



Adhesion G-protein coupled receptors: Implications for metabolic function



Oladapo E. Olaniru, Shanta J. Persaud *

Diabetes Research Group, Department of Diabetes, King's College London, Guy's Campus, London SE1 1UL, UK

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ABSTRACT

Adhesion G-protein coupled receptors (aGPCRs) are emerging as important actors in energy homeostasis. Recent biochemical and functional studies using transgenic mice indicate that aGPCRs play important roles in endocrine and metabolic functions including β -cell differentiation, insulin secretion, adipogenesis and whole body fuel homeostasis. Most aGPCRs are orphans, for which endogenous ligands have not yet been identified, and many of the endogenous ligands of the already de-orphanised aGPCRs are components of the extracellular matrix (ECM). In this review we focus on aGPCR expression in metabolically active tissues, their activation by ECM proteins, and current knowledge of their potential roles in islet development, insulin secretion, adipogenesis and muscle function.

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1. Introduction

Type 2 diabetes (T2D), a state of persistently elevated blood glucose that is associated with long term damage to multiple organs, is a chronic metabolic disorder that poses considerable economic and health challenges to individuals and society. The global rise in T2D prevalence is mainly driven by the increased incidence in obesity: in 2016 over 650 million adults were obese (WHO, 2016), approximately 425 million of whom have diabetes (IDF, 2017). The global incidence of T2D is predicted to continue to rise as a consequence of changing demographics and increases in the number of people adopting a sedentary lifestyle. It is therefore essential that effective pharmacotherapies are available

to people with T2D to ensure appropriate blood glucose control and thus minimise the complications associated with uncontrolled hyperglycaemia.

1.1. Islet GPCRs as drug targets for type 2 diabetes

GPCRs are the largest class of plasma membrane proteins, and they control many physiological processes through transducing a diverse array of signals to the cell interior through coupling to a family of heterotrimeric GTP-binding proteins. GPCRs were initially classified, based on their sequence similarities, into six alphabetically-named classes: Class A (rhodopsin-like receptors), Class B (secretin receptors), Class C (metabotropic glutamate receptors), Class D (fungal receptors), Class E (cyclic AMP receptors) and Class F (frizzled receptors). Of these, only classes A, B, C and F are found in vertebrates (Kolakowski, 1994). However, this classification did not take into account the subtle differences between the GPCRs within the same group and an alternative system was proposed that related GPCR structures to their functions and ligand preference. This alternative classification, known as the GRAFS

Abbreviations: GPCRs, G-Protein coupled receptors; aGPCRs, Adhesion G-protein coupled receptors; T2D, Type 2 diabetes; T1D, Type 1 diabetes; ECM, Extracellular matrix; GPS, GPCR Proteolytic site; GAIN, GPCR Autoproteolysis-inducing; WAT, White adipose tissue; BAT, Brown adipose tissue; HGP, Hepatic glucose production; CGCR, Glucagon receptor.

* Corresponding author.

E-mail address: shanta.persaud@kcl.ac.uk (S.J. Persaud).

system, sub-divides the GPCR superfamily into five classes: Glutamate, Rhodopsin, Adhesion, Frizzled and Secretin (Alexander et al., 2017; Fredriksson, Lagerström, Lundin, & Schiöth, 2003). Although progress has been made in identifying cognate ligands for the GPCRs, 121 out of the ~350 non-sensory GPCRs are still orphans, for which no activating ligands have been identified (Alexander et al., 2017). The rhodopsin family, which is the most studied, has 197 receptors with known ligands and about 87 of them are orphans. The frizzled family consists of 11 receptors, all of which have been de-orphanised. Of the 33 adhesion GPCRs, only 6 have been proposed to have an endogenous ligand (Alexander et al., 2017; Davenport et al., 2013).

Nearly 300 GPCRs, belonging to all classes of the GRAFS system, are expressed by human islets of Langerhans (Amisten, Salehi, Rorsman, Jones, & Persaud, 2013). The function of many of these receptors has not yet been established, but it is known that numerous islet GPCRs play important roles in regulating growth, differentiation, secretion, maturation and survival of islet cells (Ahrén, 2009; Amisten et al., 2013). As islets are crucial in maintaining glucose homeostasis through secretion of gluco-regulatory hormones, the importance of GPCR ligands in maintaining appropriate islet function has led to GPCRs being considered as attractive targets for novel T2D therapies. They have readily accessible druggable sites and are the targets of at least 30% of all prescription drugs in current use (Santos et al., 2017; Sriram & Insel, 2018), which explains why pharmaceutical industries are investing heavily in them for new drug leads (Hauser, Attwood, Rask-Andersen, Schiöth, & Gloriam, 2017; Persaud, 2017).

GPCRs exert their effects via activation and release of the $G\alpha$ -subunit from the heterotrimeric G-protein complex, although G-protein-independent effects via β -arrestins have been described (Ravier et al., 2014; Smith & Rajagopal, 2016; Tuteja, 2009). The coupling preference of GPCRs to the $G\alpha$ subtypes, $G\alpha_i$, $G\alpha_s$, $G\alpha_{q/11}$ and $G\alpha_{12/13}$, determines their effects on insulin secretion. Generally, GPCRs that signal via $G\alpha_s$ or $G\alpha_{q/11}$ increase insulin secretion through the generation of cAMP and IP_3 /DAG respectively, while signalling via $G\alpha_i$ -mediated reductions in cAMP inhibits insulin release. The roles of β -cell receptors coupled to $G\alpha_{12/13}$ are not fully understood, but actin cytoskeleton remodelling and activation of Rho-associated protein kinase downstream of these GPCRs is likely to be coupled to increased insulin secretion. Islet-expressed GPCRs that have received considerable attention for diabetes therapy include GLP-1R, GPR40, GPR119 and GPR120 (Persaud, 2017). Drugs that activate GLP-1R have been in use for the clinical management of T2D for the past 10–15 years, and those targeting GPR40, GPR119 and GPR120 are either currently undergoing clinical trials or have been discontinued due to lack of efficacy or for safety reasons. Recently, a novel GLP-1/GIP dual agonist, LY3298176, has shown very promising results in phase 2 trials in patients with T2D (Frias et al., 2018).

2. Adhesion GPCRs

The adhesion GPCR family consists of 33 members, with nine distinct subclasses (Hamann et al., 2015). A unified nomenclature was recently recommended for aGPCRs using the prefix ADGR, for adhesion G-protein coupled receptor, followed by a single letter and a number derived from their previous subfamily name and members within each subfamily, respectively (Table 1). In addition to the canonical seven transmembrane segments common to other GPCRs, aGPCRs have an extended N-terminal segment and they undergo self-cleavage during maturation at the GPCR proteolytic site (GPS) within the GPCR autoproteolysis-inducing (GAIN) domain (Fig. 1). The GAIN domain is a unique evolutionarily conserved structure of aGPCRs that is required for self-cleavage (Prömel, Langenhan, & Araç, 2013). The N and C termini re-associate upon maturation and remain non-covalently attached to each other at the GPS. The capacity of the N-terminal fragment of an aGPCR to cross-assemble with the C-terminus of a different aGPCR and vice versa, and the ability of a small proportion of the N-terminal segment, anchored independently to the cell membrane, to initiate

downstream signalling upon ligand binding, increases the complexity of aGPCR heterodimer signalling considerably (Huang, Chiang, Chang, & Lin, 2018; Silva, Lelianova, Hopkins, Volynski, & Ushkaryov, 2009; Volynski et al., 2004). The GPS is found immediately upstream of the first transmembrane loop of aGPCRs and it is rich in cysteine residues, alternating with tryptophan in a C-W-W-C-C conserved sequence (Araç et al., 2012). The exceptions to this general aGPCR structure is GPR123, which does not have a GAIN domain, and GPR111, GPR114, GPR115 and CELSR1, which do not have cleavable GAIN domains (Araç et al., 2012; Krishnan, Nijmeijer, de Graaf, & Schiöth, 2016; Wilde et al., 2016). Other aGPCRs that are predicted to have a non-cleavable GAIN domain include GPR124, GPR125, EMR1 and CELSR3, but this atypical structural feature has not yet been demonstrated (Hamann et al., 2015).

The extracellular N-termini of aGPCRs vary greatly in length and contain mucin-like motifs, which are thought to help them in their cell adhesion and cell-matrix interactions (Langenhan, Aust, & Hamann, 2013). They also contain multiple functional domains such as hormone binding domains, thrombospondin repeats, epidermal growth factor-calcium binding domain, and cadherin repeats (Bjarnadóttir et al., 2004; Hamann et al., 2015). The CELSR family members (CELSR1, CELSR 2, CELSR 3), which are associated with planar cell polarity in epithelial cells, contain four functional domains including several cadherin repeats on the uppermost part of their N-terminal segments (Wang et al., 2014), enabling them to participate in diverse physiological processes.

Most aGPCRs are widely expressed in tissues such as the reproductive tract, neurons, stomach, lungs and various tumour cells, where they play roles in angiogenesis, cell adhesion, immune recognition and neuronal migration (Simundza & Cowin, 2013). However, some aGPCRs have fairly restricted tissue expression. For example, GPR123, BAI1, BAI3 and VLGR1 have biased expression in the brain, GPR111, GPR112, GPR128 in the gastrointestinal tract and GPR110 in the kidney (Fagerberg et al., 2014), suggesting that these receptors have particular functional capacities in those organs. Inactivating mutations in aGPCRs have been linked to several human diseases including bilateral frontoparietal polymicrogyria (Piao et al., 2004), vibratory urticaria (Boyden et al., 2016) and Usher syndrome type IIc (Weston, Luijendijk, Humphrey, Möller, & Kimberling, 2004), further pointing to the importance of aGPCRs in physiological processes and disease.

2.1. Adhesion GPCR activation and signalling

As mentioned above, the N-terminal fragment of most mature adhesion GPCRs attaches non-covalently with the membrane bound C-terminal fragment at the GPS, and the cleavage of the N-terminus has been suggested to modulate receptor activity. Removal of the N-terminal domains in GPR56, CD97 and BAI1 mutants has been associated with increased receptor activities (Paavola, Stephenson, Ritter, Alter, & Hall, 2011; Stephenson et al., 2013; Ward et al., 2011), which led to the proposal that the extracellular domain of aGPCRs acts as an inverse agonist of constitutive signalling. It is now established that removal of the N-terminus, either by ligand binding or mechanical detachment, is sufficient for receptor activation (Liebscher & Schöneberg, 2016). Another signalling mechanism has been proposed based on the observation that a part of the aGPCR extracellular domain called a stachel sequence, which is buried in the GAIN segment, acts as a tethered agonist and this is exposed to the seven transmembrane domain upon ligand binding. This scenario has been demonstrated in a number of aGPCRs including GPR56, GPR64, GPR114, GPR126 and GPR133 (Wilde et al., 2016; Stoveken et al., 2015; Liebscher et al., 2014; Demberg et al., 2015; Kishore et al., 2016). Due to high sequence conservation of the aGPCR stachel region, stachel-derived peptides for a given receptor may be able to activate other aGPCRs within and beyond the same sub-family (Demberg et al., 2017). A further aGPCR activation mechanism has been identified through the observation that increased GPR126 signalling occurred when shaking forces were applied in the presence of the activating ligand laminin-211, presumably as a consequence of

Table 1

Adhesion GPCR expression in human pancreas and islets.

Expression of aGPCR proteins in human pancreas and islets is taken from immunohistochemistry data from the Human Protein Atlas Project, in which all antibodies were validated for sensitivity and reliability (www.proteinatlas.org/about/antibody+validation) (Uhlén et al., 2015). aGPCR mRNA expression in human islets is taken from qPCR and RNA-Seq data (Amisten et al., 2013; Uhlén et al., 2015).

Adhesion GPCR		Expression in human		Ligands or N-terminal interactors	Ligand action	Metabolic phenotypes in KO mice
Sub-group	Current nomenclature (previous nomenclature)	Pancreas	Islets			
I	ADGRL1 (LPHN1)	Yes	Yes (+++)	α -latrotoxin		
	ADGRL2 (LPHN2)	Not detected	Yes (+)	α -latrotoxin		
	ADGRL3 (LPHN3)	Yes	Not detected	Fibronectin leucine rich transmembrane protein 3		
	ADGRL4 (ELTD1)	Not detected	Yes (++)			
II	ADGRE1 (EMR1)	Not detected	Not detected			
	ADGRE2 (EMR2)	Not detected	Yes (+)	Chondroitin sulphate ^a		
	ADGRE3 (EMR3)	Not detected	Not detected			
	ADGRE4 (EMR4)	Not detected	Not detected			
	ADGRE5 (CD97)	Not detected	Yes (+)	CD55, $\alpha_5\beta_1$ integrin		
III	ADGRA1 (GPR123)	Not detected	Yes (+)			
	ADGRA2 (GPR124)	Not detected	Yes (+)	Glycosamino-glycans ^a		
	ADGRA3 (GPR125)	Yes	Yes (+)			
IV	ADGRC1 (CELSR1)	Not detected	Yes (+)			
	ADGRC2 (CELSR2)	Not detected	Yes (+)	N-terminal homophilic interaction		Normal endocrine cell differentiation (Cortijo et al., 2012)
	ADGRC3 (CELSR3)	Not detected	Yes (+)	N-terminal homophilic interaction		Impaired β -cell differentiation, glucose intolerance (Cortijo et al., 2012)
V	ADGRD1 (GPR133)	Yes	Yes (+)			
	ADGRD2 (GPR144)	Not detected	Not detected			
VI	ADGRF1 (GPR110)	Yes	Not detected	Synaptamide (Lee et al., 2016)		
	ADGRF2 (GPR111)	Not detected	Not detected			
	ADGRF3 (GPR113)	Not detected	Yes (+)			
	ADGRF4 (GPR115)	Not detected	Yes (+)			
	ADGRF5 (GPR116)	Not detected	Yes (+)			Hyperlipidaemia, impaired glucose tolerance and insulin resistance, decreased adipocyte size (Nie et al., 2012)
VII	ADGRB1 (BAI1)	Not detected	Not detected	Phosphatidyl-serine, lipopoly-saccharide, $\alpha_v\beta_5$ integrin, Nogo receptor-like 2 and 3 (Chong, Ohnishi, Yusa, & Wright, 2018)		
	ADGRB2 (BAI2)	Not detected	Yes (+)			
	ADGRB3 (BAI3)	Not detected	Yes (+)	C1q1 & 3, stabilin-2 (Hamoud et al., 2018)	↓ insulin secretion (Gupta et al., 2018)	
VIII	ADGRG1 (GPR56)	Yes	Yes (+++)	Collagen III ^a ,	↑ insulin secretion, ↓ apoptosis (Dunér et al., 2016; Olaniru, Pingitore, et al., 2018)	Normal glucose homeostasis (Olaniru, Pingitore, et al., 2018)
				TG2 ^a , heparin, progastrin		
	ADGRG2 (GPR64)	Yes	Not detected			
	ADGRG3 (GPR97)	Not detected	Yes (+)			
	ADGRG4	Not detected	Yes (+)			

(continued on next page)

Table 1 (continued)

Adhesion GPCR		Expression in human		Ligands or N-terminal interactors	Ligand action	Metabolic phenotypes in KO mice
Sub-group	Current nomenclature (previous nomenclature)	Pancreas	Islets			
	(GPR112)	detected				
	ADGRG5	Not	Yes (+)			
	(GPR114)	detected				
	ADGRG6	Not	Yes (+)	Collagen IV ^a , laminin ^a , prion protein		
	(GPR126)	detected				
	ADGRG7	Not	Not detected			
	(GPR128)	detected				
IX	ADGRV1	Yes	Not detected			
	(VLGR1)					

Key: Yes (+++): strongly expressed; Yes (++): moderately expressed; Yes (+): slightly expressed; Not detected: not detected or no available data, but not necessarily a proof of absence; blank cells: unknown or not yet investigated; ^a: endogenous ligands/binding partners of aGPCRs which are components of the ECM (Luo et al., 2011; Paavola, Sidik, Zuchero, Eckart, & Talbot, 2014; Petersen et al., 2015; Stacey et al., 2003; Vallon & Essler, 2006; Xu et al., 2006).

detachment of the N-terminal fragment and exposure of the stachel sequence (Petersen et al., 2015). It is therefore likely that aGPCRs are activated in a tripartite manner in vivo, such that binding of the endogenous ligand coupled with mechanical force from cell movement exposes the tethered agonist to initiate receptor activation (Fig. 2).

The hybrid and enigmatic structural features of aGPCRs have impeded understanding of their signalling mechanisms, and progress has been further limited by more than two-thirds of aGPCRs being orphan receptors. The major endogenous ligands reported so far for the de-orphanised aGPCRs are components of the extracellular matrix (ECM), a meshwork of collagens, laminins and chondroitin sulphate proteoglycans that contains secreted proteins such as cytokines and growth factors trapped within it (Table 1). CELSR2 and 3 have no known ligands but are activated by N-terminal homophilic interactions (Shima et al., 2007).

It has been postulated that aGPCRs will have multiple interacting ligands due to their unusually long N-terminal segment with adhesive motifs, and their broad expression in many tissues (Paavola & Hall, 2012). Four binding partners have been identified for the most studied aGPCR, GPR56: the ECM protein collagen III in the developing brain (Luo et al., 2011), the cross-linking enzyme transglutaminase 2 (TG2) in HEK293 cells (Xu, Begum, Hearn, & Hynes, 2006), the anti-coagulant heparin in A375 melanoma cells (Chieng et al., 2016) and the stomach prohormone progastrin in colorectal cancer cells (Jin et al., 2017). Whereas activation of GPR56 by collagen III or an antibody directed against its N-terminal has been shown to couple to RhoA through

$G\alpha_{12/13}$ (Iguchi et al., 2008; Luo et al., 2011, 2014), recruitment of downstream signalling has not been demonstrated so far for TG2, heparin or progastrin, suggesting that collagen III is the main endogenous agonist of GPR56. Complexes between GPR56 and the tetraspanins CD9 and CD81 that couple to $G\alpha_q$ have also been reported (Little, Hemler, & Stipp, 2004), but there is currently no information on whether these complexes perform a physiological function.

Another mechanism that might regulate signalling downstream of GPR56 is the generation of splice variants in cells expressing this receptor. Full length GPR56 consists of 13 exons, yielding proteins of 693 and 697 amino acids in human and mouse, respectively, and human GPR56 is known to undergo alternative splicing at exons 2, 3 and 10 to produce four isoforms termed GPR56₆₈₇, GPR56₆₉₂, GPR56₅₂₃ and GPR56₅₁₈ (Kim et al., 2010). Analysis of gene promoter activities in cells expressing GPR56 splice variants indicated that GPR56₆₈₇ and GPR56₆₉₂ increased serum response element (SRE) transcriptional activity, which may have been a consequence of deletion of six amino acids in the first intracellular loop contributing to enhanced $G\alpha_{12/13}$ /RhoA signalling (Kim et al., 2010). It has also been identified that the GPR56₅₁₈ variant, in which a frameshift deletion causes a new translation start site, has increased basal activity and it has been predicted that alternative splicing of GPR56 could diversify functionality (Salzman et al., 2016). GPR56 is not the only aGPCR that undergoes alternative splicing: functional splice variants have been identified in all other aGPCRs except for GPR111, GPR115, GPR128, GPR144, BAI3, CELSR1, ELTD1 and VLGR1 (Bjarnadóttir et al., 2007).

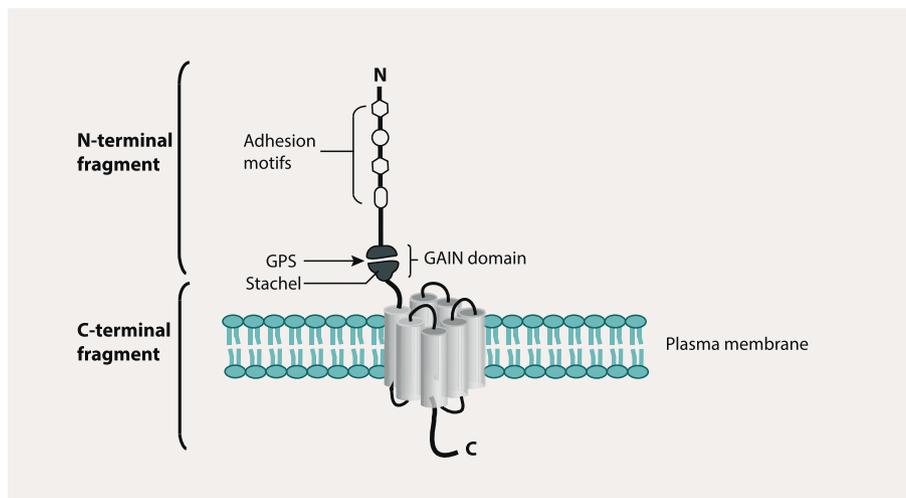


Fig. 1. Adhesion GPCR architecture. Adhesion GPCRs have unusually long extracellular N-terminal fragments (NTF) that contain several adhesive motifs, which are important in cell adhesion and cell-matrix interactions. The NTF is joined non-covalently to the C-terminal fragment at the GPCR proteolytic site (GPS) within the GPCR autoproteolysis-inducing (GAIN) domain. The stachel sequence is buried in the GAIN domain and is exposed upon ligand binding.

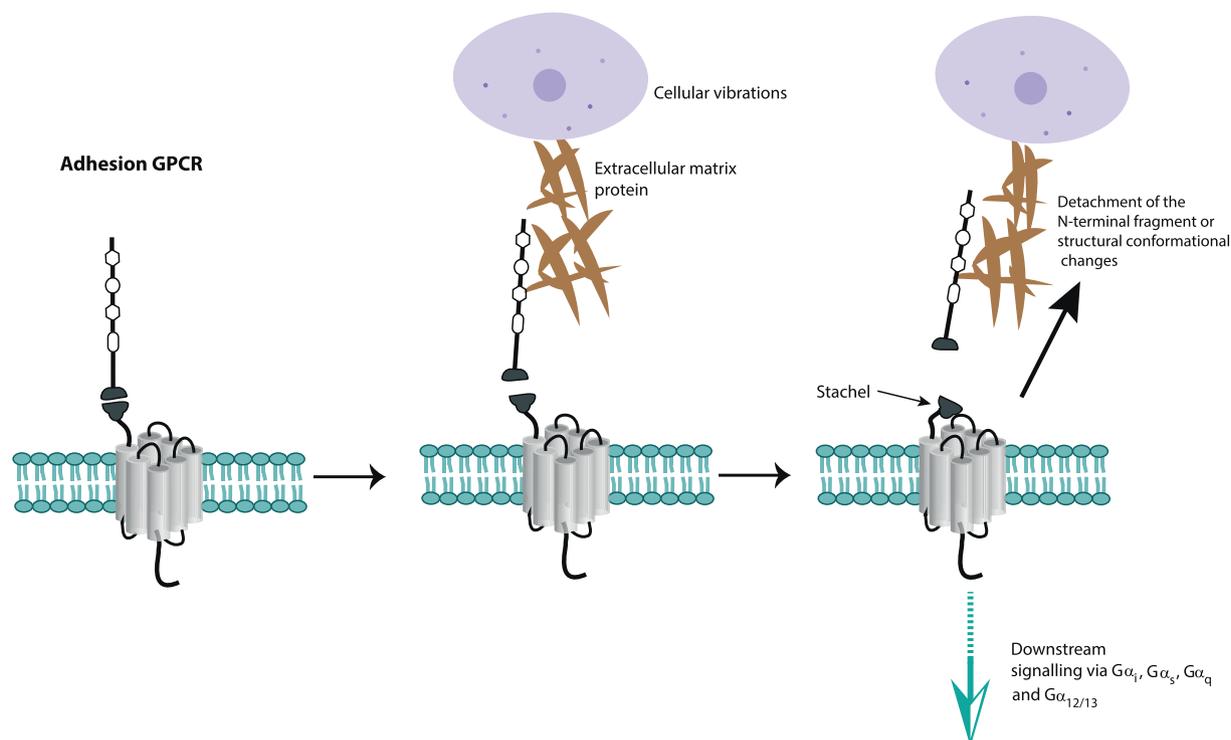


Fig. 2. Activation of aGPCRs. Dissociation of the N-terminal fragment from the C-terminal transmembrane domain is the main activation mechanism for most aGPCRs. Binding of activating ligands, which include the extracellular matrix proteins collagen III and laminin-211, leads to detachment of the N-terminal fragment of cleavable aGPCRs from the C-terminal fragment at the GPS. This exposes a stachel sequence that induces tethered agonism and subsequent downstream signalling. The stachel sequence may also be exposed by mechanical force or cellular vibrations. Receptor activation is coupled to intracellular effects through coupling to members of the heterotrimeric GTP-binding protein family ($G\alpha_s$, $G\alpha_i$, $G\alpha_q$ and $G\alpha_{12/13}$).

3. Function of adhesion GPCRs in metabolism

Quantitative trait loci analyses have revealed that the majority of human aGPCRs are associated with traits involved in metabolism such as body weight and body fat, and leptin, glucose and insulin levels (Kovacs & Schöneberg, 2016). Adhesion GPCRs have been detected in metabolically active tissues such as islets, liver, skeletal muscle and adipose tissue (Fig. 3), and TG2, a putative GPR56 interacting partner, was identified as a candidate gene for maturity onset diabetes of the young (Porzio et al., 2007).

3.1. Islets

Most aGPCRs are expressed at varying levels in islets, with GPR56 being the most highly expressed GPCR in both mouse and human islets, and ELTD1, CELSR and latrophilin family members showing moderate expression (Table 1). Both mouse and human islets express readily quantifiable levels of the latrophilins LPHN1 and LPHN2, but LPHN3 mRNA is of low abundance in mouse islets and undetectable in human islets (Amisten et al., 2017). Therefore, if latrophilins have any translational value in regulating islet function focus should be limited to LPHN1 and LPHN2. Research to date on the role played by adhesion receptors in islets has largely focused on their interaction with the ECM, and their roles in β -cell development and insulin secretion.

3.1.1. The extracellular matrix and β -cell function

Islets of Langerhans are surrounded by a capsule of ECM, made up of the peri-insular basement membrane (BM) and a subjacent interstitial matrix, and this is among the first structures to be destroyed by autoimmune assault in type 1 diabetes (Irving-Rodgers et al., 2008; Korpos et al., 2013; Winer et al., 2003). The functional significance of the ECM in normal islet function is well reported. Thus, ECM proteins are

involved in a wide range of functions such as protecting β -cells from apoptosis, enhancing insulin secretion, β -cell migration and adhesion, and they play a role in pancreas development (Arzouni et al., 2017; Davis et al., 2012; Huang et al., 2011; Kaido, Yebra, Cirulli, & Montgomery, 2004; Llacua, Faas, & de Vos, 2018; Olaniru et al., 2018; Shih, Panlasigui, Cirulli, & Sander, 2016).

A substantial amount of ECM is also distributed throughout the islet interior as the perivascular basement membrane that is associated with, and largely generated by, the microvasculature endothelium (Otonkoski, Banerjee, Korsgren, Thornell, & Virtanen, 2008). Unlike mouse islets, which have a single BM, the blood vessels of human islets have a duplex BM consisting of an outer parenchyma BM and an inner capillary BM (Virtanen et al., 2008), and this is speculated to provide extra protection against autoimmune insulinitis (Otonkoski et al., 2008). The majority of β -cells are in contact with the BM at the vasculature (Peiris, Bonder, Coates, Keating, & Jessup, 2014) and it is becoming apparent that insulin granule fusion is enriched at points where β -cells are in contact with the vascular BM (Gan et al., 2018; Low et al., 2014). In this way the ECM plays an important role in optimal insulin exocytosis by allowing targeted insulin secretion towards the vasculature.

Receptors mediating cell-ECM interactions have been identified, but their functions and signalling mechanisms are not fully understood. It is known that signals arising from ECM proteins can be transmitted into β -cells via membrane-localised adhesion receptors such as integrins, cadherins and aGPCRs, with integrin-mediated signalling cascades being the most studied (Olaniru & Persaud, 2018). Efforts to translate integrin- β -cell-ECM interactions to T2D therapies have made little progress due to the sheer complexity of integrin/ECM interactions and non-specificity of ligand binding. However, given that GPCR family members have been successful in drug development, aGPCRs may prove more tractable than integrins in translating our understanding

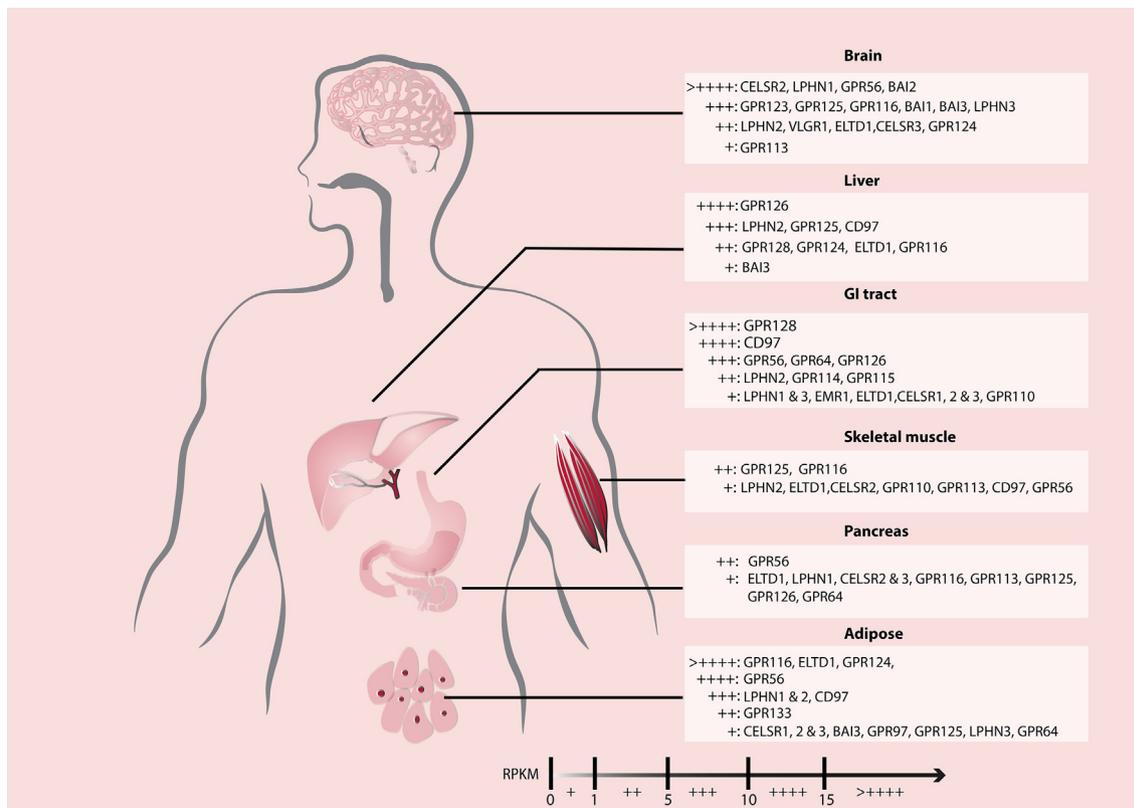


Fig. 3. Expression pattern of aGPCRs in metabolically active tissues. The relative expression of aGPCR transcripts in human brain, liver, gastrointestinal tract, skeletal muscle, pancreas and adipose tissue are indicated as RPKM (reads per kilobase of transcript per million mapped reads). + = ≤ 1 ; ++ = 1–5; +++ = 5–10; ++++ = 10–15; >++++ = ≥ 15 RPKM. Data were obtained from published RNAseq analysis (Fagerberg et al., 2014).

of β -cell-ECM interaction into novel therapeutic targets, although much research needs to be carried out in this area.

3.1.2. Islet development

Islet development starts as early as embryonic day 9 (E9) in mouse and occurs in two phases. The first phase, which is also known as primary transition, takes place between E9 and E12.5 and at this stage most of the cells are multipotent progenitor cells (MPCs) (Shih, Wang, & Sander, 2013). As the nascent pancreas enlarges and buds the MPCs, marked by their expression of transcription factors such as Pdx1, Ptf1a, Nkx2.2 and Sox9, undergo extensive proliferation (Bastidas-Ponce, Scheibner, Lickert, & Bakhti, 2017). Towards the end of the primary transition, the first wave of differentiation begins, with the majority of the differentiated cells being glucagon-expressing α -cells (Johansson et al., 2007). After E12.5, substantial differentiation occurs, giving rise to all of the endocrine cell types, with appearance of β -cells, followed by δ -cells and then pancreatic polypeptide cells (Johansson et al., 2007). This is known as phase II or secondary transition (Jensen, 2004). As the mouse matures, islet cells migrate from the epithelium to form clusters and they do not resemble the adult islet structure until E18.5 (Villasenor, Chong, & Cleaver, 2008). Some differences in human islet development have been reported, such as in the presence of a single wave of endocrine differentiation, delayed expression of key differentiation genes and the islet cytoarchitecture (Nair & Hebrok, 2015). Thus, at 30 days post-conception (dpc) in human pancreas the MPCs express key transcription factors such as Pdx1, Ptf1a, Sox9, Gata4 and Nkx6.1 but not Nkx2.2, which is only detectable after endocrine cell commitment at 10 weeks post-conception (wpc) (Jennings et al., 2013). Also, in humans insulin-positive β -cells are the first endocrine cells to appear (at 8wpc), rather than the α -cells that are observed first in developing mouse pancreas (Jeon, Correa-

Medina, Ricordi, Edlund, & Diez, 2009; Salisbury et al., 2014). In addition, approximately 30% of the early human pancreas endocrine cells express more than one hormone, as the MPCs differentiate to other endocrine cell types, whereas the appearance of polyhormonal cells in mouse islets is scarce (Herrera, 2000; Riedel et al., 2012). Despite these species-specific differences in endocrine pancreas specification the transcription factors regulating pancreas development are common to mice and humans and the overall islet structure is similar.

There is increasing evidence implicating ECM proteins and aGPCRs in pancreas development. It is now thought that ECM components provide cues for cells to migrate during organ development (Langenhan, Piao, & Monk, 2016), govern cell fate decisions of bipotent pancreatic progenitors to follow either duct or endocrine lineages (Mamidi et al., 2018), and they regulate branching morphogenesis during pancreas development (Shih et al., 2016). GPR56 is highly expressed in NGN3⁺ endocrine progenitors in the developing pancreas (Gu et al., 2004), but its function in islet development is not yet known. Studies in neuronal and seminiferous tubule development in mice have indicated that GPR56 is critical for proper formation of the cerebellum, as it allows the developing neurons to adhere to the ECM of the pial basement membrane (Li et al., 2008; Luo et al., 2011), and its absence during embryogenesis leads to reduced male fertility (Chen, Yang, Begum, & Xu, 2010). Considering the high expression of GPR56 in the developing pancreas it may play a role in islet formation, and our preliminary studies showing fewer β -cells and more α -cells in islets from neonatal GPR56 null mice support this (Olaniru et al., 2018). In addition, it has been established that CELSR3 is critical for islet development, as mice with pancreatic progenitor Pdx1-specific deletion of CELSR3 are glucose intolerant in adult life, as a result of severe islet β -cell differentiation deficiency (Cortijo, Gouzi, Tissir, & Grapin-Botton, 2012).

3.1.3. Insulin secretion

Insulin release from islet β -cells is a tightly controlled process that is mainly regulated by nutrient availability and feedback communication between heterogenous islet cells and insulin-sensitive tissues. Although the contribution of classical GPCRs, such as GLP-1R, M3 muscarinic receptors and β_2 -adrenergic receptors (β_2 -AR), to glucose-induced insulin secretion is well established (Ahrén, 2009; Kong et al., 2010; Santulli et al., 2012), the involvement of aGPCRs is only just starting to be appreciated. In our screen of all GPCRs expressed by human islets, we detected 22 of the 33 known aGPCRs, including GPR56, GPR116, latrophilins (LPHNs), BAI3, ELTD1 and CELSR family members (Amisten et al., 2013), and recent studies are beginning to reveal the effects of individual aGPCRs on islet secretory function.

Our observation that GPR56 is the most abundant GPCR in human and mouse islets (Amisten et al., 2013; Amisten et al., 2017) is consistent with its previously reported high expression in mouse pancreas (Haitina et al., 2008). Collagen III, the endogenous ligand of GPR56 (Luo et al., 2011), activates the receptor in a $G\alpha_{12/13}$ /RhoA dependent manner (Iguchi et al., 2008; Luo et al., 2014). In the islets, collagen III is not expressed by the β -cells but by the vascular endothelial cells within the islets and the basement membrane (Olaniru, Pingitore, et al., 2018; Van Deijnen, Van Suylichem, Wolters, & Van Schilfgaarde, 1994). Exposure of islets and β -cells to exogenous collagen III potentiates glucose-mediated insulin secretion and protects them from apoptosis, in a GPR56-dependent manner (Dunér et al., 2016; Olaniru, Pingitore, et al., 2018), demonstrating that islets use β -cell-expressed GPR56 to sense signals from ECM collagen III to improve β -cell mass and secretory function. Consistent with this, islets in which GPR56 expression was acutely downregulated with siRNA had less insulin content and reduced insulin secretory capacity (Dunér et al., 2016). However, GPR56 knockout mice are normal and are able to regulate blood glucose levels appropriately, and islets isolated from them respond appropriately to glucose (Olaniru, Pingitore, et al., 2018). In contrast, deletion of TG2, which is thought to be a GPR56 binding partner, resulted in glucose intolerance in mice and islets isolated from them showed reduced glucose-induced insulin secretion, although signalling via GPR56 was not explored as TG2 had not yet been identified as a GPR56 activating ligand (Bernassola et al., 2002). This role for TG2 in regulating blood glucose levels via stimulation of insulin release could not be replicated in a separate study where deletion or constitutive activation of TG2 did not affect islet insulin secretory responses to glucose or whole body glucose homeostasis (Iismaa et al., 2013).

The black widow spider neurotoxin, α -latrotoxin, was shown to induce exocytotic release of insulin from clonal β -cells that expressed latrophilin, and transient overexpression of latrophilin in a β -cell line with low endogenous latrophilin expression conferred insulin secretory responsiveness to α -latrotoxin in those cells (Lang, Ushkaryov, Grasso, & Wollheim, 1998). It was proposed that this stimulatory effect of α -latrotoxin may have been a consequence of it mimicking a natural ligand of the latrophilin receptor, but it is not yet known whether specific LPHN activation in islets is coupled to increased insulin secretion since LPHNs are still classified as orphans for which endogenous ligands have not yet been defined. Fibronectin leucine rich transmembrane proteins (FLRT) (O'Sullivan et al., 2012) and teneurins (Boucard, Maxeiner, & Südhof, 2014; Silva et al., 2011) have been proposed as endogenous binding partners for LPHNs, but nothing is known about the effects of these proteins on islet function.

Less is known about aGPCR signal transduction mechanisms than for the other GPCR families, most likely because most of them are orphans. However, there is evidence of aGPCR signalling via both stimulatory $G\alpha_s$ and inhibitory $G\alpha_i$ coupling (Hamann et al., 2015), so it might be expected that they could have inhibitory as well as stimulatory effects on insulin secretion. In this context, it has recently been reported that the secreted protein, complement 1q like-3 (C1qL3), which has been identified as an activating ligand for BAI3 (Bolliger, Martinelli, & Südhof, 2011; Hamoud et al., 2018), decreased glucose-induced insulin

secretion from mouse and human islets in a BAI3-dependent manner by inhibiting cAMP production (Gupta et al., 2018). These data were generated using C1qL3 present in conditioned medium from HEK293 cells transfected with a C1qL3 plasmid, so it would be useful to identify whether similar results are also obtained with exposure of islets to recombinant C1qL3. A related C1q domain-containing protein, C1qL4, has recently been identified as an inhibitor of BAI3 while stabilin-2 is an activator. It is thought that the relative expression of these two BAI3 binding partners is important in the regulation of myoblast fusion (Hamoud et al., 2018), but there is currently no information on BAI3 regulation by C1qL4 or stabilin-2 in islets.

3.2. Adipose tissue

The traditional function of adipose tissue is to store energy and release it in the form of fatty acids when required, but it is now accepted it plays an important role as an endocrine organ that secretes a range of adipokines that are critical for maintaining whole body energy homeostasis. The major adipokine secreted by WAT is leptin, which is involved in metabolic regulation through its anorexigenic effects to inhibit food intake (Friedman, 2016). There is an imbalance in adipokine expression in obesity, with adipocyte hypertrophy leading to up-regulation of pro-inflammatory adipokines (e.g. IL-6, leptin, resistin and TNF α) and concomitant reductions in anti-inflammatory adipokines (e.g. adiponectin, adipolin and omentin-1) (Nakamura, Fuster, & Walsh, 2014; Ohashi, Shibata, Murohara, & Ouchi, 2014). This chronic, low-grade inflammatory environment in obesity contributes to cardiovascular and metabolic disorders (Nakamura et al., 2014).

Adipose tissue is generally sub-classified as white adipose tissue (WAT) and brown adipose tissue (BAT). In addition, beige or brite adipocytes with brown-like properties have been found in WAT depots (Wu et al., 2012), and it is now generally accepted that these arise from browning of WAT rather than being a distinct type of adipocyte. WAT is the primary energy storage organ that expands and contracts under conditions of energy excess and deficit, respectively. BAT is mainly found in neonates and infants where it has an essential function to generate non-shivering heat during cold exposure. Adipocytes in BAT have many mitochondria with high expression of uncoupling protein 1 (UCP-1), allowing them to efficiently convert lipids into heat, and BAT deficiency in mice is associated with obesity, insulin resistance and reduced thermogenic ability (Hamann, Flier, & Lowell, 1998; Lowell et al., 1993). It has been calculated that 40–50 g of maximally activated BAT in adult humans could account for 20% of total energy expended (Rothwell & Stock, 1983), and the importance of BAT in energy metabolism has heightened the search for BAT activators for use as obesity and T2D therapies (Scheideler, Herzig, & Georgiadi, 2017).

Human subcutaneous WAT and mouse mature BAT express over 150 and 230 GPCRs, respectively (Amisten et al., 2015; Klepac et al., 2016). In terms of aGPCRs, GPR56, GPR116, GPR124 and ELTD1 are highly expressed in human subcutaneous adipose tissue (Amisten et al., 2015; Fig. 3) and profiling of mouse brown adipose tissue has indicated relatively high expression of GPR124, GPR125, GPR133, LPHN1 and LPHN2 (Klepac et al., 2016). Research on the role of GPCRs in adipose tissue has largely focused on β -adrenergic receptor signalling, with observations that selective activation of β_3 receptors in BAT and WAT was associated with increased energy expenditure and reduced food intake in mice (Grujic et al., 1997). However, the enthusiasm for a β_3 adrenergic receptor-directed therapy was diminished in human studies due to lack of agonist efficacy and undesirable side effects (Poekes, Lanthier, & Leclercq, 2015).

Studies have been performed to identify the role of GPR116 in white adipocyte differentiation and whole body glucose homeostasis. It was found that depletion of GPR116 in pre-adipocytes *in vitro* impaired their capacity to differentiate to mature adipocytes (Nie et al., 2012). In addition, adipose tissue-specific deletion of GPR116 produced mice that were glucose intolerant and insulin resistant, which was exacerbated by high fat feeding (Nie et al., 2012), suggesting that if ligands

are identified that selectively activate GPR116 they could be useful therapeutically in normalising glucose homeostasis.

The recent profiling of the BAT GPCRome (Klepac et al., 2016) has led to renewed interest in the possibility of targeting BAT GPCRs to combat obesity. In particular, in that study it was identified that antagonising $G\alpha_q$ signalling could provide a mechanism for increasing brown and beige adipocyte number, and this is a potential strategy for increasing energy expenditure in obesity. In addition, since aGPCRs are the second most abundant family of GPCRs (after the large rhodopsin receptor family) in BAT, and there are altered expression profiles of aGPCRs upon differentiation of pre-adipocytes to mature brown adipocytes (Klepac et al., 2016) there is strong rationale for research exploring aGPCR function in BAT. CELSR2 is down-regulated in mature brown adipocytes (Klepac et al., 2016) and the potential importance of this aGPCR in metabolic control is indicated by the correlation of single nucleotide polymorphisms in CELSR2 with altered low-density lipoprotein levels in humans (Kathiresan et al., 2008). The roles of aGPCRs that show altered expression during brown adipocyte maturation will provide important information on whether they may be targeted therapeutically, but as with identifying aGPCR function in other metabolically active tissues progress is limited by the lack of suitable ligands for most of the receptors.

3.3. Skeletal muscle

Skeletal muscle cells take up glucose following food intake through insulin-dependent translocation of GLUT4 transporters to the myocyte plasma membrane, and glucose that is not required for muscle activity is stored as glycogen (Bradley et al., 2015; DeFronzo & Tripathy, 2009). Glucose transport into myocytes can also occur in an insulin-independent manner through exercise-induced muscle contractility (Sinacore & Gulve, 1993), thus ensuring that myocytes obtain an appropriate fuel supply in the post-absorptive state. The insulin resistance that commonly occurs in obesity, T2D, and other cardiometabolic disorders impairs insulin-mediated glucose uptake via GLUT4 and it is now apparent that β_2 adrenergic receptor activation can promote glucose uptake into skeletal muscle (Sato et al., 2014). This increase in glucose clearance is dependent on GLUT4 translocation, but occurs independently of the insulin-mediated signal transduction cascade, offering the potential of circumventing myocyte insulin resistance.

The possibility of targeting aGPCRs to treat muscle disease through promoting skeletal muscle cell growth has been raised recently (White, 2016), and there is an increasing body of evidence indicating that aGPCRs are crucial for myoblast differentiation and muscle mass regulation. The majority of aGPCR family members that have been detected in human skeletal muscle are expressed at low levels (GPR56, GPR64, GPR113, CD97, BAI3, CELSR2, and ELTD1), and GPR116 and GPR125 are reported to have moderate expression (Duff et al., 2015; Jean-Baptiste, Yang, Khoury, Gaudio, & Greenwood, 2005).

Cell-cell fusion of myoblasts is a crucial and tightly regulated process in muscle formation and repair (Rochlin, Yu, Roy, & Baylies, 2010). By interacting with the conserved ELMO-DOCK1-Rac pathway, BAI3 is obligatory for myoblast fusion in myogenesis and in adult muscle regeneration (Hamoud, Tran, Croteau, Kania, & Côté, 2014). BAI3 can either inhibit or promote myoblast fusion by binding to C1q-like proteins or stabilin-2, respectively (Hamoud et al., 2018). In chicken embryos, a loss of function mutation in BAI3 blocked myoblast fusion, leading to reduced myofibre length (Hamoud et al., 2014), while BAI3 knockout mice have smaller muscle fibres that are less efficient in recovering from injury (Hamoud et al., 2018). It has been identified that GPR56 expression is upregulated at the early stage of myoblast differentiation, and its deletion resulted in reduced myoblast fusion (Wu et al., 2013). However, no difference in muscle phenotype was observed in GPR56 knockout mice (Wu et al., 2013), suggesting that GPR56 is not required for skeletal muscle development in vivo. A role for GPR56 in regulating muscle mass is supported by observations that it is up-regulated under conditions of excess load on skeletal muscle, that its overexpression

in vitro leads to myocyte hypertrophy and that it regulates PGC-14 α -mediated muscle hypertrophy in vivo (White et al., 2014). Additionally, GPR56 increases muscle hypertrophy via $G\alpha_{12/13}$ signalling, with subsequent downstream activation of mTOR and IGF-1 leading to increased protein synthesis (White et al., 2014). The sarcoplasmic reticulum of myofibres from CD97 null mice have altered morphology, but this does not translate to any changes in muscle function and the authors concluded that its role is most likely associated with skeletal muscle differentiation (Zyryanova et al., 2014). Overall, aGPCRs are important players in muscle physiology and further research is required to identify whether they also play a role in contraction-induced glucose transport or other metabolic parameters in skeletal muscle. In this context it is of interest that CD97 mRNA upregulation has been implicated in the development of skeletal muscle insulin resistance (Poelkens, Lammers, Pardoel, Tack, & Hopman, 2013), but further work is required to determine if this is a causative relationship and whether myocyte aGPCRs could be targeted therapeutically to improve glucose homeostasis.

3.4. Other metabolic tissues with potential for aGPCR function

aGPCRs are expressed by other metabolic tissues such as liver, gastrointestinal tract and hypothalamus, but much less is known about their functions in these tissues than in islets, adipose tissue and skeletal muscle.

3.4.1. Liver

The liver plays a pivotal role in regulating glucose homeostasis by acting as a storage organ in the absorptive state and by maintaining glucose levels through glycogenolysis and gluconeogenesis during the post-absorptive state and fasting. Hepatocytes express many GPCRs, which are predicted to play important roles in liver function (Regard, Sato, & Coughlin, 2008). The glucagon receptor (GCGR), a $G\alpha_s$ -coupled GPCR, is one of the most studied hepatocyte receptors since it directly controls hepatic glucose production: when blood glucose levels are low glucagon is secreted from islet α -cells and it increases liver glycogenolysis and gluconeogenesis through GCGR activation and generation of cAMP. This is an important physiological process, but it can be disrupted in T2D where reduced anabolic input from insulin and increased hepatic GCGR signalling can lead to excessive hepatic glucose production (HGP) (Lin & Accili, 2011). As $G\alpha_i$ -coupled GPCRs inhibit cAMP production it has been proposed that they could be targeted therapeutically to combat the increased HGP that occurs in T2D. This has recently been investigated by a chemogenetic approach where mice expressing a $G\alpha_i$ -coupled GPCR in their hepatocytes were exposed to a ligand that specifically activated that receptor, and the effects on glucose regulation in vivo and in vitro were evaluated (Rossi et al., 2018). Selective activation of $G\alpha_i$ in mouse hepatocytes paradoxically led to increased HGP and impaired glucose homeostasis, indicating that this is not an appropriate strategy for reducing glucose levels in T2D, most likely because antagonism of hepatocyte cAMP generation will have an impact on multiple processes in addition to blockade of HGP. The authors concluded that rather than activating hepatocyte $G\alpha_i$ -coupled signalling it would be more appropriate to antagonise it for treating T2D, but it seems likely that a more nuanced approach will be necessary.

The involvement of aGPCRs in hepatocyte function has not yet been described, but global transcriptomic analysis has revealed that multiple aGPCRs are expressed by human liver, with GPR125, GPR126, LPHN2 and CD97 showing high levels of expression, while GPR116, GPR124, GPR128 and ELTD1 were detected at moderate levels (Fagerberg et al., 2014). Our analysis of mouse liver has indicated a similar high expression pattern for GPR125 and LPHN2, and moderate expression of GPR116 and ELTD1 (Atanes and Persaud, unpublished). In contrast, while CD97 mRNA was highly expressed in human liver our quantifications indicated that it was expressed at low levels in mouse liver, as were GPR124 and GPR126, while we could not detect GPR128 in mouse liver by qPCR. Human hepatocytes are available for research,

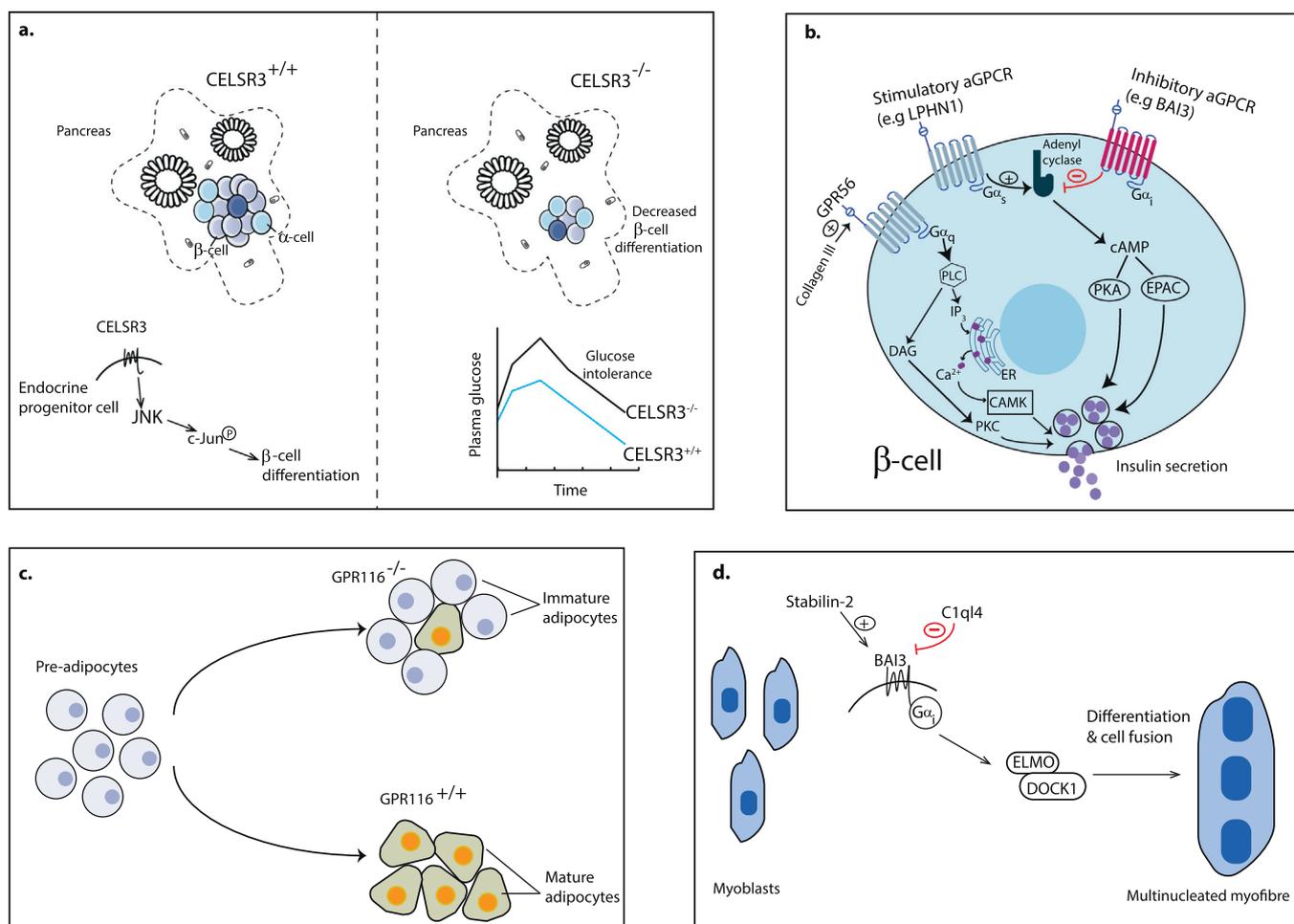


Fig. 4. Schematic summary of the signalling pathways downstream of aGPCRs that have been implicated in metabolic cell development and function. a) CELSR3 promotes differentiation of pancreas endocrine progenitors to β -cells in mice via JNK activation and phosphorylation of c-jun. CELSR3 knockout mice have severe β -cell differentiation deficiency, which leads to glucose intolerance in adulthood. b) Activation of a $G\alpha_s$ -coupled aGPCR such as LPHN1 in β -cells increases cAMP generation, which promotes insulin exocytosis through activation of protein kinase A (PKA) and/or exchange proteins activated by cAMP (EPACs). Similarly, GPR56 activation by collagen III in β -cells increases insulin secretion through $G\alpha_q$ -mediated signalling. Conversely, activation of a $G\alpha_i$ -coupled aGPCR such as BAI3 by its agonist C1q3 inhibits insulin exocytosis by decreasing cAMP production. c) Deletion of GPR116 in pre-adipocytes in vitro impaired their capacity to differentiate into mature adipocytes, and GPR116 knockout mice are glucose intolerant and insulin resistant. d) BAI3 recruits the ELMO/DOCK1 complex in myoblasts, allowing their fusion to generate multinucleated myofibres during myogenesis. This function is differentially regulated by stabilin-2 and C1ql4 regulation of BAI3: whereas stabilin-2 activates BAI3, leading to coupling to $G\alpha_i$, to promote myoblast fusion, C1ql4 inhibits it.

but as rodent samples are often used as surrogates it is important that research is focused on those rodent aGPCRs that are also expressed by human hepatocytes so that data have high translation value. Further work is required to define the function of liver aGPCRs and whether they present an opportunity for therapeutic intervention to combat liver dysfunction that occurs in fatty liver disease and diabetes.

3.4.2. Gastrointestinal tract

The gastrointestinal (GI) tract is the largest endocrine organ in mammals. It is involved in various metabolic processes such as appetite regulation, digestion, nutrient absorption and potentiation of glucose-induced insulin secretion through the release of the incretins GLP-1 and GIP from specialised enteroendocrine L cells. GLP-1 secretion is stimulated by activation of GPR40 and GPR119 by triacylglycerol metabolites and the bile acid GPCR, TGR5 (Hauge et al., 2017), and elevations in GLP-1 and PYY, another L cell-derived GPCR ligand, have been implicated in improved metabolic outcomes following bariatric surgery (Pucci & Batterham, 2018). The production of GPR119 agonists by human gastrointestinal bacteria has recently been associated with increased GLP-1 secretion and improved glucose tolerance in mice (Cohen et al., 2017). These observations indicate that there are additional physiological mechanisms regulating GLP-1 release, and open up the possibility that bacteria engineered to produce

GPR119 ligands could have therapeutic potential to treat T2D. There has been interest from pharmaceutical companies to enhance the incretin response and ligands targeting a number of enteroendocrine cell-expressed GPCRs, including GLP-1R, GPR40, GPR119 and GPR120, are undergoing investigation as potential therapies for T2D (Hoque, Ali, & Hoda, 2018; Mace, Tehan, & Marshall, 2015). It has been reported that aGPCRs expressed in the GI tract include GPR56, GPR126, GPR128, CD97, LPHN2 and CELSR1 (Fagerberg et al., 2014; Hamann et al., 2015). However, the role, if any, that GI tract aGPCRs play in regulating fuel homeostasis is currently unknown and most studies to date have focused on their contribution to colorectal carcinoma (Hilbig et al., 2018; Ji et al., 2018).

3.4.3. Hypothalamus

The importance of the hypothalamus in many metabolic processes such as feeding and energy homeostasis is well known, and many of these functions are mediated via hypothalamic GPCRs for ligands such as neuropeptide Y, opioids, serotonin and γ -amino butyric acid (Fu & van den Pol, 2010; Qiu et al., 2006, 2007). The aGPCRs GPR56, GPR64, and VLGR1 are highly expressed in the hypothalamus (Haitina et al., 2008; Liu et al., 1999) and at least 23 aGPCRs have been detected in the arcuate nucleus, which is the metabolic centre of the hypothalamus (Rønnekleiv et al., 2014). Of the aGPCRs expressed in the arcuate

nucleus, GPR56 and BAI1 are the most abundant (Rønnekleiv et al., 2014), but there is still no data available on whether these receptors or other arcuate nucleus aGPCRs are present on the NPY/AgRP or POMC/CART neurons that regulate food intake, or whether they may represent novel targets for appetite regulation in obesity.

4. Conclusion and future directions

Research defining the importance of aGPCRs in regulating appropriate energy homeostasis is still at an early stage, and considerable further research is required to determine whether members of this family of receptors may be suitable candidates for treating metabolic disorders such as obesity and T2D. Nonetheless, the expression of a wide range of aGPCRs by tissues important in ensuring that blood glucose levels are regulated within a tight range and the close association between aGPCRs and metabolic traits supports continued exploration of their utility as druggable targets.

Fig. 4 summarises some of the key information relating to aGPCR function in islet β -cells, adipocytes and myocytes, and as aGPCR metabolic research progresses we will be able to build up a clearer picture of the key candidates that may have therapeutic potential. Nonetheless, there are still barriers to rapid progress in this field and future research will be greatly facilitated by de-orphanisation of the remaining aGPCRs and identification of specific small molecule agonists and antagonists. In addition, more studies are required to fully understand the signalling mechanisms downstream of aGPCR activation, and this too will be assisted by availability of highly selective ligands. Given their broad expression, it will also be interesting to identify aGPCR splice variants that may be specifically targeted in metabolically active tissues without causing undesirable side effects.

Conflict of interest statement

The authors declare that they have no conflicting interests.

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