G protein-coupled receptors in energy homeostasis

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G-protein coupled receptors (GPCRs) comprise the largest membrane protein superfamily which play vital roles in physiological and pathophysiological processes including energy homeostasis. Moreover, they also represent the up-to-date most successful drug target. The gut hormone GPCRs, such as glucagon receptor and GLP-1 receptor, have been intensively studied for their roles in metabolism and respective drugs have developed for the treatment of metabolic diseases such as type 2 diabetes (T2D). Along with the advances of biomedical research, more GPCRs have been found to play important roles in the regulation of energy homeostasis from nutrient sensing, appetite control to glucose and fatty acid metabolism with various mechanisms. The investigation of their biological functions will not only improve our understanding of how our body keeps the balance of energy intake and expenditure, but also highlight the possible drug targets for the treatment of metabolic diseases. The present review summarizes GPCRs involved in the energy control with special emphasis on their pathophysiological roles in metabolic diseases and hopefully triggers more intensive and systematic investigations in the field so that a comprehensive network control of energy homeostasis will be revealed, and better drugs will be developed in the foreseeable future.

G-protein coupled receptor, energy homeostasis, metabolism

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G protein-coupled receptors (GPCRs), featured by a common seven-transmembrane (7TM) topology, comprise the largest protein superfamily in mammalian genomes [1,2]. The natural ligands for GPCRs include a variety of extracellular signals ranging from photons, odors, ions, amines, peptides, proteins, lipids, and nucleotides, which activate respective GPCRs and the downstream signaling [3]. The classical view of GPCR signaling has been intensively reviewed before [4]. In brief, the activated GPCR couple to heterotrimeric GTP-binding proteins (G proteins), which consists of α -, β -, and γ -subunits, and catalyze the exchange of guanine diphosphate (GDP) for guanine triphosphate (GTP) on the α -subunit, which leads to dissociation of $G\alpha$ from the dimeric $G\beta\gamma$ subunits. Based on G protein α -subunits, GPCRs are classified into several subfamilies. For instance, when GPCR couple to $G\alpha_s$ or $G\alpha_{i/o}$ proteins, adenylate cyclase (AC) will be activated or inhibited, re-

spectively, and the level of 3',5'-cyclic adenosine monophosphate (cAMP) changes accordingly and so does its downstream effectors. However, in the case of $G\alpha_q$ -coupled GPCRs, phospholipase C (PLC)- β will be activated and catalyzes the formation of inositol-1,4,5-trisphosphate (IP3), which then binds and opens the endoplasmic IP3-gated calcium channel, causing the release of calcium into the cytoplasm. It has been well-accepted that the desensitization of a given GPCR is mediated via the phosphorylation of the activated receptor by G protein coupled receptor kinases (GRKs) or its second message-activated kinases including protein kinase A (PKA) and protein kinase C (PKC), which, in turn, promotes the recruitment of β -arrestin, resulting in uncoupling of the GPCR from G proteins. Over the past decade, increasing evidence has revealed non-canonical signaling pathways of GPCRs, e.g., G protein-independent β -arrestin-mediated signaling pathways [5].

GPCRs are not only essentially involved in the regulation of fundamental physiological processes from vision, smell,

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and taste to neurological, cardiovascular, and endocrine functions, but also participate in the pathogenesis of various diseases, thus making this superfamily of receptors as the most successful category of drug targets [6,7]. However, barely 4% of known GPCRs have been successfully developed into drug targets, thus the rest of GPCR family provides a great opportunity of new targets for pharmaceutical development [8].

Energy homeostasis is vital for all kinds of cellular processes. An imbalance of energy intake and expenditure causes metabolic syndrome and subsequently leads to metabolic diseases such as obesity and diabetes mellitus. We are in such a time that the metabolic diseases and their cardiovascular complications have become not only a global medical problem but also a social burden due to the overwhelming prevalence of overnutrition and lack of physical activity. There is a compelling need to better understand how our body controls energy homeostasis, how it changes in disease development, and how we can deal with the challenge. This review is aimed to summarize our present knowledge of GPCRs that play important roles in governing energy homeostasis and discuss outstanding questions in the

field, thus to stimulate more mechanistic and translational studies that may lead to better diagnosis and therapeutics for metabolic diseases.

Energy homeostasis is precisely controlled by a large number of GPCRs. Their involvement begins even before foods enter our mouths as the odorant and visual GPCRs are activated, and then the taste GPCRs while eating. But it is much more than that as the taste GPCRs distribute not only on the taste buds but also throughout the gastrointestinal (GI) tract [9,10]. Recent findings have shown that the taste receptors, the fatty acid receptors and a few newly orphanized GPCRs act as nutrient chemosensing receptors, which sense the change of carbohydrates, protein and lipids in the gut and induce the secretion of several gut peptide hormones, including glucose dependent insulinotropic peptide (GIP), glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PYY) and cholecystokinin (CCK) [10–12]. These peptide hormones, which target respective GPCRs, play essential roles in energy homeostasis by regulating appetite, release of insulin and glucagon, and gut motility [13,14]. The most important GPCRs in the energy homeostasis are summarized in Table 1.

Table 1 GPCRs in energy homeostasis

Nomenclature	Endogenous ligands	G protein-coupling	Expression	Physiological function	Chromosome location (human)
Glucagon receptor	Glucagon>>oxyntomodulin=GLP-1	Gs, Gq	Liver and kidney with less amounts found in heart, adipose tissue, spleen, thymus, adrenal glands, pancreas, cerebral cortex, and gastrointestinal tract	Stimulate gluconeogenesis and glycogenolysis; increases cardiac glucose oxidation and glycolysis, and elicit a positive inotropic effect	17q25
GLP-1 receptor	GLP-1>>GIP=glucagon	Gs	Pancreas, hypothalamus, hippocampus, cerebral cortex, kidney, lung, heart, muscle, and GI tract	Increases insulin synthesis and release	6p21
GIP receptor	Gastric inhibitory polypeptide (GIP)	Gs	Pancreas, gut, adipose tissue, heart, pituitary, and inner layers of the adrenal cortex	Stimulates insulin and glucagon secretion and lipogenesis; inhibits lipolysis in adipocytes; enhances fatty acid uptake	19q13.3
Ghrelin receptor	ghrelin	Gs, Gq	predominantly expressed in the pituitary and at lower levels in the thyroid gland, pancreas, spleen, myocardium and adrenal gland	Stimulate food intake while decrease energy expenditure and body fat utilization	3p25–26
Y1 receptor	NPY>PYY>>PP	Gi	Brain and colon, kidney, adrenal gland, heart, placenta		4q31.3–q32
Y2 receptor	NPY>PYY>>PP	Gq	Brain and intestine, kidney proximal tubules	Inhibit gut motility, gastric emptying, acid and pancreatic exocrine secretion; control circadian rhythm and anxiety	4q31
Y4 receptor	PP>NPY=PYY	Gi, Gq	Brain, coronary artery, and intestines		10q11.2
Y5 receptor	NPY>PYY>PP	Gi	Brain, small intestine and nonepithelial tissue of colon		4q31–q32
FFA1 (GPR40)	long chain carboxylic acids	Gq, Gi, Gs	Pancreas, spleen, bone marrow	Insulin secretion stimulation, stimulating incretin release	19q13.1
FFA2 (GPR43)	short chain fatty acids	Gq, Gi	Pancreas, adipose tissue, muscle, bone marrow, spleen, GI tract, skin, lung	Stimulation of GLP-1 and leptin secretion, and adipogenesis, neutrophil chemotaxis	19q13.1
FFA3 (GPR41)	short chain fatty acids	G _i	Pancreas, vena cava, intestines	Increases leptin production	19q13.1
FFA4 (GPR120)	long-chain FFAs	Gq	Adipose tissue, pancreas, GI tract, muscle, pituitary gland	Regulates the secretion of incretin hormone GLP-1	10q23.33
GPR84	Medium-chain-length fatty acids	G _i	Brain, spinal cord, heart, colon, thymus, spleen, kidney, liver, intestine, placenta, lung, leukocytes	Chronic inflammation	12q13.13

1 Glucagon receptor

Glucagon, the counter-regulatory hormone of insulin, is primarily produced by the α -cells of the islets of Langerhans. In addition, glucagon can be converted from proglucagon by a processing enzyme, prohormone convertase 2 (PC2), in the hypothalamus. Two decades ago, both rat and human glucagon receptor (GR) genes were cloned [15,16]. The crystal structure of human glucagon receptor, a prototypical Class B GPCR, was successfully resolved at 3.4 Å resolution last year [17]. Binding of glucagon to its receptors activates both Gs and Gq signaling pathways which regulate glucose metabolism and energy homeostasis [18]. It is noteworthy that in addition to glucagon, oxyntomodulin and GLP-1 can also bind to GR with a 10-fold lower affinity as compared to glucagon [16]. The major biological function of glucagon is to stimulate hepatic glucose output through both gluconeogenesis and glycogenolysis, while it also increases cardiac glucose oxidation and glycolysis, and elicits a positive inotropic effect. Moreover, glucagon increases satiety in the hypothalamus, augments glomerular filtration and water reabsorption in the kidneys, and decreases gut motility [19], thus suppressing food intake. Human population genetic studies have revealed a loss of function mutation of GR, a single heterozygous Gly40Ser, which is associated with late-onset type 2 diabetes mellitus (T2D) [20]. While global deletion of GR increases fetal lethality and causes islet α - and δ -cell hyperplasia in mice [21], GR-deficient mice are resistant to diet-induced obesity and streptozotocin-mediated beta cell loss and hyperglycemia [22], indicating a therapeutic potential of GR in the treatment of diabetes.

2 GLP-1 receptor

On the opposite side of glucagon are the incretins, a group of gastrointestinal hormones, which decrease blood glucose level via stimulating release of insulin. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two well-characterized incretins [23]. GLP-1 is derived from the transcription product of the proglucagon gene [24] mainly in the intestinal L cells that secrete GLP-1 as a gut hormone. There are two biologically active forms of GLP-1, including GLP-1-(7-37) and GLP-1-(7-36). Remarkably, GLP-1 stimulates insulin secretion and inhibits glucagon secretion, accounting for over 70% of the insulin response following an oral glucose challenge [25,26].

GLP-1 induced insulinotropic effect is mediated by GLP-1 receptor (GLP1R), resulting in activation of adenylyl cyclase in response to an increase in extracellular glucose level [27]. Specifically, GLP-1 binds specifically to GLP1R with a greater affinity compared to other related

peptides such as GIP and glucagon which are also able to bind to GLP1R [28]. Stimulation of GLP1R leads to activation of Gs-adenylyl cyclase-cAMP-PKA pathway, resulting in increased insulin synthesis and release in pancreatic cells [29]. GLP1R is also expressed in the brain where it is involved in the control of appetite [30]. GLP1R^{-/-} mice exhibit impaired insulin secretion upon oral glucose challenge [31].

The active form of GLP-1 has a half-life of only 1–2 min, as it is rapidly inactivated by the enzyme dipeptidyl-peptidase 4 (DPP4) [32], which hampers its application in the treatment of T2D. Over the past decade, stabilized GLP1 mimetics such as exendin and DPP4 inhibitors have been developed and become one of the most important therapeutics of T2D in clinic [27]. GLP-1-based therapy exceeds the other T2D treatment, because it targets both defective insulin secretion and augmented glucagon release.

3 GIP receptor

The other incretin, GIP, also known as gastric inhibitory polypeptide, is a 42-amino acid polypeptide synthesized by K cells in the proximal small bowel [33,34]. It was originally implicated as an inhibitor of gastric acid secretion and gastrin release, but subsequently was demonstrated to potentially stimulate insulin release in the presence of elevated glucose. GIP is the first released intestine hormone in response to an enteral dose of glucose followed by GLP-1 release from L-type enteroendocrine cells of the ileum and colon [35]. Although GIP contributes at least as much as GLP-1 to the incretin effect under physiological conditions, it is not true in T2D. While pharmacological levels of GLP-1 or its DPP-IV-resistant analogues promote insulin secretion in T2D, the elevation of GIP levels fails to induce a similar insulinotropic effect [36,37]. In addition to its incretin effects, GIP also stimulates glucagon secretion from pancreatic β -cells, stimulates lipogenesis, inhibits lipolysis in adipocytes, and enhances fatty acid uptake. Due to these counterproductive effects, the clinical utility of GIP receptor agonists is limited.

The GIP receptor (GIPR) is widely expressed in various tissues including pancreatic β -cells, adipose tissue, and the brain [23,38]. GIPR belongs to subfamily 1B of the GPCR superfamily. All receptors of this subfamily are featured by a large extracellular N terminus that contains six highly conserved cysteine residues forming three disulfide bridges, a serpentine domain with seven transmembrane helices, and a short intracellular C terminus [3,39]. Activation of GIPR, a Gs-coupled receptor, evokes the adenylyl cyclase-cAMP-PKA signaling pathway. GIPR^{-/-} mice are resistant to high-fat diet-induced obesity and insulin resistance. Moreover, crossing GIPR^{-/-} with obese ob/ob (Lepob/Lepob) mice ameliorates obesity and metabolic defects [38]. In contrast, mice with double knockout of both GLP1 and GIP

receptors exhibit significantly impaired glycemic excursion, while the individual receptor knockout mice only show a modest phenotype [40]. These studies have demonstrated that GLP1 and GIP have a synergistic effect on energy homeostasis.

4 Ghrelin receptor

GH secretagogue receptor 1 (GHSR-1) was first identified in swine pituitary and hypothalamus by its ability to bind artificial compounds with growth hormone (GH)-releasing activity (hexarelin or GHRP6) in 1996 [41]. It was not until 1999 when Kojima et al. [42] identified the cognate ligand for it from rat stomach extracts, as the 28 amino acid peptide 'ghrelin'. Ghrelin, secreted mainly by the stomach and pancreas [43], is regarded as a 'hunger' hormone, as plasma levels of ghrelin peaks directly at meal initiation, followed by a postprandial decrease to baseline within the first hour after a meal [44]. Ghrelin is presently the only known circulating gut hormone which can promote a positive energy balance by stimulating food intake while decreasing energy expenditure and body fat utilization [45]. Both peripheral and central administration of ghrelin potently promotes body weight gain and adiposity through a stimulation of food intake while decreasing energy expenditure and body fat utilization [46]. Thus, it has been defined as a counterpart of leptin.

Ghrelin and GHS-R1 are involved in many important physiological processes, such as the central regulation of food intake and energy homeostasis, regulation of cardiovascular functions, stimulation of gastric acid secretion and motility, modulation of cell proliferation and survival, and inhibition of inflammation and regulation of immune function [45,47]. The active form of GPSR is GHSR1a, which coupled to both Gq and Gs signaling pathways [48]. In the arcuate nucleus (ARC), GHSR1a is co-expressed with other anabolic neuropeptides, NPY and agouti-related peptide (AgRP), which potently stimulate food intake while decreasing energy expenditure [49]. As a result, ghrelin-mediated activation of GHSR1a entails an increased expression and release of NPY and AgRP in the ARC, which, in turn, leads to the activation of anabolic downstream pathways and ultimately results in the stimulation of food intake and a decrease of energy expenditure [50,51]. Because of its orexigenic, adipogenic and diabetogenic activities, ghrelin and its receptors have emerged as an attractive target for the treatment of obesity and T2D.

5 Y receptors

The neuropeptide Y system, comprising neuropeptide Y (NPY), peptide YY (PYY), pancreatic polypeptide (PP) and the corresponding Y receptors (Y1, Y2, Y4, Y5 and Y6), is

well known for its role in the regulation of energy homeostasis and associated processes [52,53]. NPY, PYY and PP have been classified into a family of homologous peptides because of their sequence homology and common tertiary structural motif, a hairpin fold [54]. NPY is widely distributed in the sympathetic nervous system [55] and hypothalamic nuclei [56]. PYY and PP are both gut-derived, with PYY being mainly produced by the endocrine L cells of the intestines, stomach and pancreas [57], and PP being primarily produced in F type cells of the pancreas [58]. Just like GLP-1, both NPY and PYY are also processed by the specific protease-dipeptididyl peptidase-IV (DPP-IV) [59].

PYY and NPY inhibit gut motility, gastric emptying, acid and pancreatic exocrine secretion and are potent vasoconstrictors [60]. In the intestine, the Y1, Y2 and Y5 receptor subtypes have similar affinity for PYY and NPY. The Y1 receptor was the first Y receptor to be cloned [61] and was recognized as a "feeding receptor" to mediate NPY-induced hyperphagia [62]. A recent study has shown that leptin could stimulate the NPY neuron activity in the hypothalamus in diet-induced obese mice, indicating the role of NPY in leptin-mediated appetite control [63]. Several Y receptor antagonists targeting Y1, Y2, Y4 and Y5 were shown to cause weight loss or protection against diet-induced obesity in rodent models [64,65]. Furthermore, ablation of both Y2 and Y4 receptors in ob/ob mice attenuated the hyperphagia-caused obesity [66]. PP, which is a preferential agonist at Y4 receptors, is released postprandially from endocrine cells in pancreatic islets and causes a negative energy balance by decreasing food intake and gastric emptying and by increasing energy expenditure. Knockout of the Y4 gene leads to an increase in nocturnal feeding [67], while transgenic overexpression of PP in mice reduces food intake and body weight gain [68].

6 Cannabinoid receptors

The first cannabinoid (CB) receptor was first cloned from rat cerebral cortex in 1990, which we now refer to as CB1 [69], and three years later, in 1993, a second cannabinoid receptor, CB2, was identified in a human promyelocytic leukemic cell line [70]. The CB1 receptor is expressed mainly in the brain (central nervous system, CNS), but also in the lung, liver and kidney [71]. The CB2 receptor is expressed mainly on T cells of the immune system, macrophages and B cells, and hematopoietic cells [72]. Both receptors exhibit their effects mainly through activation of Gi [73], while CB1 receptors can signal through Gs proteins alternatively [74,75]. In the liver, activation of the CB1 receptor is known to increase *de novo* lipogenesis [76]. Tetrahydrocannabinol (THC) from the cannabis plant acts via CB1 receptors in the hypothalamic nuclei to directly increase appetite [77]. The amount of endocannabinoids produced is inversely correlated with the amount of leptin in

the blood [78]. When subjected to a high-fat diet, CB1 knockout mice tend to be about 60% leaner and slightly less hungry than the wild type [79]. Furthermore, inactivation of CB1 receptors reduces plasma insulin and leptin levels. Rimonabant, the first selective CB1 receptor blocker, was approved by the European Commission for the treatment of obesity and overweight [80,81], but was withdrawn from the market due to the risk of serious psychiatric problems. The study on the CB2R null mice showed that it influences the development and progression of atherosclerotic lesions by mediating the apoptotic response of macrophages to oxLDL [82].

The first of these “endocannabinoids” to be identified were N-arachidonylethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG) [83]. Accumulating evidence suggests the involvement of endocannabinoid system in energy metabolism [84,85]. For instance, patients with T2D exhibit increased 2-AG levels in visceral, but not subcutaneous adipose tissue as compared to controls [86]. Furthermore, CB1 activation induced glucose uptake and GLUT4 translocation in human primary adipocytes [87].

It has been proposed that additional cannabinoid receptors exist as the actions of compounds, such as abnormal cannabidiol that produces cannabinoid-like effects on blood pressure and inflammation, do not activate either CB1 or CB2. A few orphan receptors, namely GPCR18, GPR55, and GPR119, have been implicated as CB3 due to their sequence homology or their ability to interact with cannabinoids [85,88–90]. Among them, the association between GPR119 and metabolism is evidenced by its abundant expression in the pancreas and gastrointestinal tract and its inhibitory effects on food intake and body weight gain in rats, probably through the regulation of incretin and insulin secretion [90–92].

7 Fatty acid receptors

The free fatty acid receptors (FFARs) are G protein-coupled receptors (GPCRs) activated by free fatty acids (FFAs) [93]. GPR41 and GPR43, also known as FFAR3 and FFAR2, respectively, are activated by short-chain fatty acids, and GPR84 is activated by medium-chain FFAs, while GPR40 and GPR120 (also known as FAA1 and FAA4 respectively) by medium- and long-chain ones [93,94]. Stimulation of FFARs elicits multiple biological functions, including secretion of insulin and incretin hormones and adipocyte differentiation as well [93,95].

It has been shown that prolonged exposure to elevated FFAs results in impaired insulin secretion by inhibiting insulin biosynthesis [96,97]. However, recent evidence indicates that not all FFAs inhibit insulin secretion. For instance, FFAR1, also known as GPR40, is predominantly expressed in pancreatic β -cells and elevates insulin secretion upon medium- and long-chain FFA stimulation. A series of novel

agonists for GPR40 have been identified, with some as potential new drugs for T2D [98]. Furthermore, GPR41, GPR43 and GPCR120 promote the secretion of incretins and other energy control hormones such as leptin, adiponectin, and PYY [99–103]. GPR84 signaling is likely involved in chronic inflammation [104,105]. But the exact physiological role of GPR84 merits future investigation.

8 Other GPCRs

In addition to the aforementioned GPCRs, there are many other GPCRs involved in the energy homeostasis regulation. In particular, the multimeric amylin receptors are atypical GPCRs that are actually formed by the interaction of calcitonin receptor with receptor activity-modifying proteins (RAMPs) [106]. Amylin is cosecreted with insulin from the pancreatic β -cells and plays an important role in nutritional status via inhibiting food intake, gastric emptying and post-prandial glucagon secretion [107,108]. The Cholecystokinin A (CCKA) receptor is located mainly on pancreatic acinar cells, whereas Cholecystokinin B (CCKB) receptor is enriched mostly in the brain and stomach. CCKB receptor also binds to gastrin, a gastrointestinal hormone involved in stimulating gastric acid release and growth of the gastric mucosa. The CCK receptors are involved in the regulation of nociception, anxiety, memory and hunger [109,110]. Cholic acid (CA) administration can completely prevent high fat diet-induced changes in adipose mass and morphology, and reverse diet-induced obesity [111].

Moreover, recent studies have made the list of GPCRs in energy regulation even longer. Leucine-rich repeat-containing G-protein coupled receptor 4 (LGR4) was reported to play vital roles in metabolism as the LGR4 null mice manifested increased energy expenditure and brown adipocyte differentiation from epididymal white adipose tissue (WAT) [112]. GPR83, which is colocalised with ghrelin receptor, was shown to regulate systemic energy through both ghrelin-dependent and ghrelin-independent pathways [113]. The activation of TGR5, a bile acid (BA) receptor, significantly blunts high-fat diet induced obesity in mice [114]. Additionally, in pancreatic β -cells, activation of M3 muscarinic receptors induces insulin release during the pre-absorptive phase of feeding [115], while stimulation of sweet taste receptors (T1R2/T1R3) regulates not only the release of GLP-1 in the intestine [116] but also adipocyte differentiation and metabolism [117].

In summary, various GPCRs are involved in the regulation of energy homeostasis from nutrient sensing, appetite control to glucose and fatty acid metabolism. In particular, three classes of GPCRs, including peptide receptors (GR, GLP1R, GIPR, NPY receptors, PYY receptors), fatty acid receptors, and emerging orphan GPCRs, play important physiological and pathophysiological roles in regulating food intake and energy expenditures. These studies not only

shed new light on our understanding of energy homeostasis, but also open new avenues for the treatment of metabolic diseases including obesity and T2D. However, more systematic approaches including systems biology and omics should be innovatively adopted into the field of metabolic research and medicine, so that a comprehensive network control of energy homeostasis will be revealed, and safer and more effective drugs will be developed in the foreseeable future.

- 1 Katritch V, Cherezov V, Stevens RC. Structure-function of the G protein-coupled receptor superfamily. *Annu Rev Pharmacol Toxicol*, 2013, 53: 531–556
- 2 Lagerstrom MC, Schioth HB. Structural diversity of G protein-coupled receptors and significance for drug discovery. *Nat Rev Drug Discov*, 2008, 7: 339–357
- 3 Bockaert J, Pin JP. Molecular tinkering of G protein-coupled receptors: an evolutionary success. *EMBO J*, 1999, 18: 1723–1729
- 4 Pierce KL, Premont RT, Lefkowitz RJ. Seven-transmembrane receptors. *Nat Rev Mol Cell Biol*, 2002, 3: 639–650
- 5 Lefkowitz RJ, Shenoy SK. Transduction of receptor signals by beta-arrestins. *Science*, 2005, 308: 512–517
- 6 Overington JP, Al-Lazikani B, Hopkins AL. How many drug targets are there? *Nat Rev Drug Discov*, 2006, 5: 993–996
- 7 Kontoyianni M, Liu Z. Structure-based design in the GPCR target space. *Curr Med Chem*, 2012, 19: 544–556
- 8 Tyndall JD, Sandilya R. GPCR agonists and antagonists in the clinic. *Med Chem*, 2005, 1: 405–421
- 9 Colombo M, Trevisi P, Gandolfi G, Bosi P. Assessment of the presence of chemosensing receptors based on bitter and fat taste in the gastrointestinal tract of young pig. *J Anim Sci*, 2012, 90(suppl 4): 128–130
- 10 Rozengurt E. Taste receptors in the gastrointestinal tract. I. Bitter taste receptors and alpha-gustducin in the mammalian gut. *Am J Physiol Gastrointest Liver Physiol*, 2006, 291: G171–177
- 11 Nguyen CA, Akiba Y, Kaunitz JD. Recent advances in gut nutrient chemosensing. *Curr Med Chem*, 2012, 19: 28–34
- 12 Shirazi-Beechey SP, Daly K, Al-Rammahi M, Moran AW, Bravo D. Role of nutrient-sensing taste 1 receptor (T1R) family members in gastrointestinal chemosensing. *Br J Nutr*, 2014, 1–8
- 13 Troke RC, Tan TM, Bloom SR. The future role of gut hormones in the treatment of obesity. *Ther Adv Chronic Dis*, 2014, 5: 4–14
- 14 Murphy KG, Bloom SR. Gut hormones and the regulation of energy homeostasis. *Nature*, 2006, 444: 854–859
- 15 Lok S, Kuijper JL, Jelinek LJ, Kramer JM, Whitmore TE, Sprecher CA, Mathewes S, Grant FJ, Biggs SH, Rosenberg GB. The human glucagon receptor encoding gene: structure, cDNA sequence and chromosomal localization. *Gene*, 1994, 140: 203–209
- 16 MacNeil DJ, Occi JL, Hey PJ, Strader CD, Graziano MP. Cloning and expression of a human glucagon receptor. *Biochem Biophys Res Commun*, 1994, 198: 328–334
- 17 Siu FY, He M, de Graaf C, Han GW, Yang D, Zhang Z, Zhou C, Xu Q, Wacker D, Joseph JS, Liu W, Lau J, Cherezov V, Katritch V, Wang MW, Stevens RC. Structure of the human glucagon class B G-protein-coupled receptor. *Nature*, 2013, 499: 444–449
- 18 Quesada I, Tudurí E, Ripoll C, Nadal A. Physiology of the pancreatic α -cell and glucagon secretion: role in glucose homeostasis and diabetes. *J Endocrinol*, 2008, 199: 5–19
- 19 Gromada J, Franklin I, Wollheim CB. Alpha-cells of the endocrine pancreas: 35 years of research but the enigma remains. *Endocr Rev*, 2007, 28: 84–116
- 20 Hager J, Hansen L, Vaisse C, Vionnet N, Philippi A, Poller W, Velho G, Carcassi C, Contu L, Julier C. A missense mutation in the glucagon receptor gene is associated with non-insulin-dependent diabetes mellitus. *Nat Genet*, 1995, 9: 299–304
- 21 Vuguin PM, Kedeas MH, Cui L, Guz Y, Gelling RW, Nejathaim M, Charron MJ, Teitelman G. Ablation of the glucagon receptor gene increases fetal lethality and produces alterations in islet development and maturation. *Endocrinology*, 2006, 147: 3995–4006
- 22 Conarello SL, Jiang G, Mu J, Li Z, Woods J, Zychband E, Ronan J, Liu F, Roy RS, Zhu L, Charron MJ, Zhang BB. Glucagon receptor knockout mice are resistant to diet-induced obesity and streptozotocin-mediated beta cell loss and hyperglycaemia. *Diabetologia*, 2007, 50: 142–150
- 23 Neumiller JJ. Incretin pharmacology: a review of the incretin effect and current incretin-based therapies. *Cardiovasc Hematol Agents Med Chem*, 2012, 10: 276–288
- 24 Gosmain Y, Masson MH, Philippe J. Glucagon: the renewal of an old hormone in the pathophysiology of diabetes. *J Diabetes*, 2013, 5: 102–109
- 25 Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*, 2007, 132: 2131–2157
- 26 Paschetta E, Hvalbyrg M, Musso G. Glucose-dependent insulinotropic polypeptide: from pathophysiology to therapeutic opportunities in obesity-associated disorders. *Obes Rev*, 2011, 12: 813–828
- 27 Ahren B. Islet G protein-coupled receptors as potential targets for treatment of type 2 diabetes. *Nat Rev Drug Discov*, 2009, 8: 369–385
- 28 Fehmann HC, Jiang J, Schweinfurth J, Dörsch K, Wheeler MB, Boyd AE 3rd, Göke B. Ligand-specificity of the rat GLP-I receptor recombinantly expressed in Chinese hamster ovary (CHO-) cells. *Z Gastroenterol*, 1994, 32: 203–207
- 29 Drucker DJ, Philippe J, Mojsov S, Chick WL, Habener JF. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. *Proc Natl Acad Sci USA*, 1987, 84: 3434–3438
- 30 Kinzig KP, D'Alessio DA, Seeley RJ. The diverse roles of specific GLP-1 receptors in the control of food intake and the response to visceral illness. *J Neurosci*, 2002, 22: 10470–10476
- 31 Scrocchi LA, Brown TJ, McCluskey N, Brubaker PL, Auerbach AB, Joyner AL, Drucker DJ. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene. *Nat Med*, 1996, 2: 1254–1258
- 32 Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. *Diabetes*, 1998, 47: 1663–1670
- 33 Moody AJ, Thim L, Valverde I. The isolation and sequencing of human gastric inhibitory peptide (GIP). *FEBS Lett*, 1984, 172: 142–148
- 34 Jörnvall H, Carlquist M, Kwauk S, Otte SC, McIntosh CH, Brown JC, Mutt V. Amino acid sequence and heterogeneity of gastric inhibitory polypeptide (GIP). *FEBS Lett*, 1981, 123: 205–210
- 35 Irwin DM, Prentice KJ. Incretin hormones and the expanding families of glucagon-like sequences and their receptors. *Diabetes Obes Metab*, 2011, 13(suppl 1): 69–81
- 36 Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab*, 2004, 287: E199–206
- 37 Gromada J, Bokvist K, Ding WG, Holst JJ, Nielsen JH, Rorsman P. Glucagon-like peptide 1 (7-36) amide stimulates exocytosis in human pancreatic beta-cells by both proximal and distal regulatory steps in stimulus-secretion coupling. *Diabetes*, 1998, 47: 57–65
- 38 Yamada Y, Seino Y. Physiology of GIP—a lesson from GIP receptor knockout mice. *Horm Metab Res*, 2004, 36: 771–774
- 39 Hoare SR. Mechanisms of peptide and nonpeptide ligand binding to Class B G-protein-coupled receptors. *Drug Discov Today*, 2005, 10: 417–427
- 40 Preitner F, Ibberson M, Franklin I, Binnert C, Pende M, Gjinovci A, Hansotia T, Drucker DJ, Wollheim C, Burcelin R, Thorens B. Gluco-incretins control insulin secretion at multiple levels as revealed in mice lacking GLP-1 and GIP receptors. *J Clin Invest*, 2004, 113: 635–645
- 41 Howard AD, Feighner SD, Cully DF, Arena JP, Liberatore PA, Rosenblum CI, Hamelin M, Hreniuk DL, Palyha OC, Anderson J, Parese PS, Diaz C, Chou M, Liu KK, McKee KK, Pong SS, Chaung LY, Elbrecht A, Dashkevich M, Heavens R, Rigby M, Sirinathsinghji DJ,

- Dean DC, Melillo DG, Patchett AA, Nargund R, Griffin PR, DeMartino JA, Gupta SK, Schaeffer JM, Smith RG, Van der Ploeg LH. A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science*, 1996, 273: 974–977
- 42 Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*, 1999, 402: 656–660
- 43 Inui A, Asakawa A, Bowers CY, Mantovani G, Laviano A, Meguid MM, Fujimiya M. Ghrelin, appetite, and gastric motility: the emerging role of the stomach as an endocrine organ. *FASEB J*, 2004, 18: 439–456
- 44 Williams DL, Cummings DE. Regulation of ghrelin in physiologic and pathophysiologic states. *J Nutr*, 2005, 135: 1320–1325
- 45 Muller TD, Tschöp MH. Ghrelin—a key pleiotropic hormone-regulating systemic energy metabolism. *Endocr Dev*, 2013, 25: 91–100
- 46 Tschöp M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. *Nature*, 2000, 407: 908–913
- 47 Castañeda TR, Tong J, Datta R, Culler M, Tschöp MH. Ghrelin in the regulation of body weight and metabolism. *Front Neuroendocrinol*, 2010, 31: 44–60
- 48 Cong WN, Golden E, Pantaleo N, White CM, Maudsley S, Martin B. Ghrelin receptor signaling: a promising therapeutic target for metabolic syndrome and cognitive dysfunction. *CNS Neurol Disord Drug Targets*, 2010, 9: 557–563
- 49 Barsh GS, Schwartz MW. Genetic approaches to studying energy balance: perception and integration. *Nat Rev Genet*, 2002, 3: 589–600
- 50 Kamegai J, Tamura H, Shimizu T, Ishii S, Sugihara H, Wakabayashi I. Central effect of ghrelin, an endogenous growth hormone secretagogue, on hypothalamic peptide gene expression. *Endocrinology*, 2000, 141: 4797–4800
- 51 Kamegai J, Tamura H, Shimizu T, Ishii S, Sugihara H, Wakabayashi I. Chronic central infusion of ghrelin increases hypothalamic neuropeptide Y and Agouti-related protein mRNA levels and body weight in rats. *Diabetes*, 2001, 50: 2438–2443
- 52 Zhang L, Bijker MS, Herzog H. The neuropeptide Y system: pathophysiological and therapeutic implications in obesity and cancer. *Pharmacol Ther*, 2011, 131: 91–113
- 53 Sharman JL, Benson HE, Pawson AJ, Lukito V, Mpamhanga CP, Bombail V, Davenport AP, Peters JA, Spedding M, Harmar AJ, NC-IUPHAR. IUPHAR-DB: updated database content and new features. *Nucleic Acids Res*, 2013, 41: D1083–D1088
- 54 Holzer P, Reichmann F, Farzi A. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut-brain axis. *Neuropeptides*, 2012, 46: 261–274
- 55 Ekblad E, Edvinsson L, Wahlestedt C, Uddman R, Håkanson R, Sundler F. Neuropeptide Y co-exists and co-operates with noradrenaline in perivascular nerve fibers. *Regul Pept*, 1984, 8: 225–235
- 56 Bai FL, Yamano M, Shiotani Y, Emson PC, Smith AD, Powell JF, Tohyama M. An arcuate-paraventricular and -dorsomedial hypothalamic neuropeptide Y-containing system which lacks noradrenaline in the rat. *Brain Res*, 1985, 331: 172–175
- 57 Ekblad E, Sundler F. Distribution of pancreatic polypeptide and peptide YY. *Peptides*, 2002, 23: 251–261
- 58 Adrian TE. Pancreatic polypeptide. *J Clin Pathol Suppl (Assoc Clin Pathol)*, 1978, 8: 43–50
- 59 Mentlein R. Dipeptidyl-peptidase IV (CD26)—role in the inactivation of regulatory peptides. *Regul Pept*, 1999, 85: 9–24
- 60 Vona-Davis LC, McFadden DW. NPY family of hormones: clinical relevance and potential use in gastrointestinal disease. *Curr Top Med Chem*, 2007, 7: 1710–1720
- 61 Herzog H, Baumgartner M, Vivero C, Selbie LA, Auer B, Shine J. Genomic organization, localization, and allelic differences in the gene for the human neuropeptide Y Y1 receptor. *J Biol Chem*, 1993, 268: 6703–6707
- 62 Haynes AC, Arch JR, Wilson S, McClue S, Buckingham RE. Characterisation of the neuropeptide Y receptor that mediates feeding in the rat: a role for the Y5 receptor? *Regul Pept*, 1998, 75–76: 355–361
- 63 Lee SJ, Verma S, Simonds SE, Kirigiti MA, Kievit P, Lindsley SR, Loché A, Smith MS, Cowley MA, Grove KL. Leptin stimulates neuropeptide Y and cocaine amphetamine-regulated transcript coexpressing neuronal activity in the dorsomedial hypothalamus in diet-induced obese mice. *J Neurosci*, 2013, 33: 15306–15317
- 64 MacNeil DJ. NPY Y1 and Y5 receptor selective antagonists as anti-obesity drugs. *Curr Top Med Chem*, 2007, 7: 1721–1733
- 65 Kamiji MM, Inui A. NPY Y2 and Y4 receptors selective ligands: promising anti-obesity drugs? *Curr Top Med Chem*, 2007, 7: 1734–1742
- 66 Lee NJ, Enriquez RF, Boey D, Lin S, Slack K, Baldock PA, Herzog H, Sainsbury A. Synergistic attenuation of obesity by Y2- and Y4-receptor double knockout in ob/ob mice. *Nutrition*, 2008, 24: 892–899
- 67 Edelsbrunner ME, Painsipp E, Herzog H, Holzer P. Evidence from knockout mice for distinct implications of neuropeptide-Y Y2 and Y4 receptors in the circadian control of locomotion, exploration, water and food intake. *Neuropeptides*, 2009, 43: 491–497
- 68 Ueno N, Inui A, Iwamoto M, Kaga T, Asakawa A, Okita M, Fujimiya M, Nakajima Y, Ohmoto Y, Ohnaka M, Nakaya Y, Miyazaki JI, Kasuga M. Decreased food intake and body weight in pancreatic polypeptide-overexpressing mice. *Gastroenterology*, 1999, 117: 1427–1432
- 69 Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*, 1990, 346: 561–564
- 70 Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*, 1993, 365: 61–65
- 71 Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA, International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacol Rev*, 2010, 62: 588–631
- 72 Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? *Prog Lipid Res*, 2011, 50: 193–211
- 73 Mukhopadhyay S, Shim JY, Assi AA, Norford D, Howlett AC. CB(1) cannabinoid receptor-G protein association: a possible mechanism for differential signaling. *Chem Phys Lipids*, 2002, 121: 91–109
- 74 Glass M, Felder CC. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. *J Neurosci*, 1997, 17: 5327–5333
- 75 Jarrahian A, Watts VJ, Barker EL. D2 dopamine receptors modulate galpha-subunit coupling of the CB1 cannabinoid receptor. *J Pharmacol Exp Ther*, 2004, 308: 880–886
- 76 Osei-Hyiaman D, DePetrillo M, Pacher P, Liu J, Radaeva S, Bátkai S, Harvey-White J, Mackie K, Offertáler L, Wang L, Kunos G. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest*, 2005, 115: 1298–1305
- 77 Kirkham TC, Tucci SA. Endocannabinoids in appetite control and the treatment of obesity. *CNS Neurol Disord Drug Targets*, 2006, 5: 272–292
- 78 Di Marzo V, Sepe N, De Petrocellis L, Berger A, Crozier G, Fride E, Mechoulam R. Trick or treat from food endocannabinoids? *Nature*, 1998, 396: 636–637
- 79 Ravinet Trillou C, Delgorge C, Menet C, Arnone M, Soubrié P. CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. *Int J Obes Relat Metab Disord*, 2004, 28: 640–648
- 80 Despres JP, Lay A, Sjöström L, Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med*, 2005, 353: 2121–2134
- 81 Florentin M, Kostapanos MS, Nakou ES, Elisaf M, Liberopoulos EN. Efficacy and safety of ezetimibe plus orlistat or rimonabant in statin-intolerant nondiabetic overweight/obese patients with dyslipidemia. *J Cardiovasc Pharmacol Ther*, 2009, 14: 274–282

- 82 Buckley NE. The peripheral cannabinoid receptor knockout mice: an update. *Br J Pharmacol*, 2008, 153: 309–318
- 83 Devane W, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, 1992, 258: 1946–1949
- 84 Nogueiras R, Diaz-Arteaga A, Lockie SH, Velásquez DA, Tschöp J, López M, Cadwell CC, Diéguez C, Tschöp MH. The endocannabinoid system: role in glucose and energy metabolism. *Pharmacol Res*, 2009, 60: 93–98
- 85 Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther*, 2010, 126: 21–38
- 86 Matias I, Gonthier MP, Orlando P, Martiadis V, De Petrocellis L, Cervino C, Petrosino S, Hoareau L, Festy F, Pasquali R, Roche R, Maj M, Pagotto U, Monteleone P, Di Marzo V. Regulation, function, and dysregulation of endocannabinoids in models of adipose and beta-pancreatic cells and in obesity and hyperglycemia. *J Clin Endocrinol Metab*, 2006, 91: 3171–3180
- 87 Pagano C, Pilon C, Calcagno A, Urbanet R, Rossato M, Milan G, Bianchi K, Rizzuto R, Bernante P, Federspil G, Vettor R. The endogenous cannabinoid system stimulates glucose uptake in human fat cells via phosphatidylinositol 3-kinase and calcium-dependent mechanisms. *J Clin Endocrinol Metab*, 2007, 92: 4810–4819
- 88 McHugh D, Hu SS, Rimmerman N, Juknat A, Vogel Z, Walker JM, Bradshaw HB. N-arachidonoyl glycine, an abundant endogenous lipid, potently drives directed cellular migration through GPR18, the putative abnormal cannabidiol receptor. *BMC Neurosci*, 2010, 11: 44
- 89 Johns DG, Behm DJ, Walker DJ, Ao Z, Shapland EM, Daniels DA, Riddick M, Dowell S, Staton PC, Green P, Shabon U, Bao W, Aiyyar N, Yue TL, Brown AJ, Morrison AD, Douglas SA. The novel endocannabinoid receptor GPR55 is activated by atypical cannabinoids but does not mediate their vasodilator effects. *Br J Pharmacol*, 2007, 152: 825–831
- 90 Lan H, Vassileva G, Corona A, Liu L, Baker H, Golovko A, Abbondanzo SJ, Hu W, Yang S, Ning Y, Del Vecchio RA, Poulet F, Laverty M, Gustafson EL, Hedrick JA, Kowalski TJ. GPR119 is required for physiological regulation of glucagon-like peptide-1 secretion but not for metabolic homeostasis. *J Endocrinol*, 2009, 201: 219–230
- 91 Ning Y, O'Neill K, Lan H, Pang L, Shan LX, Hawes BE, Hedrick JA. Endogenous and synthetic agonists of GPR119 differ in signalling pathways and their effects on insulin secretion in MIN6c4 insulinoma cells. *Br J Pharmacol*, 2008, 155: 1056–1065
- 92 Swaminath G. Fatty acid binding receptors and their physiological role in type 2 diabetes. *Arch Pharm (Weinheim)*, 2008, 341: 753–761
- 93 Hara T, Kimura I, Inoue D, Ichimura A, Hirasawa A. Free fatty acid receptors and their role in regulation of energy metabolism. *Rev Physiol Biochem Pharmacol*, 2013, 164: 77–116
- 94 Tazoe H, Otomo Y, Kaji I, Tanaka R, Karaki SI, Kuwahara A. Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. *J Physiol Pharmacol*, 2008, 59: 251–262
- 95 Newman L, Haryono R, Keast R. Functionality of fatty acid chemoreception: a potential factor in the development of obesity? *Nutrients*, 2013, 5: 1287–1300
- 96 Kashyap S, Belfort R, Gastaldelli A, Pratipanawatr T, Berria R, Pratipanawatr W, Bajaj M, Mandarino L, DeFronzo R, Cusi K. A sustained increase in plasma free fatty acids impairs insulin secretion in nondiabetic subjects genetically predisposed to develop type 2 diabetes. *Diabetes*, 2003, 52: 2461–2474
- 97 Ritz-Laser B, Meda P, Constant I, Klages N, Charollais A, Morales A, Magnan C, Ktorza A, Philippe J. Glucose-induced preproinsulin gene expression is inhibited by the free fatty acid palmitate. *Endocrinology*, 1999, 140: 4005–4014
- 98 Feng XT, Leng J, Xie Z, Li SL, Zhao W, Tang QL. GPR40: a therapeutic target for mediating insulin secretion (review). *Int J Mol Med*, 2012, 30: 1261–1266
- 99 Xiong Y, Swaminath G, Cao Q, Yang L, Guo Q, Salomonis H, Lu J, Houze JB, Dransfield PJ, Wang Y, Liu JJ, Wong S, Schwandner R, Steger F, Baribault H, Liu L, Coberly S, Miao L, Zhang J, Lin DC, Schwarz M. Activation of FFA1 mediates GLP-1 secretion in mice. Evidence for allosterism at FFA1. *Mol Cell Endocrinol*, 2013, 369: 119–129
- 100 Nagasaki H, Kondo T, Fuchigami M, Hashimoto H, Sugimura Y, Ozaki N, Arima H, Ota A, Oiso Y, Hamada Y. Inflammatory changes in adipose tissue enhance expression of GPR84, a medium-chain fatty acid receptor: TNF α enhances GPR84 expression in adipocytes. *FEBS Lett*, 2012, 586: 368–372
- 101 Zaibi MS, Stocker CJ, O'Dowd J, Davies A, Bellahcene M, Cawthorne MA, Brown AJ, Smith DM, Arch JR. Roles of GPR41 and GPR43 in leptin secretory responses of murine adipocytes to short chain fatty acids. *FEBS Lett*, 2010, 584: 2381–2386
- 102 Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F, Gribble FM. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes*, 2012, 61: 364–371
- 103 Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, Sugimoto Y, Miyazaki S, Tsujimoto G. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat Med*, 2005, 11: 90–94
- 104 Suzuki M, Takaishi S, Nagasaki M, Onozawa Y, Iino I, Maeda H, Komai T, Oda T. Medium-chain fatty acid-sensing receptor, GPR84, is a proinflammatory receptor. *J Biol Chem*, 2013, 288: 10684–1091
- 105 Wang J, Wu X, Simonavicius N, Tian H, Ling L. Medium-chain fatty acids as ligands for orphan G protein-coupled receptor GPR84. *J Biol Chem*, 2006, 281: 34457–34464
- 106 Hay DL, Christopoulos G, Christopoulos A, Sexton PM. Amylin receptors: molecular composition and pharmacology. *Biochem Soc Trans*, 2004, 32: 865–867
- 107 Cooper GJ. Amylin compared with calcitonin gene-related peptide: structure, biology, and relevance to metabolic disease. *Endocr Rev*, 1994, 15: 163–201
- 108 Higham CE, Hull RL, Lawrie L, Shennan KI, Morris JF, Birch NP, Docherty K, Clark A. Processing of synthetic pro-islet amyloid polypeptide (proIAPP) 'amylin' by recombinant prohormone convertase enzymes, PC2 and PC3, *in vitro*. *Eur J Biochem*, 2000, 267: 4998–5004
- 109 Noble F, Wank SA, Crawley JN, Bradwejn J, Seroogy KB, Hamon M, Roques BP, International Union of Pharmacology. XXI. Structure, distribution, and functions of cholecystokinin receptors. *Pharmacol Rev*, 1999, 51: 745–781
- 110 Dufresne M, Seva C, Fourmy D. Cholecystokinin and gastrin receptors. *Physiol Rev*, 2006, 86: 805–847
- 111 Watanabe M, Houten SM, Matak C, Christoffolete MA, Kim BW, Sato H, Messaddeq N, Harney JW, Ezaki O, Kodama T, Schoonjans K, Bianco AC, Auwerx J. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature*, 2006, 439: 484–489
- 112 Wang J, Liu R, Wang F, Hong J, Li X, Chen M, Ke Y, Zhang X, Ma Q, Wang R, Shi J, Cui B, Gu W, Zhang Y, Zhang Z, Wang W, Xia X, Liu M, Ning G. Ablation of LGR4 promotes energy expenditure by driving white-to-brown fat switch. *Nat Cell Biol*, 2013, 15: 1455–1463
- 113 Müller TD, Müller A, Yi CX, Habegger KM, Meyer CW, Gaylinn BD, Finan B, Heppner K, Trivedi C, Bielohuby M, Abplanalp W, Meyer F, Piechowski CL, Pratzka J, Stemmer K, Holland J, Hembree J, Bhardwaj N, Raver C, Ottaway N, Krishna R, Sah R, Sallee FR, Woods SC, Perez-Tilve D, Bidlingmaier M, Thorner MO, Krude H, Smiley D, DiMarchi R, Hofmann S, Pfluger PT, Kleinau G, Biebermann H, Tschöp MH. The orphan receptor Gpr83 regulates systemic energy metabolism via ghrelin-dependent and ghrelin-independent mechanisms. *Nat Commun*, 2013, 4: 1968
- 114 Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K. The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. *J Hepatol*, 2011, 54: 1263–1272
- 115 Gautam D, Han SJ, Hamdan FF, Jeon J, Li B, Li JH, Cui Y, Mears D, Lu H, Deng C, Heard T, Wess J. A critical role for beta cell M3

- muscarinic acetylcholine receptors in regulating insulin release and blood glucose homeostasis *in vivo*. *Cell Metab*, 2006, 3: 449–461
- 116 Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, Kim HH, Xu X, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF, Egan JM. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci USA*, 2007, 104: 15069–15074
- 117 Simon BR, Parlee SD, Learman BS, Mori H, Scheller EL, Cawthorn WP, Ning X, Gallagher K, Tyrberg B, Assadi-Porter FM, Evans CR, MacDougald OA. Artificial sweeteners stimulate adipogenesis and suppress lipolysis independently of sweet taste receptors. *J Biol Chem*, 2013, 288: 32475–32489

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