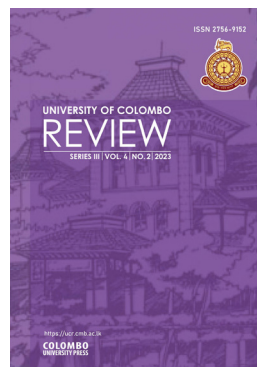


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Overview of G-protein coupled receptors (GPCRs) in adipose tissues and their regulatory roles in the pathophysiology of human diseases

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ABSTRACT

Despite the advancement of allopathic medicine, G-protein coupled receptors (GPCRs) are investigated as ideal drug targets for a range of chronic diseases including cancers, obesity, type II diabetes mellitus, non-alcoholic fatty liver, cardiovascular diseases, and neurodegeneration. During the past decades, scientists have been directly focused on the deep understanding of GPCR signaling pathways involved in the regulation of energy homeostasis and glucose metabolism which can hopefully direct towards the synthesis of novel drug compounds. Regulation of energy homeostasis is always aligned with the GPCRs associated with adipose tissues in which obesity is identified as one of the major diseases. However, evidence has not been provided on Food and Drug Administration (FDA) approved therapeutics for obesity that can directly affect the metabolism of adipose tissues yet. With the aid of these findings related to adipose tissue biology, further expansion and metabolic activation of white adipose tissues, brown adipose tissues, and beige adipose tissues will be potential target therapy for a variety of human diseases in the future. Therefore, the present review primarily focuses on the GPCRs present in adipose tissues and their regulatory roles in the pathophysiology of human diseases.


KEYWORDS:

Adipose tissues; Chronic diseases; Obesity

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Introduction

As a consequence of evolution, the new generation focused their attention on consuming instant-energy-rich foods in terms of life survival, growth, and development. Obesity and related non-communicable diseases have increased due to frequent calorie-rich diet consumption and the lack of physical activities (Barella et al., 2021). Over the last three decades, obesity prevalence has doubled among the world population, which increases the risk of cardiovascular diseases, type II diabetes mellitus, multiple cancers, non-alcoholic fatty liver disease, and neurodegeneration (Heng et al., 2013). According to previous studies, excess calorie intake cause resistance of insulin in the liver and adipose tissues, which in turn promotes adipose tissue expansion, hyperlipidemia, and liver steatosis (Suchý et al., 2020). Recent studies found that the regulation of specific signaling pathways associated with distinct tissues or cells is an ideal approach for novel drug therapy (Klepac et al., 2019). Among those approaches, GPCRs are the most comprehensively studied in contemporary medicine (Klepac et al., 2019). GPCRs are also known as seven-pass-transmembrane domain receptors, 7TM receptors, and G-protein-linked receptors that are considered as the largest group of membrane receptors mainly present in eukaryotic cell membranes. They are mainly categorized into six classes as secretin receptors, frizzled receptors, cyclic adenosine monophosphate (cAMP) receptors, rhodopsin receptors, metabotropic glutamate receptors, and fungal mating pheromone receptors depending on the functional similarity and sequence homology (Klepac et al., 2016).

In general, GPCRs are composed of a long protein chain consisting of three distinct regions: N-terminus, C-terminus, and the middle segment. N-terminus is the extracellular portion, C-terminus is the intracellular portion while the middle segment is composed with seven transmembrane domains. GPCR forms a cavity inside the plasma membrane after organizing it into a tertiary structure by assembling a barrel with transmembrane helices (Suchý et al., 2020) (Figure 1). When a ligand/drug is bound with the corresponding GPCR, it may undergo conformational changes which in turn are responsible for the activation of Guanine exchange (Sveidahl Johansen et al., 2022). After this process, GPCR can activate G-proteins associated with it via exchanging the bounded GDP (Guanosine diphosphate) for a GTP (Guanosine triphosphate). Then the alpha (α) subunit of the G-protein which is already bound with GTP can be set apart from the remaining beta (β) and gamma (γ) subunits and directly affect the intracellular signaling molecules for further signal transduction.

As past studies revealed, GPCRs are responsible for a vast range of metabolic and physiological functions such as growth and metastasis of cancer types, immune system boosting and regulation of inflammation, increment of the sense of smell, taste, visuality, and gustatory sense, mood and behavioral stimulation, insulin action, insulin secretion and glucose uptake regulation, and differentiation of different cell

types (Heng et al., 2013). The present review mainly highlights G-protein coupled receptors (GPCRs) in adipose tissues and their regulatory roles in the pathophysiology of human diseases.

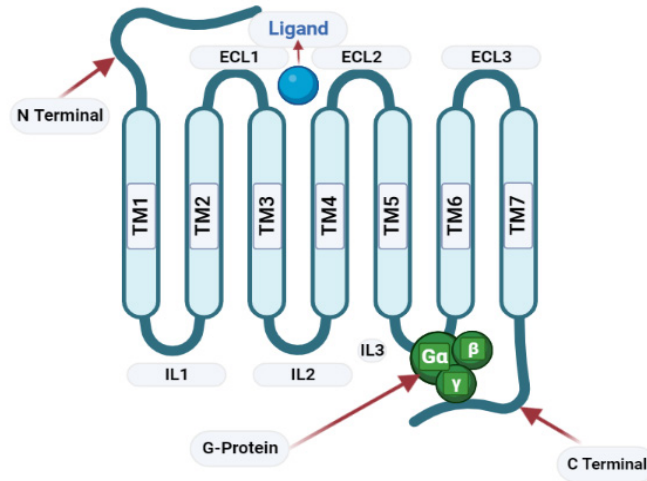


Figure 1: Schematic representation of the GPCR

Metabolic function of GPCRs associated with adipose tissues

Hypertrophy and hyperplasia are two cellular adaptations of adipocytes that can lead to the development of obesity directly (Im et al., 2021). Adipose tissues are usually composed of 90% adipocytes whereas the rest consists of a variety of stem cells, endothelial cells, fibroblasts, and immune cells (Im et al., 2021). Adipocytes are mainly categorized into three types as brown adipocytes, white adipocytes, and beige adipocytes. Among those three types, white adipocytes are responsible for the accumulation of extra energy as triacylglycerols and fats (Digby et al., 2010). Furthermore, brown adipocytes contain the highest number of mitochondria which is responsible for the expression of UCP1 (Uncoupling protein-1). Similar to the brown adipose tissues (BAT), beige adipocytes are also responsible for heat generation (Sidossis & Kajimura, 2015) (Figure 2).

According to present knowledge, existing drugs have the ability to activate beige adipocytes and brown adipocytes, which in turn impact the fat accumulation within the adipose tissues and act as the hallmark for treating different metabolic diseases like type II diabetes (Barella et al., 2021). Apart from that, GPCRs are found to regulate different kinds of adipocyte functions such as glucose handling, cytokine and adipokine secretion, thermogenesis, and lipolysis in BAT (Eisenstein & Ravid,

2014) (Figure 2). Currently, there are hundreds of identified GPCR expressions related to mouse and human adipose tissues with the aid of high-throughput sequencing analysis. GPCRs are generally classified into six classes as, class A – Rhodopsin like receptors, class B - Secretin family, class C - Metabotropic glutamate receptors, class D - Fungal mating pheromone receptors, class E - cAMP receptors, and class F – Frizzled and smoothened receptors (Hu et al., 2017). Among those identified GPCRs of both human and mouse adipose tissues, 75% are related to class A.

Beta-adrenergic receptors (β ARs) can be considered as the most widely studied type of GPCR belonging to class A that is responsible for the regulation of lipid and glucose metabolism in adipose tissues (Yu et al., 2011). Usually, mice contain all three types of β ARs (β 1ARs, β 2ARs, β 3ARs) while its β 3ARs expression level is relatively high compared to other types (Marian, 2006). When considering humans, it is the other way around. That means the β 3ARs expression level of human adipose tissues is comparatively lower than that of the other two types of β ARs (Valet et al., 2000). However, activation of β 3ARs in a healthy individual after interacting with its corresponding agonist mirabegron, leads to the increment of the rate of metabolic resting followed by the alteration of BAT activity (Klepac et al., 2016).

Recent research has demonstrated that mouse white adipocytes may internalize agonist-stimulated β 3ARs via a beta-arrestin-2-dependent pathway (Im et al., 2021). As a result, mice with a low number of beta-arrestin-2 in adipocytes showed enhanced β 3AR-induced metabolic effects. In contrast to nonbiased β 3AR agonists, biased β 3AR agonists that transfer signal through Gas and without attracting beta-arrestin-2 are hence anticipated to exhibit improved effectiveness in a clinical scenario (Im et al., 2021). In addition to that, ATP is produced from sympathetic nerve terminals as a co-transmitter together with NE and is quickly converted to adenosine which has an effect on adenosine receptors A1, A2A, A2B, and A3 separately (Valet et al., 2000). Gi-coupled A1 receptors are primarily responsible for adenosine signaling in White adipose tissues (WAT), but Gs-coupled receptors: A2A and A2B are crucial for brown fat activity (Jamwal et al., 2019). In mouse white adipocytes, activation of A1 receptors suppresses cAMP, lowers PKA (protein kinase A) activity, prevents lipolysis, and also contributes to leptin synthesis, adipogenesis, and lipogenesis (Qiao et al., 2011). Apart from that, A2A and A2B receptor activation increases lipolysis (cAMP-mediated) in murine and human adipocytes, in contrast to A1 receptor stimulation. Either receptor A2A or A2B associated agonist activation in mice enhances being in WAT and energy expenditure as well. Despite everything, if A2A or A2B receptors in the BAT were genetically deleted, it will render the BAT inoperable and decrease oxygen uptake throughout the body (Im et al., 2021). Most significantly, A2A or A2B receptor activation in HFD (high fat diet) mice resulted in body weight reduction, body glucose tolerance enhancement, and protection against diet-induced obesity in mice. Gs-linked glucagon receptors (GCGRs) are

activated by glucagon in white adipocytes, which results in a rise in the stimulation of hormone-sensitive lipase-mediated lipolysis (HSL-mediated), intracellular cAMP and an increase in oxygen utilization (Barella et al., 2021; Zhao et al., 2020). The expression of body temperature, thermogenic genes, body fat consumption, FFA, and plasma glycerol levels rise in mice when glucagon is present (Beaudry et al., 2019). Thermogenesis in BAT mediated by β 3AR is induced by central glucagon administration and is impaired by pro-glucagon gene deletion. Therefore, it is expected that glucagon will affect adipose tissue through a combination of direct and indirect actions (Townsend et al., 2019).

Additionally, adhesion GPCR expression by adipocytes has received attention recently, even though the GPCRs class is distinguished by an abnormally wide region of extracellular N-terminal domain (Suchý et al., 2020). There is a kind of Gs-coupled adhesion GPCR in white adipocytes of mice known as GPR64 that is abundantly expressed and are in charge of raising the level of intracellular cAMP, which in turn increases lipolysis. Apart from that, this receptor is involved in mouse adipocyte maturation and adiponectin secretion inhibition after the stimulation. Despite the knowledge of receptor functions in body glucose plus energy metabolism, this would undoubtedly considerably improve by the development and study of GPR64 knockout in mice that are specifically adipocyte-specific (Suchý et al., 2020; Barella et al., 2021). The endocannabinoid systems, both peripheral and central, are crucial to energy metabolism, including adipocyte activity (Rossi et al., 2018; Sidibeh et al., 2017). In both mouse and human WAT, Cannabinoid receptor 1 (CB1) activation caused down-regulation of the expression of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1- α), which in turn degrades mitochondrial performance, and boosts lipogenesis (Tedesco et al., 2010; Tedesco et al., 2008; Silvestri & di Marzo, 2013). It is a well-known fact that adipocytes lack CB1 receptors affected for the increment of activated macrophage abundance (De Azua et al., 2017; Murphy & Foll, 2020). Correspondingly, CB1 receptor blockade resulted in the elevation of beta-oxidation, lipolysis, and energy expenditure as well (Bajzer et al., 2011). With the aid of these investigations, it is hypothesized that CB1 antagonists are potent candidates for the treatment of a range of metabolic diseases including type II diabetes, obesity, cardiovascular diseases, etc.

Also, Gi-link receptors associated with adipocytes including hydroxycarboxylic-acid receptors (HCA) influenced the down-regulation of the lipolysis process (Offermanns, 2014; Singh et al., 2014). These HCA receptors are mainly composed of three segments as HCA1, HCA2, and HCA3 which are also named as GPR81, GPR109A, and GPR109B respectively (Blad et al., 2011). Among these three HCA receptor types, HCA1 is identified as the predominant one expressed within the adipose tissues while HCA2 along with the HCA3 are located within the peripheral tissues. During the adipocyte differentiation, the expression

level of both HCA1, HCA2 receptors are rising while HFD consumption involves the reduction of its expression level in advance (Offermanns, 2017). Regardless, long-term use of HCA2 agonists like nicotinic acids are unable to help type II diabetes patients maintain euglycemia situations (Tunaru et al., 2003; Shen & Colletti, 2009). Furthermore, the extracellular succinate has an effect by signalling with the help of the Sucnr1/GPR91 succinate receptor, as demonstrated by the significantly higher levels of succinate circulation in both humans and rodents with obesity. (Ariza et al., 2012). Specially in rodent WAT, GPR91 receptor expression is relatively high. In addition to that, McCreath et al. (2015) reveal that GPR91 receptor shortage affects the increment of lipolysis and are involved in the activation of protection against diet-induced obesity.

Further, FFA receptor series (FFA1- FFA4) are also engaged in many of these properties and functions as well. Amidst these four FFA receptors, FFA2 and FFA4 receptors are highly expressed in adipocytes while FFA2 is regulated with the aid of short-chain FFA and after interacting with Gq and Gi type G proteins (McCreath et al., 2015; Keiran et al., 2019). This receptor controls the synthesis of adipokines and lipolysis inhibition as well. In addition to that, lean phenotypes can be observed as a result of FFA2 overexpression of rodent adipose tissues, and the favorable metabolic phenotype demonstrated by this mouse strain was lost when the animals were given antibiotic therapy or kept in a germ-free, sterile environment (McCreath et al., 2015; Keiran et al., 2019). FFA-2 agonist activation is also responsible for the diminishment of insulin signaling and fat accumulation deduction within adipose tissues (Keiran et al., 2019).

Numerous saturated long-chain fatty acids produced during lipolysis activate the FFA4. Generally, GPR120 or FFA4 is a type of Gq coupled receptor encountered for significant roles in metabolic activities upon activation. Most interestingly, its expression level is enhanced following HFD feeding (Ulven, 2012). Some studies reveal that GPR120 activation leads to the induction of WAT browning and in the enhancement of BAT thermogenesis followed by FGF21 secretion (Quesada-López et al., 2016). In mammalian cells like 3T3 cells, GPR120 shortage is responsible for the reduction of GLUT4 protein levels, lipid accumulation, and adipocyte differentiation (Quesada-López et al., 2016). Some studies conclude that PPARc activation via thiazolidinediones (TDZ) affect the increment of GPR120 expression in WAT as well (Paschoal et al., 2020). Furthermore, scientists have shown that activating PPARc receptors in adipocytes and stimulating GPR120 receptors in macrophages increases insulin sensitivity in rodents, indicating that using a GPR120 agonist in combination with a TDZ medication may be a potential strategy for treating type II diabetes (Paschoal et al., 2020). Finding agonists and antagonists that can specifically target a GPCR in a metabolic tissue while avoiding side effects on other remaining tissues will be the main hurdle in the development of viable therapeutic

GPCR-based medicines (Paschoal et al., 2020). Anyway, a deeper knowledge of the metabolic roles played by GPCRs is essential as it may result in the creation of brand-new medications for treating cancers and diverse metabolic diseases including type II diabetes, nonalcoholic steatohepatitis and nonalcoholic fatty liver disease in the future.

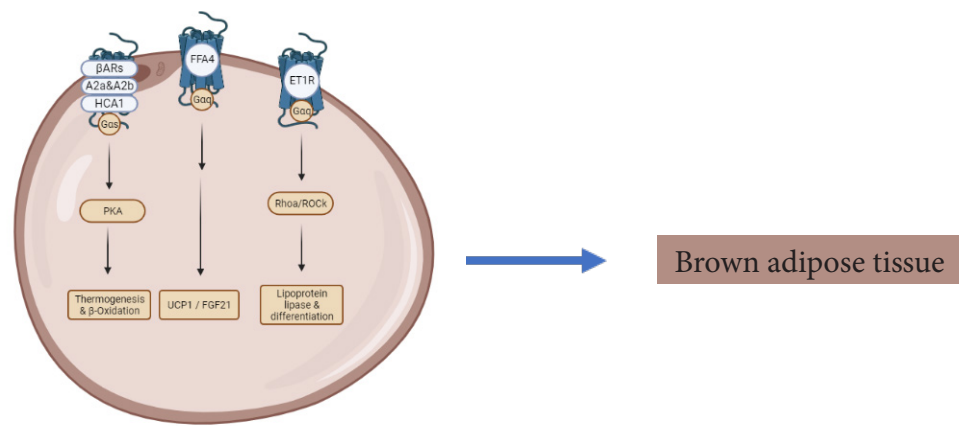


Figure 2: GPCRs are founded to be regulate different kinds of adipocyte functions such as glucose handling, cytokine and adipokine secretion, thermogenesis and lipolysis in BAT

Table 1: Common GPCRs related with adipocytes and their metabolic functions

Receptor name	Transduction mechanism	Function	References
FFAR-2 (Free fatty acid receptor 2)	Gi and Gq	Lipolysis inhibition in WAT	(Paschoal et al., 2020; Oh et al., 2014)
FFAR4 / GPR120 (Free fatty acid receptor 4)	Gq	Increment of adipogenesis, glucose uptake, and beiging in WAT, thermogenesis enhancement in BAT	(Paschoal et al., 2020; Oh et al., 2014)
β 3AR (β 3-adrenoceptor)	G α_s	Enhancing beiging, lipolysis and mitochondrial respiration in WAT, thermogenesis enhancement of BAT	(Valet et al., 2000; Marian, 2006; Yu et al., 2011)
A1 (Adenosine A1 receptor)	G α_i	Increase lipogenesis and decrease lipolysis in WAT	(Eisenstein & Ravid, 2014)

A2A and A2B (Adenosine A2A & A2B receptors)	G α s	Increase lipolysis and beiging in WAT, mitochondrial respiration enhancement in BAT	(Eisenstein & Ravid, 2014; Jamwal et al., 2019)
HCA1 / GPR81 (Hydroxycarboxylic acid receptor 1)	G α s	Lipolysis enhancement in WAT, enhancement of thermogenesis in BAT	(Ge et al., 2008)
ET1R	G α q	Brown adipocyte differentiation inhibition	(Barella et al., 2021; Sidossis & Kajimura, 2015)
LPA4 (Lysophosphatidic acid receptor 4)	G12 / 13	Reduction of the expression of mitochondrial marker genes, adiponectin and adipogenesis in WAT	(Qiao et al., 2011)
GCGR (Glucagon receptor)	G α s	Increase oxygen consumption and HSL-mediated lipolysis in WAT	(Barella et al., 2021; Klepac et al., 2016)
GPR64 (G-protein coupled receptor 64)	G α s	Inhibits the secretion of adiponectin and lipolysis enhancement in WAT	(Townsend et al., 2019)
CB1 (Cannabinoid receptor 1)	G α i	Lipogenesis enhancement and mitochondrial function impairment in WAT	(Rossi et al., 2018; Sidibeh et al., 2017; Tedesco et al., 2008, 2010)
HCA2 / GPR109A (Hydroxycarboxylic acid receptor 2)	G α i	Lipolysis inhibition in WAT	(Ge et al., 2008)
Sucnr1/GPR91 (Succinate receptor)		Lipolysis enhancement in WAT	(Barella et al., 2021)

Role of GPCRs in cancers

Cancer continues to be a leading cause of morbidity and death despite decades of scientific and clinical research as well as trials of promising new treatments. Nevertheless, the most common observations associated with the disease includes an aberrant apoptotic process with abnormal cell proliferation (Matthews et al., 2022). Numerous GPCRs with various roles have been connected to the pathophysiology of cancer and are now being researched as possible targets for pharmacological therapies (Heng et al., 2013; Lappano & Maggiolini, 2011). Depending on the implication of cancer pathogenesis, GPCRs can be designated into groups according to their function, involvement in abnormal cell growth and proliferation, differentiation

pathways, cell fate modulation, metastasis, control mechanisms, angiogenesis, and normal apoptotic pathway alterations (Lappano & Maggiolini, 2011).

Generally, cancer cells constitutively overexpressed corresponding GPCRs of different potent mitogens including lysophosphatidic-acid receptors (LCA), prostaglandin receptors, protease-activated receptors (PARs), sphingosine-1-phosphate receptors plus a wide array of neuropeptide receptors like endothelin, gastrin-releasing peptide, bradykinin, cholecystokinin, angiotensin II and neuromedin B receptors (Murakami & Yamamoto, 2010; Roosenburg et al., 2011; Figueroa et al., 2012; Rosenthal & Gavras, 2009). In addition to cell proliferation, some GPCRs have various pleiotropic effects on the development of cancer, including metastasis, apoptosis suppression, and angiogenesis (Bagnato et al., 2011). When a GPCR signaling route is activated, it can sometimes drive the synthesis and secretion of its corresponding ligand, which amplifies the signaling pathway further with the aid of a paracrine or autocrine loop (Mills & Moolenaar, 2003).

Apart from straight provoke of cell development and proliferation via signaling GPCRs, multilayered cross-talk linking with GPCRs and non-GPCRs may lead to abnormal cancer cell proliferation (Bhola & Grandis, 2008). Perhaps the most well-known examples of how GPCRs interact with tyrosine kinase receptors, such as insulin receptors (InsR), EGFR (epidermal growth factor receptor) and IGF1R (insulin-like growth factor-1 receptor), are in the development of various cancers. (Kisfalvi et al., 2007; Rozengurt et al., 2010). Through the provocation of thrombin activity followed by the stimulation of EGFR signaling, it drives the growth of breast cancer. Moreover, ovarian and breast cancer cells induce their proliferation as a result of interacting EGFR signaling with ETAR (Endothelin-A subtype receptor) (Arora et al., 2008; Mills & Moolenaar, 2003). On the other hand, pancreatic malignant cells are prevented from growing and proliferating when the anti-diabetic medication metformin interferes with the regulatory cross-talk among GPCR signaling and InsR/IGF1R receptors (Kisfalvi et al., 2007).

Nevertheless, enhancement of angiogenesis and vascularization within malignant tissues are the only ways to supply the nutrition and oxygen that cancer cells frequently need for their growth, and some GPCRs are identified as the regulators for these two mechanisms which are significant in cancer-related therapies (Richard et al., 2001). It is particularly intriguing for therapeutic reasons when cancer cells manipulate chemokine networks with their associated GPCRs to promote the migration and penetration of endothelial cells into malignant tissues (Strieter et al., 2004). These chemokines either directly affect stromal components and endothelial cells, or they function indirectly by causing immune cells and stromal cells to produce additional pro-angiogenesis mediators like vascular endothelial growth-factor (VEGF) (Strieter et al., 2006).

Prostaglandin-E2 receptor, sphingosine-1-phosphate receptor (S1PR1) and protease activate receptors are other GPCR systems that regulate vasculogenesis and angiogenesis throughout the progression of cancer (Tsopanoglou & Maragoudakis, 2004). Pro-angiogenic chemokines like CCL5 and IL-8 are produced and secreted in greater quantities as a result of the interaction between prostaglandin-E2 and its corresponding GPCR, EP2 (Tsopanoglou & Maragoudakis, 2004; Pöld et al., 2004). Upon the activation by its specific ligand, sphingosine-1-phosphate, S1PR1 receptor which is widely expressed in endothelial cells, promotes the generation and secretion of VEGF. This secreted VEGF has the ability to induce sphingosine-1-kinase translocation towards the plasma membrane, which in turn affects the activation of S1PR1 followed by sphingosine-1-phosphate accumulation (Hla, 2003). It is a well-known fact that GPCRs that are involved in the control of cell fate along with differentiation pathways play a significant part in the pathophysiology of cancer (Rozengurt et al., 2010). According to current knowledge, the body's matured stem cells can become aberrant and give rise to cancer (Katoh & Katoh, 2007). As evidenced by the overexpression of Wnt receptors with corresponding ligands in malignant tissues, several cancer forms are linked to excessive Wnt/catenin signaling (Katoh & Katoh, 2007). For instance, smoothened receptor (SMO), a major GPCR implicated in Hedgehog signaling, is inhibited by the 12-transmembrane receptor patch upon the attachment of a range of hedgehog proteins like sonic hedgehog (SHH) with PCTH and this stimulates the initiation of SMO-receptor signaling at the end (Ayers & Thérond, 2010). This occurrence initiates the oncogenesis process upon the activation of transcription factor, glioma-associated oncogene homologue (Gli) (Ayers & Thérond, 2010; Kasper et al., 2006).

Nevertheless, one of the most promising therapeutic drugs, Cyclopamine, is now undergoing phase I clinical trials along with its analog receptor IPI-926 and it is thought that both compounds block the SMO receptor after interacting with associated hepta-helical bundle (Gould & Missailidis, 2011). On the other hand, cancer cells move through the process of metastasis from the primary tumor location in one tissue or organ to a secondary location and make the use of a chemokine network with related GPCRs to promote metastasis, just like angiogenesis does (Ali & Lazennec, 2007). However, the majority of malignant cells express CXCR4 receptors aberrantly and translocate with regard to SDF1 which are released by tissues or organs including lungs, bone marrow, lymph nodes, liver, etc. (Ali & Lazennec, 2007; Gelmini S et al., 2008). It is well accepted that CXCR4 overexpression in cancer cells is an indicator for identifying metastatic enhancement (Cao & Prescott, 2002). GPCRs can aid metastasis in addition to directly influencing chemotaxis and migration by degrading the extracellular matrix, as is the case with the EP2 receptor. In the majority of solid tumors, activation of EP2 receptor signaling with the aid of prostaglandin-E2 promotes the production and secretion of metalloproteinase

enzymes, thereby provoking the cancer cell infiltration and translocation from primary sites to the secondary sites (Cao & Prescott, 2002). Apart from that, the resistance of cancer cells to apoptosis is another distinctive trait where the apoptotic pathway mediated by p53 is much more significant as half of existing tumors are composed of its inactivating mutations. Anyway, a wide array of cancer types, including those without p53 mutations, have abnormal GPCR signaling, which alters the p53-associated pathways (Haupt & Haupt, 2016). For instance, cellular levels and nuclear location of p53 are decreased when the signaling of lysophosphatidic-acid receptor is activated and it suppresses apoptosis in lung cancer cells (Murph et al., 2007). GPCR87 is another instance, which is crucial for p53-dependent cell survival with regard to genotoxic stress (Zhang et al., 2009). Depending on the stimulus and cell lineage, the same GPCR may occasionally mediate either anti-apoptotic or pro-apoptotic actions in occasions where GPCRs connected to the NF-B pathway including adenosine A3, endothelin ET1, and angiotensin II receptors. (Fraser, 2008).

Role of GPCRs in human metabolic diseases

GPCRs associated with obesity

The incidence of obesity and closely related metabolic illnesses, such as hypertension, type II diabetes, and cardiovascular diseases has been gradually rising nowadays due to dietary and lifestyle variables (Nair & Ren, 2009). There are some identified GPCRs associated with adipocytes which are ideal targets in treating obesity and associated metabolic illnesses (Barella et al., 2021; Sveidahl Johansen et al., 2022). There is rising evidence that neuropeptide ligands of GPCRs that control hunger may play a significant role in the pathophysiology of obesity, even though the underlying physiology of obesity is incredibly complicated and multifaceted (Sidossis & Kajimura, 2015).

Melanin-concentrating hormone system, Ghrelin system, orexins/hypocretins system, melanocortin system, and the neuropeptide A/B system are five major neuropeptide-GPCR systems that are especially intriguing (De Ambrogi et al., 2003). An amino-acid peptide called ghrelin links the central and peripheral neural systems to regulate energy balance. The growth hormone secretagogue (GSH) receptor, which is its corresponding GPCR, is mostly expressed in the hypothalamus and somatroph of the pituitary gland (De Ambrogi et al., 2003). It is primarily synthesized in the stomach. Experiments related to both animal and human models have shown that continuous fasting and food restriction raise ghrelin secretion levels, whereas eating increases circulating ghrelin levels (Cummings et al., 2001). Ghrelin agonists have been demonstrated to enhance appetite and elicit a feeling of hunger in human subjects (Laferrère et al., 2006). It is shown that, appetite enhancement of human subjects and hunger sensation stimulation occur upon the activation of GSH receptor with the aid

of a ghrelin agonist (Laferrère et al., 2006). Previous experiments done using rodents revealed that persistent administration of ghrelin along with its corresponding agonist leads to the elevation of weight gain as a result of the over-consumption of foods (Palus et al., 2011). In contrast, injection of [D-Lys-3]-GHRP-6, a ghrelin receptor antagonist, caused a fast decrease in fat mass and body mass as a result of reduced food consumption (Maletínská et al., 2011).

For instance, the Melanin-concentrating hormone (MCH) is composed of corresponding MCH-1 and MCH-2 receptors which in turn are capable of regulating energy homeostasis after food consumption (Saito & Nagasaki, 2008). Previous in-vivo experiments concluded that chronic MCH administration was responsible for fat mass and rapid weight elevations at once while MCH-receptor antagonists administration led to the opposite result (Shearman et al., 2003). Among all the existing treatment methods for obesity, the MCH system was considered as the most promising target (Shearman et al., 2003). The expression of MC3R and MC4R receptors are very strong in brain areas related to eating behavior and food intake, just like MCH and ghrelin. Both MC3R and MC4R can be activated by one of three main neuropeptide ligands agouti-related protein (AgRP), neuropeptide Y and α -melanocyte stimulating hormone (α -MSH) (Mountjoy, 2010; Xu et al., 2011).

In addition to that, prepro-orexin, a precursor peptide cleaves to create two neuropeptides named orexin A (hypocretin-1) and orexin B (hypocretin-2) to form orexin (hypocretin) system. Nevertheless, orexin system is identified as the best treatment method with regulatory feedback with regards to obesity out of MCH, ghrelin and melanocortin systems (Willie et al., 2001). As suggested by its name, the neuropeptide-B/neuropeptide-W (NPB/NPW) system consists of two different neuropeptides and GPR7, GPR8 are their corresponding receptors (Hondo et al., 2008). Both of these neuropeptides have the ability to bind with their corresponding receptor well where NPB is found as the one with a higher affinity for binding with GPR7 while NPW has the highest affinity for GPR8 (Brezillon et al., 2003). Disparate MCH and ghrelin, these neuropeptides minimize food uptake, boost metabolism and enhance energy expenditure followed by chronic administration (Aikawa et al., 2008). Apart from the NPB/NPW system, TGR5 – bile acid receptor also can be considered as a GPCR target, ideal for obesity treatments (Chen et al., 2011). Apart from the aforementioned neuropeptides, TGR5 owed a different mechanism for the regulation of energy homeostasis. TGR5 receptor activation causes an increase in cAMP levels in brown adipose tissues and skeletal muscles, which then triggers the D2 enzyme (type 2 iodothyronine deionase) (Watanabe et al., 2006). This D2 enzyme involves in the formation of active thyroid hormone using inactive thyroxine to elevate heat generation and energy depletion via mitochondrial activity (Watanabe et al., 2006).

GPCRs associated with type II diabetes

Type II diabetes is a global health issue related to the group of metabolic disorders which arises as a result of the disfunctioning of β -cells, aberrant glucose homeostasis, and insulin resistance (Barella et al., 2021). The onset of this disorder is accountable for a wide range of secondary complications including cardiovascular diseases, kidney failures, and retinopathy. Compared to the rest of the non-infectious diseases, type II diabetes is a considerable reason for high morbidity and mortality worldwide (Lam & LeRoith, 2012). Many GPCRs linked to pancreatic function and glucose homeostasis have recently been linked to the pathophysiology of this illness in an effort to identify potential therapeutic targets. (Heng et al., 2013). These GPCRs associated with type II diabetes can be categorized into five groups as neurotransmitter receptors, somatostatin receptors, glucagon receptors, free fatty acid binding GPCRs, incretin receptors, and pancreatic islet-associated GPCRs (B. Holst et al., 2009; J. J. Holst et al., 2009). Among these receptors, incretin is a type of gastrointestinal peptide secreted from islet β -cells prior to the glucose level elevation and after the intake of food (B. Holst et al., 2009; J. J. Holst et al., 2009). Still there are only two well-known incretin types that can be considered as GPCR ligands like GLP-1 (Glucan like peptide-1) present in pancreatic β -cells and GIP (Glucose-dependent insulintropic polypeptide) expressed in the pancreas (Tornehave et al., 2008).

Increment of the secretion of insulin enzyme and inhibition of the secretion of glucagon occurs as a result of GLP-1 receptor activation. In addition to that, it can inhibit apoptosis and elevate the β -cell proliferation as well (Tornehave et al., 2008; Scott Heller et al., 1997). There is a range of GLP-1-derived synthetic compounds available to treat type II diabetic patients (Montanya, 2012). When GIP receptors bind with their respective ligand, they inhibit the apoptosis of β -cells and elevate the secretion of insulin and glucagon (Widenmaier et al., 2010). Upon interaction with respective GPCRs, free fatty acids (FFA) which are released as a byproduct of bacterial fermentation which occurs inside the colon, play the role of signaling molecules in advance (Fujimoto et al., 1978). FFA-GPCRs interaction is able to maintain glucose homeostasis inside the human body and GPR40, GPR41, GPR43, GPR119, and GPR120 are such types of GPCRs interact with FFA (Rayasam et al., 2007).

FFA is responsible for the stimulation of glucose and glucagon secretion (Ferry et al., 1992). In adipose tissues, GPR43 is most abundant compared to the other types of GPCRs. The β 2-adrenergic receptor is the corresponding GPCR for norepinephrine (Liggett et al., 2000). There are three corresponding GPCR subtypes for galanin as GAL1, GAL2, GAL3, and neuropeptide Y has five corresponding GPCR subtypes as Y1, Y2, Y3, Y4, Y5 (Branchek et al., 2000; Chambers & Woods, 2012). All these neurotransmitters promote glucagon secretion while inhibiting

insulin release induced by glucose. CGRP (Calcitonin gene-related peptide), is known as the main type of neurotransmitter that exists in the sensory nerves that suppresses glucose-stimulated insulin production by interacting with its corresponding GPCR (Bretherton-Watt et al., 1992).

The liver and kidneys are the primary sites of glucagon receptor expression and are essential for maintaining glucose homeostasis. After the activation of glucagon, it enhances the circulation level of blood glucose by translating liver glucagon to glucose (Qureshi et al., 2004). The abnormal activation of the glucagon receptor, which raises circulating glucagon and consequently glucose levels, is frequently linked to type II diabetes and small compounds/monoclonal antibodies that inhibit glucagon receptor function have shown promising outcomes in the treatment of type II diabetes (Gu et al., 2009). Other types of GPCRs expressed in the islets like vasopressin receptors, GPR54 and purinergic receptors are involved in the maintenance of glucose homeostasis via regulating glucagon or insulin secretion (Hauge-Evans et al., 2006). Upon the stimulation of GPR54 receptor by its corresponding ligand, kisspeptin, it regulates the secretion of glucose-stimulated insulin. Although there is some empirical evidence to prove the role of glucose homeostasis within the islets, there is limited knowledge of GPCRs for its expression within islets (Hauge-Evans et al., 2006).

GPCRs associated with cardiovascular diseases

Cardiovascular diseases can be considered as closely related to obesity, which is highly prevalent among younger and older generations living in developed countries (Després, 2012). Activation of different GPCR signaling pathways represents the pathophysiology of heart malfunctioning and diseases where acute activation might be beneficial for short-term diseased hearts while chronic activation benefits long-term cardiac function deterioration (Tang & Insel, 2003).

As investigations reveal, cardiac cells expressed about 200 known GPCRs like fibroblasts, cardiomyocytes and endothelial cells (Tang & Insel, 2003). Among these investigated GPCRs, a very small amount of GPCRs are well known for ideal drug target capacity for cardiac treatments and enriched with well-characterized capabilities in the heart disease-associated pathophysiology. This well-characterized portion of GPCRs includes endothelin (Anand et al., 2004), adenosine (Ely & Berne, 1992), angiotensin (Cohn & Tognoni, 2001) and adrenergic receptors (Woo & Xiao, 2012). Amidst these receptors, Angiotensin II is compromised with its cognate GPCR (AT1R) which is considered as the ideal drug target for a variety of cardiac treatments (Meggs et al., 1993). Angiotensin receptor is well characterized as an antagonist in ACE (Angiotensin-converting enzyme) inhibition which in turn is responsible for the reduction of reverse cardiac remodeling and hypertrophy and delays the heart failure progression in myocardial infarction (Pitt et al., 1999).

In addition, endothelin-1 receptor activation with the aid of endothelin ligand leads to the promotion of diseased heart remodeling and hypertrophy (Anand et al., 2004; Asano et al., 2002). Cardiac tissues are mainly composed of three α -adrenergic sub-receptors as $\alpha 1A$, $\alpha 1B$, $\alpha 1D$ and three β -adrenergic receptors as $\beta 1$, $\beta 2$, $\beta 3$. All of these receptors are involved in transferring chemical signals to a cardiac response from the sympathetic nervous system (Woo & Xiao, 2012). When heart failure has occurred, the expression of α -adrenergic receptors is enhanced which in turn modulates the contractile, blood pressure and hypertrophic responses. Among all three β -adrenergic sub-receptors, $\beta 1$ receptor is nominated as the most highly expressed one in healthy hearts and it is responsible for the regulation of contractility and heartbeat rate (Perez & Doze, 2011; Woo & Xiao, 2012). $\beta 2$ -adrenergic receptors are involved in heart contractility, glycogenesis and smooth muscle relaxation in advance. Cardiac tissues have a very a smaller number of $\beta 3$ -adrenergic receptors and they are well characterized in playing thermogenesis and lipolysis roles (Tilley & Rockman, 2006). Adenosine receptors owe a cardioprotective propensity and they can stimulate coronary vasodilation upon myocardial ischemia (McIntosh & Lasley, 2012). According to previous studies, the enhancement of the function of the left ventricle and minimizing of the size of the infarct can happen as a result of adenosine receptor activation via straight adenosine administration in the time of reperfusion following myocardial infarction (Babbitt et al., 1989; Ely & Berne, 1992).

Conclusion

Overall, this article suggests that GPCRs are potential therapeutic targets for a variety of chronic illnesses, such as cancer, obesity, type II diabetes, non-alcoholic fatty liver disease, cardiovascular disease, neurodegeneration, etc. Finding agonists and/or antagonists that specifically target a GPCR in tissues while avoiding side effects on other tissues will be the main challenge in the development of effective therapeutic GPCR-based drugs. Confirming that the mouse-identified GPCR signaling networks are also active in humans is a crucial issue. Therefore, the creation of novel drugs for the treatment of different metabolic disorders, such as T2D, NAFLD, and NASH, as well as numerous other illnesses like cancers, may result from a deeper knowledge of the metabolic roles played by GPCRs in the future.

Conflict of interest

The authors have no conflict of interest to declare.

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