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G Protein–Coupled Receptors Targeting Insulin Resistance, Obesity, and Type 2 Diabetes Mellitus

Darren M. Riddy, Philippe Delerive, Roger J. Summers, Patrick M. Sexton, and Christopher J. Langmead

Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia (D.M.R., R.J.S., P.M.S., C.J.L.); and Institut de Recherches Servier, Pôle d'Innovation Thérapeutique Métabolisme, Suresnes, France (P.D.)

Address correspondence to: Dr. Christopher J. Langmead, Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, VIC 3052, Australia. E-mail: chris.langmead@monash.edu

Abstract——G protein–coupled receptors (GPCRs) continue to be important discovery targets for the treatment of type 2 diabetes mellitus (T2DM). Many GPCRs are directly involved in the development of insulin resistance and β-cell dysfunction, and in the etiology of inflammation that can lead to obesity-induced T2DM. This review summarizes the current literature describing a number of well-validated GPCR targets, but also outlines several new and promising targets for drug discovery. We highlight the importance of understanding the role of these receptors in the disease pathology, and their basic pharmacology, which will pave the way to the development of novel pharmacological probes that will enable these targets to fulfill their promise for the treatment of these metabolic disorders.

I. Introduction

A. Pathophysiology and Diagnosis of Type 2 Diabetes Mellitus

Data from the International Diabetes Federation Atlas (2015) indicates that over 415 million people have been diagnosed with diabetes, a figure that by 2040 is projected to rise to more than 642 million. In almost 90% of cases, the patients have been diagnosed with type 2 diabetes mellitus (T2DM). Although countries such as China, Brazil, and the United States have the largest number of people with T2DM, it is predicted that countries in the Middle East and Africa will soon have the greatest increase in prevalence. Clinically it is proving difficult to determine the onset of T2DM, with estimates of 5–10 years prior to diagnosis being suggested (Cooper, 2012). Typically, in the first 2 years following diagnosis, pancreatic β-cell function can decrease by 40%–70%, indicating that early diagnosis is critical to identifying the most suitable patient care (Cooper, 2012).

Current therapies for T2DM focus on restoring glycemia levels to those of healthy subjects. The American Diabetes Association has recommended that the glycemic goal for T2DM patients be an HbA1c level $\leq$7%, with an optimal level of 6.5%. Traditionally treatments for T2DM have focused on pancreatic β-cell dysfunction and insulin resistance; however, additional pathophysiological mechanisms associated with T2DM, including hyperglucagonemia in pancreatic α-cells, increased glucose reabsorption in the kidneys (Mazzola, 2012) and tissue inflammation (Donath, 2014), are gaining greater recognition. Due to a close link between obesity and T2DM, the initial treatment prescribes a change in lifestyle with a specific focus on diet and inactivity. However, current adherence of obese and/or prediabetic patients to lifestyle recommendations to prevent the development of overt T2DM is low. Furthermore, the impact of intensive lifestyle intervention focusing on weight loss does not significantly reduce the rate of cardiovascular events in obese with T2DM (Wing et al., 2013). Therefore, pharmacological intervention is often eventually required to aid in glycemic control (García-Pérez et al., 2013).

T2DM is a multifaceted disease involving pancreatic α- and β-cells, skeletal muscle, adipose tissue, liver, intestine, kidney, and the central nervous system (CNS) (DeFronzo, 2009; Lin and Sun, 2010). In healthy people, during fasting conditions, glucagon is released from α-cells in the liver (Gylfe and Gilon, 2014), which helps to maintain normal blood glucose concentrations. Following food intake, blood glucose levels increase, and this, in turn, causes the pancreas to secrete insulin from pancreatic β-cells to inhibit glycogenolysis and gluconeogenesis and increase glycogen synthesis (Perley and Kipnis, 1967). In addition, the biologically active incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released from endocrine cells following food intake, and act on GLP-1 receptor (GLP-1R) and GIP receptors expressed on pancreatic β-cells, causing a direct potentiation of insulin secretion. Furthermore, insulin increases blood glucose uptake by skeletal muscle and adipose tissue, mediated by translocation of glucose transporter 4 (GLUT4) (Mueckler, 1992). Insulin also promotes the storage of glucose as glycogen in the liver and inhibits lipolysis from adipose tissue (Kalupahana et al., 2012). Once blood glucose levels revert to normal, insulin secretion ceases and normoglycemia is restored (Wilcox, 2005).

B. β-Cell Dysfunction and Insulin Resistance

Glucose-stimulated insulin secretion from β-cells occurs due to an increase in calcium (Ca^{2+}) influx into the cell following closing of ATP-sensitive potassium (K^+) channels and activation of the protein kinase C

(PKC) signaling pathway (Cooper, 2012). A decrease in insulin-stimulated glucose uptake in insulin-sensitive tissues such as skeletal muscle is termed insulin resistance and leads to progressive hyperglycemia (Fig. 1) (Olefsky and Glass, 2010). The molecular mechanism by which insulin resistance occurs includes activation of the serine/threonine kinase pathway by translocation of PKCε, leading to phosphorylation of insulin receptor substrate (IRS)-1 (Morino et al., 2006). Furthermore, dysregulation in the levels of ceramides, sphingolipids, triacylglycerols, and diacylglycerols, through an increase in dietary fat sources, can further impair IRS phosphorylation, culminating in a deficiency of the downstream signaling of the insulin cascade (Galbo et al., 2013; Camell et al., 2015; Iqbal et al., 2017). An increase in these ectopic lipids is associated with complications of T2DM, including nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH) (Shulman, 2000; Samuel and Shulman, 2012).

Phosphorylation of IRS-1 promotes negative feedback that interferes with normal insulin signaling (Cooper, 2012). This reduced function in insulin-sensitive tissues causes pancreatic β-cells to increase insulin secretion and cellular mass (Donath and Shoelson, 2011; Cerf, 2013). Activation of membrane-bound G protein–coupled receptors (GPCRs) enhances insulin secretion via PKC activation or through an increase in cAMP, which activates protein kinase A and potentiates the Ca^{2+} influx (Heit et al., 2006; Vangoitsenhoven et al., 2012). An increase in pancreatic β-cell proliferation has been suggested to be caused by signaling through IRS-2, which causes protein kinase B phosphorylation, and inhibition of the forkhead-O transcription factor 1

(Heit et al., 2006; Prentki and Nolan, 2006). Expression of the transforming growth factor (TGF)-β superfamily signaling inhibitor, SMAD7, in pancreatic β-cells, has also been implicated as it promotes cell proliferation in vivo by increasing CyclinD1 and CyclinD2 expression (Xiao et al., 2014). The increased insulin secretion is initially sufficient to overcome the higher demand, but over time exhausted β-cells cannot cope with the increased insulin demand, resulting into exacerbated insulin resistance (Chawla et al., 2011; Kalupahana et al., 2012; Lee and Lee, 2014).

It is important to note that T2DM may develop as a consequence of early β-cell dysfunction in certain patients, whereas in others insulin resistance precedes the defects in the β-cells (Færch et al., 2013, 2015). T2DM is therefore considered as a very heterogeneous disease.

C. Obesity-Induced Type 2 Diabetes Mellitus

In recent years, evidence has emerged linking immune cell infiltration into adipose tissue to causes of chronic low-grade inflammation (Fig. 2) that has a key role in the pathogenesis of obesity-induced insulin resistance (Olefsky and Glass, 2010; Chawla et al., 2011; Donath and Shoelson, 2011; Shu et al., 2012; Krinninger et al., 2014). Although these changes can be ascribed to the natural ageing process, there is a contribution from increasingly sedentary lifestyles and the consumption of high-fat foods that causes a change in metabolic and immune cells, including adipocytes and macrophages (Tanti et al., 2013). Further insight into the mechanistic link between insulin resistance and inflammation has revealed activation of B cells by
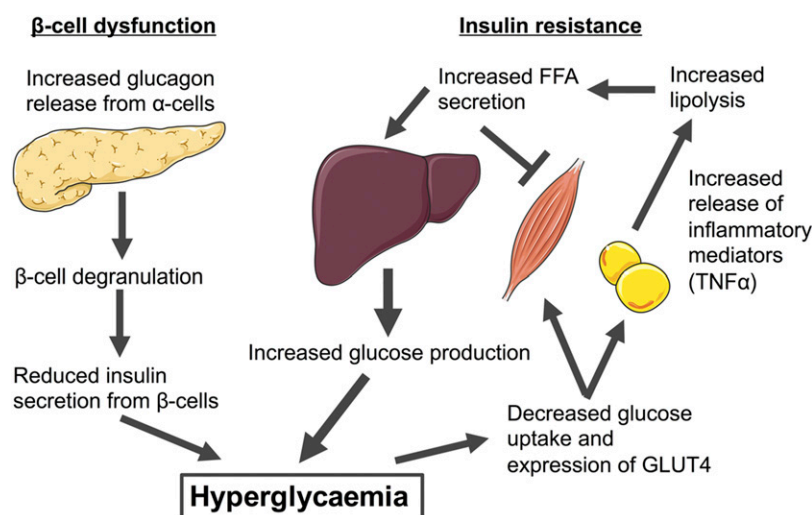
Fig. 1. Pathology of T2DM. β-cell dysfunction occurs following insult from increased FFA levels, obesity, insulin resistance, and inflammation. Initially the β-cell compensates by increasing the release of insulin; however, over time this compensatory mechanism fails and reduction in β-cell mass is evident. The loss of β-cell mass occurs from cellular degranulation, resulting in an increase in glucagon from α-cells and a decrease in insulin secretion. The reduced plasma insulin results in an increase in glucose levels. Glucose-sensitive tissues, including skeletal muscle and adipocytes, are unable to accommodate the increased glucose concentration. Increased fat accumulation in adipocytes also leads to an increase in proinflammatory cytokine release and increased lipolysis. A further release of FFAs stimulates the liver to increase glucose production. Persistent glucose release preserves the hyperglycemic environment, leading ultimately to T2DM.
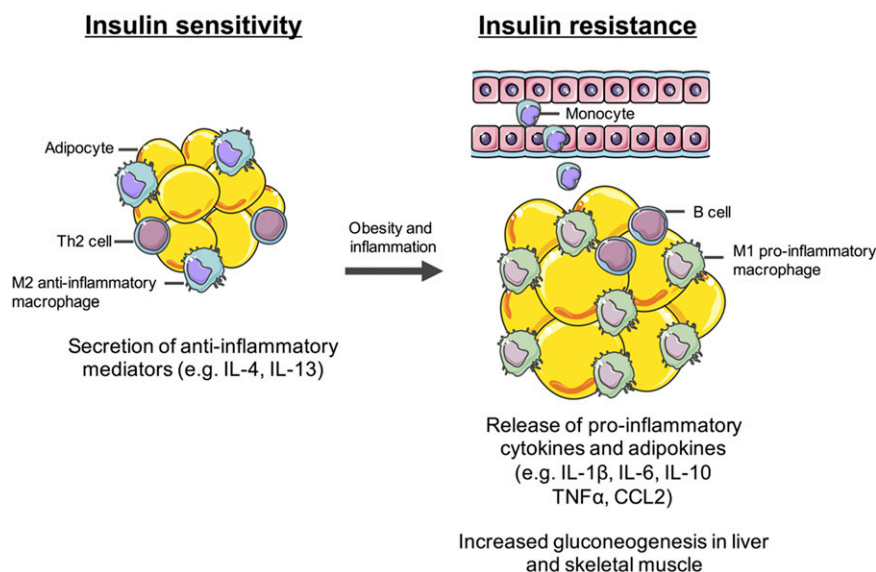
Fig. 2. Inflammation and insulin resistance. Under normal conditions, tissue-resident M2 macrophages surround adipocytes and secrete anti-inflammatory mediators, including IL-4 and IL-13, maintaining an insulin-sensitive environment. Increased levels of nutrients, including fat, FFAs, and proinflammatory mediators, result in adipocyte hypertrophy, lipolysis, and ER stress. In addition, further release of proinflammatory mediators, including IL-6, IL-10, and CCL2 (MCP-1), results in transition, differentiation, and polarization of the tissue-resident M2 macrophages into M1 proinflammatory macrophages. Furthermore, recruitment and differentiation of circulating peripheral blood monocytes result in an increase in the proinflammatory milieu. Other metabolic tissues, including the liver and skeletal muscle, are also susceptible to the increased levels of cytokine production, ER stress, and macrophage recruitment, resulting in an increase in glucose production, fueling the hyperglycemic state further.

nuclear factor κ light-chain enhancer (NF-κB) and the inhibitor of κB kinase (IKK)-β, resulting in an increase in the expression and release of proinflammatory cytokines and in expression of their cognate receptors (Donath and Shoelson, 2011; Osborn and Olefsky, 2012). Similarly, the suppressor of cytokine signaling protein family, which interacts directly with Janus-activated kinases, is upregulated in obese patients (Tanti et al., 2013). Activation of the c-Jun N-terminal kinase (JNK) pathway, which is increased in obesity, causes a further release of proinflammatory cytokines in response to NF-κB activation (Donath and Shoelson, 2011).

Schroder et al. (2010) demonstrated that the inflammasome, which contains the nucleotide-binding oligomerization domain–like receptor, caspase-1, and the apoptosis-associated speck-like protein containing a caspase recruitment domain adapter protein, was capable of controlling the secretion of proinflammatory cytokines, including interleukin (IL)-1β and IL-18. Increased activation of the inflammasome has also been observed in macrophages of obese animals and humans, in which the levels of caspase-1 and IL-1β are significantly upregulated (Tanti et al., 2013; Esser et al., 2014, 2015). Furthermore, obese mice lacking nucleotide-binding oligomerization domain like protein pyrin domain-containing 3 displayed improved insulin resistance and glucose homeostasis as a direct result of a reduction in IL-18 and interferon-γ expression and an enhancement in insulin signaling (Vandanmagsar et al., 2011).

The relationship between inflammation and insulin resistance is not new because benefits on glycemic control have been noted in diabetic patients taking sodium salicylate, the active ingredient in the nonsteroidal anti-inflammatory drug, aspirin (Williamson, 1901). Unfortunately, this theory was not reconsidered until 1993, when it was demonstrated that tumor necrosis factor (TNF)-α was expressed in the adipose tissue of obese animals and insulin-resistant patients (Hotamisligil et al., 1993, 1995), thus identifying a direct connection between obesity, inflammation, and insulin resistance.

Under normal conditions, M2 macrophages surround adipocytes in adipose tissue and secrete anti-inflammatory mediators, including IL-4 and IL-13, that maintain an insulin-sensitive environment (Fig. 2). Increased levels of nutrients, including fat, free fatty acids (FFAs), and proinflammatory mediators, cause adipocyte hypertrophy, lipolysis, and endoplasmic reticulum (ER) stress (Hotamisligil, 2010). In addition, further release of proinflammatory mediators, including IL-6, IL-10, and C-C-chemokine ligand (CCL) 2 [also known as monocyte chemoattractant protein (MCP)-1], results in differentiation and polarization of anti-inflammatory M2 macrophages into M1 proinflammatory macrophages. Furthermore, recruitment and differentiation of circulating peripheral blood monocytes result in an increase in the proinflammatory milieu. Other metabolic tissues, including the liver and skeletal muscle, are also susceptible to the increased levels of cytokine production, ER stress, and macrophage recruitment, resulting in an increase in glucose production and hyperglycemia.

Current anti-inflammatory targets for the treatment of T2DM include IKK-β–NF-κB [salsalate; Schwarz Pharma (now part of UCB, Brussels, Belgium) &

Elan Pharma, Dublin, Ireland], IL-6 (tocilizumab; Roche, Basel, Switzerland), IL-1β (canakinumab, Novartis, Basel, Switzerland; LY2189102, Eli Lilly, Indianapolis, IN), and TNF-α (CDP571; Celltech Therapeutics, Slough, UK). At present the number of clinical trials evaluating anti-inflammatory compounds and biologics for the treatment of T2DM is limited, with results to date indicating a modest effect on insulin resistance and β-cell dysfunction (Goldfine et al., 2011, 2013; Esser et al., 2015). Although encouraging, this raises the question of the level of biologic redundancy that exists within these inflammatory pathways, and whether modulation of a single mediator, or pathway, would prevent the development of insulin resistance or T2DM. Moreover, it is still unclear whether low-grade inflammation is the main driver of the development of T2DM or part of a wider pathology (for a comprehensive review, see Kusminski et al., 2016). As the mechanism behind obesity-induced insulin resistance is still unknown, there is still conjecture as to whether targeting inflammation will prove an effective strategy in T2DM (Kraakman et al., 2014; Liu et al., 2016). Therefore, further trials are required to understand whether a relationship exists; such studies may enable investigation into other facets of the disease, including effects on adipocytes and adipose tissue, β-cell function, and complications that typically arise with T2DM, including microvascular and macrovascular disease (Fowler, 2008) and NASH (Michelotti et al., 2013; Wree et al., 2013).

Although targeting inflammation appears to be potentially a useful approach, targeting different mechanisms to current therapies for T2DM, it is important to note that different preclinical mouse models are divergent in their immune cell populations. For example, BALB/c mice demonstrate a T helper (Th)2-type (anti-inflammatory) cytokine bias, whereas the C57BL/6 strain shows bias toward a Th1-type cytokine phenotype that includes proinflammatory mediators; however, in humans, including those diagnosed with T2DM, there appears to be little or no bias (Lee and Lee, 2014). Greater use of human cells and tissues during target validation and preclinical stages would allow better translation to be achieved earlier, enabling greater confidence in the target and compounds before committing to expensive clinical trials.

D. Involvement of G Protein–Coupled Receptors

Currently, there are more than 30 GPCRs that have been implicated in the development and progression of β-cell dysfunction, insulin resistance, obesity, and T2DM (Fig. 3; Table 1). However, at present, only the GLP-1R has been successfully targeted therapeutically. As this receptor has been comprehensively reviewed (Donnelly, 2012; Meier, 2012; Koole et al., 2013; Cantini et al., 2016; Graaf et al., 2016), it will be discussed only briefly in the following section. Although some of the other receptors listed in Table 1 have been reviewed elsewhere (Ahrén, 2009; Thorburn et al., 2014), these will be mentioned together with a more detailed examination of recently identified GPCRs, many of which are still classified as orphans, making them potentially less well characterized as drug targets for exploitation.

II. G Protein–Coupled Receptors and β-Cell Dysfunction and Insulin Resistance

A. Adrenoceptors

Activation of the sympathetic nervous system, with consequent release of the catecholamines, adrenaline
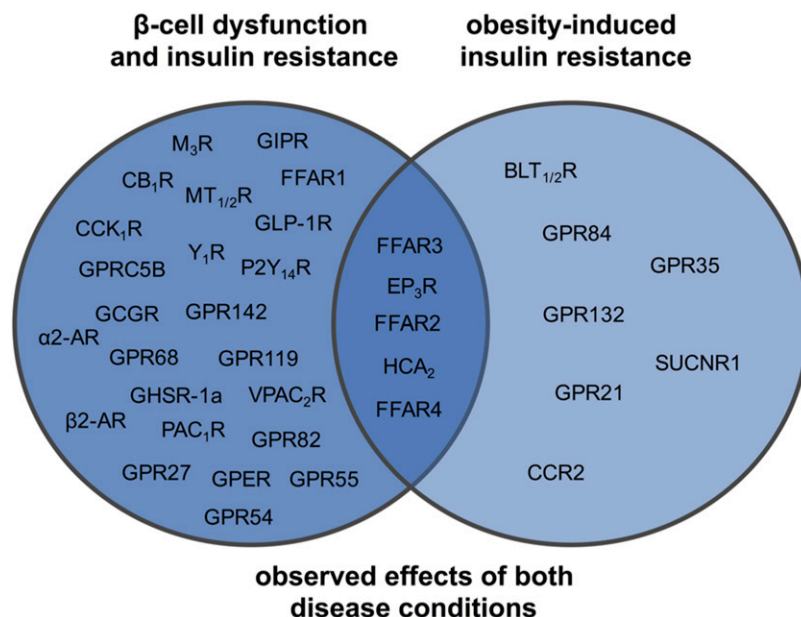
Fig. 3. Venn diagram illustrating GPCRs, as described in Table 1, involved in the development and/or progression of β-cell dysfunction, insulin resistance, and obesity-induced T2DM. Some overlap between these two groups exists, which will continue to expand with our increased understanding of these receptors and the disease pathophysiology. The number of targets illustrated perhaps reflects focus on β-cell function over the past 20–30 years.

TABLE 1
Summary of published GPCRs involved in the development and progression of β-cell dysfunction, insulin resistance, obesity, and type 2 diabetes mellitus
Nomenclature as described in "The Concise Guide to Pharmacology 2015/16" (Alexander et al., 2015).

GPCR	Endogenous Ligand(s)	Family	G Protein Coupling	Compounds Available	Expression Profile	(Pathophysiologic Effects)	References
α_{1A}-AR	Noradrenaline	A	$G\alpha_{q/11}$	A61603, Dabuzalgron, Oxymetazoline	Pancreatic β-cells, liver, muscle, and heart	Direct and indirect influence on glucose metabolism	Cheng et al. (2012); Piascik and Perez (2001); Wier and Morgan (2003); Evans et al. (2011); Beak et al. (2017); Willis et al. (2016)
α_{2A}-AR	Noradrenaline	A	$G\alpha_{i/o}$	Idazoxan, MK-912	Pancreatic α- and β-cells	Activation on α-cells increases glucagon secretion, and on β-cells decreases insulin secretion	Gonzalez-Manchon et al. (1989); Limbird (1988); Ortiz-Alonso et al. (1991); Ostenson et al. (1988); Rosengren et al. (2010)
β_2-AR	Adrenaline, noradrenaline	A	$G\alpha_s$	BRL37344, Clenbuterol	Widely expressed	Vasodilation, increased insulin secretion from β-cells in the pancreas and directly by stimulating insulin-independent glucose uptake in skeletal muscle	Nevzorova et al. (2002, 2006); Dehvari et al. (2012); Sato et al. (2014); Evans et al. (2010)
β_3-AR	Noradrenaline	A	$G\alpha_{i/o}$ $G\alpha_s$	BRL26830, BRL35135, BRL37344, L755507, Mirabegron	Bladder, heart, gastrointestinal tract, adipose tissue	Improvement in insulin sensitivity is related to downregulation of TNF-α expression	Arch et al. (1984, 2008)); Emorine et al. (1989); Ghorbani et al. (2012); Michel and Gravas (2016); Nedergaard and Cannon (2014); Roth Flach et al. (2013)
$BLT_{1/2}R$	Leukotriene B4	A	$G\alpha_{q/11}$ $G\alpha_{i/o}$	Solabegron	Immune cells, endothelial cells	Insulin resistance in hepatocytes and myocytes	Li et al. (2015b); Spite et al. (2011); Yokomizo et al. (2001)
CB_1R	Anandamide, 2-AG	A	$G\alpha_{i/o}$	JD5037, Rimonabant	Pancreatic β-cells, brain	Stimulation of food intake	Gruden et al. (2016); Jourdan et al. (2014)
CCK_1R	CCK	A	$G\alpha_{q/11}$		Pancreatic β-cells, gastrointestinal tract, pancreas	Stimulation of exocrine pancreatic and gall bladder contraction	Ahrén et al. (2000)
CCR2	CCL2, CCL7, CCL8, CCL11, CCL13	A	$G\alpha_{i/o}$	CCX140-B, Cenicriviroc, NOX-E36	Immune cells	Obesity-induced insulin resistance by macrophage proinflammatory activity	de Zeeuw et al. (2015); Gutierrez et al. (2011); Kawano et al. (2016); Lefebvre et al. (2016); Menne et al. (2017); Sullivan et al. (2013a,b); Weisberg et al. (2006)
EP_3R	Prostaglandin E_2	A	$G\alpha_{q/11}$ $G\alpha_{i/o}$	DG-041	Brain, kidney	Negatively regulates glucose and hormone-stimulated insulin secretion	Ceddia et al. 2016; Kimple et al. (2013); Neuman and Kimple (2013)
FFAR1 (GPR40)	MCFAs (C9–C22): linoleic acid	A	$G\alpha_{i/o}$ $G\alpha_{q/11}$ $G\alpha_s$	Compound 15i, GW9508, LY2881835, LY2922470, TAK-875	Pancreatic β-cells, enteroendocrine cells, brain, liver, muscle, omental adipocytes, islet α-cells	Indirect release of GLP-1 from intestinal endocrine cells; insulin secretion from pancreatic β-cells	Blad et al. (2012); Defossa and Wagner (2014); Houthuizen (2016); Husted et al. (2017); Mancini and Poitout (2013, 2015); Bindels et al. (2013); McKenzie et al. (2015); Thorburn et al. (2014)

(continued)

TABLE 1—Continued

GPCR	Endogenous Ligand(s)	Family	G Protein Coupling	Compounds Available	Expression Profile	(Pathophysiologic Effects)	References
FFAR2 (GPR43)	SCFAs (C2–C7): formate, acetate, propionate, butyrate, pentanoate	A	$G\alpha_{i/o}$ $G\alpha_{q/11}$	2-Methylacrylic acid, AZ1729 (PAM), Compound 34, Compound 4, Compound 58	Pancreatic β-cells, innate immune cells, enteroendocrine cells, gut epithelium, white adipose tissue, spleen, bone marrow	G protein bias, inhibition of lipolysis, immune function, insulin-mediated fat accumulation, control of body energy	Blad et al. (2012), Bolognini et al. (2016), Husted et al. (2017), Bindels et al. (2013); McKenzie et al. (2015), Smith et al. (2011), Thorburn et al. (2014)
FFAR3 (GPR41)	SCFAs (C3–C7): formate, acetate, propionate, butyrate, pentanoate	A	$G\alpha_{i/o}$		Pancreatic β-cells, adipocytes, enteroendocrine cells, brain, lung, immune cells	Anti-inflammation, involved in energy expenditure and metabolic regulation; activation causes release of leptin	Husted et al. (2017), Inoue et al. (2014), Thorburn et al. (2014), Ulven (2012)
FFAR4 (GPR120)	Long-chain unsaturated fatty acids (C14–C18): docosahexaenoic acid	A	$G\alpha_{q/11}$	Compound A, GW9508	Pancreatic β-cells, enteroendocrine cells, macrophages	Stimulation of GLP-1 secretion, involvement of G protein–dependent and independent pathways, proinflammation	Hirasawa et al. (2005), Houthuijzen (2016), Husted et al. (2017), Im (2016), Konno et al. (2015), Li et al. (2015a), Oh et al. (2010), Stone et al. (2014), Ulven and Christiansen (2015)
GCGR	Glucagon	B	$G\alpha_{s}$		Pancreatic β-cells, hepatocytes	Stimulates hepatic glucose output	Kieffer et al. (1996)
GHSR-1a	Ghrelin	A	$G\alpha_{q/11}$ $G\alpha_{i/o}$ $G\alpha_{12/13}$		Pancreatic β-cells, widely expressed	Stimulates ghrelin secretion	Dezaki et al. (2008)
GIPR	GIP	B	$G\alpha_{s}$		Pancreatic β-cells, adipocytes, small intestine, stomach, adrenal cortex, lung, pituitary, heart, testis, bone, brain	Stimulates GLP-1 secretion, inhibits gastric emptying, induces adipocyte differentiation	Flatt (2008)
GLP-1R	GLP-1-(7–36), GLP-1-(7–37)	B	$G\alpha_{s}$	Albiglutide, Dulaglutide, Exenatide, Liraglutide, Semaglutide, Taspoglutide	Pancreatic β-cells, brain, heart, kidney, gastrointestinal tract	Satiety, inhibits gastric emptying, inhibits glucagon secretion	Donnelly (2012), Graaf et al. (2016), Meier (2012), Secher et al. (2014), Sisley et al. (2014)
GPER (GPR30)	17β-estradiol (E2)	A	$G\alpha_{i/o}$ $G\alpha_{s}$	ICI 182, 780, Tamoxifen, Raloxifene, G-1, G15, G36	Pancreatic β-cells, placenta, lung, liver, prostate, ovary, brain	Promotes insulin production, β-cell survival and adipogenesis	Balhuizen et al. (2010), Davis et al. (2014), Dennis et al. (2009, 2011), Kumar et al. (2011), Sharma et al. (2013, 2017), Wang et al. (2016)
GPR21		A	$G\alpha_{q}$		Macrophages, brain, heart	Coordinates macrophage proinflammatory activity in the context of obesity-induced insulin resistance	Gardner et al. (2012), Osborn et al. (2012)
GPR27		A	$G\alpha_{q/11}$		Pancreatic β-cells	Positive insulin promoter and glucose-stimulated insulin secretion	Ku et al. (2012)
GPR35	Kynurenic acid, pamoic acid, lysophosphatidic acid	A	$G\alpha_{i/o}$		Monocytes, neutrophils, gastrointestinal tract, peripheral nervous tissue, mast cells	Indirect release of GLP-1	MacKenzie et al. (2011), Maravillas-Montero et al. (2015), Shore and Reggio (2015)

(continued)

TABLE 1—*Continued*

GPCR	Endogenous Ligand(s)	Family	G Protein Coupling	Compounds Available	Expression Profile	(Pathophysiologic Effects)	References
GPR54 (KiSS1R)	Kisspeptin	A	$G\alpha_{q/11}$		Pancreatic β-cells, brain, blood vessels, placenta	Inhibition of tumor growth	Popa et al. (2008)
GPR55	Lysophosphatidylinositol	A	$G\alpha_{q/11}$ $G\alpha_{12/13}$		Brain	Energy homeostasis through the regulation of food intake, fuel storage in adipocytes, gut motility, and insulin secretion	Liu et al. (2015a); Meadows et al. (2015); Ross (2009); Simcocks et al. (2014)
GPR68	Proton sensing (pH 6–7.6)	A	$G\alpha_{i/o}$ $G\alpha_{q/11}$	Lorazepam, Ogerin (PAM)	Widely expressed	Controls pancreatic β-cell response to acidic microenvironment	Chandra et al. (2016); Huang et al. (2015b)
GPR82		A			Gastrointestinal glands, gall bladder, and pancreas	Influences food intake, energy, and body weight balance	Engel et al. (2011)
GPR84	MCFAs (C9–C14): capric acid, 6-n-octylaminouracil	A	$G\alpha_{i/o}$	Compound 1	Immune cells, adipocytes, macrophages	Obesity-induced insulin resistance by macrophage proinflammatory activity	Blad et al. (2012); Suzuki et al. (2013); Talukdar et al. (2011); Thorburn et al. (2014); Wang et al. (2006)
GPR119	Lipid amines	A	$G\alpha_{s}$	GSK2041706, GSK1292263, MBX2982, PSN821	Pancreatic β-cells, enteroendocrine cells, brain	Causes release of GLP-1 and GIP; Release of insulin from pancreatic β-cells	Chu et al. (2008); Hansen et al. (2012); Ritter et al. (2016); Yang et al. (2016)
GPR132	Long-chain n-acyl amides, pH, commensal metabolites	A	$G\alpha_{s}$ $G\alpha_{13}$	Compound 1	Macrophages, adipose tissue, skeletal muscle	Involved in the cell cycle and promotes chemotaxis and proliferation	Cohen et al. (2015); Shehata et al. (2015)
GPR142		A	$G\alpha_{q}$	CLP-3094, Compound 33	Exclusively pancreatic β-cells	Stimulates insulin secretion under conditions of high blood glucose	Du et al. (2012); Lizarzaburu et al. (2012); Toda et al. (2013); Yu et al. (2013)
GPRC5B		C	$G\alpha_{12/13}$		Pancreatic β-cells	Increased expression contributes to reduced insulin secretion and β-cell viability	Kim et al. (2012); Kurabayashi et al. (2013); Soni et al. (2013)
GPRC6A	L-Arginine, L-Lysine, L-Ornithine, Osteocalcin	C	$G\alpha_{q}$	Compound 7, Compound 34b	Pancreatic β-cells	Increased pancreatic β-cell proliferation, and insulin release from pancreatic islets	Di Nisio et al. (2017); Jørgensen et al. (2017); Pi et al. (2008, 2011, 2016); Johansson et al. (2015); Rueda et al. (2016); Smajilovic et al. (2013)
HCA$_2$ (GPR109A)	SCFAs (C4–C8): butyrate, nicotinic acid	A	$G\alpha_{i/o}$	GSK256073	Adipocytes, neutrophils, macrophages, intestinal epithelial cells	Intracellular triglyceride lipolysis in adipocytes; activation causes unwanted flushing side effect, activation may cause insulin resistance in skeletal muscle	Dobbins et al. (2013, 2015); Thorburn et al. (2014); Wanders and Judd (2011)
M$_3$R	Acetylcholine, choline	A	$G\alpha_{q/11}$		Pancreatic β-cells, widely expressed	Enhanced glucose-stimulated insulin secretion from pancreatic β-cells	Gautam et al. (2008)
MT$_{1/2}$R	Melatonin	A	$G\alpha_{i/o}$ $G\alpha_{q/11}$		Pancreatic α- and β-cells	Inhibition of glucose-stimulated insulin secretion, involvement in sleep/wake cycle	Jockers et al. (2016); Tuomi et al. (2016); Lane et al. (2016)

(continued)

TABLE 1—*Continued*

GPCR	Endogenous Ligand(s)	Family	G Protein Coupling	Compounds Available	Expression Profile	(Pathophysiologic Effects)	References
P2Y$_{14}$R (GPR105)	UDP and UDP-glucose	A	Gα$_{i/o}$		Pancreatic β-cells, smooth muscle, lung	Insulin secretion from pancreatic β-cells	Abbracchio et al. (2003) Carter et al. (2009) Fricks et al. (2008) Meister et al. (2014) Xu et al. (2012)
PAC$_1$R	PACAP	B	Gα$_s$		Pancreatic β-cells, widely expressed	Stimulation of glucagon and adrenaline secretion	Harmar et al. (2012) Moody et al. (2011)
SUCNR1 (GPR91)	Succinate	A	Gα$_{i/o}$ Gα$_{q/11}$	Compound 5 g	Adipose tissue, kidney, nervous system, dendritic cells, liver, spleen	Hypertensive effects, activation of renin angiotensin system	Carmone et al. (2015) Littlewood-Evans et al. (2016) McCreath et al. (2015) Rubic et al. (2008) Van den Bossche et al. (2017)
VPAC$_2$R	VIP and PACAP	B	Gα$_s$		Pancreatic β-cells, widely expressed	Stimulation of glucagon and adrenaline secretion, vasodilation	van Diepen et al. (2017) Harmar et al. (2012) Moody et al. (2011)
Y$_1$R	NPY	A	Gα$_{i/o}$		Pancreatic β-cells, widely expressed	Vasoconstriction	Brothers and Wahlestedt (2010)

from the adrenals, and noradrenaline from sympathetic nerve endings, is one of the most efficient ways of increasing blood glucose levels. The actions of the catecholamines are mediated by a group of nine GPCRs; these adrenoceptors are divided into three subgroups, α_1, α_2, and β, based on their sequence similarities and dominant signaling pathways. The α_1-adrenoceptor subgroup couples primarily to Gα$_{q/11}$ to activate phospholipase C, causing hydrolysis of phosphatidylinositol 4,5-bisphosphate to diacylglycerol, which activates protein kinase C (PKC), and inositol 1,4,5-trisphosphate, which releases Ca^{2+}, causing a variety of effects in many tissues (Piascik and Perez, 2001; Wier and Morgan, 2003); α_2-adrenoceptors are Gα$_{i/o}$-coupled receptors that inhibit adenylyl cyclase to reduce cAMP production, activate K$^+$ channels, and inhibit voltage-gated Ca^{2+} channels (Limbird, 1988); and β-adrenoceptors are Gα$_s$-coupled receptors that activate adenylyl cyclase to increase intracellular levels of cAMP. Each of the adrenoceptor subgroups has representatives that have a wide variety of effects on glucose metabolism; this is influenced by the receptor populations and signaling components expressed in particular cell types.

1. α_1-Adrenoceptor. Activation of α_1-adrenoceptors in liver, muscle, and adipose tissue has direct metabolic effects, but activation in other tissues, such as the heart, vasculature, and brain, can indirectly influence glucose metabolism. An association between the Arg347Cys polymorphism of the α_{1A}-adrenoceptor and severe metabolic abnormalities has been reported (Cheng et al., 2012). In skeletal muscle and adipose tissue, activation of α_{1A}-adrenoceptors mediates insulin-independent glucose uptake by a mechanism operating downstream of Ca^{2+} release and involving calmodulin-dependent protein kinase kinase and 5′ adenosine monophosphate–activated protein kinase (Cheng et al., 2000; Hutchinson and Bengtsson, 2006). Similar findings have been reported in response to α_1-adrenoceptor agonists in human adipose tissue (Boschmann et al., 2002; Flechtner-Mors et al., 2004). Of particular interest is the evidence that α_{1A}-adrenoceptors are cardioprotective in heart failure. Activation of α_1-adrenoceptors in the heart reduces pathologic remodelling, inhibits cell death, and improves myocyte contractility (Jensen et al., 2011; O'Connell et al., 2013; Willis et al., 2016; Beak et al., 2017) by mechanisms that include facilitation of glucose uptake (Tian and Abel, 2001; Shi et al., 2016). The role of α_{1A}-adrenoceptors in the failing heart is increasingly important for a number of reasons. In the normal heart, cardiac energy requirements are met primarily by ATP derived from fatty acid oxidation, but, in the failing heart, augmentation of energy production by glucose uptake becomes important for contractile function (Jaswal et al., 2011). In addition, whereas downregulation of β_1-adrenoceptors is a feature of heart failure, it is accompanied by upregulation of α_{1A}-adrenoceptors that provide an alternative insulin-independent mechanism

for promotion of glucose uptake and improved contractile function (Shi et al., 2016). In vivo these direct effects of α_1-adrenoceptor activation that promote glucose uptake into tissues may be offset by vasoconstriction that reduces blood flow and glucose uptake and by gluconeogenesis and glycogenolysis in the liver. Nevertheless, α_{1A}-adrenoceptors remain a potential target of interest for the treatment of metabolic disease with the discovery of biased agonism that may identify agonists that enhance glucose uptake without unwanted effects in the liver and on the vasculature (Evans et al., 2011).

2. α_2-Adrenoceptor. The metabolic effect of activation of α_2-adrenoceptors is mainly on the pancreas, adipose tissue, and the adrenals. α_{2A}-Adrenoceptors are present on both α- and β-cells of pancreatic islets, and activation on α-cells increases glucagon secretion and on β-cells decreases insulin secretion. Interestingly, there is a genetic association between α_{2A}-adrenoceptors and T2DM. In Goto-Kakizaki rats (model of T2DM), there is a locus containing *Adra2a* that was associated with a reduction in glucose-stimulated insulin secretion and a marked increase in α_{2A}-adrenoceptors in β-cells (Rosengren et al., 2010). The authors went on to examine whether single-nucleotide polymorphisms associated with ADRA2A in humans were associated with these traits and with T2DM. They found an association for one single-nucleotide polymorphism rs553668 that displayed reduced insulin secretion and an increased risk of T2DM. However, it has also been pointed out that the contribution of this mutation to overall T2DM is likely to be very small in line with the condition being polygenic and greatly influenced by lifestyle factors (Liggett, 2009). α_{2A}-Adrenoceptors also decrease lipolysis in adipocytes, suggesting that agonists would decrease glycerol available for hepatic gluconeogenesis (Gonzalez-Manchon et al., 1989). It has been suggested that α_2-adrenoceptor antagonists may provide a mechanism to improve insulin secretion and glucose tolerance, but studies in humans have been equivocal (Ostenson et al., 1988; Ortiz-Alonso et al., 1991).

3. β_2-Adrenoceptor. β_2-Adrenoceptors are the most widely distributed of the β-adrenoceptor subgroup and are expressed in skeletal muscle, cardiac muscle, and blood vessels, as well as liver, pancreas, and adipose tissue. Physiologic activation of β_2-adrenoceptors is mainly by adrenaline that is about two orders of magnitude more potent than noradrenaline at this receptor. Activation can lead to increased glucose uptake by a number of mechanisms—indirectly by vasodilation and by increasing insulin secretion from β-cells in the pancreas and directly by stimulating insulin-independent glucose uptake in skeletal muscle (Nevzorova et al., 2002, 2006). In the liver, stimulation of β_2-adrenoceptors causes glycogenolysis (Chu et al., 2000) and a significant increase in blood glucose levels. However, in skeletal muscle, activation of β_2-adrenoceptors

causes an increase in glucose uptake involving cAMP (Nevzorova et al., 2002, 2006), G protein receptor kinase (Dehvari et al., 2012), activation of mTORC2, and translocation of GLUT4 to the cell surface (Sato et al., 2014). The translocation of GLUT4 to the cell surface following β_2-adrenoceptor activation does not involve either Akt or AS160 as required by insulin (Sato et al., 2014). Administration of the long-acting β_2-adrenoceptor agonist clenbuterol to Goto-Kakizaki rats or obese C57BL/6J mice improves glucose tolerance (Sato et al., 2014). However, in addition, in adipose tissue there is increased lipolysis, and in a number of tissues including muscle and adipose tissue, β_2-adrenoceptor activation inhibits insulin-mediated glucose uptake (Hunt et al., 2002; Eriksson et al., 2004). Because ligand-directed signaling bias is also a feature of β_2-adrenoceptor signaling, it may be possible to develop therapies to lower blood glucose by actions on muscle without promoting glycogenolysis in the liver (Evans et al., 2010).

4. β_3-Adrenoceptor. The β_3-adrenoceptor has long been a potential target for the development of antiobesity drugs. Even before the β_3-adrenoceptor was cloned (Emorine et al., 1989), atypical β-adrenoceptor agonists had been developed that selectively stimulated lipolysis in brown adipocytes (Arch et al., 1984), an effect later shown to be mediated by β_3-adrenoceptors. mRNA encoding β_3-adrenoceptors is found in the bladder, heart, gastrointestinal tract, and adipose tissue, with particularly high concentrations in rodent brown fat (Evans et al., 1996, 1999; Emilsson et al., 1998). Although several studies have examined effects of β_3-adrenoceptor agonists on lipolysis and heat production in brown fat, it was apparent even in early studies that β_3-adrenoceptor (or atypical β-adrenoceptor) agonists improve glucose tolerance and insulin sensitivity (Cawthorne et al., 1984; Sennitt et al., 1985; Williams et al., 1999). Recent studies suggest that the improvement in insulin sensitivity is related to downregulation of TNF-α expression (Ghorbani et al., 2012). In contrast, it has been shown that β_3-adrenoceptor activation upregulates E-selectin to induce neutrophil infiltration and inflammation in adipose tissue (Roth Flach et al., 2013). Unfortunately, further development of the β_3-adrenoceptor as a therapeutic target stopped when it was discovered that the β_3-adrenoceptor agonists BRL26830, BRL37344, and BRL35135, developed on the basis of their actions on rodent brown fat, had much lower efficacy in humans. In addition, it became widely accepted that adult humans possessed little brown fat. Although subsequent studies have revealed that brown fat in humans is present and activated by cold (Nedergaard et al., 2007; Nedergaard and Cannon, 2014), there is some doubt as to whether metabolic effects on brown fat in humans are mediated by β_3-adrenoceptors (Arch, 2008). The recent introduction of the human selective β_3-adrenoceptor agonists mirabegron and solabegron for the treatment of overactive

bladder (Michel and Gravas, 2016) may allow the reinvestigation of the metabolic effects of β_3-adrenoceptor agonists (Arch, 2002).

B. CB$_1$R

Cannabinoid receptors are highly expressed in the CNS and on immune and inflammatory cells. There are two cannabinoid receptors, CB$_1$R and CB$_2$R, which are activated by the bioactive lipid molecules anandamide and 2-arachidonoylglycerol. Activation of CB$_1$R in the CNS causes an increased food intake that is further enhanced by the mesolimbic system. However, activation of CB$_1$R in metabolic tissues, including both white and brown adipocytes, causes an increase in fatty acid synthesis and reduction in lipolysis (Gruden et al., 2016); in Zucker diabetic fatty rats, overstimulation of CB$_1$R expressed on macrophages caused a marked increase in the activation of the inflammasome, apoptosis, and loss of β-cell function (Rohrbach et al., 2012). More recently, increased activation and signaling of the CB$_1$R in podocytes have been implicated in the development of type 2 diabetic nephropathy (Jourdan et al., 2014). Multiple studies have shown an improvement in metabolic phenotype when treated with CB$_1$R antagonists, including SR141716 (Rimonabant; Sanofi-Aventis, Paris, France) (Lafontan et al., 2007; Scheen, 2007; Nam et al., 2012). However, development of suitable therapeutics has proved challenging due to on-target neuropsychiatric effects. To overcome this, antagonists, such as JD5037, have been developed that do not penetrate the brain and improve pancreatic β-cell function and decrease cell loss in animal models (Chorvat, 2013; Jourdan et al., 2014); however, no human studies with this compound have yet been initiated. For a comprehensive review on the endocannabinoid system, see Gruden et al. (2016).

C. EP$_3$R

Prostaglandin E$_2$ is derived from arachidonic acid and is the endogenous ligand for the EP$_3$R. In the BTBR mouse strain, containing the leptin$^{ob/ob}$ mutation to cause obesity and diabetes, the EP$_3$R negatively regulates insulin secretion, and upregulation of both the ligand and receptor inhibits GLP-1R signaling (Neuman and Kimple, 2013). In a recent study by Neuman et al. (2017), enrichment of pancreatic islets with eicosapentaenoic acid, the precursor to prostaglandin E$_3$, caused a marked decrease in arachidonic acid, improved glucose-stimulated insulin secretion, a reduction in IL-1β production, and an improvement in glucose tolerance and β-cell function. Thus, blockade of EP$_3$R in pancreatic islets may be a viable therapy and recently new EP$_3$R antagonists have been disclosed (Abdel-Magid, 2015). However, data from Vanderbilt University (Nashville, TN) researchers have shown conflicting data. $Ep3r^{-/-}$ mice, generated on the C57BL/6 background and fed a high-fat diet, displayed an increase in macrophage infiltration, increased ectopic lipid accumulation in skeletal muscle and liver, and hepatic steatohepatitis, culminating in increased obesity, lipolysis, and increased insulin resistance (Ceddia et al., 2016). These discrepancies highlight the need for further investigation into EP$_3$R as a metabolic target and emphasize the context dependency of data between different animal models.

D. Free Fatty Acid Receptors: FFAR1, FFAR2, and FFAR3 (GPR40, GPR43, and GPR41)

The benefits of dietary fiber have been recognized for decades, although the identification of the targets involved in these effects has only recently been established (Thorburn et al., 2014; Alvarez-Curto and Milligan, 2016). FFA receptor (FFAR)1, FFAR2, and FFAR3 bind short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, produced from the fermentation of undigested carbohydrates and dietary fibers by colonic bacteria (Bindels et al., 2013; McKenzie et al., 2015), and have subsequently been termed metabolite-sensing GPCRs. SCFAs produce many beneficial effects, including maintenance of immune and gut homeostasis, regulation of T cell activation, and control of various immune pathways, specifically via the inhibition of NF-κB signaling (Thorburn et al., 2014). Each receptor is widely expressed in multiple metabolically important tissues, including pancreatic β-cells, immune cells, adipocytes, and enteroendocrine cells (Table 1); for comprehensive reviews, see Blad et al. (2012), Husted et al. (2017), and Milligan et al. (2017).

1. FFAR1. FFAR1 is a target of great therapeutic interest after the phase II clinical trial with fasiglifam (TAK-875), a FFAR1 agonist, yielded lowering of HbA1c without unwanted side effects, including hypoglycemia or tachyphylaxis (Burant, 2013). In animal models of T2DM, FFAR1 agonists increase levels of insulin secretion and may indirectly release GLP-1 from intestinal endocrine cells (Defossa and Wagner, 2014). FFAR1 appears to couple exclusively to G$\alpha_{q/11}$ proteins to produce an increase in cytosolic Ca^{2+} concentration, phospholipase C activation (Ahrén, 2009), and insulin secretion.

Perhaps surprisingly, fasiglifam acts allosterically at a secondary binding site, distinct to that used by the endogenous SCFA ligands (Lin et al., 2012), and was recently used to facilitate solution of the crystal structure of FFAR1 (Srivastava et al., 2014). Interestingly, the structure revealed a unique binding mode in which fasiglifam appears to access the allosteric binding pocket in the lipid bilayer. These data corroborate the allosteric mechanism identified from traditional binding studies and functional assays. One issue surrounding FFAR1 is the potential link with glucolipotoxicity by chronically elevated SCFA levels, which promotes β-cell dysfunction (Mancini and Poitout, 2013). Although most studies using FFAR1 agonists demonstrate an

improvement in glycemic control, further studies are required to ascertain whether long-term use has detrimental consequences. The recent phase III trial of fasiglifam was terminated due to high levels of hepatotoxicity caused by off-target inhibition of hepatobiliary transporters, including the efflux transporter (multidrug resistance-associated protein 2), and the uptake transporter (organic anion-transporting polypeptide) (Li et al., 2015c).

Encouragingly, new FFAR1 agonists developed by Eli Lilly, including LY2881835 and LY2922470, are in phase I and reduce hyperglycemia and increase GLP-1 secretion in both rats and humans (Mittermayer et al., 2015; Hamdouchi et al., 2016), suggesting that these compounds may still prove beneficial for the treatment of T2DM.

2. FFAR2. FFAR2 was deorphanized in 2003 (Brown et al., 2003); it is activated by SCFAs, including propionate and butyrate (Bindels et al., 2013), and pleiotropically couples to at least $G\alpha_i$ and $G\alpha_q$. Interestingly, activation of these signaling pathways causes opposing effects. $G\alpha_i$ inhibits glucose-stimulated insulin secretion, whereas $G\alpha_q$ increases glucose-stimulated insulin secretion (McKenzie et al., 2015). The existence of signaling bias as well as multiple endogenous SCFA ligands provides both additional layers of complexity and therapeutic opportunities for targeting FFAR2. Due to the close homology between FFAR2 and FFAR3, identification of selective ligands has been important for greater understanding of the signaling and pharmacology of these receptors. Three key amino acids, E166, L183, and C184, within the orthosteric binding pocket, govern the selectivity between FFAR2 and FFAR3 for metabolite binding (Schmidt et al., 2011). Multiple compounds that bind to either the orthosteric or allosteric binding pocket have now been discovered (Lee et al., 2008; Milligan et al., 2009; Bindels et al., 2013). Recently, AZ1729 was shown to display novel allosteric $G\alpha_i$ signaling bias in mouse colonic preparations and human neutrophils (Bolognini et al., 2016).

It has been suggested that there is a link between FFAR2 and/or FFAR1 (Wang et al., 2015) and the peroxisome proliferator-activated receptor γ, an established target for the glitazones currently used as a treatment of T2DM. In mouse 3T3-L1 cells, a reduction in *Ffar2* expression with small infering RNA (siRNA), or addition of a peroxisome proliferator-activated receptor γ agonist, produced changes in expression of both receptors. However, Bindels et al., (2013) recently showed that this effect does not translate from mouse to human. *Ffar2*$^{-/-}$ mice also display contradictory phenotypes, in which in one study an increase in energy expenditure and a decrease in body mass were observed (Bjursell et al., 2011), whereas in a second study, using the knockout (KO) animals on the same background, an increase in body mass of mice fed either normal chow or a high-fat diet was found, and the mice did not display phenotypic differences in glucose homeostasis or insulin resistance (Kimura et al., 2013).

Activation of FFAR2 by SCFA also causes the recruitment and migration of neutrophils. Changes in the migratory ability of these cells during inflammation may contribute to the pathophysiology of T2DM (Sina et al., 2009; Vinolo et al., 2011; Corrêa-Oliveira et al., 2016). Although FFAR2 appears to be an attractive target, further investigation into its signaling profile, development of compounds that display similar affinities in both rodent and human recombinant systems, and confirmation of the effects observed in KO mouse studies in human samples and patients will be necessary.

3. FFAR3. As described above, there is close homology between FFAR2 and FFAR3, and therefore, FFAR3 is activated by similar SCFAs, including formate, acetate, propionate, and butyrate (Ulven, 2012), although the rank orders differ between the receptors. Development of synthetic compounds for FFAR3 has been slow, with only a handful of compounds identified to date. These include both orthosteric and allosteric compounds (Milligan et al., 2017). One such allosteric compound is AR420626 (Arena Pharmaceuticals), which caused GLP-1 release from mouse colonic crypt cells (Nøhr et al., 2013). However, the poor potency of this, and other identified allosteric compounds, limits their suitability for in vivo studies.

FFAR3 has been shown to be involved in energy expenditure and metabolic regulation, although, unlike FFAR1 and FFAR2, most data have been obtained from KO mouse studies (for a comprehensive review, see Ulven, 2012 and Tang et al., 2015). Controversy exists as to whether FFAR3 is expressed in adipose tissue and if its activation causes the release of leptin, or whether another receptor, possibly FFAR2, is involved (Inoue et al., 2014), suggesting that KO of both FFAR2 and FFAR3 is required to identify any specific effects (Tang et al., 2015). Little is known of the signaling pathways involved in energy homeostasis by FFAR3 (Inoue et al., 2014). Although modulation of FFAR3 appears to warrant further investigation, no progress can be made until more potent and selective compounds are developed.

E. Glucagon-Like Peptide 1 Receptor

GLP-1 is a key incretin, promoting glucose-dependent insulin secretion in response to meal ingestion. It has broad physiologic effects, including preservation of β-cell mass, and inhibition of glucagon secretion, gastric emptying, and food intake, in addition to its incretin role (Baggio and Drucker, 2014; Graaf et al., 2016). GLP-1 is also cardio- and neuroprotective (Salcedo et al., 2012; Graaf et al., 2016; Wiberg et al., 2016). Endogenous GLP-1 is rapidly degraded by endopeptidases, most prominently dipeptidyl peptidase-IV (DPP-IV), and has a very short plasma half-life, making it unsuitable as a therapeutic.

As such, targeting of the GLP-1R has focused on peptide mimetics resistant to enzymatic degradation, and with prolonged plasma half-life (Hui et al., 2002). These peptide agonist mimetics lower HbA1c in T2DM, acting both directly on the pancreatic β-cell and via vagal afferents (Trujillo et al., 2015; Krieger et al., 2016). In addition, GLP-1R agonists cause increased β-cell proliferation, regeneration, and neogenesis, in both animal models and in vitro cultures of human islets (Tian et al., 2011), and decreased apoptosis (Vilsbøll, 2009), collectively contributing to preservation of β-cell mass. However, these effects may be specific to mouse models. There are now multiple GLP-1R agonists approved for T2DM treatment, including exenatide, albiglutide, and liraglutide (reviewed in detail; Meier 2012; Graaf et al., 2016).

Importantly, long-term treatment with GLP-1R agonists promotes satiety and weight loss in both diabetic and obese patients (van Bloemendaal et al., 2014). GLP-1R is expressed on the vagus nerve, linking the gut to the CNS, and abundantly in the hypothalamus, paraventricular nucleus, dorsomedial nucleus, and arcuate nucleus (Baggio and Drucker, 2014). The weight loss is most likely driven by combination of GLP-1 action to inhibit gastric emptying, as well as direct actions in the CNS; direct activation of propiomelanocortin expressing arcuate nucleus neurons by liraglutide induced weight loss, which was blocked by the GLP-1R antagonist exendin (9–39) (Secher et al., 2014; Sisley et al., 2014). Nonetheless, KO of GLP-1R in the CNS using nestin-$Cre\ Glp1r^{fl/fl}$ mice, or vagus nerve using $Phox2b$-$Cre\ Glp1r^{fl/fl}$ mice, did not affect food intake or body weight of animals fed normal chow or a high-fat diet, suggesting that activation of receptors at either site alone may have limited benefit. Beneficial weight loss is well-documented for treatment with exenatide and liraglutide (Raun et al., 2007; Buse et al., 2009), the earliest drugs to market; liraglutide has also been approved independently for treatment of obesity in the United States (Iepsen et al., 2015). These initial drugs are metabolically stable peptide mimetics of GLP-1 that require daily injections, and much recent work has focused on development of drugs with extended half-lives, including sustained release formulation (taspoglutide), albumin fusion (albiglutide), and linkage to modified Fc of immunoglobulin (dulaglutide), for once-weekly injection (Smith et al., 2016). Overall, GLP-1 mimetics have an excellent safety profile; the most prevalent side effects include injection-site reactions, nausea, diarrhea, or vomiting, and these effects can be dose limiting in patients. The latter events are thought to be primarily related to effects on the gastrointestinal tract; however, these tend to abate with time (Buse et al., 2009). Of note, taspoglutide was withdrawn from phase III clinical trials due to high risk for nausea (Zaccardi et al., 2016). All approved mimetics improve HbA1c levels, although the longer-acting formulations appear to have reduced efficacy for control of body weight, with limited effect on gastric emptying (Dungan et al., 2014; Pratley et al., 2014). A new generation mimetic with reversible albumin binding, semaglutide, formulated for once-weekly dosing, has shown promising effects on HbA1c and body weight control (Blundell et al., 2017), whereas implantable technologies for osmotic slow release (Intarcia) are currently in phase III clinical trials for delivery of exenatide over a 6-month period. Evidence is now emerging that liraglutide (Velez et al., 2015) and semaglutide may also have beneficial effects with respect to cardiovascular function and mortality (Marso et al., 2016), increasing the potential benefit of this drug class for treatment of T2DM patients at risk for cardiovascular disease.

There is increasing interest in benefits of dual-specificity peptide ligands that have activity at multiple glucagon-peptide family receptors, combining activity at GLP-1 and glucagon receptors (Day et al., 2009), or GLP-1 and GIP receptors (De and DiMarchi, 2010); these peptide agonists have shown promise in preclinical studies for obesity treatment with greater weight loss than seen with GLP-1 agonism alone (Day et al., 2009; De and DiMarchi, 2010). This dual targeting strategy is being pursued by companies, including Zealand Pharma and Transition Therapeutics. Moreover, combination of GLP-1 agonists with other anorectic peptides such as amylin is reported to provide synergistic effects on weight loss (Roth et al., 2012).

The GLP-1 receptor has been refractory to small-molecule drug development, and this may in part be explained by the extended pharmacophore recently revealed by structural studies (Jazayeri et al., 2017; Song et al., 2017; Zhang et al., 2017), which would create difficulties for development of mimetics acting via the orthosteric peptide binding site. A number of small-molecule compounds have been disclosed (Willard et al., 2012), but none have yet been developed for therapeutic use. Many of these act as allosteric ligands, and indeed, at least one class acts on the intracellular face of the receptor (Nolte et al., 2014). As an alternative, a range of modified peptides of ~11 amino acids has been developed, some of which retain high affinity and potency (Huang et al., 2015a; Jazayeri et al., 2017), and are resistant to degradation (Jazayeri et al., 2017). These peptides have both overlapping and unique interactions with GLP-1 at targeting GLP-1 receptors (Jazayeri et al., 2017; Zhang et al., 2017). It is believed that such peptides may be better suited for oral formulation. Nonetheless, semaglutide has been trialled in oral formulation, and, despite limited bioavailability, can still achieve therapeutically viable concentrations (Jensen et al., 2017), with high enough dose.

The GLP-1R is a secretin-like class B GPCR (Donnelly, 2012) and is pleiotropically coupled to multiple G proteins, including $G\alpha_i$, $G\alpha_o$, and $G\alpha_{q/11}$, as well as other effector/regulatory proteins, most notably the arrestins (Koole et al., 2013; Graaf et al., 2016), and this

has very broad consequences for intracellular signaling. Virtually all GLP-1 ligands that have been assessed appropriately exhibit biased agonism relative to the principal endogenous GLP-1 peptide [GLP-1(7-36)(NH$_2$)] (Koole et al., 2010; Graaf et al., 2016; Wootten et al., 2017). This is evident for both natural ligands of the receptor (e.g., oxyntomodulin) and GLP-1 mimetics (e.g., exendin-4), with divergent effects of each of these peptides in pancreatic β-cell–like INS-1 insulinoma cells (Wootten et al., 2016). This is likely to impact on treatment outcomes with different GLP-1 mimetic drugs. Indeed, although principally considered in the context of altered pharmacokinetics, there are diverse outcomes observed with currently approved therapeutics for body weight, gastric emptying, and cardiovascular improvement, as well as the extent of unwanted side effects (Graaf et al., 2016) that may also arise from biased agonism of these peptides. Of particular note, a recently discovered analog of exendin-4, termed exendin-P5, which had a different signaling bias to exendin-4, displayed a distinct impact in preclinical models of diabetes and obesity (Zhang et al., 2015). Both peptides reduced plasma glucose; however, in contrast to exendin-4, exendin-P5 was only a weak insulinotrope and caused altered adiposity. Thus, altered signaling bias could provide novel therapeutic potential for this target. To date, we have only a poor understanding of which signaling pathways interplay for beneficial effects in both the pancreas and extrapancreatic tissues that control appetite, gastric emptying, and cardio- and/or neuroprotection. Nonetheless, this promises to be a fruitful area of research for development of new-generation GLP-1R drugs.

F. G Protein–Coupled Estrogen Receptor

G protein–coupled estrogen receptor (GPER), the nongenomic receptor for estrogen, previously denoted GPR30, is widely expressed in the heart, intestines, reproductive tissues, immune cells, and metabolic tissues, including adipose, skeletal muscle, and liver (Sharma et al., 2017). Furthermore, GPER expression has been reported on pancreatic β-cells, with expression levels notably higher in islets from both female mice and humans compared with those derived from male mice (Balhuizen et al., 2010; Kumar et al., 2011). The estrogen receptor agonist, 17β-estradiol, activates GPER with nanomolar affinity (Wang et al., 2016), and the genomic estrogen receptor modulators tamoxifen and raloxifene also have moderate GPER activity (Sharma et al., 2017). Recently, a selective GPER agonist (G-1) was identified that displays no activity at the estrogen receptors ERα or ERβ (Bologa et al., 2006), and selective GPER antagonists have also been discovered (G15 and G36) (Dennis et al., 2009, 2011). Activation of GPER by 17β-estradiol and G-1 revealed coupling to both Gα_s and Gα_i proteins, yielding a net increase in both cAMP and intracellular Ca^{2+}

(Martensson et al., 2009). More recently, data suggest that GPER can signal from the plasma membrane and also intracellular compartments, including the Golgi and ER (Otto et al., 2008; Cheng et al., 2011).

GPER KO mouse studies have yielded a range of reported metabolic outcomes. In one study, female $Gper1^{-/-}$ mice fed a high-fat diet displayed reduced body weight and were protected from obesity-induced insulin resistance; however, no significant effects were observed in male animals (Wang et al., 2016). Contrary to these findings, Sharma et al., (2013) demonstrated that both female and male $Gper1^{-/-}$ mice had increased body weight compared with wild-type controls and developed insulin resistance. More subtly, Davis et al., (2014) showed that this increased body weight in females was delayed by 6 weeks in comparison with males. Female $Gper1^{-/-}$ mice aged 6 months also displayed impaired glucose tolerance, increased blood pressure, and reduced bone growth (Mårtensson et al., 2009). These disparities most likely result from different methods used to generate the transgenic animals and variations in the length of feeding, but overall they indicate that deletion of GPER results in a similar phenotype obtained from ERα KO models, suggesting that activation of GPER by estrogen may be necessary to maintain glucose homeostasis (Sharma et al., 2017). Although GPER remains an interesting drug target, further studies are required to understand the mechanism of GPER activation in metabolic tissues. Furthermore, confirmation of the effects observed in KO mouse studies in humans, both male and female, will be necessary. For a comprehensive review of GPER, see Sharma et al. (2017).

G. GPR55

GPR55 is activated by endocannabinoids and was initially classified as the third cannabinoid receptor (Ross, 2009). Subsequently, it has also been shown to be activated by lipids, including lysophospholipid, and L-α-lysophosphatidylinositol (Henstridge et al., 2010). Unlike many of the GPCRs involved in insulin resistance or pancreatic β-cell dysfunction that predominantly couple to Gα_s or Gα_i, GPR55 couples primarily to G$\alpha_{q/11}$ and G$\alpha_{12/13}$ (Ross, 2009; Simcocks et al., 2014). The glucose-lowering and insulinotropic effects of a range of GPR55 agonists in vivo have been recently described, demonstrating the therapeutic potential for this target (McKillop et al., 2013). However, many of these ligands lack specificity, thus limiting conclusions from these studies. Recently, studies show that $Gpr55^{-/-}$ mice develop increased insulin resistance, adiposity, and fat mass (Meadows et al., 2015) together with a significant reduction in physical activity, even though muscle function was unaffected. These data therefore support the developmental potential of GPR55 selective agonists. For a more comprehensive review of the role of GPR55 in metabolism, see Liu et al. (2015a).

H. GPR82

GPR82 belongs to the $P2Y_{12}$-like family, which also contains the ADP receptor $P2Y_{13}R$, the UDP-glucose receptor $P2Y_{14}R$, and the orphan receptors GPR87 and GPR171, all of which couple to $G\alpha_i$ (Cattaneo, 2015). Little else is known about the receptor, but, interestingly, $Gpr82^{-/-}$ mice display a lean phenotype, have decreased serum triglyceride levels, increased insulin sensitivity, and glucose tolerance when challenged with a Western diet (32.8% sugar/21.2% raw fat) (Engel et al., 2011). Unfortunately, no further information is available regarding the physiologic role of the receptor. The lack of a synthetic or endogenous ligand has limited further studies into the receptor signaling.

I. GPR119

GPR119 is highly expressed on pancreatic β-cells and enteroendocrine cells (Hansen et al., 2012). Multiple endogenous ligands for the receptor have been identified with varying potencies, including oleoylethanolamide, *N*-oleyldopamine, olvanil, and 1-oleoyl-lysophosphatidylcholine (18:1-lysoPC) (Ahrén, 2009; Hansen et al., 2012; Al-Barazanji et al., 2015). The steroid glycoside, gordonoside F, from the popular herbal weight loss supplement *Hoodia gordonii*, activates GPR119 (Zhang et al., 2014). This plant has been used medicinally for thousands of years by Xhomani Bushmen as an anorexant (Zhang et al., 2014) without known side effects, suggesting gordonoside F may represent a novel class of compounds for further investigation. Like the FFARs, GPR119 causes the release of GLP-1 and GIP, upon activation from L and K cells, respectively (Chu et al., 2008; Lauffer et al., 2009). GPR119 couples to $G\alpha_s$ to increase glucose-stimulated insulin release from pancreatic β-cells via the formation of cAMP (Chu et al., 2008). GPR119 controls enteral glucose tolerance by three main complementary mechanisms: 1) direct activation of insulin secretion in islets, 2) promotion of secretion of incretins such as GLP-1 and GIP to potentiate glucose-stimulated insulin secretion (Panaro et al., 2017), and 3) delay of gastric emptying via, at least in part, the enhancement of PYY action (Hansotia et al., 2007; Flock et al., 2011). The glucoregulatory properties of GPR119 led to the development of multiple synthetic agonists for the treatment of T2DM, including GSK1292263 (GSK), MBX-2982 (CymaBay Therapeutics), and PSN821 (Astellas/Prosidion) (Hansen et al., 2012; Nunez et al., 2014; Liu et al., 2015c; Mittermayer et al., 2015; Ritter et al., 2016). However, both GSK1292263 and MBX-2982 were discontinued due to lack of efficacy in phase II trials, in which neither compound improved glycemia handling. Clinical failure of these compounds has cast doubt on the utility of targeting GPR119 for the treatment of T2DM (Kang, 2013), but may in part be due to suboptimal compounds with low potencies or lack of sufficient exposure and

activity to cause release of insulin and the incretins (Ritter et al., 2016), as most of the molecules assessed in clinical trials failed to trigger robust increases in gut hormones (Ritter et al., 2016). Nonetheless, GPR119 agonists may be effective when used in combination with current T2DM treatments. GSK2041706 in combination with metformin in diet-induced obese mice showed a synergistic effect to reduce body weight (Al-Barazanji et al., 2015). In contrast, another GPR119 agonist, GSK1292263, in combination with metformin and sitagliptin in patients with T2DM yielded no additional improvement in glycemic control (Nunez et al., 2014). Although disappointing, this latter study was performed for only 14 days, and longer-term studies may be needed to better address these key questions. The lack of complete translation of the rodent pharmacology in type 2 patients with diabetes may also result from species-specific biology of the receptor. Of note, GPR119 has been found by single-cell RNA Seq to be highly expressed in human glucagon-producing α-cells (10-fold higher levels than β-cells), where its function remains largely unknown (Blodgett et al., 2015). Interestingly, an unexpected role of GPR119 in the liver has been uncovered with some potential consequences for the treatment of fatty liver diseases (Yang et al., 2016). Whereas expression of GPR119 in hepatocytes has been a subject of debate (Odori et al., 2013), Yang et al. (2016) showed that hepatocytes do express GPR119 at both mRNA and protein levels in both mice and humans. Moreover, pharmacological activation of GPR119 led to a suppression of de novo lipogenesis via activation of AMP kinase and subsequent inhibition of the LXR-SREBP1c transcriptional cascade, ultimately resulting in a significant reduction of hepatic steatosis. These effects were abolished in $Gpr119^{-/-}$ KO mice (Yang et al., 2016). Further studies are required to determine whether GPR119 agonists might be useful for the treatment of nonalcoholic fatty liver diseases.

J. GPR142

Numerous publications describe synthetic phenylalanine derivatives as agonists acting at GPR142 (Du et al., 2012; Lizarzaburu et al., 2012; Toda et al., 2013; Yu et al., 2013; Guo et al., 2016). All of these compounds were developed based on the understanding that the receptor is activated by tryptophan, an essential amino acid that is the biologic precursor to serotonin (Wurtman and Anton-Tay, 1969), and niacin (Ikeda et al., 1965). GPR142 is highly expressed on pancreatic β-cells and signals via $G\alpha_q$ (Wang et al., 2016a). Activation of the receptor enhances glucose-stimulated insulin release from pancreatic β-cells, but it is not known whether GPR142 has any further role beyond glycemic control. This limited effect may prevent GPR142 from being considered a suitable (or commercially viable) target for drug discovery. However, recent data suggest that serum tryptophan levels are

increased in T2DM patients with a higher degree of insulin resistance (Chen et al., 2016), suggesting that inhibition of the receptor could prove beneficial. Furthermore, $Gpr142^{-/-}$ mice display reduced levels of sensitivity to a collagen antibody-induced arthritis model of inflammation (Murakoshi et al., 2016). A similar effect was observed with a GPR142 antagonist (CLP-3094) (Murakoshi et al., 2016). Identification of better tool compounds will enable greater target validation and clarification of the pathophysiological processes controlled by GPR142.

K. GPRC5B

GPRC5B is a class C GPCR that was first cloned as a retinoic acid–inducible orphan receptor (Robbins et al., 2000); its ligand, if any, remains unknown. GPRC5B is widely expressed across different tissues at the level of mRNA, with highest levels in the CNS and lowest in liver and bone marrow (Regard et al., 2008). Although relatively little is known about the function of receptor, evidence has emerged that GPRC5B plays roles in different tissues relevant to metabolic function. GPRC5B expressed in pancreatic islets negatively regulates insulin secretion, potentially by reducing cell viability, as shown by cytokine challenge in murine insulin-secreting MIN6 cells (Soni et al., 2013). Control of Gprc5b expression is thought to skew macrophage populations to the M2, anti-inflammatory phenotype (Hohenhaus et al., 2013), and a copy number variant very close to Gprc5b has been shown to be associated with body mass index (Speliotes et al., 2010). Following this latter report, Gprc5b deficiency was found to protect mice from diet-induced obesity and insulin resistance and was associated with abolition of GPRC5B-dependent inflammation in white adipose tissue (Kim et al., 2012). GPRC5B interacts with and regulates Fyn kinase, which in turn controls proinflammatory IKK-ε–NF-κB signaling. These data converge to suggest that an antagonist of GPRC5B could be effective to reduce pathophysiology and symptomology of metabolic syndrome at a number of levels. However, to date, no known small-molecule ligands of the receptor have been discovered.

L. GPRC6A

GPRC6A is a class C GPCR that has been cloned from human, mouse, rat, goldfish, and bonobo chimpanzee. The receptor mediates responses to basic L-amino acids, such as arginine, ornithine, and lysine, which bind in the N-terminal (Venus flytrap) domain of the receptor (Wellendorph and Bräuner-Osborne, 2009) in a manner analogous to the binding of L-glutamate to metabotropic glutamate receptors.

In line with its amino acid pharmacology, GPRC6A was originally thought of as a nutrient-sensing receptor. Recent studies suggest that GPRC6A is involved in an array of metabolic, endocrine, and inflammatory processes (Pi et al., 2008, 2011, 2012; Wellendorph et al., 2009; Rossol et al., 2012; Clemmensen et al., 2013a,b; Smajilovic et al., 2013), although the evidence is equivocal. One $Gprc6a^{-/-}$ mouse strain displays manifestations of metabolic syndrome, with increased fasted plasma glucose levels and impaired insulin sensitivity (Pi et al., 2008), and a polymorphism in the Gprc6a gene that is associated with insulin resistance in normal weight and obese subjects has been identified (Di Nisio et al., 2017). However, a different KO mouse strain has a much less pronounced phenotype, with no evidence of disrupted glucose handling or insulin sensitivity, and impairments in glucose metabolism only observed when the mice were fed a high-fat diet (Smajilovic et al., 2013).

Perhaps the biggest area of contention with respect to GPRC6A and metabolic disorders has been the enigmatic role of the bone-derived peptide, osteocalcin (OCN). The decarboxylated form of this osteoblast-derived protein exerts a number of beneficial metabolic and endocrine effects, including control of energy expenditure regulated by the pancreas (Lee et al., 2007); $Ocn^{-/-}$ mice display reduced pancreatic cell proliferation, impaired glucose handling, and insulin resistance. Furthermore, systemic administration of OCN increases circulating insulin levels in wild-type but not $Gprc6a^{-/-}$ mice (Pi et al., 2011). OCN has also been shown to increase pancreatic β-cell proliferation, insulin release from pancreatic islets, insulin sensitivity, energy expenditure, and testosterone synthesis in the gonads in mice (Lee et al., 2007; Oury et al., 2011). Furthermore, OCN-mediated insulin and GLP-1 release have also been reported in immortalized pancreatic β-cell lines, effects that are blocked by siRNA targeting Gprc6a (Pi et al., 2011; Mizokami et al., 2013). However, a recent study suggests that OCN does not increase GLP-1 release from enteroendocrine cells or insulin release from islets or immortalized β-cells (Rueda et al., 2016), adding further intrigue to the biology.

The positive effects of OCN, combined with the lack of OCN efficacy in $Gprc6a^{-/-}$ mice, both in vivo and ex vivo, have led to suggestions that decarboxylated OCN acts directly via GPRC6A to exert its metabolic and endocrine effects. Despite this evidence, verification of a direct action of decarboxylated OCN on GPRC6A has proven somewhat elusive. Several reports have shown that OCN stimulates cAMP accumulation or extracellular signal-regulated kinase 1/2 phosphorylation in HEK293 cells recombinantly expressing GPRC6A (although the species tested is not always stated) (Pi et al., 2011, 2012; Pi and Quarles, 2012; Oury et al., 2013), suggesting that the signaling of the receptor may not be limited to $G\alpha_q$-coupled pathways originally reported for L-amino acids. Furthermore, recent reports have used computational approaches to predict the binding locus for OCN on GPRC6A

(Pi et al., 2016) and suggested that OCN shares its binding site with testosterone (De Toni et al., 2016). However, two further laboratories have evaluated the pharmacology of mouse GPRC6A and failed to replicate either the agonist activity of OCN or GPRC6A-mediated cAMP signaling (Jacobsen et al., 2013; Rueda et al., 2016), leading both groups to conclude that the receptor is primarily a $G\alpha_q$-coupled, basic L-amino acid receptor.

Given the complexities of the pharmacology of GPRC6A, it is unclear whether targeting the receptor therapeutically could replicate the effects of OCN; small-molecule chemistry targeting the receptor has been restricted to a limited number of low-potency negative allosteric modulators, which target the transmembrane domain of GPRC6A (Gloriam et al., 2011; Johansson et al., 2015). A further challenge is the potential differences between orthologs of the receptor; a recent study explained the challenges of expressing and interrogating the pharmacology of the human receptor by virtue of an insertion/deletion variation in the third intracellular loop that leads to intracellular retention (Jørgensen et al., 2017). It remains unclear whether the pharmacology of the human receptor differs markedly from its murine ortholog—or indeed, what role the human receptor might have in vivo if not expressed at the cell surface.

M. Hydroxycarboxylic Acid Receptor 2 (GPR109A)

The receptor for nicotinic acid, or niacin, was identified in 2003 and subsequently shown to be highly expressed in adipocytes and immune cells (Wanders and Judd, 2011). Activation of hydroxycarboxylic acid receptor 2 (HCA_2) by niacin in adipocytes causes inhibition of lipolysis, but also via the epidermal Langerhans cells the harmless, yet unwanted side effect of flushing (Wanders and Judd, 2011). In addition to binding niacin, the receptor also binds the SCFA butyrate, suggesting that HCA_2 is involved in gut homeostasis, similar to the FFARs described above. KO mouse studies revealed a marked increase in adiponectin concentrations (Plaisance et al., 2009). Interestingly, niacin activation of HCA_2 stimulates sodium-glucose cotransporter 1 and GLUT2 jejunal glucose uptake, indicating potential additional benefits that would improve glycemic control (Wong et al., 2015).

The pursuit of HCA_2 agonists for the treatment of T2DM has recently increased, with a focus on identifying compounds without the flushing side effect. GSK256073, in a trial of 39 diabetic patients, caused a significant decrease in serum nonesterified fatty acids and glucose concentrations when dosed three times over 2 days (Dobbins et al., 2013). These improvements in glucose tolerance were attributed to an increase in insulin sensitivity with an associated decrease in insulin concentrations. Encouragingly, no flushing or adverse effects on the gastrointestinal tract were observed (Sprecher et al., 2015). However, recent data from a randomized 12-week trial revealed

that GSK256073 did not meet its primary end point in reducing HbA1c compared with placebo (Dobbins et al., 2015). Lack of efficacy could be due to an inability of the compound to produce sustained suppression of plasma nonesterified fatty acid concentrations, thought to be required for the effects on insulin sensitivity.

However, a recent publication has questioned the validity of targeting HCA_2 (Fraterrigo et al., 2012). Niaspan, an extended release form of niacin, produced insulin resistance in skeletal muscle, most probably due to increased levels of adiponectin. These opposing effects suggest that further investigation of HCA_2 as a target is required. Its close homolog, HCA_3 (GPR109B), differs by only 15 amino acids and results from a gene duplication only present in humans (Ahmed et al., 2009). This receptor does not bind niacin with high affinity, but, like HCA_2, couples to $G\alpha_i$. 3-OH-octanoic acid is an endogenous ligand for HCA_3 (Ahmed et al., 2009), and activation of the receptor by this ligand controls adipocyte lipolysis by a negative feedback loop involving counteraction of prolipolytic stimuli in situations of increased fatty acid oxidation. Targeting HCA_3 may therefore be an alternative approach to HCA_2, especially if the HCA_2-mediated side effects can be avoided.

N. Melatonin Receptors (MT_1R and MT_2R)

Melatonin (MT) is primarily secreted by the pineal gland during the dark phase, but can also be secreted to a lesser extent from the innate immune system, the gastrointestinal tract, and the retina. The effects of MT are mediated by two homologous but distinct GPCRs, namely MT_1R and MT_2R, encoded by two distinct genes, *MTNR1A* and *MTNR1B*, respectively. MTs are $G\alpha_i$-coupled and expressed in a cell-specific fashion in mice and in humans (see Jockers et al., 2016 for recent review). MTs are involved in numerous physiologic and neuroendocrine functions. Interest in MT in the pathogenesis of T2DM derived initially from three independent genome-wide association studies that led to the identification of several frequent polymorphisms located near the *MTNR1B* gene that were associated with increased fasting plasma glucose, a reduction of early insulin response to glucose, and ultimately an increased risk of developing T2DM (Bouatia-Naji et al., 2009; Lyssenko et al., 2009). This genetic association is very robust and was subsequently replicated by several groups in other populations (Ronn et al., 2009; Renström et al., 2015). Surprisingly, the influence of MT on insulin secretion is still debated, with conflicting results generated in vitro using rodent and human islets (Lyssenko et al., 2009; Costes et al., 2015). Furthermore, MT receptors are expressed at low levels in both α- and β-cells. In a recent study, Tuomi et al. (2016) demonstrated elegantly that the common rs10830963 variant located in the *MTNR1B* intron is an expression quantitative trait locus conferring

increased expression (two- to fourfold) of the receptor in islets, as measured by RNA Seq in 204 Scandinavian donors, whereas *MTNR1A* expression is not altered by either genotypes (GG versus CC).

MT inhibits glucose-stimulated insulin secretion in INS-1 cells overexpressing *MTNR1B*/MT$_2$R by, at least in part, reducing glucose-stimulated cAMP production. Pertussis toxin treatment completely abolished this effect (Tuomi et al., 2016). The authors also characterized in depth the phenotype of $Mt2^{-/-}$ KO mice. These mice display increased insulin release in response to an intravenous glucose tolerance test and impaired hepatic insulin sensitivity, as determined by hyperinsulinemic-euglycemic clamp. This exacerbated insulin response was documented both ex vivo and in vivo. Increased β-cell mass and increased cAMP levels in response to glucose stimulation are the main reasons for this altered insulin response. Tuomi et al. (2016) showed that MT treatment at bedtime for 3 months in nondiabetic individuals resulted in a significant reduction in insulin secretion in GG allele carriers (Tuomi et al., 2016). It is noteworthy that sleep duration and quality were similar in both groups in response to MT treatment. Another group reported a negative effect of acute MT treatment on glucose clearance during a 2-hour oral glucose tolerance test in a genotype-specific fashion in healthy young female athletes (Garaulet et al., 2015). Taken together, these studies suggest that increased MT signaling is a risk factor for T2DM. However, analysis of rare loss-of-function MTNR1B variants suggested that reduced MT signaling increases T2DM risk (Prokopenko et al., 2009; Bonnefond et al., 2012). Furthermore, reduced MT secretion is associated with an increased risk for diabetes in the general population (McMullan et al., 2013). Although it appears difficult to assign a definitive role of MT on insulin secretion from all these human and mouse genetic studies, the role of MT and its receptors in the CNS on energy and glucose homeostasis should be further investigated because sleep restriction and circadian misalignment are recognized as major risk factors for the development of cardio-metabolic diseases (Scheer et al., 2009). Indeed, Lane et al. (2016) recently reported that the *MTNR1B* risk allele influences dynamics of MT secretion with consequences on the sleep/wake cycle. Nevertheless, the species-specific receptor distribution and downstream biology complicate translation of the preclinical pharmacology into the clinical space for cardio-metabolic diseases.

III. G Protein–Coupled Receptors and Obesity-Induced Type 2 Diabetes Mellitus

A. C-C Motif Chemokine Receptor 2

CCR2 belongs to the C-C motif chemokine receptor (CCR) and C-X-C motif chemokine receptor superfamily.

These receptors are involved in many inflammatory responses and are expressed on multiple inflammatory cell types, including monocytes, macrophages, T-cells, and B-cells. However, these receptors are also widely expressed in the periphery, with some expression also located in the CNS. Like many chemokine receptors, CCR2 is activated by multiple agonists, including CCL7 (MCP-3), CCL8 (MCP-2), CCL11 (eotoxin), and CCL13 (MCP-4), which all bind with similar low nanomolar affinities. However, the principal agonist for CCR2 is CCL2 (MCP-1), which binds with sub-nM affinity. Many of these agonists also bind to multiple receptors, for example, CCL2 binds with low affinity (>1000-fold compared with CCR2) to CCR4. This multireceptor, multiligand behavior suggests that a large degree of redundancy must occur across the biologic functions (Boring et al., 1997). It has been shown that the different endogenous ligands for CCR2 are able to bind and stabilize different confirmations of the receptor, enabling the activation of both G protein–dependent and independent pathways (Berchiche et al., 2011). In addition, multiple binding sites have been identified using radiolabeled antagonists (Zweemer et al., 2013). Recently, the crystal structure of inactive CCR2 was solved using a T4L fusion construct (Zheng et al., 2016) in a ternary complex with both an orthosteric (BMS-681) and an allosteric [CCR2-RA-(R)] antagonist, indicating that the receptor is able to accommodate multiple ligands at any one time. The next challenge is to identify whether the receptor could accommodate multiple endogenous agonists simultaneously, thus giving an insight into redundancy among chemokine receptors/ligands. However, this may prove too challenging, as to date over 90% of all GPCR structures have been solved in the inactive confirmation, with either an antagonist and/or an allosteric modulator bound. Of note, the double-antagonist CCR2 crystal structure is the most inactive, therefore most stable, structure solved (Zheng et al., 2016). Therefore, a double-agonist bound structure may yet be outside the current technical capabilities.

During infection, activation of the innate immune response occurs, and binding of CCL2 to CCR2 causes recruitment of Ly6C^{hi} monocytes. The levels of expression of CCL2 rapidly increase within inflamed tissues, and its release is further stimulated by the release of proinflammatory mediators (Shi and Pamer, 2011), although the mechanism involved is largely unknown. It has been suggested that CCL2 produces a chemokine gradient toward the site of inflammation, enabling the recruitment of circulating monocytes (Shi and Pamer, 2011). In addition, the levels of CCR2 expression are also modulated during tissue inflammation, by granulocyte-macrophage colony-stimulating factor (Croxford et al., 2015). Therefore, the increased levels of both receptor and ligand help resolve the site of infection.

It is unsurprising, based on the expression profile of CCR2, that this receptor has been implicated in the

pathophysiology of T2DM. In $Ccr2^{-/-}$ mice fed a high-fat diet, a reduction in food intake, macrophage recruitment, inflammatory markers in adipose tissue, and an improvement in glucose homeostasis and insulin sensitivity have been reported (Weisberg et al., 2006). A similar phenotype has also been described with siRNA knockdown of CCR2 (Kim et al., 2016). In global $Ccr2^{-/-}$ and hematopoietic (bone marrow) $Ccr2^{-/-}$ mice fed a high-fat diet for 12 weeks, flow cytometry revealed differences in the F4/80$^+$ myeloid cell population compared with their wild-type counterparts. In the adipose tissue from all cohorts, CD11b^{hi}F4/80$^+$ cells were detected; however, in both KOs, a population of CD11b^{lo}F4/80^{lo} was seen. It was only when this population of cells was absent from adipose tissue, following 20 weeks of the high-fat diet, that improvements in adipose tissue inflammation were detected (Gutierrez et al., 2011). Loss of CCR2 resulted in the accumulation of CD11b^{lo}F4/80^{lo} cells in adipose tissue, whereas in wild-type mice transient expression of these cells was identified. No explanation was given as to why these cells disappeared with increased feeding. Further data reveal that migration of monocytes from bone marrow is dependent on both CCR2 and CCL2, whereas migration of monocytes from the circulation into inflamed tissues appears to be dependent on CCR2, CCL2, and CCL7 (Tsou et al., 2007). To further explore monocyte migration, Kawano et al. (2016) generated colonic macrophage-specific $Ccr2^{-/-}$ (M-Ccr2KO) and intestinal epithelial cell–specific tamoxifen-inducible $Ccl2^{-/-}$ (Vil-Ccl2KO) mice. Although both strains gained significant body weight when fed a high-fat diet, only the $Ccr2^{-/-}$ displayed improved glucose tolerance and insulin sensitivity. Interestingly, in a whole-body $Ccl2^{-/-}$, when fed a similar diet, an increase in adiposity and metabolic dysfunction was observed, suggesting that global CCL2 is required for the protection of sensitive metabolic tissues (Cranford et al., 2016).

As there is clear redundancy in the immune system and receptor/ligand polygamy, targeting chemokine receptors therapeutically, especially with small molecules, may appear extremely challenging. However, recent data have shown some promise with CCR2 antagonists for the treatment of T2DM and its associated complications, nonalcoholic fatty liver disease/NASH. In mice fed a high-fat diet, and in db/db mice, CCX140-B (ChemoCentryx) fully blocked the recruitment of inflammatory macrophages into adipose tissue, resulting in an improvement in glucose homeostasis, insulin sensitivity, hepatic glycogen, and triglyceride content (Sullivan et al., 2013a). Similar effects were observed in human CCR2 knock-in mice, with no increase in circulating CCL2 levels in plasma, or increased blood monocyte numbers (Sullivan et al., 2013b). Encouragingly, treatment of 110 patients with T2DM and nephropathy in a phase II trial with CCX140-B resulted in renoprotection and improved

glucose handling, although there was no overall improvement in insulin resistance (de Zeeuw et al., 2015). As no improvement in insulin resistance was seen, the compound is now being further investigated in models of chronic kidney disease. Similarly, use of the Spiegelmer, NOX-E36 (Noxxon; emapticap pegol), which neutralizes CCL2, has shown promise in a phase IIa exploratory study in patients with T2DM and albuminuria (Menne et al., 2017) and in mouse models of NASH and chronic hepatic injury (Baeck et al., 2012). Finally, use of a dual CCR2/CCR5 antagonist Cenicriviroc (Allergan) has shown potent anti-inflammatory and antifibrotic effects in animal models of NASH and fibrosis (Lefebvre et al., 2016). A phase IIb combination study with the farnesoid X receptor agonist LJN 452 (Novartis) is planned to assess safety, efficacy, and tolerability. Results of these studies may further enforce the rationale for targeting CCR2 for the treatment of T2DM and chronic liver diseases.

B. FFAR4 (GPR120)

FFAR4 is a metabolite-sensing FFA GPCR activated by unsaturated long-chain FFAs (Hirasawa et al., 2005), leading to the release of GLP-1 and an increase in circulating insulin. Omega-3 polyunsaturated fatty acids display the highest potency for FFAR4 in vitro (Im, 2016), but other endogenous ligands also activate FFAR4, including docosahexaenoic acid and eicosapentaenoic acid (Oh et al., 2010; Kim et al., 2015). FFAR4 exerts its biologic effects by both G protein–dependent and independent pathways. Coupling to $G\alpha_q$ causes release of intracellular Ca^2 to promote the release of cholecystokinin and GLP-1. In addition, activation of extracellular signal-regulated kinase phosphorylation and phosphoinositide 3-kinase leads to AKT phosphorylation and GLUT4 translocation, leading to the regulation of adipogenesis and adipogenic differentiation (Li et al., 2015a). Moreover, FFAR4 is expressed specifically on mouse pancreatic δ-islet cells, but not on β-islet cells, and activation of FFAR4 in these cells regulates the secretion of somatostatin (Stone et al., 2014).

FFAR4 may also inhibit inflammation promoted by other mechanisms. For example, activation of Toll-like receptor 4 and TNF receptor by lipopolysaccharide (LPS) and TNF-α, respectively, causes TGF-β–activated kinase 1 binding protein and TGF-β–activated kinase 1 to colocalize and activate the IKK, JNK, and NF-κB pathways, leading to inflammation (Oh et al., 2010; Talukdar et al., 2011; Li et al., 2015a; Liu et al., 2015b; Ulven and Christiansen, 2015). However, agonist activation of FFAR4 causes recruitment of β-arrestin 2, leading to the sequestration of TGF-β–activated kinase 1 binding protein away from TGF-β–activated kinase 1 and an anti-inflammatory effect (Oh et al., 2010), suggesting that signaling bias may exist for this receptor, and this may provide a means of inhibiting inflammation.

FFAR4 is highly expressed in adipose tissue, proinflammatory macrophages, and eosinophils (Konno et al., 2015), suggesting that it may provide a link between metabolic diseases and inflammation (Oh et al., 2010). In the monocyte RAW 264.7 cell line and mouse intraperitoneal macrophages, FFAR4-mediated anti-inflammatory effects, including reduction of proinflammatory M1, increased anti-inflammatory M2 macrophage levels and reduced cytokine levels that were abrogated when FFAR4 was knocked down using siRNA. Similar effects were observed in $Ffar4^{-/-}$ mice on a high-fat diet with or without omega-3 polyunsaturated fatty acid supplementation. The KO phenotype indicated that a FFAR4 agonist may alleviate insulin resistance. GW9508, which has FFAR1 and FFAR4 agonist activity (Briscoe et al., 2006), inhibited LPS-induced phosphorylation of JNK, IKKβ, I$\kappa\beta$ degradation, cytokine secretion, and inflammatory gene expression in RAW 264.7 cells. A FFAR4-selective agonist Cpd A (Oh et al., 2014) reduced chronic inflammation in obese mice, but also improved insulin sensitivity, glucose tolerance, and decreased hyperinsulinemia. Other FFAR4 agonists have since been developed and display similar attributes (Li et al., 2015a; Liu et al., 2015b; Ulven and Christiansen, 2015). However, FFAR4 desensitizes rapidly upon chronic activation, which has hampered the progression of FFAR4 agonists in the clinic (Alvarez-Curto et al., 2016). Furthermore, increased FFAR4 expression and signaling both in vitro and in vivo are associated with an increase in colorectal carcinoma tumor growth, promotion of angiogenesis, increased motility, and induced epithelial–mesenchymal transition of human colorectal carcinoma cells (Wu et al., 2013). Further studies are therefore required to delineate the effects of FFAR4 agonist activity on tumor progression before committing to human studies.

C. GPR21

GPR21 is an orphan receptor that couples to Gα_q (Bresnick et al., 2003), but as no ligand, synthetic or endogenous, has yet been identified, further conclusions about signaling are difficult to make. It has been suggested that the endogenous ligand is a FFA (Kakarala and Jamil, 2014), and/or could be found within serum as serum-starved GPR21-expressing cells display reduced AKT phosphorylation (Leonard et al., 2016). However, no strong experimental evidence has emerged to confirm these findings.

Two independent studies using $Gpr21^{-/-}$ mice indicate that GPR21 may be involved in obesity-induced insulin resistance (Gardner et al., 2012; Osborn et al., 2012). In the first study, $Gpr21^{-/-}$ mice showed a robust improvement in glucose tolerance and systemic insulin sensitivity after a high-fat diet, culminating in a modest lean phenotype that was suggested to be due to a reduction in tissue inflammation caused by a decrease

in the migratory ability of macrophages into adipose tissue (Osborn et al., 2012). To examine these effects in a human model, lentiviral short hairpin RNA knockdown of GPR21 in a human monocyte-like cell line (U-937) was performed and showed similar inhibition of migration. In the second study, there was a clear reduction in proinflammatory mediators in $Gpr21^{-/-}$ mice, along with an improvement in glucose tolerance and systemic insulin sensitivity after a high-fat diet (Gardner et al., 2012). However, subsequently, the same group generated an alternative KO mouse model using transcription activator-like effector nucleases (TALENS) technology (Wang et al., 2016b). This was necessary because the $Gpr21$ gene resides within the intron of the RAB GTPase-activating protein 1 ($Rabgap1$) gene, and the authors showed that this gene was disrupted in the original $Gpr21^{-/-}$ mice. Although there was no effect on the expression of $Rabgap1$ in the TALENS $Gpr21^{-/-}$ KO, no improvement in glycemic control was reported. Why no beneficial phenotype was observed is unclear, and no head-to-head comparison between the two KO strains was made, nor was a high-fat diet regimen tested in the TALENS KO, making interpretation of these observations challenging. However, although GPR21 appears to be a promising target, the orphan status, and the lack of any suitable tool molecule, inhibits further investigation.

D. GPR35

GPR35 is an orphan GPCR that is highly expressed in the pancreas, immune cells, and to a lesser extent adipose tissue, liver, and skeletal muscle (MacKenzie et al., 2011). Recently, it has been reported that GPR35 can be activated by the chemokine CXCL17 (Maravillas-Montero et al., 2015). Based on this finding, it was proposed that the receptor be renamed C-X-C motif chemokine receptor 8 (Maravillas-Montero et al., 2015). Multiple other endogenous ligands have been associated with GPR35, including kynurenic acid and 2-oleoyl lysophosphatidic acid (Shore and Reggio, 2015). In addition, a vast array of synthetic agonists and antagonists has been developed for this receptor (for a summary, please see MacKenzie et al., 2011). To further add complexities to the pharmacology of GPR35, the concept of ortholog selectivity and ligand bias has been demonstrated for this receptor (Milligan, 2011). Although the expression profile of GPR35 would support its potential as a suitable target for obesity-induced T2DM, little experimental data exist to support this theory. It has been shown that CXCL17 causes the migration of macrophages from the lungs of wild-type mice, but not from $Cxcl17^{-/-}$ mice, indicating a role in inflammation (Maravillas-Montero et al., 2015). However, no further investigation into the potential metabolic effect of GPR35 was performed. Further studies are required to elucidate the potential of GPR35,

such as a high-fat diet study in $Gpr35^{-/-}$ animals. Unfortunately, due to the complex pharmacology and multiple endogenous ligands known, interest in this receptor is perhaps limited.

E. GPR84

Medium-chain fatty acids (MCFAs), including capric, undecanoic, and lauric acid, bind and activate GPR84, resulting in Ca^{2+} mobilization and inhibition of cAMP (Wang et al., 2006). These responses are pertussis toxin sensitive, indicating that GPR84 couples to $G\alpha_{i/o}$. GPR84 is predominantly present on immune cells and more particularly in monocytes, macrophages, and neutrophils (Wang et al., 2006). In the periphery, GPR84 is mainly expressed in bone marrow, spleen, lung, and peripheral blood leukocytes. In the CNS, GPR84 expression is restricted to microglia (Bouchard et al., 2007). Interestingly, MCFAs caused significant upregulation of the LPS-induced proinflammatory cytokine IL-12 p40 (IL12B), which has a pivotal role in promoting cell-mediated immunity by inducing and maintaining Th1 cell responses and inhibiting Th2 response. In agreement with these results, $Gpr84^{-/-}$ mice had increased levels of Th2 cytokines (Wang et al., 2006). Furthermore, under proinflammatory conditions, $Gpr84$ expression in macrophages is increased (Talukdar et al., 2011) and regulates TNF-α secretion from LPS-stimulated macrophages (Müller et al., 2017). Moreover, Nagasaki et al. (2012) demonstrated, using a 3T3-L1 (adipocyte) and RAW264.7 (macrophage) coculture, a clear upregulation in $Gpr84$ expression in the presence of TNF-α, with a concomitant downregulation of adiponectin, and concluded that the release of TNF-α from infiltrating macrophages caused the increase in $Gpr84$ expression.

To add further weight to this hypothesis, Suzuki et al. (2013) demonstrated, using MCFAs and a surrogate agonist, 6-n-octylaminouracil, that GPR84 agonists caused chemotaxis of human leukocytes and macrophages. Likewise, LPS stimulation increased the release of proinflammatory cytokines, IL-8 and TNF-α, in these human leukocytes and macrophages, respectively. Finally, $Gpr84$ was shown to be upregulated under inflammatory conditions in both the microglia and astrocytes (Madeddu et al., 2015). In line with these observations, $Gpr84$ gene deficiency significantly reduces microgliosis (Audoy-Remus et al., 2015). Because several groups have established a role for glia in energy balance regulation and obesity pathogenesis (see Douglass et al., 2017 for review), it is tempting to speculate that GPR84 may have a metabolic role under inflammatory conditions. Although all these studies suggest a link between GPR84 and chronic low-grade inflammation, its role in energy and glucose homeostasis remains unclear. Surprisingly, recent studies performed by Du Toit et al. (2017) indicate that $Gpr84$ gene deficiency does not significantly affect glucose or energy homeostasis in response to a low-chain fatty acid (LCFA)- or MCFA-enriched diet. Interestingly, the authors found that $Gpr84^{-/-}$ KO mice displayed significantly increased liver triglyceride levels in response to the low-chain fatty acid diet, although infiltration of immune cells in the liver as well as expression markers of inflammation under these conditions was unfortunately not documented. Whether the exacerbated steatosis observed in $Gpr84^{-/-}$ KO animals is due to cross-talk between hepatocytes and immune cells remains to be established. Further studies using KO mice and bone marrow transplantations are required to determine whether there is a major role for GPR84 in metabolic disease.

F. Leukotriene BLT$_1$ Receptor

Leukotriene B$_4$ (LTB$_4$) is a proinflammatory cytokine produced from arachidonic acid (Tager and Luster, 2003) that binds with high and low affinity to the leukotriene B4R1 (BLT$_1$) and B4R2 (BLT$_2$) receptors, respectively. In addition, other lipoxygenase and thromboxane synthase products, including 12-hydroxyeicosatetraenoic acid and 12-hydroxyheptadecatrienoic acid, bind and activate the BLT$_2$ receptor. In a recent study, $Blt_1^{-/-}$ mice placed on a high-fat diet had reduced levels of CD11b$^+$ monocytes in adipose tissue compared with the wild-type controls, a clear reduction in M1 proinflammatory adipose tissue macrophages, and a reduction in the expression of proinflammatory chemokine genes, including $IL6$ and $Ccl2$ (Spite et al., 2011). Deletion of the BLT$_1$ receptor reduced inflammation in adipose tissue and liver, resulting in protection from hepatic steatosis and insulin resistance. This suggested a novel role for the BLT$_1$ receptor in monocyte chemotaxis, culminating in high levels of chronic inflammation and obesity.

It has also been shown that LTB$_4$ causes insulin resistance in obese mice associated with enhanced macrophage chemotaxis, stimulation of proinflammatory pathways, reduced insulin-stimulated glucose uptake into myocytes, and impaired insulin-mediated suppression of hepatic glucose secretion in mouse hepatocytes (Li et al., 2015b). All of these effects were reversed or severely blunted in the $Blt_1^{-/-}$ mouse. These studies suggest that BLT$_1$ receptor inhibition may be a useful way of preventing obesity-induced T2DM. However, to date, all studies have been performed using only $Blt_1^{-/-}$ mice. As LTB$_4$ also binds and activates the BLT$_2$ receptor, further studies are required to understand whether a compensatory mechanism is present, using the $Blt_2^{-/-}$, or a double $Blt_1^{-/-}/Blt_2^{-/-}$ KO. Finally, whereas the BLT$_1$ receptor appears to couple exclusively to $G\alpha_i$ proteins, the BLT$_2$ receptor couples to both $G\alpha_i$ and $G\alpha_q$ proteins (Yokomizo et al., 2001). Therefore, perhaps specifically inhibiting the activation of the $G\alpha_i$ pathway via the BLT$_1$ receptor may be sufficient to obtain the desired anti-inflammatory phenotype.

G. SUCNR1 (GPR91)

SUCNR1 is expressed on immature dendritic cells and macrophages. The receptor is activated by succinate, which is generated from citrate via the tricarboxylic acid cycle. Citrate is involved in the production of prostaglandin and fatty acid synthesis. Under homeostasis, M2 macrophages break down succinate by succinate dehydrogenase (SDH). However, under levels of high inflammation, SDH is inhibited by itaconate, an antimicrobial metabolite (Nemeth et al., 2016), and inhibition of SDH causes accumulation of succinate within the macrophage. This accumulation adds to the inflammatory phenotype by increasing LPS-induced hypoxia-inducible factor 1α equilibrium, resulting in an increase in IL-1β expression (Van den Bossche et al., 2017). Activation of SUCNR1 causes maturation and migration of these immune cells into metabolic tissues, further increasing the production of IL-1β (Rubic et al., 2008). Moreover, activation of SUCNR1 by succinate causes a SUCNR1-dependent recycling of the agonist fueling the inflammation in a paracrine mechanism, a concept termed immunometabolism (Littlewood-Evans et al., 2016). In differentiated bone marrow macrophages obtained from wild-type and $Sucnr1^{-/-}$ mice,

macrophage migration and IL-1β production were abrogated in the KO animals (Littlewood-Evans et al., 2016). However, $Sucnr1^{-/-}$ mice fed a high-fat diet for 16 weeks exhibited improved insulin resistance (Carmone et al., 2015; van Diepen et al., 2017), whereas a similar study only showed an initial improvement, with the animals becoming progressively hyperglycemic (McCreath et al., 2015). Finally, in another study, $Sucnr1^{-/-}$ mice developed dry age-related macular degeneration (Favret et al., 2013). Due to these conflicting data sets, interest in targeting SUCNR1 for metabolic disorders may be limited.

IV. Conclusions and Perspectives

The worldwide prevalence of type 2 diabetes mellitus is increasing rapidly, culminating in a significant financial and resource burden on the various health care systems and health professionals. Although in recent years there has been a moderate increase in the number of available treatments, including the newly approved sodium-glucose cotransporter-2 inhibitors (Chao, 2014), there is a clear unmet medical need. The roles of β-cell dysfunction and insulin resistance were
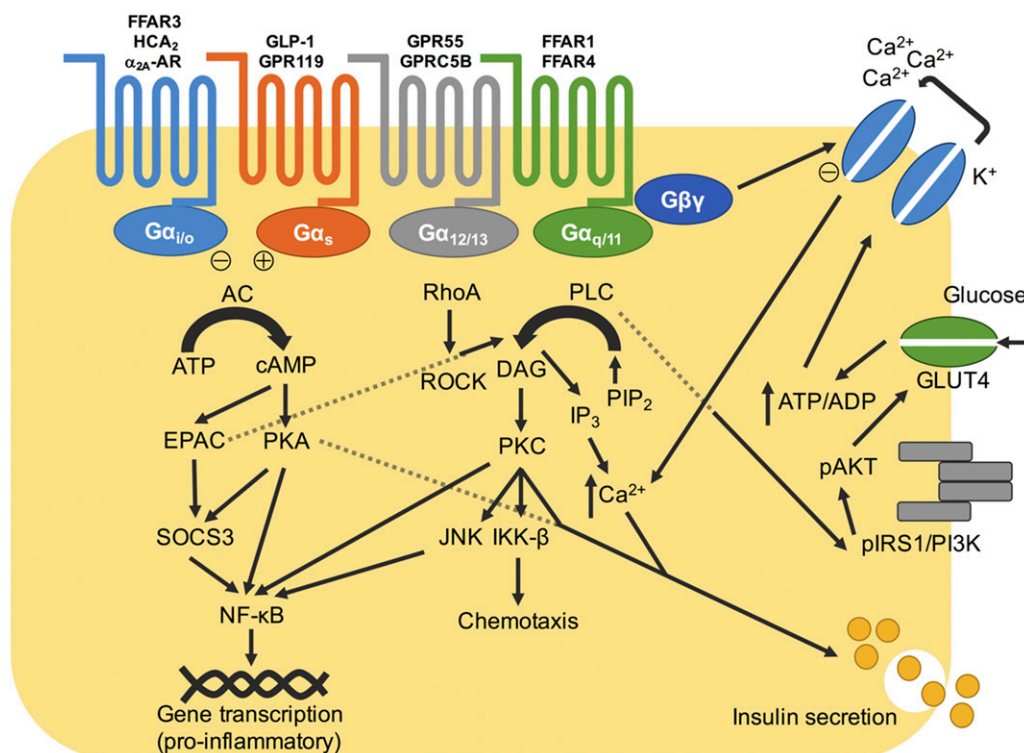

Fig. 4. Schematic diagram of a pancreatic β-cell illustrating GPCR-involved β-cell dysfunction, insulin resistance, and obesity-induced T2DM and the signaling pathways of downstream G protein activation. Typically, insulin secretion occurs when glucose is taken up into the cell, which increases the ATP/ADP ratio. This change causes a reduction in the ATP-regulated K$^+$ channel activity. The increased levels of K$^+$ within the cell cause depolarization of the cellular membrane, which in turn causes opening of voltage-dependent Ca^{2+} channels. This influx of Ca^{2+} causes the exocytosis of insulin from insulin-storing secretory granules. Phosphorylation of the insulin receptor by phospholipase C and activation of the serine/threonine kinase pathway enhance glucose uptake into the relevant tissues. The involvement of GPCRs causes an increase in the level of insulin exocytosis either via the stimulation of the Gα_s signaling pathway, which causes an increase in protein kinase A, or via the Gα_q signaling pathway, which causes an increase in both PKC and intracellular Ca^{2+} concentrations. The levels of insulin secretion can be inhibited by the G$\beta\gamma$ subunit complex, inhibiting the voltage-dependent Ca^{2+} channel activity. GPCRs can also cause an increase in the gene transcription of multiple proinflammatory genes and increased chemotaxis via activation of IKK-β, JNK, and NF-κB signaling pathways.

first described by Yalow and Berson (1960) when they developed an immunoassay to measure endogenous plasma insulin levels in humans and observed clear differences in nondiabetic and early diabetic subjects following an oral glucose tolerance test. As such, the main focus for developing new therapeutics over the past 50 years has been to improve β-cell function and insulin sensitivity. However, more recently, the effect of low-grade tissue inflammation has emerged as a mechanism to target therapeutically (Donath, 2014). Nonetheless, there is some debate within the diabetes field as to whether inflammation is a driver of insulin resistance and T2DM or just an additional symptom of the disease. To definitively answer this question, an increase in clinical trials using anti-inflammatory compounds is required. In addition, whether targeting GPCRs for this indication will prove successful is still yet unknown, but combinational therapies including anti–IL-1β and anti-TNF with small molecular weight agonists or antagonists may prove beneficial, complementing effects on the different pathways involved in inflammation.

The number of GPCRs potentially involved in the development and progression of T2DM has dramatically increased since the beginning of the millennium, likely due to greater access to transgenic animal models and an increased understanding of GPCR pharmacology. With over 40% of all marketed drugs activating or inhibiting GPCRs (Wise et al., 2002), targeting these proteins is likely to be both tractable and beneficial. However, many challenges in targeting these receptors still persist, particularly as many are orphans or, like FFA and chemokine receptors, have a large number of endogenous ligands that make tractability more challenging. Changes in the expression and/or function of the receptors highlighted in this review can influence the development and progression of T2DM. In some cases, the downstream signaling pathways involved are known, at least for β-cells (Fig. 4), but more studies are required within other relevant metabolic tissues, including skeletal muscle, liver, and brain to dissect the interplay of downstream events. Interestingly, no clear relationship between specific G proteins and the disease exists (Fig. 4; Table 1).

A lack of understanding of basic receptor pharmacology makes development of therapeutic compounds immensely difficult. Even with KO animal data supporting many of these GPCRs, as promising targets, progressing these into candidates for drug development remains challenging. In many cases, limited or conflicting data have hindered the translation of many of these KO studies into humans and indicate that more rigorous early-stage target validation is required. Nonetheless, with the constant advances of technological platforms, including improved compound screening techniques, deorphanization strategies, novel targeting mechanisms, including signaling bias and allostery, and the explosion in GPCR structural biology, the possibility of successfully targeting these proteins is ever increasing. Further research into these highly desirable targets is warranted, but may require novel approaches ultimately led by an increased understanding of the pathophysiology of T2DM.

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