 230 in rats ⁵³. On the other hand, a study by Hayes et al provided no direct evidence to support the 231 hypothesis that intestinal gluconeogenesis contributes to the resolution of T2D seen after 232 gastric bypass of obese and diabetic patients, when compared to obese non diabetic patients 233 ⁵⁴. The authors interpreted the net increase in portal glucose concentration observed in the 234 non-diabetic subjects as weak ⁵⁴. However, the role of intestinal blood flow, which is known 235 to be very high ⁵⁵, was not taken into consideration, in this study. Taking into account 236 237 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 than 25% of the total glucose production of the body ⁵⁵. Moreover, in the diabetic subjects, the 239 portal glucose concentration was equal to that of the peripheral glucose concentration ⁵⁵. This 240 has been shown to be sufficient, at least in rodents, in activating portal glucose sensing and in 241 promoting its benefits on glucose and energy homeostasis ^{13, 26, 53}. Finally, it is noteworthy 242 that the beneficial effects of intestinal gluconeogenesis on insulin sensitivity, and of GLP 1 243 on insulin secretion, may act in synergy to account for the whole systemic effect of bypass on 244 glucose control ⁵⁶. A pending question in this area is why and how intestinal gluconeogenic 245 genes expression is induced after gastric bypass. Since MORs are widely expressed along the 246 gut ⁴⁹, the possibility that they might be involved in this induction in relation with the protein 247 content of the diet is attractive and warrants careful testing (see "Outstanding Questions"). 248

As outlined above, the benefits of portal glucose sensing may operate during the postabsorptive period (time of occurrence of satiety) rather than during the postprandial period (time of occurrence of satiation). Whether gastric bypass might also induce a process compatible with the time of "satiation", i.e. deriving directly from the digestion of nutrients,

deserves further investigation. Indeed, it was recently shown that a jejunal lipid-sensing 253 mechanism might account for the effect of gastric bypass on glucose control in rats ¹⁴. 254 Interestingly, in the situation of gastric bypass, glucose absorption might concur to the effects 255 observed on glucose control ¹⁴. Again, the mechanistic chain of events involves the extrinsic 256 gastrointestinal nervous afferents¹⁴. 257

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

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CONCLUDING REMARKS AND FUTURE PERSPECTIVES

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

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 282 decrease appetite and food intake, and how important are the extrinsic nerves of the 283 gastrointestinal system in sensing and conveying these signals to the brain. Much remains to 284 be known relating to the specificities underlying the mechanisms initiated by lipids, proteins 285 or glucose, especially regarding to their routing and their brain targets. Continuing efforts is 286 warranted, since the future knowledge could offer novel paradigms of food intake control, 287 288 which may provide as much as novel approaches of treatment and/prevention of metabolic diseases. 289

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291 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?

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• Does the portal glucose signal modulate the activity of the brain regions involved in the reward system?

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305 **TEXT BOX 1:** Satiation or satiety: a question of definition and time of occurrence

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

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324 GLOSSARY
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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.

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

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

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

Glucose stimulated insulin secretion (GSIS): refers to the fraction of insulin, which is released in response to an increase in blood glucose concentration and adds to the basal insulin release. Intrinsic gastrointestinal nervous system: refers to the nerves closely surrounding the gut mucosa (the so-called Meisner's plexus) and those of the gut muscular layer (the so-called 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.

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.

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496 **FIGURE LEGEND:**

497 Figure 1: Sequential events controlled by food protein and glucose via the 498 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.

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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