Citation for published version (APA):
Atanes Juiz, P., Ashik, T., & Persaud, S. (2021). Obesity-induced changes in human islet G protein-coupled receptor expression: Implications for metabolic regulation. Pharmacology and Therapeutics, 228.
Obesity-induced changes in human islet G protein-coupled receptor expression: implications for metabolic regulation

Abstract:
G protein-coupled receptors (GPCRs) are a large family of cell surface receptors that are the targets for many different classes of pharmacotherapy. The islets of Langerhans are central to appropriate glucose homeostasis through their secretion of insulin, and islet function can be modified by ligands acting at the large number of GPCRs that islets express. The human islet GPCRome is not a static entity, but one that is altered under pathophysiological conditions and, in this review, we have compared expression of GPCR mRNAs in human islets obtained from normal weight range donors, and those with a weight range classified as obese. We have also considered the likely outcomes on islet function that the altered GPCR expression status confers and the possible impact that adipokines, secreted from expanded fat depots, could have at those GPCRs showing altered expression in obesity.
Obesity-induced changes in human islet G protein-coupled receptor expression: implications for metabolic regulation

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Keywords: obesity, diabetes, GPCRs, adipose, human islets, insulin secretion
ABSTRACT

G protein-coupled receptors (GPCRs) are a large family of cell surface receptors that are the targets for many different classes of pharmacotherapy. The islets of Langerhans are central to appropriate glucose homeostasis through their secretion of insulin, and islet function can be modified by ligands acting at the large number of GPCRs that islets express. The human islet GPCRome is not a static entity, but one that is altered under pathophysiological conditions and, in this review, we have compared expression of GPCR mRNAs in human islets obtained from normal weight range donors, and those with a weight range classified as obese. We have also considered the likely outcomes on islet function that the altered GPCR expression status confers and the possible impact that adipokines, secreted from expanded fat depots, could have at those GPCRs showing altered expression in obesity.
ABBREVIATIONS

- ACTB: beta-actin.
- ACTH: adrenocorticotropic hormone.
- ADGRs: adhesion receptors.
- ADORAs: adenosine receptors.
- ADRs: adrenergic receptors.
- AVP: vasopressin.
- AVPRs: vasopressin receptors.
- BAT: brown adipose tissue.
- BMI: body mass index.
- C3a: complement component 3a.
- C3AR: complement component 3a receptor.
- cAMP: cyclic adenosine monophosphate.
- CCLs: C-C chemokine ligands.
- CCRs: C-C chemokine receptors.
- CCRLs: C-C chemokine receptors-like.
- CELSRs: cadherin EGF LAG seven-pass g-type receptors.
- CNRs: cannabinoid receptors.
- CXCLs: CXC chemokine ligands.
- CXCRs: CXC chemokine receptors.
- DDRs: dopamine receptors.
- EST: expressed sequence tag.
- F2RLs: F2R like trypsin receptors.
- FFA: free fatty acids.
- FFARs: free fatty acid receptors.
- FZDs: frizzled receptors.
- **GAPDH**: glyceraldehyde 3-phosphate dehydrogenase.
- **GLP-1**: glucagon-like peptide-1.
- **GLP-1RAs**: glucagon-like peptide-1 receptor agonists.
- **GPCRB**: G protein-coupled receptor family C group 5 member B.
- **GPCRs**: G protein-coupled receptors.
- **GPRs**: G protein-coupled receptors.
- **GRAFS system**: G (Glutamate); R (Rhodopsin); A (Adhesion); F (Frizzled); S (Secretin) system.
- **GSHR**: Growth hormone secretagogue receptor.
- **HbA1c**: glycated haemoglobin.
- **HCA**: hydroxycarboxylic acid.
- **HCAR**: hydroxycarboxylic acid receptors.
- **HFD**: high-fat diet.
- **HTRs**: serotonin receptors.
- **LPA**: lysophosphatidic acid.
- **LPARs**: lysophosphatidic acid receptors.
- **LTB4**: leukotriene B4.
- **MC2R**: melanocortin 2 receptor.
- **MRGPRXs**: Mas-related G-protein coupled receptors.
- **mRNA**: messenger ribonucleic acid.
- **NMUR1**: neuromedin U receptor 1.
- **NPY**: neuropeptide Y.
- **NPY1R**: neuropeptide Y receptor type 1.
- **OXT**: oxytocin.
- **OXTR**: oxytocin receptor.
- **P2RYs**: purinergic receptors.
- **PGs**: prostanoid ligands.
- **PNX**: phoenixin.
- **PPIA**: peptidylprolyl isomerase A.
- **PRLHR**: Prolactin-releasing peptide receptor.
- **PrRP**: prolactin-releasing peptide.
- **PTGERs**: prostaglandin receptors.
- **PTH**: parathyroid hormone.
- **PTH2R**: parathyroid hormone 2 receptor.
- **qPCR**: quantitative polymerase chain reaction.
- **QRFPR**: pyroglutamylated RFamide peptide receptor.
- **RXFPs**: relaxin receptors.
- **S1P**: sphingosine 1-phosphate.
- **S1PRs**: sphingosine 1-phosphate receptors.
- **Shh**: Sonic hedgehog.
- **SNP**: single-nucleotide polymorphism.
- **SST**: somatostatin.
- **SSTR**: somatostatin receptors.
- **TAS2Rs**: bitter-taste receptors.
- **T2D**: type 2 diabetes.
- **TBP**: TATA-binding protein.
- **TFRC**: transferrin receptor.
- **TSH**: thyroid stimulating hormone.
- **TSHR**: thyroid stimulating hormone receptor.
- **TUDCA**: taouroursodeoxycholic acid.
- **WAT**: white adipose tissue.
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3.0. Conclusions and perspectives
1. Introduction

The most recent global analysis of obesity incidence was published by the World Health Organisation in 2016, which indicated that 650 million people worldwide had a BMI in excess of 30kg/m² and were thus classified as having obesity. Re-analysis of existing data suggests that nearly 50% of US adults will have obesity by 2030 (Ward, et al., 2019) and it is now apparent that overweight and obesity contribute to over 23% of deaths in England and Scotland (Ho, et al., 2021). The alarming rise in worldwide obesity prevalence is not the product of overnutrition and underactivity alone: socioeconomic, genetic, environmental, biological and behavioural factors all play roles in development of this “globesity phenomenon” (Costa-Font & Mas, 2016; Lee, Cardel, & Donahoo, 2000). Regardless of aetiology, obesity is characterised by expansion of visceral fat depots that are located around and within abdominal organs and there is also increased subcutaneous fat accumulation, although, given its location, there is less capacity for this to expand. The metabolic consequences of growing visceral adiposity are of great concern: it has been known for many years that expanded visceral fat mass in obesity leads to insulin resistance (Lebovitz & Banerji, 2005), which predisposes towards several comorbidities, such as type 2 diabetes (T2D) and cardiovascular disease.

Much focus to date has been on the deleterious effects of dietary saturated fatty acids such as palmitate and free fatty acids generated by lipolysis of adipocyte triacylglycerols, but adipocytes are sources of biological signalling mediators termed adipokines, which are key regulators of metabolic competence. It is known that levels of some adipokines are altered in obesity (Zorena, Jachimowicz-Duda, Ślęzak, Robakowska, & Mrugacz, 2020) and that the adipokines secreted from adipocytes can have endocrine effects to regulate function of tissues involved in glucose homeostasis, such that metabolic control is either improved or impaired.

1.1. Cross-talk between adipocytes and islets

Adipose tissue is sub-divided into physiologically distinct white (WAT) and brown (BAT) adipose tissue compartments, based on cellular differences in morphology, gene expression,
localisation and primary metabolic functions (Miura, 2015). BAT is mainly localised to the axilla and supraclavicular region (Sacks & Symonds, 2013) and it houses an abundance of mitochondria that express and utilise uncoupling protein 1, which uncouples respiration to generate heat through a process known as “non-shivering thermogenesis” (Lee, et al., 2014). Details of BAT in relation to metabolic control have emerged with its stimulation shown to improve insulin sensitivity and glucose disposal (Stanford, et al., 2013), and BAT depots have been identified as possible pharmacological targets for obesity and diabetes therapies (Lee, et al., 2014).

In contrast to the small volume of BAT, WAT has a significantly greater capacity for lipid storage. Mature adipocytes represent ~80% of WAT volume due to the large triacylglycerol droplets within their cytoplasm (Bourgeois, et al., 2019) and adipocyte plasticity accommodates even further tissue expansion in the event of chronic energy intake (Bourgeois, et al., 2019). WAT is a highly active source of secretory products that are synthesised and released in response to various hormonal and central afferent signals (Kershaw & Flier, 2004). Leptin and adiponectin are among the best characterised adipokines, with well-established effects to regulate feeding status and insulin sensitivity (Stern, Rutkowski, & Scherer, 2016). Adipose tissue remodelling in the form of fibrosis, angiogenesis and adipocyte hypertrophy is associated with a highly inflammatory milieu, oxidative stress and DNA damage (Ryan, et al., 2019). Subsequently, the fine balance in the secretion of pro-inflammatory, pro-diabetic and anti-inflammatory, anti-diabetic factors is disrupted in favour of the former. For example, in obese humans, decreased adiponectin and elevated leptin levels, as a consequence of increased adiposity, are associated with insulin resistance. There is also evidence that these adipokines act in an endocrine manner to regulate β-cell function (Kang, et al., 2016; Weisberg, et al., 2003) whereby leptin inhibits glucose-induced insulin secretion (Cochrane, et al., 2020; Fehmann, et al., 1997) while adiponectin potentiates it (Gu, et al., 2006). Therefore, the increased leptin and decreased adiponectin levels in obesity can contribute to β-cell secretory insufficiency. In addition, adipocytes also secrete less well known adipokines such as chemerin, adipoin and apelin, all of which have stimulatory effects on insulin secretion (Lo, et al., 2014; O’Harte, Parthsarathy, Hogg, &
It is therefore clear that adipokines can function as true endocrine mediators, with effects at islets that may ameliorate or exacerbate the deleterious effects of an obesogenic environment.

The receptors responsible for transducing downstream signalling in response to leptin and adiponectin have been known for some time. Thus, leptin acts at Ob-R type I cytokine receptors to activate the cytoplasmic tyrosine kinase JAK2 and the subsequent phosphorylation of STAT proteins leads to changes in gene expression (Marroquí, et al., 2012). Adiponectin exerts its effects by binding to AdipoR1 and AdipoR2 receptors belonging to the progestin and adipoQ (PAQR) family of proteins that are coupled to AMP kinase and PPARγ activation (Kupchak, Garitaonandia, Villa, Smith, & Lyons, 2009). Chemerin activates the G protein-coupled receptors (GPCRs) ChemR23 and GPR1, both of which signal via mitogen-activated protein kinase and RhoA/ROCK cascades. Adipsin has recently been shown to protect β-cells by increasing complement peptide C3a levels (Gómez-Banoy, et al., 2019), a ligand that is known to improve islet function via the GPCR C3aR (Atanes, Ruz-Maldonado, Pingitore, et al., 2018). Apelin is an agonist for the receptor APJ, which signals via Gαi to inhibit adenylate cyclase activity and reduce cyclic AMP generation (Chapman, Dupre, & Rainey, 2014).

There is evidence that alterations in circulating adipokine levels are associated with changes in expression of the GPCRs through which they act and that there are tissue-dependent effects of GPCR modulation following changes in ligand levels in obesity. For example, circulating chemerin levels are reported to increase by more than 2-fold in mice fed a high-fat diet (HFD), and this is accompanied by reduced Gpr1 expression in skeletal muscle (Rourke, Muruganandan, Dranse, McMullen, & Sinal, 2014). In addition, serum levels of apelin are increased in obesity (Hehir & Morrison, 2012), while levels of its receptor, APJ, are reduced in skeletal muscle (Ji, Gong, Wang, He, & Zhang, 2017), but elevated in adipose tissue (Dray, et al., 2010). Weight status therefore has the capacity to modify the cross-talk between adipocytes and islets such that adipose expansion in obesity will lead to increased secretion of adipokines, and, for those that signal via GPCRs, this may be accompanied by changes in levels of the target GPCRs and modified responses to those ligands.
1.2. Overview of islet GPCR expression

Approximately 800 GPCRs have been identified in humans, around half of which encode receptors responsible for sensory functions such as olfaction. All GPCRs have seven transmembrane helices consisting of intracellular, transmembrane and extracellular domains (Unal & Karnik, 2012). This configuration facilitates the transduction of extracellular stimuli from the cell surface into the cytoplasm to trigger various signalling cascades that include enzyme recruitment and cytoskeletal remodelling, hormone synthesis/secretion and alterations in gene expression (Atanes & Persaud, 2020). The overall effect of individual GPCR activation depends on several key factors:

1) the nature and availability of the occupying GPCR ligand;
2) the associated Gα-protein (Gαs, Gαi/o, Gαq/11 and Gα12/13), which distinguish the GPCR subclasses, and the coupled downstream effector(s);
3) receptor, system- or ligand-bias that results in preference for either G protein signalling or β-arrestin recruitment and GPCR desensitisation;
4) the localisation of the expressed GPCR and its cell- or tissue-dependent pharmacological profiles.

The structural and functional features of GPCRs mean that this large and versatile family of receptors has a high capacity for signalling output. In β-cells, this equates to positive or negative effects on insulin mRNA expression, insulin protein production and packaging, glucose-stimulated vesicle fusion and insulin exocytosis, and β-cell growth, proliferation and apoptosis (Kowluru, 2020). The importance of GPCRs in glucose regulation and overall metabolic homeostasis is becoming clearer, but there still remains incomplete knowledge regarding the functions of many islet GPCRs and the identities of their corresponding ligands (Amisten, Salehi, Rorsman, Jones, & Persaud, 2013). Complete profiling of the islet GPCRomes of both mouse and humans has aided in bridging this knowledge gap and we have previously reported that human and C57BL/6 mouse islets express mRNAs encoding 293 and 227 GPCRs, respectively (Amisten, et al., 2017; Amisten, Salehi, Rorsman, Jones, & Persaud, 2013). The adhesion receptor, ADGRG1, is the most highly expressed islet GPCR mRNA in both species.
(Amisten, et al., 2017) and its activation by collagen III protects islets against cytokine-induced apoptosis and potentiates glucose-stimulation insulin secretion (Olaniru, et al., 2018). In addition, reduced expression of ADGRG1 mRNA in islets from diabetic subjects indicates the potential involvement of this GPCR in glucose dysregulation (Duner, et al., 2016). Analysis of islets retrieved from normal weight and obese donors has also revealed alterations in islet GPCR expression that links obesity to altered islet function (Atanes, Lee, Huang, & Persaud, 2020).

1.3. Targeting islet GPCRs to treat type 2 diabetes

The capacity for GPCRs as druggable entities is considerable (Atanes & Persaud, 2020). Indeed, this large family of receptors represents ~35% of all current drug targets for treatment across a wide range of diseases (Sriram & Insel, 2018). However, there are only three pharmacotherapies for diabetes that directly target GPCRs, only one of which acts at an islet GPCR (Atanes & Persaud, 2020). Thus, glucagon-like peptide-1 receptor agonists (GLP-1RAs) activate β-cell GLP-1 receptors to mimic the actions of endogenous GLP-1 to potentiate glucose stimulated insulin secretion; bromocriptine, an activator of dopamine D2 receptors, improves postprandial glycaemia by modulating dopamine levels; and pramlintide, an amylin analogue, acts centrally at calcitonin receptor/receptor activity-modifying protein heterodimers to reduce food intake, slow gastric emptying and delay glucose absorption. GLP-1RAs, such as exenatide and liraglutide, are widely prescribed and through their effects to increase insulin secretion and slow gastric emptying they are very effective in lowering postprandial plasma glucose levels and glycated haemoglobin (HbA1c), without risk of hypoglycaemic events (Gilbert & Pratley, 2020; Sposito, Berwanger, de Carvalho, & Saraiva, 2018). The additional anorectic properties of GLP-1RAs, which are mediated by GLP-1 receptors on POMC/CART appetite-controlling hypothalamic nuclei, further contribute to improved glycaemic control (Secher, et al., 2014). Furthermore, GLP-1 receptors are also expressed by islet α-cells and binding of GLP-1RAs to these receptors suppresses glucagon secretion, which ameliorates the detrimental hyperglucagonaemia that occurs in T2D. Until recently, daily or weekly subcutaneous injections of
GLP-1RAs meant that their route of administration was impractical or undesirable for many people with T2D, but the recent clinical introduction of a GLP-1RA in tablet form, oral semaglutide, will undoubtedly improve the attractiveness of this class of pharmacotherapy (Pratley, et al., 2021).

Nonetheless, further research and drug development are required as T2D is a progressive disorder, with ongoing deterioration of glycaemic control: it is important that alternative therapeutic options are available when individuals fail to maintain HbA1c <7%, as prolonged hyperglycaemia is responsible for the range of diabetic complications that have a detrimental impact on people with poorly controlled diabetes. Therefore, novel pharmacotherapies are necessary to improve quality of life, and, based on cumulative evidence implicating visceral adipose tissue in diabetes pathophysiology, it is sensible to direct attention towards possible adipose tissue-derived peptides modifying β-cell function through GPCR activation. This review will focus on altered islet GPCR expression in obesity and consideration will be made of potential cross-talk between adipocytes and islets through secreted adipokines binding to islet GPCRs. Figure 1 shows a schematic indicating expansion of visceral adipose tissue in obesity and secretion of the established adipokines, leptin and adiponectin, which act at non-GPCRs as well as novel adipokines that may reach islets via the circulation to modify β-cell function by binding to GPCRs.

2. Obesity-induced changes in human islet GPCR mRNA expression

2.1. Quantification of GPCR mRNA expression in islets from lean and obese donors

To identify the impact of obesity on human islet GPCR mRNA expression, a revised TRIzol protocol was employed to extract total RNA from human islets that had been isolated from heart-beating non-diabetic donors within a healthy weight range (BMI 22.5±0.9; n=4; “low BMI”) and those in an obese range (BMI 33.5±1.2; n=4; “high BMI”) (Amisten, Salehi, Rorsman, Jones, & Persaud, 2013; Huang, et al., 2004). TaqMan RT-PCR kits were used to generate human islet cDNA templates and expression of 385 non-odorant GPCRs were quantified using QuantiTect qPCR primers and QuantiFast kits (Figure 2A). The gender, age and BMI of individual donors are shown in Figure 2B. Gene expression
was expressed relative to the housekeeping genes ACTB, GAPDH, PPIA, TBP and TFRC in the same samples, as described elsewhere (Amisten, et al., 2017), and mean expression of these genes in islets from lean and obese donors is shown in Figure 2C. Different nomenclatures have been proposed to group GPCRs into sub-families based on features including their sequence homology, functional similarity or evolutionary relationships (Hu, Mai, & Chen, 2017). For this review we have used the GRAFS (G: Glutamate; R: Rhodopsin; A: Adhesion; F: Frizzled; S: Secretin) system (Fredriksson, Lagerstrom, Lundin, & Schioth, 2003), as shown in Figure 2A.

2.2. Summary of human islet GPCR mRNA expression in lean and obese donors

Analysis of expressed sequence tag (EST) databases has revealed that only 0.01-0.001% of ESTs match GPCRs, indicating that GPCRs usually have low expression levels (Fredriksson & Schiöth, 2005). In our qPCR analysis human islet GPCR mRNA levels were sub-divided as “Expressed”, “Trace” and “Absent/non-quantifiable” based on their expression relative to the housekeeping genes. Thus, genes in the “Expressed” category were present at levels >0.001% of the mRNA expression of the five reference genes, while those whose expression was between 0.0001-0.001% of housekeeping gene levels were considered to be present only at trace level. The absent/non quantifiable genes were either not expressed by the islets or expressed at such low levels that it was not possible to quantify them. The Venn diagrams in Figure 2D show these three categories with stratification of GPCR mRNA expression in islets from lean (green) and obese (pink) donors and the extent of commonality in expression is shown in grey. In summary, in islets from both low and high BMI subjects, a core set of 186 GPCR mRNAs were detected above trace levels, 89 were detected at trace levels and 20 receptors were not quantifiable or absent. We have also examined the impact of obesity on individual GPCRs from lean and obese donors to stratify the top 10 most upregulated (Figure 2E) and downregulated (Figure 2F) islet GPCR mRNAs, which have been illustrated in heatmaps showing expression values and fold-change ratios expressed as high/low BMI. Islet GPCR mRNAs with fold-change values of 1 had no alterations in expression, while genes with values above 1 were upregulated and below 1 were
downregulated in islets from high BMI donors. Consistent with this, we have recently reported that
the chemokine receptor CCR9, which showed the highest upregulation in expression in islets from
obese donors, could be explored as a possible target for antagonism in T2D based on the deleterious
impact on β-cell function elicited by its endogenous ligand CCL25 (Atanes, et al., 2020). The most
downregulated gene from our qPCR analysis was TSHR. It is known that circulating levels of its
endogenous ligand, TSH, are increased in high BMI subjects (Bastemir, Akin, Alkis, & Kaptanoglu,
2007), and that deletion of Tshr in mice protects against HFD-induced obesity (Ma, et al., 2015).
However, Tshr activation in rodent β-cells is associated with increased insulin secretion (Lyu, et al.,
2018), so if this also occurs in human β-cells the down-regulation of TSHR in islets in obesity could lead
to reduced capacity of islets to secrete sufficient insulin to overcome the obesity-induced insulin
resistance.

2.3. GRAFS stratification of human islet GPCR mRNA expression in lean and obese donors

To explore our GPCR mRNA quantifications in islets from low and high BMI donors in more
detail, Figure 3 shows all detectable GPCR mRNAs in each of the GRAFS families and we have identified
those showing significantly changed expression in obesity. Therefore, the following sections
summarise available published information on the roles of significantly upregulated/downregulated
islet GPCRs in glucose homeostasis, with particular focus on whether they can be activated by adipose-
derived ligands and their function in islets.

2.3.1 Glutamate receptors

This GPCR family is composed of five subfamilies: calcium-sensing (CASK and GPRC6A),
gamma-amino-butyric acid (GABA) type B, metabotropic glutamate (GRM), taste (TAS1R) and orphan
receptors. Our qPCR analysis of islets isolated from lean and obese donors indicated that of the
twenty-two members of this receptor family, three mRNAs were significantly upregulated in obesity.
There are no reported adipokines for any of the Glutamate family GPCRs that show altered expression
in obesity. One GPCR showing a small but significant increase in islets of obese donors is \textit{GPCR5B}, a retinoid-acid inducible orphan receptor that has previously been reported to have deleterious metabolic effects by promoting inflammation in adipocytes and causing diet-induced obesity and insulin resistance (Kim, Sano, Nabetani, Asano, & Hirabayashi, 2012). These detrimental findings are in agreement with our observations that transfection of MIN6 β-cells with a Gprc5b plasmid increased pro-apoptotic signalling pathways (Atanes, Ruz-Maldonado, Hawkes, et al., 2018). However, the extent of increase of islet \textit{GPCR5B} in obesity is very small, and it is therefore unlikely to be a major contributor to islet dysfunction and β-cell loss. In contrast, the poorly characterised orphan receptor \textit{GPR156} was increased over 30-fold in islets from donors with high BMI. There is a previous report that \textit{Gpr156} is downregulated in adipocytes from obese C57 mice (Choi, et al., 2015) while its upregulation in adipocytes has also been reported under similar conditions (Voigt, Agnew, van Schothorst, Keijer, & Klaus, 2013). It is difficult to analyse functional effects of orphan receptors since activating ligands are not available, and a further difficulty of working with \textit{Gpr156} is that it lacks an N-terminus domain, which contains the orthosteric binding site for the liganded members of this class (Hauser, Attwood, Rask-Andersen, Schioth, & Gloriam, 2017). Additional information is therefore required to better understand its functional effects in islets and other cell types. The third receptor in this family that was significantly upregulated in islets from obese donors is \textit{GPR158}, another orphan GPCR. \textit{GPR158} is highly expressed in the brain, where it has been implicated in the regulation of energy balance (Wagner, Bernard, Derst, French, & Veh, 2016). In addition, it interacts closely with two other genes, CACNA1B and RGS7, both of which are reported to promote obesity in their respective knockout mice (Orlandi, et al., 2015; Takahashi, et al., 2005), but its function in islets has not been established.

\textbf{2.3.2 Rhodopsin receptors}

The rhodopsin family of GPCRs is the largest component of the GPCR superfamily of receptors, and we have separated it into twenty-one distinct subfamilies (Joost & Methner, 2002) that includes the nineteen standard subfamily members plus sensory bitter-taste receptors and a group of orphan
receptors that have been allocated to subfamily A21 based on their similarities to other Rhodopsin receptors.

2.3.2.1. Subfamily A1

Subfamily A1 comprises receptors for chemokines and an orphan member (GPR137). The only islet receptor with a significant alteration in expression was CCR1, which was upregulated 3-fold in obesity, while CCR2, CCRL2 and XCR1 showed upregulatory trends in islets from high BMI donors. CCR1 is involved in monocyte and macrophage infiltration in obesity-induced adipose inflammation (Conroy, et al., 2016; Noh, et al., 2014) so it is possible that its increased expression in islets in obesity is secondary to passenger immune cells expressing CCR1 infiltrating the islets of obese individuals, rather than the upregulation occurring in the islet endocrine cells *per se*. Upregulation in CCR1 mRNA expression is not a result of cross-talk between secreted adipokines and islets as the main endogenous ligands for CCR1, CCL15 and CCL23, are plasma chemokines (Zlotnik & Yoshie, 2012). However, other ligands for subfamily A1 receptors are adipokines. For example, CCL2 is a CCR2-binding adipocyte-secreted chemoattractant involved in macrophage recruitment. This ligand is upregulated in mice fed a HFD (Chen, et al., 2005) and it is overexpressed in adipose tissue and elevated in plasma in insulin-resistant obese individuals (Tan, Chong, Tan, & Tan, 2012), which may be related to the increase observed for CCR2 in islets from obese donors. Similarly, CCRL2 is moderately increased in islets from high BMI donors and levels of its activating ligand, CCL19, are significantly higher in adipose tissue of obese individuals (Kochumon, et al., 2019). Furthermore, studies with HFD-fed rats showed increased XCL1 expression in WAT (Wang, et al., 2017), and it is possible that upregulation of this adipokine in obesity is linked to the 4-fold increase in XCR1, its cognate receptor, that we observed in islets of obese donors.

2.3.2.2. Subfamily A2
The second subfamily of Rhodopsin receptors consists of the remaining chemokine receptors, and it also includes a GPCR for estrogen (GPER) and an orphan receptor (GPR182). Two of the subfamily A2 receptors, CCR9 and GPR182, were significantly upregulated in islets from obese donors and another, CCRL1, was downregulated. CCR9 has been previously linked with inflammatory bowel disease and allergy (Koenecke & Forster, 2009) and a growing body of literature has reported a close association of CCR9 with pancreas inflammation (Cosorich, McGuire, Warren, Danta, & King, 2018; McGuire, et al., 2011). CCL25, the endogenous ligand for CCR9, is upregulated in KKAY mice fed a HFD (Lee, et al., 2009), and we have recently reported that CCL25 has a CCR9-specific inhibitory role on β-cell function in both mouse and human islets (Atanes, et al., 2020). We did not observe differences in the effects of CCL25 on insulin secretion from islets obtained from obese and lean human donors, suggesting that CCR9 upregulation in islets from high BMI donors could have been secondary to its expression by passenger immune cells rather than by islet β-cells (Atanes, et al., 2020). There are no reports of altered expression of GPR182 in obesity, and the few publications available for this orphan receptor are cancer-related (Kechele, et al., 2017; Tian, et al., 2020). CCRL1 can be activated by CCL19, CCL21, a lymphoid chemokine that is upregulated by HFD-induced obesity (Zhao, et al., 2017) and also by CCL25, the endogenous ligand for CCR9. As indicated above, the effects of CCL25 on insulin secretion are similar in islets from lean and obese donors (Atanes, et al., 2020), so downregulation of CCRL1 in obesity does not affect signalling via CCL25, but the effects of CCL19 and CCL21 on islet function of low and high BMI donors have not yet been established. The situation is complicated by the promiscuity of chemokine ligand binding to their receptors: for example, in addition to activating CCRL1, CCL19 is also a ligand for the subfamily A1 receptor CCRL2, which shows a small elevation in expression in islets from high BMI donors. If we consider adipokines targeting this subfamily of receptors, CXCL12 is well known to promote macrophage infiltration and induce insulin resistance (Kim, et al., 2014; Shin, et al., 2018). In addition, this chemokine is reported to have effects on β-cell differentiation, regeneration and survival that are mediated by its activation of CXCR4 (Vidakovic, et al., 2015). However, as with many of the other chemokines, CXCL12 can also bind to other receptors,
including CXCR3 and CXCR7. Levels of CXCL13, a fat-derived ligand that exclusively activates CXCR5, are reported to be higher in WAT from HFD-fed mice (Kusuyama, et al., 2019) and increased serum levels of CXCL1, an activator of CXCR1, have been linked to obesity, hyperglycaemia and impaired islet function (Nunemaker, et al., 2014). Many other adipokines for receptors of this subfamily are increased during obesity, including CCL20, which activates CCR6 and CXCR3 (Duffaut, et al., 2009), CXCL16 which activates CXCR6 (Kurki, Shi, Martonen, Finckenberg, & Mervaala, 2012) and CXCL5 which activates CXCR5 and DARC (Chavey, et al., 2009). All of these chemokine receptors were expressed in islets above trace levels, but no significant differences were observed between lean and obese donors. This suggests that it is alterations in concentrations of these activating ligands in plasma that may affect islet function in obesity rather than changes in expression of their target receptors.

2.3.2.3. Subfamily A3

The third subfamily includes receptors for angiotensin, apelin, bradykinin and two orphan receptors. All of these GPCR mRNAs were detectable in islets from lean and obese donors and their levels were not altered in obesity. Apelin, the endogenous ligand for APLNR, is produced and secreted by mature adipocytes (Boucher, et al., 2005), and circulating levels of apelin are increased in diabetes (Habchi, et al., 2014). Considering its established role in improving glucose uptake (Zhu, et al., 2011), its protective effect against oxidative stress and apoptosis (Wysocka, Pietraszek-Gremplewicz, & Nowak, 2018), its ability to increase insulin sensitivity and improve lipid profile in HFD mice (O’Harte, Parthasarathy, Hogg, & Flatt, 2018b), and its direct effects at β-cells to potentiate insulin release (O’Harte, et al., 2018a), APLNR is an exciting target for the treatment of obesity-related diabetes.

2.3.2.4. Subfamily A4

Receptors for neuropeptide B/W, opioids and somatostatin, and the orphan receptor GPR1, comprise the fourth subfamily of Rhodopsin receptors. Some of these were downregulated in islets from high BMI donors, including OPRM1, OPRL1, SSTR2 and SSTR5, and islet GPR1 mRNA levels were
increased in obesity. However, the only significant change was SSTR1, which showed increased expression in islets from high BMI individuals compared to lean ones. It is well-established that somatostatin (SST) inhibits insulin secretion (Strowski, Parmar, Blake, & Schaeffer, 2000) and this has been proposed as a promising strategy to treat associated hyperinsulinemia in obesity (Srivastava & Apovian, 2018). Upregulation of this SST receptor subtype in obesity may lead to increased paracrine signalling between δ-cells and β-cells to reduce insulin secretion. However, SST is also an agonist at SSTR2 and SSTR5, receptors with a downregulatory trend in islets from obese individuals so the functional consequences of obesity on SST signalling in islets from obese donors are not clear and requires further research using receptor-specific ligands.

2.3.2.5. Subfamily A5

This subfamily includes receptors that are activated by cysteinyl leukotrienes, galanin, kisspeptin, leukotriene B4 (LTB4), 5-hydroxyeicosatetraenoic acid, melanin-concentrating hormone, relaxin and urotensins. The islet GPCR mRNA profiles for members of this subfamily were largely unaffected by BMI status although the relaxin receptor RXFP4 showed increased expression in samples from high BMI donors, and RXFP1 was significantly upregulated. Relaxin, the endogenous ligand for all RXFP receptors, can reverse insulin resistance in mice on a HFD by promoting skeletal muscle glucose uptake (Bonner, et al., 2013). Circulating relaxin-2 levels are increased in prediabetic and T2D individuals and this is associated with improved β-cell function (Gao, Li, Wang, & Chen, 2018). As relaxin-2 is a selective ligand for RXFP1 and also RXFP2, which is absent in islets, it is possible that it acts at upregulated islet RXFP1 receptors to enhance β-cell function as a compensatory mechanism against the obesogenic environment.

2.3.2.6. Subfamily A6

The sixth subfamily of Rhodopsin receptors consists of members that are activated by cholecystokinin, gonadotropin releasing hormone, neuropeptide FF, orexin, pyroglutamylated
RFamide peptide, vasopressin and oxytocin, and it also contains the orphan receptors GPR22 and GPR176. Most of the endogenous ligands for receptors of this subfamily are neuropeptides and no adipokine ligands have been described. There were significantly higher mRNA levels encoding three of the receptors in islets from obese donors (QRFP, OXTR and GPR22) while another receptor, AVPR1A, showed reduced expression in obese islet samples. QRFP has two endogenous ligands, QRFP26 and QRFP43, both of which stimulate food intake and trigger obesity in mice (do Rego, Leprince, Chartrel, Vaudry, & Costentin, 2006; Moriya, et al., 2006), suggesting a role for this receptor in the development and maintenance of the obese status. In addition, QRFP26 has been reported to regulate glucose homeostasis by enhancing insulin sensitivity and increasing insulin secretion (Prevost, et al., 2015). QRFP26 is predominantly expressed by the hypothalamus, but it is also expressed by the gut, where it has been proposed to be a novel incretin (Prevost, et al., 2015; Chartrel et al., 2016), and it is also synthesised in adipose tissue where it regulates adipogenesis (Mulumba et al., 2010). Given that we have identified that QRFP is upregulated 15-fold in islets from obese donors and circulating levels of QRFP26 are significantly higher in obese individuals (Prevost, et al., 2019), this neuropeptide is an attractive candidate for regulating glycaemic control. Studies focusing on the role of oxytocin (OXT) in glucose homeostasis have shown improvements with single-dose intranasal OXT delivery to obese (Thienel, et al., 2016) and healthy (Klement, et al., 2017) individuals. Oxytocin can also promote glucose uptake and stimulate insulin secretion (Elabd & Sabry, 2015) so the upregulation of OXTR observed in islets from obese donors may be a compensatory mechanism to improve glycaemic levels, highlighting OXT analogues as promising approaches to combat glucose intolerance and diabetes. Little is known about GPR22, which was also upregulated in obese donor islets, although it has been linked to development of diabetic complications using a T1D rat model (Ruiz-Hernandez, et al., 2015). The only receptor significantly downregulated in islets from obese donors, AVPR1A, has been implicated in dysglycaemia since treatment with an antagonist can attenuate glucose intolerance in obese Zucker rats (Taveau, et al., 2015) and chronic excess of vasopressin in metabolic dysfunction can trigger further deteriorations in glucose tolerance (Ding & Magkos, 2019). However, exogenous
vasopressin (AVP) is reported to stimulate insulin secretion, effects that are blocked in a rodent β-cell line by selective antagonists of Avpr1a and Avpr1b (Mohan, Moffett, Thomas, Irwin, & Flatt, 2019). It is therefore possible that reductions in islet AVPR1A in obesity are associated with reductions in insulin secretion, although it would be expected that the more abundant AVPR1B could compensate for this decrease.

2.3.2.7. Subfamily A7

Receptors in subfamily A7 respond to a range of peptide ligands including bombesin, endothelin, ghrelin, motilin, neuromedin U, neuropeptide S, neurotensin, thyrotropin-releasing hormone and two that are designated as orphan receptors (GPR37 and GPR39) are also included. Our qPCR analysis indicated that expression levels of the majority of these receptor mRNAs in islets were not affected by obesity, with only three showing significantly higher expression (GHSR, NMUR1 and GPR39). Ghrelin, the endogenous ligand for GHSR, is an orexigenic hormone that stimulates food intake in a dose-dependent manner (Nakazato, et al., 2001) and serum ghrelin levels are generally lower in obese individuals (Makris, et al., 2017). In addition, ghrelin is an inhibitory agent in terms of insulin secretion and glucose tolerance (Tong, et al., 2010), so GSHR overexpression in islets from obese donors could enhance the detrimental effects of ghrelin on glycaemic control. Neuromedin U deletion in mice leads to development of obesity, whereas mice overexpressing neuromedin U are lean and hypophagic (Peier, et al., 2009). However, neuromedin U and a selective NMUR1 agonist can signal at β-cells via NMUR1 to suppress glucose-stimulated insulin secretion (Zhang, Sakoda, & Nakazato, 2020) so, as for GSHR, it is possible that upregulation of NMUR1 in obese donors could lead to compromised β-cell function. Although GPR39 is classified as an orphan, it has been proposed as a receptor for obestatin (Zhang, et al., 2005) and, more recently, as a zinc-sensing receptor (Hershfinkel, 2018). Maintenance of Gpr39 knockout mice on a HFD is associated with increased obesity (Petersen, et al., 2011) and also decreased serum insulin levels and hyperglycaemia (Tremblay, et al., 2009). Gpr39 deletion also has direct effects at islets, where glucose-stimulated insulin secretion is reduced
so its upregulation in islets from obese donors could be associated with improved insulin secretion. However, GPR39 agonists do not potentiate insulin secretion from mouse islets (Fjellstrom, et al., 2015), so further work is required to establish the role of islet GPR39.

2.3.2.8. Subfamily A8

The eighth subfamily includes anaphylatoxin, chemerin, formyl peptide and orphan receptors. There are several adipokines that target receptors from this subfamily. For example, the anaphylatoxin ligands C3a and C5a, which are generated by cleavage of complement components C3 and C5, are released from adipose tissue (Copenhaver, Yu, & Hoffman, 2019; Osaka, et al., 2016), and we have previously reported that both ligands act at C3AR and CSAR1 to have stimulatory effects on β-cell function by enhancing insulin secretion and protecting against apoptosis (Atanes, Ruz-Maldonado, Pingitore, et al., 2018). Annexin A1, which is a ligand for the N-formyl peptide receptors FPR1-3, is upregulated in adipose tissue in obesity and its deletion is associated with hyperglycaemia and insulin resistance (Akasheh, Pini, Pang, & Fantuzzi, 2013; Purvis, et al., 2019). Increased serum levels of annexin A1 have been reported in obese individuals (Pietrani, et al., 2018), and its action at islet FPR1-3 receptors would be expected to potentiate insulin secretion and protect islets from apoptosis (Rackham, et al., 2016). Serum levels of another adipokine, chemerin, are increased in obesity (Buechler, Feder, Haberl, & Aslanidis, 2019) and chemerin stimulates insulin secretion in mice via Cmklr1 (Takahashi, et al., 2011). CMKLR1 mRNA was undetectable in islets from obese donors so our data suggest that any increases in chemerin that occur during obesity would not be translated into increased insulin release. We found that mRNAs encoding MAS1L and MRGPRX4 were significantly upregulated in islets from obese donors. Genetic map positioning of MAS1L has highlighted it as a candidate gene for T1D susceptibility (Noble & Valdes, 2011), but there are no published reports on its role in obesity or on islet function. The physiological role of MRGPRX4 is unknown, although it has recently been identified as a novel bile acid receptor that may play a role in cholestatic pruritus and the bile acids deoxycholic acid, ursodeoxycholic acid, taurodeoxycholic acid, taurochenodeoxycholic
acid and taurocholic acid have been identified as MRGPRX4 activating ligands (Meixiong, Vasavda, Snyder & Dong, 2019). Bile acids such as tauroursodeoxycholic potentiate insulin secretion (Vettorazzi, et al., 2016) and β-cell mass (Bronczek, et al., 2019), but thus far their effects have been ascribed to activation of the GPCR TGR5 (GPBAR1) and it is not yet known if MRGPRX4 contributes to the beneficial action of bile acids in islets.

2.3.2.9. Subfamily A9

Receptors in this subfamily are activated by melatonin, neuropeptides NPY and PPY, prokineticin, prolactin-releasing peptide and tachykinin, and subfamily A9 also contains three orphan receptors (GPR50, GPR75 and GPR83). Our analysis of islets from obese donors indicated that mRNAs encoding NPY1R, PROKR2 and PRLHR were significantly increased. Neuropeptide Y (NPY) is an orexigenic peptide mainly secreted by arcuate nucleus neurons in the hypothalamus, but it is also known to be present in visceral adipose tissue (Yang, Guan, Arany, Hill, & Cao, 2008). Circulating NPY levels are elevated in obese individuals (Baranowska, Wolinska-Witort, Martynska, Chmielowska, & Baranowska-Bik, 2005) and its overexpression is known to contribute to obesity and insulin resistance in mice (Vahatalo, et al., 2015). NPY is also present in pancreatic nerves and exogenous NPY inhibits insulin release via activation of NPY1R (Morgan, et al., 1998; Pettersson, Ahrén, Lundquist, Böttcher, & Sundler, 1987). Increased NPY and islet NPY1R overexpression in obesity is therefore likely to have a detrimental impact on glucose homeostasis. Nonetheless, NPY can also activate NPYSR, which is expressed by human islets and coupled to protection against apoptosis (Franklin, et al., 2018), so receptor-specific approaches are required to better elucidate its impact within the islet environment. Prokineticin 2 is a hypothalamic neuropeptide with a clear inhibitory role in food intake (Gardiner, et al., 2010), and its plasma levels are reported to be negatively correlated to T2D and BMI (Mortreux, et al., 2019). However, no studies so far have reported on its role in islets, a source of information that will be useful to understand the physiological importance of PROKR2 upregulation in human islets in obesity. Prolactin-releasing peptide (PrRP) is the endogenous ligand for PRLHR. There is no
information on the role of PrRP in islet function, but PrRP deletion in mice is associated with adult-onset hyperphagia, obesity, insulin-resistance and impaired glucose tolerance (Takayanagi, et al., 2008). Consistent with this, Prhr/− mice demonstrated marked obesity and decreased glucose tolerance with a chow diet, similar to the phenotype of wild-type littermates fed a HFD (Gu, Geddes, Zhang, Foley, & Stricker-Krongrad, 2004), findings which highlight the importance of this ligand-receptor tandem in the regulation of energy homeostasis. Palmitoylation of the biologically active 31 amino acid peptide (PrRP31) increases its in vivo bioavailability and subcutaneous administration of this analogue resulted in reduced food intake, weight loss and improved glucose tolerance in mouse (Prazienkova, et al., 2017) and rat (Kunes, et al., 2016; Mikulaskova, et al., 2018) obese models, establishing PRLHR as an exciting target to be exploited for the treatment of obesity-related dysglycaemia.

2.3.2.10. Subfamily A10

The tenth Rhodopsin receptor subfamily consists exclusively of glycoprotein hormone receptors and three orphan receptors (LGR4-6). Of these, only TSHR mRNA was significantly affected by obesity, being downregulated 30-fold in islets from high BMI donors. Serum TSH levels are elevated in obesity (Bastemir, et al., 2007) and deletion of Tshr in mice is reported to protect against HFD-induced obesity (Ma, et al., 2015). However, islets from Tshr knockout mice have reduced glucose-stimulated insulin secretion and upregulation of pro-apoptotic markers (Yang, et al., 2019), and if the same signalling occurs in human islets the reduction in TSHR in obesity could lead to reduced functional β-cell mass.

2.3.2.11. Subfamily A11

Constituents of subfamily A11 include receptors activated by free fatty acids (FFA), hydroxycarboxylic acid (HCA), oxoglutarate, adenine nucleotides and succinate, plus two orphan receptors (GPR31 and GPR82). Based on our qPCR analysis, all HCAR receptors showed significant
upregulation in islets from high BMI subjects. HCAR1 (also known as GPR81) is solely activated by lactate, with plasma levels of this glycolysis product reported to be elevated in obese subjects (Jones, et al., 2019). Although circulating lactate is mainly produced by skeletal muscle, it has also been described as an adipose-derived product (DiGirolamo, Newby, & Lovejoy, 1992), with an ability to stimulate insulin secretion (Akiyoshi, Iwamoto, & Nakaya, 1999). These findings are consistent with studies revealing that HCAR1 activation improved systemic glucose levels in mice fed a HFD by increasing glucose uptake into BAT (Kwon, Yoo, Joung, & Jo, 2020). HCAR2 (also known as GPR109A) is activated by butyric acid, and previous studies have shown that butyric acid treatment not only increased insulin-stimulated glucose uptake and inhibited lipolysis in primary rat adipocytes (Heimann, Nyman, & Degerman, 2015), but also ameliorated the development of insulin resistance and obesity in HFD C57BL/6 mice (Gao, et al., 2009). As butyrate can also bind to FFAR2 and FFAR3, it is difficult to distinguish receptor-specific activity, but the effects of the butyrate prodrug tributyrin to improve glucose tolerance in diet-induced obese mice were not seen following Hcar2 deletion, leading to the proposal that tributyrin activation of Hcar2 could be harnessed as an obesity therapy (Sato, et al., 2020). However, HCAR2 is coupled to Goi and its activation inhibits insulin secretion, at least in a rodent cell line (Wang, et al., 2016), so its upregulation in human islets in obesity could be deleterious through reducing insulin output. The endogenous ligand of HCAR3 is 3-hydroxyoctanoic acid, a fatty acid molecule mainly produced by adipocytes, immune cells and intestinal epithelium (Offermanns, 2017). HCAR3 is known to regulate adipocyte lipolysis and immune functions under conditions of increased FFA (Offermanns, 2017), but its role in islets has not been established.

2.3.2.12. Subfamily A12

The twelfth subfamily of Rhodopsin receptors consists of additional P2RY receptors, a receptor for platelet-activating factor and three orphan receptors (GPR34, GPR87 and GPR171). We detected significantly elevated mRNA levels encoding P2RY12 and P2RY14 in islets from obese donors. P2RY12, which can be activated by ADP or ATP, has been previously identified in human islets (Lugo-
and the effects of adenine nucleotides on insulin secretion depend on the balance between stimulatory signalling via the Gαq-coupled purinergic receptors in subfamily A11 and the inhibitory Gαi-coupled receptors in this subfamily. Studies using a P2ry14 knockout mouse model have generated conflicting results. Thus, there is a report that P2ry14 deletion improves glucose tolerance and insulin sensitivity in HFD mice (Xu, et al., 2012) whereas another study has indicated that P2ry14−/− mice have significantly impaired glucose tolerance, no change in insulin sensitivity and reduced glucose-induced insulin secretion (Meister, et al., 2014). This observation of decreased insulin secretion from islets isolated from P2ry14−/− mice is unexpected given that, similar to P2YR12, it signals via Gαi. Therefore, additional information is required for better understanding of the impact of obesity-elicited P2RY14 upregulation on islet function.

2.3.2.13. Subfamily A13

Receptors for cannabinoids, lysophosphatidic acid (LPA), melanocortin and sphingosine 1-phosphate (S1P), plus the orphan receptors GPR3, GPR6 and GPR12 comprise the thirteenth subfamily of Rhodopsin receptors. Of these, six GPCRs displayed significant alterations in expression in obesity: three were upregulated in islets from high BMI donors (CNR1, MC2R and S1PR2) and three were downregulated in the same samples (S1PR3, S1PR5 and GPR6). During obesity, the endocannabinoid/CNR1 system is upregulated (Bluher, et al., 2006), and the CNR1 antagonist rimonabant was previously used as an anti-obesity drug (Bifulco, Grimaldi, Gazzerro, Pisanti, & Santoro, 2007). In line with the potential of rimonabant to reduce basal insulin hypersecretion in islets from obese rats (Getty-Kaushik, et al., 2009), studies using an analogue of this antagonist, BAR-1, have shown improved islet function in both prediabetic and diabetic mice (Nava-Molina, et al., 2020). We have demonstrated that activation of mouse islet Cnr1 increases intracellular calcium and potentiates glucose-stimulated insulin secretion (Li, Bowe, Jones, & Persaud, 2010), and stimulatory effects of CNR1 activation on insulin secretion have also been observed in isolated human islets (Li, et al., 2011). Therefore, our identification of islet CNR1 mRNA upregulation in obesity may be linked to enhanced
insulin secretion to mitigate the hyperglycaemia present in obesity. Adrenocorticotrophic hormone (ACTH) is a ligand for all five melanocortin receptors, but when plasma ACTH levels and receptor sensitivity are taken into account, it only physiologically activates MC2R (Schnabl, Westermeier, Li, & Klingenspor, 2018). MC2R activation has been linked to a lipolytic effect in adipocytes (Moller, et al., 2011) and studies using Mc2r<sup>−/−</sup> and Acth<sup>−/−</sup> mice have found that 75% of their litters die immediately after birth due to neonatal hypoglycaemia (Chida, et al., 2007). We have found that ACTH stimulates insulin secretion from mouse and human islets (Al-Majed, et al., 2004) so the nearly 40-fold increase observed for MC2R mRNA in obesity may represent a compensatory role for this receptor in islets.

The last obesity-upregulated receptor in this subfamily, S1PR2, has been associated with adipocyte hypertrophy and glucose intolerance in obesity, and its deletion in mice leads to improved metabolic profiles (Kitada, et al., 2016). The S1PR2 ligand, S1P, is elevated in plasma from obese humans and rodents (Kowalski, Carey, Selathurai, Kingwell, & Bruce, 2013), and it enhances insulin secretion (Shimizu, et al., 2000), promotes β-cell proliferation and reduces islet apoptosis (He, Shi, Zhao, & Sui, 2019). However, as S1P can also bind to nine other GPCRs, additional information using receptor-specific gene deletion or targeted antagonists are required to fully elucidate the effects of this ligand in islets. The S1PR2 antagonist JTE-013 has been successfully used to rescue β-cell damage in HFD-fed mice (Japtok, et al., 2015), suggesting that the beneficial effects of S1P in islets are not via S1PR2 activation, and these observations implicate the elevated S1PR2 mRNA levels in islets from obese donors in increased β-cell dysfunction.

In contrast to the upregulation of S1PR2, S1PR3 and S1PR5 were downregulated in islets obtained from obese donors. Hyperglycaemia can trigger S1P/S1PR3 signalling in bone-marrow-derived macrophages and the S1PR3 antagonist CAY10444 is reported to reduce hyperglycaemia-induced liver injury (Hu, et al., 2019). In addition, the S1PR1/3 antagonist VPC-23019 inhibits adipocyte proliferation and promotes adipogenic differentiation (Kitada, et al., 2016). Interestingly, this antagonist has also been used to confirm a role for S1PR1/3 in apolipoprotein M-induced insulin secretion, an action elicited by maintaining S1P levels (Kurano, et al., 2014). SP1 also activates S1PR5,
a receptor whose activation reduces age-related cognitive decline in mice (Hobson, et al., 2015). Little is known about the role of S1PR5 in obesity or islet function, but a study analysing genomic copy number variants documented deletions at the S1PR5 locus in obese children (Glessner, et al., 2010). Although some publications have suggested that SP1 can activate GPR6 (Uhlenbrock, Gassenhuber, & Kostenis, 2002), this receptor is still considered to be an orphan that is constitutively active to stimulate cAMP production via Gαs coupling (Uhlenbrock, et al., 2002). Additional studies are required to elucidate its impact on glycaemic control and whether its downregulation in islets in obesity is physiologically relevant.

2.3.2.14. Subfamily A14

The fourteenth subfamily of Rhodopsin receptors is comprised exclusively of prostanoid receptors. The most well-defined source of prostanoid ligands is the pulmonary vascular endothelium, but many reports have indicated that PGI2, PGE2 (Richelsen, 1992), PGD2 (Virtue, et al., 2015) and PGF2α (Pisani, et al., 2014) can be also produced and secreted by macrophages in adipose tissue. These ligands are highly promiscuous, with almost all of them being able to bind to other prostanoid receptor subtypes beyond their cognate receptors so a refinement of receptor-specific agonists/antagonists is necessary to elucidate their impact on glycaemic control and obesity. We found that PTGDR and PTGER2 mRNAs were upregulated in islets from obese donors and PTGER4 was significantly downregulated in the same samples. Activation of PTGDR is reported to reduce weight gain in HFD-fed mice (Kumar, Palaia, Hall, & Ragolia, 2018). In addition this receptor is expressed by islet α-cells, and the enzyme responsible for synthesis of its ligand, PGD2, inhibits glucagon secretion (Davani, Kumar, Palaia, Hall, & Ragolia, 2015). Thus, it is possible that PTGDR upregulation in islets in obesity protects against excessive glucagon secretion, which contributes to impaired glucose tolerance in obesity and diabetes. The PTGER2 antagonist AH6809 improves retinopathy in STZ-induced diabetic rats (Wang, et al., 2019), implicating the endogenous ligand for this receptor, PGE2, in the pathogenesis of diabetic retinopathy. In contrast, we have previously shown that PGE2 has direct
effects at human islets to stimulate insulin secretion (Persaud, et al., 2007), which may occur via $G\alpha_s$-coupled PTGER2, and upregulation of this receptor in obesity has the capacity to allow sufficient insulin secretion to overcome obesity-induced insulin resistance. On the other hand, it should be borne in mind that PGE$_2$ activates all four PTGER receptors and as $G\alpha_s$-coupled islet PTGER4 is downregulated in obesity the overall net effect of PGE$_2$ signalling in islets is likely to be similar to that of non-obese individuals.

2.3.2.15. Subfamily A15

This Rhodopsin subfamily includes the remaining LPA and P2RY receptors, plus proteinase-activated and orphan receptors. Of these, LPAR4, LPAR5 and F2RL2 were upregulated and F2RL3 was downregulated in islets from high BMI donors. Lpar4$^{-/-}$ mice are protected against WAT inflammation, hepatosteatosis and insulin resistance (Yanagida, et al., 2018) and selective LPAR5 antagonists have been profiled as promising pharmacological agents to block LPA-induced pro-inflammatory signalling cascades (Plastira, et al., 2019). Circulating levels of LPA, which activates LPAR1-6, are increased in HFD-fed mice (Li, Kim, & Long, 2020), and this phospholipid derivative is known to exacerbate insulin resistance and impair insulin secretion (D'Souza, Paramel, & Kienesberger, 2018; Rancoule, et al., 2014). Therefore, increased plasma LPA and the marked upregulation of LPAR4 and LPAR5 in islets in obesity would be expected to reduce insulin secretory output. Thrombin, the endogenous ligand for all proteinase-activated receptors except F2RL1, is a key component of the blood coagulation pathway. The thrombin inhibitor dabigatran reduces HFD-induced obesity development (Kopec, et al., 2017), while thrombin stimulates insulin secretion via activation of protease-activated receptor-3, the GPCR encoded by F2RL2 (Andrades, et al., 2007), which is upregulated 3-fold in islets from obese donors. In contrast to upregulation of F2RL2, the related protease-activated family member, F2RL3, was downregulated 4-fold in obesity. Deletion of F2rl3 in mice protects against HFD-induced insulin resistance and glucose intolerance (Kleeschulte, Häussinger, & Bode, 2019), similar to the phenotype
of obese mice treated with a thrombin inhibitor (Kopec, et al., 2017), implicating protease-activated receptors in induction of dysglycaemia despite the ability of thrombin to stimulate insulin secretion.

2.3.2.16 Subfamily A16

The sixteenth subfamily consists solely of opsin receptors, with OPN5 showing significantly increased expression in islets from obese donors. Little is known about this GPCR apart from its role as a photoreceptor responsive to wavelengths in the ultraviolet range (Yamashita, et al., 2010). However, a recent publication has shown that Opn5−/− mice have overactive BAT and increased thermogenesis and body temperature when cold-challenged (Zhang, et al., 2020). As it is a Gαi-coupled receptor its upregulation in obesity could result in reduced insulin secretion, but no data are yet available on whether it plays a role in β-cell function.

2.3.2.17 Subfamily A17

Subfamily A17 consists of receptors activated by ligands including serotonin, adrenergic neurotransmitters, dopamine, histamine and trace amines. Our qPCR analysis indicated that three of these, HTR2B, ADR2B and DDR4, were significantly upregulated in islets from high BMI donors. The main source of serotonin is the intestine and central nervous system, but it can also be produced by islets and adipose tissue (Berger, Gray, & Roth, 2009), and increased circulating levels of serotonin have been detected in HFD mice (Kim, et al., 2011). A recent publication using a β-cell specific Htr2b−/− mouse model has shown that this receptor is key for adequate perinatal β-cell proliferation and glycaemic control (Moon, et al., 2020). In addition, the HTR2B agonists AMS and BW723C86 have been reported to enhance glucose-stimulated insulin secretion from mouse and human islets (Bennet, et al., 2016; Nagata, et al., 2019). Therefore, the 12-fold upregulation of human islet HTR2B in obesity could allow compensatory increases in β-cell mass and insulin secretion. In addition to genetic studies demonstrating an association between the ADRB2 SNP rs1042713 and increased odds of insulin resistance (Mitra, Tan, & Amini, 2019), β2-adrenergic receptor agonists are known to improve cellular
glucose uptake and metabolism (Ziegler, Elayan, Milic, Sun, & Gharibeh, 2012), exert protective effects against the kidney and reduce cardiovascular diabetic complications (Noh, et al., 2017), and also increase insulin secretion from human islets (Lacey, et al., 1990). The increased ADRB2 expression observed in islets in obesity may therefore add to the capacity of β-cells to hypersecrete insulin in prediabetes to compensate for obesity-induced insulin resistance. Dopamine activates all dopamine receptors (DRD1-5) and many studies have investigated the impact of dopamine receptor subtype knockout in mouse models and/or the effects of DRD2 and DRD3 agonists on islet function, delineating a clear inhibitory role on insulin secretion (Ustione, Piston, & Harris, 2013). Less is known about the role of DRD4, but as it is also Gαi-coupled it would also be predicted to inhibit insulin release and its upregulation in obesity would be expected to restrict the capacity of β-cells to respond appropriately to an insulin resistant, hyperglycaemic environment.

2.3.2.18. Subfamily A18

The eighteenth subfamily consists of adenosine, histamine and muscarinic receptors, plus fourteen orphan receptors. Of these, ADORA1, GPR21, GPR52, GPR161 and GPR173 were significantly upregulated in islets from high BMI donors. Deletion of Adora1 in mice is reported to increase fat mass and impair glucose tolerance, with a HFD drastically enhancing this phenotype (Faulhaber-Walter, et al., 2011). Conversely, another study using an Adora1 knockout mouse model reported improved glucose tolerance on a chow diet but not with a HFD (Yang, Fredholm, Kieffer, & Kwok, 2012), so it is not currently clear from those studies what role adenosine A1 receptors play in whole body fuel homeostasis. Nonetheless, promising partial and selective agonists and antagonists for ADORA1 have been proposed as regulators of lipid and carbohydrate metabolism (Wojcik, Zieleniak, & Wozniak, 2010). Adenosine inhibits glucose-induced insulin secretion from rodent islets (Bertrand, Nenquin, & Henquin, 1989; Ismail, El Denshary, & Montague, 1977), most likely via Gαi-coupled ADORA1 and/or ADORA3, and the 4-fold upregulation of islet ADORA1 in obesity could lead to an adenosine-triggered reduction in insulin output. The orphan receptor GPR21 was recently proposed as an attractive
antidiabetic target, as its overexpression revealed a negative impact on insulin signalling (Leonard, Kinsella, Benetti, & Findlay, 2016) while Gpr21−/− mice have a marked improvement in glucose tolerance and insulin sensitivity, mainly attributed to the role of GPR21 in coordinating macrophage proinflammatory activity (Gardner, et al., 2012; Osborn, et al., 2012). It is therefore possible that the 5-fold upregulation of GPR21 that we detected in obesity was due to infiltration of GPR21-expressing passenger immune cells into islets, that could lead to increased islet inflammation. There is little information available about the orphan receptor GPRS2, with the main focus being on the use of selective ligands as antipsychotic agents in murine models (Hatzipantelis, Lu, Spark, Langmead, & Stewart, 2020). However, a recent study has reported a role for GPRS2 in HFD-induced fatty acid synthesis in the liver and demonstrated that Gpr52−/− mice are lean and show enhanced insulin sensitivity as a consequence of decreased hepatic de novo lipogenesis (Wada, et al., 2021). Its 3-fold upregulation in islets during obesity may also be coupled to detrimental lipid accumulation in islet cells, but no studies have yet been carried out to investigate this. GPR161, another orphan receptor, is reported to be a negative regulator for Sonic hedgehog (Shh) signalling in cilia (Tschaikner, Enzl, Torres-Quesada, Aanstad, & Stefan, 2020), but there is no information available on its role in fuel homeostasis or islet function, so it is not clear whether its upregulation in obesity would have an impact on islet viability, β-cell mass or insulin secretion. Studies in zebrafish using phoenixin (PNX), which has been proposed as a GPR173 ligand, have linked this ligand-receptor tandem to reduced food intake (Rajeswari, Blanco, & Unniappan, 2020). PNX is known to stimulate insulin secretion and β-cell proliferation (Billert, Kolodziejski, Strowski, Nowak, & Skrzypski, 2019), therefore the 5-fold increase in GPR173 mRNA in islets from obese donors and readily quantifiable circulating PNX levels in obese subjects (Hofmann, et al., 2017) suggests that GPR173 activation by PNX could improve islet functional mass in obesity.

2.3.2.19. Subfamily A19
The nineteenth Rhodopsin receptor subfamily consists of the remaining serotonin receptors not included in subfamily A17. Most of these were absent or expressed at low levels apart from HTR1F, a receptor linked to reduced α-cell cAMP production and glucagon secretion (Almaça, et al., 2016). None of the subfamily A19 receptors showed significant differences in mRNA expression when comparing islets from obese and lean donors.

2.3.2.20. Subfamily A20

The bitter-taste receptors (TAS2Rs) are similar to the Rhodopsin family of GPCRs, so for simplicity we have included these twenty-four receptors as subfamily A20. Our qPCR analysis indicated that mRNAs encoding TAS2R3 and TAS2R16 were significantly upregulated in islets from obese donors while TAS2R1 and TAS2R38 mRNAs were downregulated in the same samples. The TAS2R1 agonist KDT501 improves glucose tolerance in HFD-fed mice by enhancing GLP-1 secretion (Kok, et al., 2018) and emetine, another TAS2R1 agonist, increases ghrelin secretion in a concentration-dependent manner in fundic cultures from obese individuals (Wang, et al., 2019). Genetic variations for TAS2R38 have been detected in obese individuals (Ortega, et al., 2016) leading to a reduced bitter taste sensitivity (Pilic, et al., 2020), and the TAS2R38 agonist PTU has been identified as a stimulator of GLP-1 release (Pham, et al., 2016). However, nothing is known about these receptors in terms of islet function, making it difficult to evaluate an impact of their changes in expression in islets from obese donors.

2.3.2.21. Subfamily A21

The last subfamily of Rhodopsin receptors is formed exclusively of orphan receptors, with GPR143, GPR146 and GPR157 mRNAs showing significant upregulation in islets from high BMI donors and GPR148 showing reduced expression in the same samples. Not much is known about GPR143 except for its role in pigmentation (De Filippo, Manga, & Schiedel, 2017), but it has recently been suggested that the precursor of dopamine, levodopa, can signal via GPR143 (Goshima, Masukawa,
Kasahara, Hashimoto, & Aladeokin, 2019). GPR146 was proposed to be the elusive C-peptide receptor (Kolar, Grote, & Yosten, 2017), but questions remain about whether this ligand-receptor tandem is physiologically relevant (Lindfors, et al., 2020). Very little is known about GPR157, apart from its role in neurogenesis (Takeo, Kurabayashi, Nguyen, & Sanada, 2016), but as it is Gαq-coupled its upregulation in islets provides a route for increased insulin secretion. GPR148 is a human-specific GPCR that does not exist in the mouse genome (Amisten, et al., 2017), and there is no information on whether it has a role in obesity or diabetes. In addition, there are no reports of signalling via these receptors in islets so the potential for them playing a role in altering islet function in obesity is unknown. Furthermore, given that these receptors are classified as orphans, it is difficult to establish if the alterations observed in expression in islets from obese and lean individuals reflect alterations in circulating levels of their activating ligands.

2.3.3 Adhesion receptors

The Adhesion GPCR family consists of thirty-three members, and we have previously reviewed the expression and function of this receptor family in metabolically active tissues (Olaniru & Persaud, 2019). Islet adhesion receptors are not restricted to the adhesion GPCRs, and it is well-established that integrins and cadherins are expressed by islet cells, where they play roles in cell-cell and cell-extracellular matrix protein interactions (Olaniru & Persaud, 2018). In our current qPCR analysis, we focused on adhesion GPCRs and found that ADGRA3, ADGRC1, ADGRF1, ADGRG6 and ADGRL1 mRNAs were significantly increased in islets from high BMI donors and ADGRC3 mRNA was downregulated. Adgra3 expression is increased in subcutaneous and visceral fat pads of obese mice (Suchy, et al., 2020), consistent with our qPCR analysis in islets and as elevated ADGRA3 is linked to Wnt/β-catenin signalling inactivation (Wu, et al., 2018), its overexpression in islets in obesity may lead to β-cell dysfunction. Genetic variants of ADGRC1 have been associated with susceptibility to hypertension (Ueyama, et al., 2013) and, agreeing with our observation in islets, this receptor is also upregulated in adipose tissue from obese human donors (Suchy, et al., 2020). It has been proposed that ADGRF1 is
the receptor for the docosahexaenoic acid metabolite N-docosahexaenoylethanolamine, and that it is important in neuronal development (Lee, et al., 2016), but its role in fuel homeostasis, if any, has not yet been defined. Type IV collagen has been suggested as the activating ligand for ADGRG6 (Paavola, Sidik, Zuchero, Eckart, & Talbot, 2014), and this extracellular matrix protein is known to increase insulin secretion (Kaido, et al., 2006) and reduce islet apoptosis (Pinkse, et al., 2006), effects that are of obvious benefit in maintaining glycaemia under conditions of obesity-induced insulin resistance. Adgrl1 expression is elevated in subcutaneous fat pads of obese mice (Suchy, et al., 2020) and in visceral adipose tissue of obese human donors (Del Corno, et al., 2019), in agreement with our observed 2-fold upregulation in islets from high BMI donors. α-latrotoxin, a neurotoxin from black widow spider venom, has been proposed as a latrophilin receptor agonist in β-cells where it increases insulin secretion (Lang, Ushkaryov, Grasso, & Wollheim, 1998) and Adgrl1 increases cAMP generation in MIN6 β-cells (Rothe, et al., 2019). These results suggest a potentially protective effect of increased islet ADGRL1 expression in obesity, by stimulating insulin secretion. Adgrc3 is known to play a critical role in differentiation of endocrine progenitors into β-cells (Cortijo, Gouzi, Tissir, & Grapin-Botton, 2012), but there is no information on whether it has a functional role in mature β-cells nor whether its downregulation in obesity would be expected to have any effect on islet function.

2.3.4 Frizzled receptors

This family is classically described as frizzled receptors, but the smoothened receptor (SMO) is also included here as it shows high sequence homology with the other subfamily members. The ten FZD receptors are activated by a family of nineteen Wnt ligands with a high degree of promiscuity, so additional information and receptor-specific pharmacological strategies will be key to understanding the specific role of each receptor in glycaemic control. Several Wnt proteins are synthesised by adipocytes (Bagchi, et al., 2020) and Wnt5a shows high expression in fat depots and in the circulation (Akoumanakis, et al., 2019), and circulating Wnt3a levels are increased in a prediabetic mouse model (Kozinski, et al., 2016). Our qPCR analysis revealed that FZD4 and FZD9 were significantly upregulated
in islets from obese donors and FZD5 was downregulated. Interestingly, FZD4 gene expression is downregulated in \( \beta \)-cell-enriched pancreas samples from T2D donors (Marselli, et al., 2010), which is in contrast to our observations of its 3-fold upregulation in islets of obese donors. It is therefore possible that FZD4 mRNA overexpression in islets during obesity could facilitate increased Wnt/\( \beta \)-catenin signalling to allow compensatory \( \beta \)-cell hyperplasia during the prediabetic state, but by the time overt diabetes develops this receptor is downregulated and Wnt signalling is impaired. Not much is currently known about FZD9 apart from its role in osteoblast function via a non-canonical Wnt pathway (Albers, et al., 2011), and that it is activated by Wnt2 (Kalkman, 2012), which is not expressed by human islets (Heller, et al., 2003). The role of FZD9 in islets is therefore not clear and nor are the functional effects, if any, of its large upregulation in islets in obesity. Exposure of islets to Wnt5a, an endogenous ligand for FZD5, increases insulin secretion (Xu, et al., 2019), while knockdown of Fzd5 in MIN6 \( \beta \)-cells decreases insulin gene transcription and secretion (Zhang, et al., 2020), so reduced FZD5 in islets in obesity may be coupled to reduced insulin secretory output.

### 2.3.5 Secretin receptors

The Secretin receptor subfamily consists of fifteen receptors that are activated by a range of peptide ligands. The only mRNA that showed altered expression was that encoding PTH2R, which was significantly upregulated in islets from high BMI subjects. PTH2R is reported to be expressed at higher levels in BAT than WAT in humans (Kovanicova, et al., 2020), with a suggested role in thermoregulatory control (Tupone, Madden, & Morrison, 2014). BMI is known to be positively correlated with increased circulating PTH (Saab, et al., 2010), the ligand for PTH2R, which can induce insulin resistance by downregulating insulin receptors (Nachankar, Kotwal, Upreti, Verma, & Hari Kumar, 2018). PTH potentiates glucose-induced insulin secretion (Fadda, Akmal, Lipson, & Massry, 1990) so upregulation of islet PTH2R in islets from obese donors could provide a mechanism for increased insulin release to alleviate the PTH-induced insulin resistance.
3.0. Conclusions and perspectives

Islets of Langerhans are critically important in the appropriate maintenance of glucose homeostasis and factors that regulate the number of β-cells in islets and their ability to secrete insulin can have a major impact on blood glucose levels. It has been known for a long time that islets respond to parasympathetic input at M3 muscarinic receptors to potentiate glucose-induced insulin secretion (Gilon & Henquin, 2001) while sympathetic activation of α2 adrenoreceptors results in profound inhibition of insulin release (Persaud, Jones, & Howell, 1989). More recently, the identification that GLP-1RAs can normalise glycaemia has led to them being used to treat T2D, but the GLP-1 receptor is currently the only islet GPCR approved for T2D therapy. This is perhaps surprising given that GPCRs have been exploited to treat a wide range of diseases, including asthma, hypertension and neurodegenerative disorders (Heng, Aubel, & Fussenegger, 2013), and we have previously demonstrated that nearly 300 GPCR mRNAs are expressed by human islets (Amisten, et al., 2013). In this review we have therefore quantified obesity-induced alterations in islet GPCR mRNAs as a starting point to better understand signalling networks in human islets that may affect β-cell mass and insulin secretion in obesity.

It is known that the secretory profiles of adipose-derived ligands vary with BMI, as has been reported, for example, for TSH (Bastemir, et al., 2007), QRFP26 (Prevost, et al., 2019), NPY (Baranowska, et al., 2005) and PTH (Saab, et al., 2010), so it is possible that ligands secreted from the expanded visceral fat depots travel in the bloodstream to highly vascularised islets to up- or downregulate expression of their cognate GPCRs and in doing so modify the signalling capacity of these ligands in islets. In addition to adipokines that reach the islets via the circulation, ectopic adipose depots that accumulate in the pancreas in obesity are also known to synthesise and secrete adipokines (Gerst, et al., 2019), which may act locally to regulate islet GPCR expression and function. Another possible reason for obesity-elicited changes in islet GPCR expression could be through the presence of an increased number of passenger infiltrating immune cells, mainly islet-associated macrophages, derived from expanding adipose tissue repositories (Horii, et al., 2020). For example, analysis of
purified human islet macrophages indicate that they selectively express P2RY6 (Weitz, et al., 2020), so our identification of this purinergic receptor in islets from obese but not lean donors (Rhodopsin subfamily A11) most likely reflects macrophage accumulation in islets in obesity. Similarly, the chemokine receptor CCR9, which is known to be expressed by macrophages (Schmutz, et al., 2010), was only detected in islets obtained from obese donors. Thus, macrophage accumulation in islets in obesity has the capacity to lead to altered levels of islet GPCR mRNAs in samples from low and high BMI subjects, either due to the physical presence of an increased population of obesity-triggered islet macrophages with a different GPCR repertoire to islets or due to the release of cytokines from islet-resident macrophages, which could alter GPCR expression in islets. More complete understanding of the contribution of human islet-associated macrophages to the human islet GPCRome profiles of low and high BMI donors requires a parallel cell sorting approach in which the macrophages are purified from the islets and GPCRome qPCR analyses performed on them and also on the macrophage-free islet populations.

We have summarised possible consequences on islet function of islet GPCRs that show altered expression in an obesogenic environment, but several limitations have impeded us from presenting unambiguous verdicts:

1) the changes that we have quantified here are at the mRNA level and although it is highly likely that these changes also occur at the protein level it was not possible to establish that for the wide range of GPCRs under investigation;

2) if the observed up- and downregulation in mRNAs are confirmed at the protein level it is still not certain that altered expression will lead to changes in islet function, since this is dependent on ligand availability and overall receptor density. However, there are many examples of functional correlations between experimentally-induced GPCR overexpression or depletion that provides a basis for expecting that the altered mRNA levels that we observed would be translated into modified islet function;
3) we used whole islets for our qPCR analyses and while β-cells are the majority endocrine cell type some GPCRs will be expressed by non-β-cells, therefore further work using single cell RNA sequencing, in situ hybridisation and immunohistochemistry will be useful in delineating cellular localisation of GPCRs of interest;

4) some GPCR ligands, such as chemokines, prostanoids and Wnts, can bind to more than one receptor and some of their cognate receptors also have multiple described ligands so refined strategies to determine the effects of receptor-specific agonists and antagonists are necessary to confirm the effects of promising islet GPCRs on glycaemic control.

5) many of the GPCRs that we have quantified are still classified as orphan receptors, which means that their endogenous ligands have not been identified. This makes it difficult to establish their role in islets and determine whether alterations in levels of adipocyte-derived activating ligands play a role in the significant changes in islet mRNA levels observed for these orphan GPCRs.

In conclusion, this review adds a new layer of complexity to the already intricate repertoire of human islet GPCRs, by considering the impact of obesity on their mRNA expression levels and this is complemented by reference to published studies reporting on the roles in islets of GPCRs showing significantly altered expression. In doing so, we have identified islet GPCRs that are altered in obesity and further work is now required to fully investigate the functional effects of these receptors in human islets and whether any could be targeted therapeutically for appropriate glycaemic regulation.

Conflict of Interest statement

The authors declare that they have no conflicting interests.

Acknowledgements

We are grateful to Diabetes UK for funding our research on islet GPCRs. We are also very grateful to the families of donors for making available pancreases and to Dr. Guo Cai Huang for providing human islets for the GPCRome data that we have included in this review. Human islets were isolated at the
King’s College Hospital Islet Transplantation Unit, with appropriate ethical approval (KCL Human Islet Research Tissue Bank, IRAS project ID: 244510).
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FIGURE LEGENDS

**Figure 1**: Cross-talk between visceral adipose tissue and islet β-cells through the secretion of adipokines. Adipocytes synthesise and secrete a variety of adipokines, levels of which change following adipose tissue expansion in obesity. The well-characterised adipokines leptin and adiponectin are known to have central effects to regulate food intake and they also act at specialised non-GPCR receptors on β-cells to modify insulin output. Other adipokines, such as apelin and chemerin act at islet GPCRs to regulate insulin secretion, and it is likely that other, as yet uncharacterised, adipokines also bind to islet GPCRs to regulate functional β-cell mass. In obesity β-cells are surrounded by ectopic adipose tissue that can secrete locally produced adipokines and by accumulating macrophages that secrete cytokines, both of which may alter islet GPCR expression and activity.

**Figure 2**: The human islet GPCR mRNA repertoire and its regulation by obesity. A) Islets isolated from donors with BMI in the healthy weight range (22.5±0.9; n=4; “low BMI”) and those in the obese range (33.5±1.2; n=4; “high BMI”) were processed for RNA extraction/cDNA generation and qPCR was employed to quantify all non-odorant islet GPCR mRNAs, and the number of receptors per family are shown grouped by the GRAFS nomenclature. B) Table showing characteristics of the lean (green) and obese (pink) pancreas donors, including gender, age (years) and BMI (kg/m²). C) Mean Ct values obtained for qPCR amplification of the reference genes ACTB, GAPDH, PPIA, TBP and TFRC in human islets isolated from four lean (white bars) and four obese (grey bars) pancreas donors. D) Venn diagrams representing exclusive or overlapping patterns for expressed, trace or absent/non-quantifiable human islet GPCR mRNAs from lean (green) and obese (pink) donors. Heatmaps showing individual expression values for the 10 most upregulated (E) and downregulated (F) human islet GPCR mRNAs, with fold change ratios expressed as high/low BMI.

**Figure 3**: Comparison of human islet GPCR mRNA expression between lean and obese donors. Data are presented as mean+SEM of non-olfactory human islet GPCR mRNAs distributed using the GRAFS nomenclature in samples from low BMI (white bars) and high BMI (grey bars) donors, expressed
relative to the reference genes ACTB, GAPDH, PPIA, TBP and TFRC. Data were generated using non-
pooled islet RNA from eight donors (four lean, four obese). *p < 0.05; **p < 0.01; ***p < 0.001; ****p
< 0.0001; analysed using unpaired t-tests.
Insulin secretion
Proliferation
Apoptosis
Gene expression

Circulating adipokines

Visceral adipose tissue
Obesity-induced adipocyte hypertrophy, immune cell infiltration, inflammation, hypoxia and fibrosis

Central nervous system
Regulation of appetite and reward responses, food intake and energy balance

Pancreas

β-cell
Surrounded by intrapancreatic ectopic adipose tissue and accumulating macrophages
**A)**

BMI < 25

BMI > 30

n=4

Islets of Langerhans

Quantification of 385 non-odorant islet GPCR mRNAs

**B)**

| Donor | Gender | Age (years) | BMI (kg/m²) |
|-------|--------|-------------|-------------|
| #1    | ♂     | 41          | 20          |
| #2    | ♀     | 55          | 24          |
| #3    | ♂     | 50          | 24          |
| #4    | ♂     | 53          | 22          |
| #5    | ♀     | 47          | 36          |
| #6    | ♂     | 60          | 32          |
| #7    | ♀     | 51          | 35          |
| #8    | ♀     | 42          | 31          |

**C)**

![Graph showing Ct values for ACTB, GAPDH, PP1A, TBP, and TRFC across BMI categories](image)

**D)**

Expressed

Trace levels

Absent/Non quantifiable

**E)**

Low BMI

High BMI

Fold-change

| Gene  | Low BMI | High BMI | Fold-change |
|-------|---------|----------|-------------|
| CCR9  |         |          | 92.1        |
| MC2R  |         |          | 32.1        |
| CCR1  |         |          | 30.3        |
| GPR155|         |          | 26.5        |
| MAS1L |         |          | 23.1        |
| FZD9  |         |          | 18.9        |
| PTH2R |         |          | 13.7        |
| QRFP3 |         |          | 13.1        |
| TAS2R16|        |          | 12.5        |
| HTR2B |         |          | 10.3        |

**F)**

Low BMI

High BMI

Fold-change

| Gene  | Low BMI | High BMI | Fold-change |
|-------|---------|----------|-------------|
| OPRM1 |         |          | 0.42        |
| TAS2R1|         |          | 0.39        |
| ADGRC3|         |          | 0.39        |
| TAS2R38|        |          | 0.38        |
| NPY5R |         |          | 0.34        |
| S1PR5 |         |          | 0.27        |
| F2RL3 |         |          | 0.26        |
| HCRTR1|         |          | 0.26        |
| S1P4  |         |          | 0.23        |
| TSHR  |         |          | 0.03        |
Glutamate receptors

- CASR
- GPRC6A
- GABBR1
- GABBR2
- GRM1
- GRM2
- GRM3
- GRM4
- GRM5
- GRM6
- GRM7
- GRM8
- TAS1R1
- TAS1R2
- TAS1R3
- GPR156
- GPR158

Expression relative to ACTB, GAPDH, PPIA, TBP and TFRC

Rhodopsin receptors

Subfamily A1

- CCR1
- CCR2
- CCR3
- CCR4
- CCR5
- CCR8
- CCRL2
- CX3CR1

Expression relative to ACTB, GAPDH, PPIA, TBP and TFRC
Subfamily A2

Expression relative to ACTB, GAPDH, PPIA, TBP and TFRC

Subfamily A3

Expression relative to ACTB, GAPDH, PPIA, TBP and TFRC
Expression relative to ACTB, GAPDH, PPIA, TBP and TFRC

Subfamily A19
Frizzled receptors

Expression relative to ACTB, GAPDH, PPIA, TBP and TFRC

Secretin receptors

Expression relative to ACTB, GAPDH, PPIA, TBP and TFRC
