Review

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The relevance of adhesion G protein-coupled receptors in metabolic functions

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Abstract: G protein-coupled receptors (GPCRs) modulate a variety of physiological functions and have been proven to be outstanding drug targets. However, approximately one-third of all non-olfactory GPCRs are still orphans in respect to their signal transduction and physiological functions. Receptors of the class of Adhesion GPCRs (aGPCRs) are among these orphan receptors. They are characterized by unique features in their structure and tissue-specific expression, which yields them interesting candidates for deorphanization and testing as potential therapeutic targets. Capable of G-protein coupling and non-G protein-mediated function, aGPCRs may extend our repertoire of influencing physiological function. Besides their described significance in the immune and central nervous systems, growing evidence indicates a high importance of these receptors in metabolic tissue. RNAseq analyses revealed high expression of several aGPCRs in pancreatic islets,

adipose tissue, liver, and intestine but also in neurons governing food intake. In this review, we focus on aGPCRs and their function in regulating metabolic pathways. Based on current knowledge, this receptor class represents high potential for future pharmacological approaches addressing obesity and other metabolic diseases.

Keywords: adipose tissue; aGPCR; metabolism; pancreatic islet.

Introduction

G protein-coupled receptors (GPCRs) are important drug targets based on their well-known signaling pathways and good accessibility for ligands. Although two-thirds of non-olfactory GPCRs have been intensively characterized and assigned to endogenous agonists there is still a reasonable portion that remains orphan (Schöneberg and Liebscher 2021). The entire adhesion-type class of GPCRs (aGPCRs) belongs to these unstudied receptors, yet, their remarkable characteristics have the potential to establish new paradigms in treatment of metabolic diseases. These receptors share the common structure of all GPCRs containing an extracellular *N*-terminus, an intracellular *C*-terminus, and seven α -helical transmembrane helices connected by three extra- and intracellular loops (7TM domain) (Liebscher et al. 2013). Their large *N*-termini contain several functional domains not found in most other GPCRs, which are essential for several of the unusual functions that they display (Figure 1A) (Hamann et al. 2015; Langenhan 2020; Vizurraga et al. 2020). The structural hallmark of the aGPCR *N*-terminus is the GPCR autoproteolysis-inducing (GAIN) domain (Araç et al. 2012; Araç et al. 2016), which features the GPCR proteolytic site (GPS) at which the receptor undergoes autoproteolytic processing in the endoplasmic reticulum (Chang et al. 2003; Lin et al. 2004).

Besides splitting the receptor protein into two functional units (the *N*-terminal fragment and the *C*-terminal fragment), the GAIN domain like some of the other domains of the *N*-terminus, can bind extracellular matrix (ECM)

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Figure 1: Adhesion GPCR structure and activation.

(A) Schematic presentation of the aGPCR structure. Adhesion GPCRs possess a 7-transmembrane (7TM) domain and a large *N*-terminus containing several adhesive domains, which are depicted here schematically as star, ellipse, and hexagon. The characteristic feature of aGPCRs is the GAIN (GPCR autoproteolysis-inducing) domain where autoproteolytic cleavage occurs within the GPS (GPCR proteolytic site). The resulting *N*-terminal fragment (NTF) and C-terminal fragment (CTF) remain non-covalently attached to each other. The extracellular portion of the CTF harbors the tethered agonist sequence, called the *Stachel*. (B) Activation of aGPCRs can occur by interaction with extracellular matrix (ECM), mechanical force, or small molecule agonists. Artificial activation is achieved by peptides derived from the tethered agonist sequence. Another feature of aGPCRs is the possibility of *trans*-signaling by interaction with and activation of receptors from other cells.

components (Figure 1B) (Dunn et al. 2019; Luo et al. 2011; Petersen et al. 2015; Wandel et al. 2012). Also, interactions between the aGPCR *N*-terminus and surface antigens of neighboring cells were observed (Wang et al. 2005). Some of these ligands, such as collagen IV on GPR126 (Paavola et al. 2014), appear to activate the respective receptor directly, while others require additional mechanical forces to achieve a downstream signal. This has been demonstrated for the activation of GPR126 with laminin-211, which is dependent

on mechano-stimulation (Petersen et al. 2015). Furthermore, it has been proposed for GPR56 that mechanical force together with the interaction of collagen III is required for platelet activation (Yeung et al. 2020). However, mechanical stimuli can also activate aGPCRs without the addition of a ligand (Figure 1B). Mechano-stimulation of GPR114 results in adenylyl cyclase activation and cAMP formation (Wilde et al. 2016) and the drosophila Latrophilin homolog CIRL decreases intracellular cAMP in response to mechano-

stimulation (Scholz et al. 2015; Scholz et al. 2017). Thus, the large extracellular portion of these receptors integrates several context-specific signals via an encrypted tethered agonist sequence embedded within the GPS, referred to as the *Stachel* sequence (Balenga et al. 2017; Brown et al. 2017; Liebscher and Schöneberg 2016; Liebscher et al. 2014; Müller et al. 2015; Stoveken et al. 2015; Wilde et al. 2016). Peptides derived from this sequence can be used to activate aGPCRs (Figure 1B), thus giving rise to potential therapeutics, while mechano-sensing could provide a more localized approach to modulate receptor activity levels. Another highly interesting aspect of aGPCR function is the so-called trans-signaling, which is mediated solely by the interaction of the receptor's N-terminus with membrane receptors of neighboring cells (Figure 1B) (Prömel et al. 2012; Tu et al. 2018). The targets of this external signaling are largely unknown but future studies will further elucidate this fascinating signaling mechanism.

Given the growing interest in aGPCRs their nomenclature has recently been homogenized (Hamann et al. 2015). However, the new nomenclature features various inconsistencies (Scholz et al. 2019), thus, the historical denomination is still commonly used, including in this review. So far, functional studies on aGPCRs address mainly their roles in the neuronal (Ackerman et al. 2018; Bolliger et al. 2011; Giera et al. 2015; Krasnoperov et al. 1996; Mogha et al. 2013; Piao et al. 2004; Sugita et al. 1998) and immune systems (Lin et al. 2017) as well as in developmental processes (Langenhan et al. 2009; Tissir and Goffinet 2013). Six human pathologies have been shown to be directly caused by mutations in aGPCRs (Schöneberg and Liebscher 2021). For example, the Usher Syndrome is a combined blind-deafness caused by malfunctioning of VLGR1 (Weston et al. 2004) and the bilateral frontal polymicrogyria results from mutations within GPR56 (Piao et al. 2004). In contrast, much less is known about aGPCR involvement in metabolic functions although many of these receptors are highly expressed in adipose tissue, the liver, the endocrine pancreas, and the gut. This review aims to summarize what is known about the contribution of aGPCRs to healthy and disease-state tissue functions that are recognized for their major role in metabolism.

Adipose tissue

Adipose tissue was long considered as an inert organ with the sole purpose of storing excess energy. However, in the last decades it has been identified as a key endocrine organ

with an active role in maintaining the body's energy homeostasis (Coelho et al. 2013). It is categorized in brown (BAT) and white (WAT) subtypes with the latter being subdivided into subcutaneous (SAT) and visceral (VAT) adipose tissue with distinct functions, morphology, and development (Belaj and Eller 2012). While primary functions of WAT are storing energy-rich triacylglycerols and hormonal signaling, BAT is mainly active in non-shivering thermogenesis. WAT and BAT are located in distinct depots all over the body, yet some WAT depots are susceptible to browning in response to stimuli, such as cold exposure. The browning results in beige (also referred to as “brite”) adipocytes with shared characteristics of both brown and white adipocytes (Jong et al. 2015; Young et al. 1984).

In adipose tissue, expression of numerous GPCRs has been demonstrated and the activation of G protein-signaling pathways regulates adipocyte function (Amisten et al. 2015). Increased cAMP levels due to activation of the Gs protein are indispensable for inducing adipogenesis (Petersen et al. 2008) and have also been shown to reduce hormone secretion and glucose uptake while increasing lipolysis (Frühbeck et al. 2014). Accordingly, the inhibition of adenylyl cyclases by Gi/o proteins has the opposite effects on lipolysis and hormone secretion (Caron et al. 2018; Stich et al. 1999). Interestingly, activation of Gi as well as Gs signaling in adipose tissue has been reported to positively impact glucose homeostasis under obese conditions (Caron et al. 2019; Wang et al. 2020). Furthermore, cAMP levels are connected to non-shivering thermogenesis in BAT as well as WAT browning (Barbatelli et al. 2010; Cannon and Nedergaard 2004; Jiang et al. 2017). Activation of Gq/11-protein signaling increases glucose uptake and interferes with WAT browning (Balasubramanian et al. 2014; Klepac et al. 2016). In general, Gq/11 signaling inhibits adipogenesis and BAT functioning, and induces BAT whitening (Klepac et al. 2016).

White adipose tissue

Initially, the expression of 11 aGPCRs was demonstrated in human WAT using a qPCR approach (Amisten et al. 2015). Additional studies have provided deeper insight into aGPCR expression by proteomic approaches (Fagerberg et al. 2014; Uhlén et al. 2015) and RNAseq of human and mouse WAT including changes depending on dietary conditions (Dalgaard et al. 2016; Suchý et al. 2020). Ultimately, expression has been observed for 14 aGPCRs in mouse VAT (Suchý et al. 2020; Vernia et al. 2016) and 17 aGPCRs in human SAT (Dalgaard et al. 2016) (Table 1).

Table 1: Expression of aGPCRs in human (Dalgaard et al. 2016) and mouse (Vernia et al. 2016) WAT under changed nutritional conditions determined by RNAseq as well as expression in mouse brown preadipocytes and mature adipocytes determined by qPCR analysis (Klepac et al. 2016). RNAseq expression is given in FPKM values (+++ > 50; ++ > 10; + > 1; – < 1) and expression determined by qPCR is given in ΔCt values (+++ < 19; ++ < 23; + < 27; – > 32).

aGPCR	Human WAT		Mouse WAT		Mouse BAT	
	Lean	Obese	Chow	High-fat	Preadipocytes	Adipocytes
<i>Adgrl1/Lphn1</i>	++	++	+	+	+++	+++
<i>Adgrl2/Lphn2</i>	++	++	+	++	+++	+++
<i>Adgrl3/Lphn3</i>	+	+	–	–	++	+
<i>Adgrl4/Eltd1</i>	+++	+++	++	++	+	–
<i>Adgre1/Emr1</i>	+	+	++	+++	+	++
<i>Adgre2/Emr2</i>	+	+				
<i>Adgre3/Emr3</i>	+	+				
<i>Adgre4/Emr4</i>	+	+	–	–	–	–
<i>Adgre5/Cd97</i>	++	++	+++	+++	+++	+++
<i>Adgra1/Gpr123</i>	–	–	–	–	–	–
<i>Adgra2/Gpr124</i>	++	++	+	+	+++	+++
<i>Adgra3/Gpr125</i>	++	++	+	+	+++	++
<i>Adgrc1/Celsr1</i>	–	+	–	–	+	–
<i>Adgrc2/Celsr2</i>	+	+	+	+	+	+
<i>Adgrc3/Celsr3</i>	–	–	–	–	–	–
<i>Adgrd1/Gpr133</i>	++	+	++	++	+	++
<i>Adgrd2/Gpr144</i>	–	–				
<i>Adgrf1/Gpr110</i>	–	–	–	–	–	–
<i>Adgrf2/Gpr111</i>	–	–	–	–	–	–
<i>Adgrf3/Gpr113</i>	–	–	–	–	–	–
<i>Adgrf4/Gpr115</i>	–	–	–	–	+	+
<i>Adgrf5/Gpr116</i>	+++	+++	+++	++	+	+
<i>Adgrb1/Bai1</i>	–	–	–	–	+	–
<i>Adgrb2/Bai2</i>	+	+	+	–	+	+
<i>Adgrb3/Bai3</i>	+	+	–	–	–	–
<i>Adgrg1/Gpr56</i>	++	++	+++	++	++	+
<i>Adgrg2/Gpr64</i>	+	+	++	+	+	+
<i>Adgrg3/Gpr97</i>	+	+	+	–	–	–
<i>Adgrg4/Gpr112</i>	–	–	–	–	–	–
<i>Adgrg5/Gpr114</i>	–	–	–	–	+	–
<i>Adgrg6/Gpr126</i>	+	+	+	+	–	–
<i>Adgrg7/Gpr128</i>	–	–	–	–	–	–
<i>Adgrv1/Vlgr1</i>	–	–	–	–	–	–

Only limited studies are available regarding the function of aGPCRs in adipose tissue (Figure 2). A comprehensive analysis identified 11 aGPCRs to be significantly expressed during differentiation of the adipocyte model cell line 3T3-L1 (Suchý et al. 2020). Reducing the expression of six aGPCRs (*Lphn2*, *Gpr124*, *Gpr125*, *Gpr116*, *Gpr64*, and *Gpr126*) via transient knock-down impeded adipogenesis (Suchý et al. 2020) (Figure 2A). Furthermore, the knock-down of *Gpr126* and *Gpr64* altered the pattern of free fatty acids accumulated in 3T3-L1 cells (Suchý et al. 2020). Analysis of preadipocytes in Haiyang Yellow chicken revealed dynamic expression of *Gpr133* during adipogenesis combined with an interaction with *gga-miR-135a-*

5p (Chen et al. 2019), a regulator of adipogenesis in 3T3-L1 cells (Chen et al. 2014). However, a regulatory function of *Gpr133* in WAT has not been demonstrated, yet.

Gpr116 was found to be abundantly expressed in mouse primary adipocytes (Nie et al. 2012) as well as in differentiated 3T3-L1 cells, and its upregulation during adipogenesis was the highest among all aGPCRs (Suchý et al. 2020). This suggested a functional role for *Gpr116* in adipogenesis and mature adipocytes. Interestingly, this receptor is coupled to Gq/11 proteins (Brown et al. 2017; Demberg et al. 2017) and inhibition of *Gpr116* expression reduced lipid accumulation in primary mouse adipocytes (Nie et al. 2012) and 3T3-L1 cells (Suchý et al. 2020).

Figure 2: Adhesion GPCR functions in WAT and BAT.

(A) *Gpr124*, *Gpr125*, *Gpr116*, *Gpr56*, *Gpr64*, *Gpr126*, and *Lphn2* are involved in adipogenesis and knock-down of these receptors results in impaired differentiation of preadipocytes. (B) *GPR64* and *GPR116* are expressed on mature adipocytes and influence their function. Activation of *GPR64* elevates intracellular cAMP and, such, stimulates protein kinase A, which regulates glucose uptake and lipolysis. Furthermore, elevated cAMP levels reduce adiponectin secretion. *GPR116* modulates secretion of adiponectin and resistin most likely by activation of the $G_q/11$ pathway. (C) Adipose tissue-specific deletion of *Gpr116* results in insulin resistance and ectopic fat accumulation in liver and skeletal muscle underlining the importance of this receptor in maintaining body's energy homeostasis. (D) *GPR64* is discussed to induce whitening of BAT.

Furthermore, adipose tissue-specific knock-out of *Gpr116* resulted in insulin resistance and glucose intolerance while reducing adipocyte size and adiponectin secretion (Nie et al. 2012) (Figure 2B). Additionally, when challenged with high-fat diet, knock-out animals manifested ectopic lipid accumulation in liver and muscle as well as higher levels of circulating free fatty acids and triacylglycerol (Nie et al. 2012), highlighting the important role of *Gpr116* in lipid metabolism (Figure 2C). Unfortunately, the endogenous signal that leads to activation of *GPR116* is still unknown, even though interaction with $\alpha 5$ integrin has been suggested in vascular development (Lu et al. 2017). Because $\alpha 5$ integrin expression declines from

preadipocytes to mature adipocytes (Liu et al. 2005a), it seems unlikely that the adipose tissue function of *GPR116* is induced by interaction with this integrin.

The most abundant aGPCR in WAT is *Gpr56*, which is dynamically regulated during differentiation (Al Hasan et al. 2020; Suchý et al. 2020) and downregulated in VAT of obese rats (Al Hasan et al. 2020). Collagen III, a ligand of *GPR56*, is an integral part of the adipose tissue ECM (Khan et al. 2009). Remodeling of ECM including an up-regulation of *Col3a1* has been shown in obesity (Khan et al. 2009), which could be assumed to increase *GPR56* signaling. Thus, the observed down-regulation of *Gpr56* might constitute a mechanism counteracting this, considering

that knock-down of this receptor in 3T3-L1 cells resulted in reduced differentiation and a complete knock-out decreased adhesion and proliferation of these cells (Al Hasan et al. 2020). Interestingly, *Gpr56* knock-out also displayed altered expression of ECM components (Al Hasan et al. 2020) yielding GPR56 a potential target to interfere with ECM remodeling and induction of adipose tissue fibrosis.

Also, the functional role of *Gpr64* in adipocytes has been demonstrated in 3T3-L1 cells (Suchý et al. 2020). The receptor couples to Gs-, Gi-, and Gq proteins (Demberg et al. 2015). Activation with a tethered agonist-derived peptide increased intracellular cAMP levels in 3T3-L1 cells, thereby accelerating lipolysis and reducing glucose uptake and adiponectin secretion (Suchý et al. 2020) (Figure 2B).

Conclusively, significant progress was achieved in deciphering the roles of aGPCR in WAT. However, many aspects like the identification of receptor ligands and activation mechanisms remain to be subject for further research to entirely elucidate the function of aGPCRs in WAT physiology.

Brown adipose tissue

Similar to WAT, a multitude of GPCRs, including aGPCRs, are expressed in BAT (Klepac et al. 2016; Li et al. 2020). A comparative analysis of isolated human pre- and mature adipocytes found 14 aGPCRs to be expressed in both and four aGPCRs only in preadipocytes (Klepac et al. 2016) (Table 1). Furthermore, proteome analysis of murine BAT has demonstrated LPHN2, LPHN3, CD97, and GPR116 expression (Li et al. 2020). As G protein-signaling pathways have been connected to BAT activation and, subsequently, regulate non-shivering thermogenesis, these receptors are promising targets to increase energy expenditure and reduce blood glucose levels.

However, the role of aGPCRs in BAT function was not intensively investigated, although, there is evidence that aGPCRs are involved therein. For example, GPR64 has been connected to whitening of BAT, which is generally associated with activation of Gq/11 protein-signaling pathways (Klepac et al. 2016) (Figure 2D). This connection is based on the observation that *Gpr64* expression, which is usually lower in mature brown adipocytes compared to preadipocytes, increases upon knock-out of *Prdm16*, a transcription factor regulating thermogenic genes (Harms et al. 2014; Klepac et al. 2016). Upregulation of *Gpr64* expression is accompanied by inducing a white fat-like phenotype of BAT (Harms et al. 2014). Considering the multiple signaling options of this receptor (see above), one

can speculate that selectively activating its G-protein preference may be an interesting strategy to inhibit whitening of BAT or even induce WAT browning. In this line, the upregulation of the Gs protein-coupled aGPCR *Gpr133* (Bohnekamp and Schöneberg 2011) in mature brown adipocytes compared to brown preadipocytes (Klepac et al. 2016) may indicate an involvement of this receptor in browning and thermogenesis.

In sum, information about aGPCRs expressed in BAT is still scarce and future investigations will need to shed further light on the specific role of these receptors in this adipose tissue.

Pancreatic islets

Blood glucose levels are mainly regulated by the hormones insulin and glucagon secreted from pancreatic islets, also known as islets of Langerhans, which were discovered by Paul Langerhans in 1869 (Quesada et al. 2006). They are organized in cell clusters composed of five different types of endocrine cells, which secrete hormones required for maintaining glucose homeostasis. The most abundant cells (80%) are insulin-producing β cells which are found in the core of mouse pancreatic islets. Glucagon-secreting α cells, which represent 15% of mouse pancreatic islet cells, and somatostatin-releasing δ cells (5%) are located in the islet periphery (Arrojo e Drigo et al. 2015; Cabrera et al. 2006). Pancreatic polypeptide (PP) cells and ϵ cells secreting pancreatic polypeptide and ghrelin, respectively, represent only small cell populations located in the islet mantle (Andralojc et al. 2009; Wang et al. 2013).

The blood glucose level is the main signal for the regulated secretion of insulin or glucagon. While insulin is secreted after a meal to lower blood glucose levels, glucagon's function is to raise blood glucose levels during fasting periods. Both hormones have pivotal roles in glucose homeostasis, and their correct interplay is required for physiological blood glucose levels (Aronoff et al. 2004). It is well-established that GPCRs modulate pancreatic hormone secretion via activation of different G protein-signaling pathways (Åhrén 2009). Gq/11-coupled receptors activate phospholipase C resulting in elevated IP₃ concentrations, which induce release of Ca²⁺ from intracellular storage. Increasing cytosolic Ca²⁺ concentrations enhance the secretory response of pancreatic hormones (Winzell and Åhrén 2007). In addition, the second messenger cAMP influences hormone release by activation of protein kinase A and Epac, which stimulate the exocytosis of vesicles. Thereby, Gs protein-coupled receptors stimulate and Gi/o protein-coupled receptors inhibit hormone secretion from

Table 2: Publicly available and own RNAseq data was analyzed to determine aGPCR expression in human pancreatic islets (Dunér et al. 2016) and sorted α - and β cells (Blodgett et al. 2015) as well as mouse pancreatic islets (Meister et al. 2014) and sorted islet cells (Adriaenssens et al. 2016; DiGruccio et al. 2016). RNAseq expression is given in FPKM values (+++ > 20; ++ > 2; + > 0.5; - < 0.5) or TPM values (+++ > 2; ++ > 0.2; + > 0.02; - < 0.02).

aGPCR	Human		Mouse	
	Whole islet	Cell type	Whole islet	Cell type
<i>Adgrl1/Lphn1</i>	+	$\alpha = \beta$	++	$\alpha = \beta = \delta$
<i>Adgrl2/Lphn2</i>	++	$\alpha > \beta$	+	$\delta > \alpha = \beta$
<i>Adgrl3/Lphn3</i>	-	-	+	$\beta > \alpha > \delta$
<i>Adgrl4/Eltd1</i>	++	-	++	-
<i>Adgre1/Emr1</i>	-	-	+	-
<i>Adgre2/Emr2</i>	-	-	-	-
<i>Adgre3/Emr3</i>	-	-	-	-
<i>Adgre4/Emr4</i>	-	-	-	-
<i>Adgre5/Cd97</i>	+	$\alpha > \beta$	++	$\delta > \alpha > \beta$
<i>Adgra1/Gpr123</i>	-	-	-	-
<i>Adgra2/Gpr124</i>	+	$\alpha > \beta$	+	$\alpha > \delta > \beta$
<i>Adgra3/Gpr125</i>	++	$\alpha = \beta$	++	$\delta > \beta = \alpha$
<i>Adgrc1/Celsr1</i>	-	-	+	$\beta = \delta > \alpha$
<i>Adgrc2/Celsr2</i>	+	$\alpha > \beta$	++	$\alpha = \delta > \beta$
<i>Adgrc3/Celsr3</i>	+	$\alpha > \beta$	++	$\alpha = \delta > \beta$
<i>Adgrd1/Gpr133</i>	-	-	-	-
<i>Adgrd2/Gpr144</i>	-	-	-	-
<i>Adgrf1/Gpr110</i>	++	-	-	-
<i>Adgrf2/Gpr111</i>	-	-	-	-
<i>Adgrf3/Gpr113</i>	-	-	-	-
<i>Adgrf4/Gpr115</i>	+	-	-	-
<i>Adgrf5/Gpr116</i>	++	-	++	$\delta > \alpha = \beta$
<i>Adgrb1/Bai1</i>	-	-	-	-
<i>Adgrb2/Bai2</i>	-	-	-	-
<i>Adgrb3/Bai3</i>	-	-	++	$\delta > \beta = \alpha$
<i>Adgrg1/Gpr56</i>	+++	$\beta > \alpha$	+++	$\delta > \alpha = \beta$
<i>Adgrg2/Gpr64</i>	-	$\alpha > \beta$	-	-
<i>Adgrg3/Gpr97</i>	-	$\alpha > \beta$	-	-
<i>Adgrg4/Gpr112</i>	-	-	-	-
<i>Adgrg5/Gpr114</i>	+	$\alpha > \beta$	-	-
<i>Adgrg6/Gpr126</i>	+	-	+	-
<i>Adgrg7/Gpr128</i>	-	-	-	-
<i>Adgrv1/Vlgr1</i>	+	$\beta > \alpha$	+	$\beta > \alpha = \delta$

endocrine pancreatic cells (Winzell and Ahren 2007). The influence of G12/13-protein signaling is not well-understood, but it is discussed that this pathway contributes to vesicle discharge and activation increases glucose-stimulated insulin release (Rives et al. 2018). Besides their impact on pancreatic hormone secretion there is evidence that G protein-signaling pathways are involved in islet development. For example, the Gs-coupled adenosine receptor A2a promotes β -cell proliferation and regeneration (Schulz et al. 2016). Furthermore, while Gi-protein signaling reduces β -cell mass during development

(Berger et al. 2015), activation of the Gq/11-protein pathway increases β -cell amount and insulin content in adult mice (Jain et al. 2013).

Pancreatic islet cells express numerous GPCRs, which have been widely discussed to be potential therapeutic targets for type 2 diabetes (T2D) (Amisten et al. 2017; Amisten et al. 2013; Madiraju and Poitout 2007). Recent transcriptome analyses also revealed considerable expression of 16 aGPCRs (Meister et al. 2014) (Table 2), of which *Celsr3*, *Lphn1*, *Lphn3*, *Bai3*, and *Gpr56* have been functionally characterized.

The most abundant aGPCR in mouse and human pancreatic islets is *Gpr56* (Amisten et al. 2013, 2017; Dunér et al. 2016; Meister et al. 2014). Its expression is down-regulated by long-term glucose stimulation and reduced in islets of T2D patients (Dunér et al. 2016). Activation with its ligand collagen III stimulates glucose-dependent insulin secretion of isolated pancreatic islets (Figure 3A) (Dunér et al. 2016; Olaniru et al. 2018). However, the exact mechanism is still not completely solved. The coupling preferences of GPR56 include Gq/11- and G12/13 signaling, however, elevation of cAMP and protein kinase A activation have been suggested as well (Dunér et al. 2016; Olaniru et al. 2018). Furthermore, *Gpr56* expression and collagen interaction regulate apoptosis and viability of pancreatic β cells. With collagen III being part of the ECM surrounding pancreatic islets (Korpos et al. 2013), these results indicate that ECM molecules regulate β -cell function.

High levels of expression have also been observed for receptors of the Latrophilin family. Interestingly, transcriptome analysis of sorted pancreatic islet cells has revealed equal expression of *Lphn1* in α -, β -, and δ cells, whereas *Lphn2* and *Lphn3* are most abundant in δ - and β cells, respectively (Adriaenssens et al. 2016; DiGruccio et al. 2016) (Table 2). Already more than 20 years ago, it was demonstrated that α -Latrotoxin, a ligand of LPHN1, induces insulin secretion in primary islets and β -cell lines (Lang et al. 1998). However, there are controversial reports whether this effect is receptor-mediated (Lajus et al. 2006; Liu et al. 2005b; Silva et al. 2005). Recently, tethered peptide-based activation demonstrated coupling of LPHN1 and LPHN3 to Gs- and Gi proteins in pancreatic islets, respectively (Müller et al. 2015; Röthe et al. 2019). *In vitro* and *ex vivo* analyses have revealed increased insulin secretion following LPHN1 activation, whereas activation of LPHN3 resulted in reduced insulin release (Figure 3A). Furthermore, down-regulation of *Lphn3* increased basal insulin secretion in the β -cell line MIN6, indicating that the receptor has a regulative function in β cells even without activation (Röthe et al. 2019).

Figure 3: Impact of aGPCRs on pancreatic islet function and development.

(A) Insulin secretion is modulated by G protein-signaling pathways induced by aGPCRs expressed on pancreatic β cells. Activation of LPHN1 increases intracellular cAMP and, therefore, insulin secretion, while LPHN3 and BAI3 reduce intracellular cAMP and insulin release upon activation. Gpr56 regulates β -cell viability and increases insulin secretion when activated by its ligand collagen III. (B) Deletion of *Celsr3* in Pdx-positive islet progenitor cells results in reduced β -cell amount, eventually leading to impaired insulin secretion.

BAI3 activation by its ligand complement 1q-like-3 protein (C1ql3) has been shown to reduce insulin secretion in primary islets and β -cell lines by decreasing intracellular cAMP levels and PKA activity (Gupta et al. 2018) (Figure 3A). Similar to *Lphn3*, *Bai3* knock-down increases insulin secretion, suggesting a ligand-independent inhibitory effect of the receptor. Interestingly, *C1ql3* expression is increased in plasma of obese patient indicating that BAI3 might be an interesting target in the regulation of insulin secretion in obesity-associated T2D (Shanaki et al. 2016). However, it needs to be noted that *Bai3* expression in human islets is very low (Dunér et al. 2016) (Table 2).

Even though aGPCRs have been implicated in developmental processes in other tissues little is known about their impact on islet development. Thus far, only *Celsr3* has been linked to β -cell development. Deletion of *Celsr3* in Pdx-positive pancreatic progenitor cells diminishes β -cell amount leading to an impaired glucose tolerance (Cortijo et al. 2012) (Figure 3B). Transcriptome analysis of human fetal β cells revealed the highest aGPCR expression for *Gpr97*, although the receptor is not expressed in adult human and mouse islets (Blodgett et al. 2015) (Table 2). It has been demonstrated that glucocorticoid-activated GPR97 reduces intracellular cAMP levels via the Gi/o protein-signaling pathway (Gupte et al. 2012; Ping et al. 2021). Interestingly, glucocorticoids as well as activation of Gi/o proteins have been shown to interfere with proper islet development

leading to reduced amount of mature β cells (Berger et al. 2015; Dumortier et al. 2011; Gesina et al. 2004). Thus, one can speculate that GPR97 might have a role during β -cell development.

Expression in other tissues connected to energy homeostasis

The liver is one of the main organs controlling and coordinating glucose homeostasis, lipid and amino acid metabolism, and several other processes which are modulated by GPCRs. Gs-protein signaling induced by, for example, glucagon, results in protein kinase A activation and subsequently in glycogen degradation and gluconeogenesis whereas activation of Gi/o proteins has opposite effects (Rossi et al. 2018). Gluconeogenesis and glycogenolysis are also induced by receptors coupled to Gq/11 proteins like the V1b vasopressin receptor (Li et al. 2013).

To date, there is no report of the functional relevance of any aGPCR in hepatic metabolic processes available. However, many aGPCRs are expressed in the liver (Fagerberg et al. 2014; Yang et al. 2016) and, specifically, in hepatocytes (MacParland et al. 2018; Schaum et al. 2018) (Table 3). Evidence for functional relevance has been found in different mouse models of hepatosteatosis, in which

Table 3: Meta-analysis of aGPCR expression in human liver (Fagerberg et al. 2014) and hepatocytes (MacParland et al. 2018) as well as mouse liver (Yang et al. 2016) and hepatocytes (Schaum et al. 2018). RNAseq expression is given in FPKM values (+++ > 20; ++ > 2; + > 0.5; − < 0.5). Hepatocyte-specific expression was determined using single cell expression atlas for human and mouse liver.

aGPCR	Human		Mouse	
	Liver	Hepatocyte	Liver	Hepatocyte
<i>Adgrl1/Lphn1</i>	+	−	+	−
<i>Adgrl2/Lphn2</i>	+++	+++	++	+
<i>Adgrl3/Lphn3</i>	+	−	−	−
<i>Adgrl4/Eltd1</i>	++	++	++	+
<i>Adgre1/Emr1</i>	+	−	+++	−
<i>Adgre2/Emr2</i>	++	−		
<i>Adgre3/Emr3</i>	−	−		
<i>Adgre4/Emr4</i>	−	−	++	−
<i>Adgre5/Cd97</i>	++	−	+++	−
<i>Adgra1/Gpr123</i>	−	−	−	−
<i>Adgra2/Gpr124</i>	++	−	++	−
<i>Adgra3/Gpr125</i>	+++	+++	++	++
<i>Adgrc1/Celsr1</i>	++	++	++	+
<i>Adgrc2/Celsr2</i>	+	++	−	+
<i>Adgrc3/Celsr3</i>	−	+	−	−
<i>Adgrd1/Gpr133</i>	++	+	−	−
<i>Adgrd2/Gpr144</i>	−	−		
<i>Adgrf1/Gpr110</i>	−	−	−	+
<i>Adgrf2/Gpr111</i>	−	−	−	−
<i>Adgrf3/Gpr113</i>	−	+	−	−
<i>Adgrf4/Gpr115</i>	−	−	−	−
<i>Adgrf5/Gpr116</i>	++	+	++	+
<i>Adgrb1/Bai1</i>	−	−	−	−
<i>Adgrb2/Bai2</i>	−	−	−	−
<i>Adgrb3/Bai3</i>	−	−	−	−
<i>Adgrg1/Gpr56</i>	++	+	+	+
<i>Adgrg2/Gpr64</i>	−	−	+	+
<i>Adgrg3/Gpr97</i>	++	−	++	−
<i>Adgrg4/Gpr112</i>	−	−	−	−
<i>Adgrg5/Gpr114</i>	−	−	−	−
<i>Adgrg6/Gpr126</i>	+++	+++	+	−
<i>Adgrg7/Gpr128</i>	++	++	−	−
<i>Adgrv1/Vlgr1</i>	++	++	−	+

Gpr110 has been identified among the 50 strongest regulated genes referred to as common indicators of non-alcoholic fatty liver disease (Lede et al. 2017). Further support comes from several genome-wide association studies. An intergenic single nucleotide polymorphism (SNP) close to the 3' UTR of the *Celsr2* gene has been associated with altered levels of LDL cholesterol. This LDL-associated SNP was strongly correlated with *Celsr2* transcript levels in human liver (Kathiresan et al. 2008). Similarly, several other SNPs in or in close proximity to aGPCR genes are associated with liver metabolism. For example, GWAS and QTL analyses linked *Lphn3* to HDL

Table 4: Expression of aGPCRs in hypothalamic AgRP and POMC neurons under fasted and fed conditions in the mice (Henry et al. 2015). RNAseq expression is given in TPM values (+++ > 50; ++ > 10; + > 1; − < 1).

aGPCR	AgRP		POMC	
	Fasted	Fed	Fasted	Fed
<i>Adgrl1/Lphn1</i>	+++	+++	+++	+++
<i>Adgrl2/Lphn2</i>	++	++	++	++
<i>Adgrl3/Lphn3</i>	++	++	+++	+++
<i>Adgrl4/Eltd1</i>	−	−	−	−
<i>Adgre1/Emr1</i>	−	−	−	−
<i>Adgre4/Emr4</i>	−	−	−	−
<i>Adgre5/Cd97</i>	−	−	−	−
<i>Adgra1/Gpr123</i>	+++	+++	+++	+++
<i>Adgra2/Gpr124</i>	−	+	+	−
<i>Adgra3/Gpr125</i>	++	++	+	++
<i>Adgrc1/Celsr1</i>	−	−	−	−
<i>Adgrc2/Celsr2</i>	−	−	−	−
<i>Adgrc3/Celsr3</i>	−	−	−	−
<i>Adgrd1/Gpr133</i>	−	+	+	+
<i>Adgrf1/Gpr110</i>	−	−	−	−
<i>Adgrf2/Gpr111</i>	+	−	+	−
<i>Adgrf3/Gpr113</i>	−	−	−	+
<i>Adgrf4/Gpr115</i>	−	+	+	+
<i>Adgrf5/Gpr116</i>	−	−	−	−
<i>Adgrb1/Bai1</i>	++	+++	++	++
<i>Adgrb2/Bai2</i>	++	+	++	++
<i>Adgrb3/Bai3</i>	++	+++	+++	++
<i>Adgrg1/Gpr56</i>	+++	+++	+++	+++
<i>Adgrg2/Gpr64</i>	+++	+	+	+
<i>Adgrg3/Gpr97</i>	−	−	−	−
<i>Adgrg4/Gpr112</i>	−	−	−	−
<i>Adgrg5/Gpr114</i>	−	−	−	−
<i>Adgrg6/Gpr126</i>	+	++	−	+
<i>Adgrg7/Gpr128</i>	−	−	−	−
<i>Adgrv1/Vlgr1</i>	−	+	+	+

cholesterol levels, *Gpr125* to LDL particle size, and *Vlgr1* to apolipoprotein A2 levels (summarized in Kovacs and Schöneberg 2016). However, causal or mechanistic links between liver metabolism and aGPCR gene variants remain to be determined.

Food intake and energy homeostasis are regulated by hypothalamic neurons of the arcuate nucleus, namely agouti-related peptide (AgRP) and pro-opiomelanocortin (POMC) neurons. POMC neurons release melanocyte-stimulating hormone activating melanocortin type 4 receptor (MC4R) expressing neurons central for inhibiting food intake and increasing energy expenditure. AgRP secreted from AgRP neurons is an inverse agonist of MC4R, thus, inducing food intake. Therefore, activated AgRP neurons promote food intake and activation of POMC neurons has anorexigenic effects (Adan et al. 2006).

The function of these neurons is modulated by G protein-signaling pathways. While induction of Gs- and Gq/11-protein pathways increases neuron activity, Gi protein-coupled receptors inhibit it (Krashes et al. 2011; Zhan et al. 2013). Transcriptome analysis has revealed expression of several aGPCRs in these neurons (Table 4) (Henry et al. 2015). Interestingly, *Bai3* is expressed in both types of neurons and during fasting periods its expression is down-regulated in AgRP neurons and up-regulated in POMC neurons (Henry et al. 2015). Such, it appears likely that BAI3 has a regulative role in food intake. As BAI3 signaling has been linked to Gi/o-protein activation (Gupta et al. 2018), it can be presumed that its activation silences POMC neurons under fasting conditions and inhibits AgRP neurons under feeding.

Expression of aGPCRs has also been demonstrated throughout the gastro-intestinal tract (Badiali et al. 2012; Fagerberg et al. 2014). High expression in intestine has been reported for *Gpr128* and knock-out of the receptor resulted in reduced body weight (Ni et al. 2014). Of specific interest are enteroendocrine cells which secrete hormones, such as the gastric inhibitory polypeptide (GIP), and regulate whole-body metabolic homeostasis. GPCRs expressed in these cells are described to function as sensors for metabolites. Interestingly, RNAseq analysis has revealed a high expression of *Gpr112* in enteroendocrine cells compared to enterocytes (Sommer and Mostoslavsky 2014) indicating a specific function of this aGPCR in these cells.

Future perspectives and concluding remarks

Whole body energy homeostasis depends on the rigorous regulation of tissue interplay and GPCRs have been demonstrated to be involved in several of these processes. Their specific expression in metabolically relevant tissues has made GPCRs promising targets to treat obesity and its associated pathologies, among them the free fatty acid receptors 1–4 (Christiansen et al. 2008; Da Oh et al. 2010; Li et al. 2019; McNelis et al. 2015; Milligan et al. 2015; Miyamoto et al. 2017; Mohammad 2016; Park et al. 2016; Shim-pukade et al. 2012; Son et al. 2021; Ueno et al. 2019), the glucose-dependent insulinotropic peptide receptor (Killian et al. 2020; Sachs et al. 2021), the glucagon-like peptide 1 receptor (Campbell 2020; Chadda et al. 2020; Maselli and Camilleri 2021; McLean et al. 2020; Willard et al. 2020), and MC4R (Clément et al. 2020; Gonçalves et al. 2018; Kievit

et al. 2013; Kühnen et al. 2019). Only limited information is available for the class of aGPCRs albeit their high expression in metabolically relevant tissues. Ongoing research on these receptors will further elucidate their signaling properties and physiological relevance and may expose their potential targetability to treat metabolic disorders such as obesity, T2D, fatty liver disease, and cardiovascular disease. As outlined above, some aGPCRs specifically modulate functions of adipocytes and pancreatic islet cells. Their dual structural characteristics of having a large *N*-terminus and a 7TM domain opens the possibility to modulate their functions, classically by 7TM-binding drugs or *Stachel*-derived peptides but also through targeting the adhesive extracellular domains. These binding partners can be identified using affinity purification approaches, as demonstrated for GPR56 and collagen III (Luo et al. 2011). Small molecules binding at the 7TM domain of aGPCRs and modulating receptor's signal transduction have been identified for GPR56, GPR97, GPR114, and GPR126 using drug screening studies (Bradley et al. 2019; Gupte et al. 2012; Stoveken et al. 2016). Autoantibodies against the *N*-terminus of GPCRs modulating receptor activity are well-known from autoimmune diseases (Schöneberg and Liebscher 2021) but are more and more generated as specific therapeutics to treat diverse pathologies (Hutchings 2020). The large *N*-termini are ideal epitopes to develop specific antibodies blocking aGPCR interactions with other cells and/or ECM or even influencing aGPCR signaling. Examples for successful applications have been shown for CD97, whose interaction with its binding partner CD55 can be abolished using an antibody targeting the EGF domains of the receptor (Eichler et al. 2019) and EMR2, which can be activated by incubation with an antibody targeting its GAIN domain (Bhudia et al. 2020; Yona et al. 2008).

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