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THEMED ISSUE REVIEW

G protein-coupled receptor-mediated autophagy in health and disease

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G protein-coupled receptors (GPCRs) constitute the largest and most diverse superfamily of mammalian transmembrane proteins. These receptors are involved in a wide range of physiological functions and are targets for more than a third of available drugs in the market. Autophagy is a cellular process involved in degrading damaged proteins and organelles and in recycling cellular components. Deficiencies in autophagy are involved in a variety of pathological conditions. Both GPCRs and autophagy are essential in preserving homeostasis and cell survival. There is emerging evidence suggesting that GPCRs are direct regulators of autophagy. Additionally, autophagic machinery is involved in the regulation of GPCR signalling. The interplay between GPCR and autophagic signalling mechanisms significantly impacts on health and disease; however, there is still an incomplete understanding of the underlying mechanisms and therapeutic implications in different tissues and disease contexts. This review aims to discuss the interactions between GPCR and autophagy signalling. Studies on muscarinic receptors, beta-adrenoceptors, taste receptors, purinergic receptors and adhesion GPCRs are summarized, in relation to autophagy.

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1 | INTRODUCTION

Cells rely on homeostatic mechanisms which require a timely response to extracellular challenges. **G protein-coupled receptors** represent the largest and most diverse superfamily of mammalian transmembrane (TM) proteins. Members of this family of receptors mediate signalling pathways in different cells and play key roles in human physiology and health. GPCRs are considered ideal drug targets because of their ability to bind and respond to agonists, antagonists and allosteric modulators. This is not surprising given the

Abbreviations: β1-AAB, β1-AR auto antibodies; β_1-AR, β_1-adrenoceptor; Aβ, amyloid β; ACh, acetylcholine; ADGRs, adhesion GPCRs; AMPK, AMP kinase; FFA, free fatty acid receptor; FLTD, frontotemporal lobar degeneration; GIP, glucose-dependent insulinotropic peptide; GLP, glucagon-like peptide; HR, hypoxia-reoxygenation; IP_3, inositol triphosphate; LC3, microtubule-associated protein 1 light chain 3; mAChR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor; mTOR, mammalian target of rapamyci; mTORC1, mTOR complex1; PINK1, PTEN-induced putative kinase 1; PIP_2, phosphatidylinositol 4,5 biphosphate; SCFAs, short-chain fatty acids; T1R, taste receptor type 1; T2R, taste receptor type 2; TM, transmembrane; TRPM5, transient receptor potential channel M5; VLGR1, very large G protein-coupled receptor-1.

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presence of more than 800 GPCRs expressed in human tissues and that these receptors mediate signal transduction in almost every cell.

This superfamily has been arranged into families based on sequence homology and functional similarity or phylogenetic criteria (Attwood & Findlay, 1994; Ghosh et al., 2015; Schiöth & Fredriksson, 2005). According to the first classification based on sequence homology and functional similarities, GPCRs are grouped under six major families: Family A (rhodopsin-like), Family B (secretin-like), Family C (metabotropic glutamate), Family D (parasitic mating pheromone), Family E (cyclic AMP) and Family F (frizzled and smoothened) (Attwood & Findlay, 1994). On the basis of phylogenetic criteria, human GPCRs are clustered into five principal families, namely glutamate (G), rhodopsin (R), adhesion (A), frizzled/taste (F) and secretin (S) and forming the GRAFS classification system (Fredriksson et al., 2003). The main difference between the A–F and GRAFS systems involves the additional subdivision of family B into adhesion and secretin families within GRAFS. Among these families, the largest is the **rhodopsin (Class A) family**, which also includes **Class A orphan GPCRs** for which endogenous ligands are not known or are unclear (Kobilka, 2007). GPCRs possess different binding domains, namely, orthosteric and allosteric domains that bind structurally diverse ligands. Members of this superfamily are diverse in structure and function but they also share some structural elements. The conserved structure of GPCRs consists of seven TM domains, each containing roughly 25–35 amino acids. These moderately hydrophobic residues form alpha helices that span the plasma membrane. The most variable structures reside in the carboxy terminus, the intracellular loop spanning TM5 and TM6, and the amino terminus, exhibiting the greatest diversity. The largest amino terminus domains are found in the **adhesion family receptors** (Kobilka, 2007). The ligand binding domains for many GPCRs are variable, with some binding within the TM segments, others to the amino terminus or extracellular sequences joining the TM domains (Rosenbaum et al., 2009; Weis & Kobilka, 2018).

GPCRs are essential for cell growth under physiological conditions. Also, GPCRs have been implicated in several disorders, including metabolic disorders, neurodegeneration and inflammatory diseases. Furthermore, an increasing number of studies has demonstrated that GPCRs can behave as agonist-dependent oncogenes (Gutkind, 1998; Heng et al., 2013).

Autophagy is a highly regulated intracellular pathway essential for the preservation of cellular homeostasis. In health, autophagy serves to degrade damaged proteins and organelles into their building blocks. The breakdown products are then recycled during nutrient depletion. Autophagy can prevent aggregation of misfolded proteins and provide protection against diseases. On the other hand, increased autophagy due to dysregulation has been linked to various diseases (Klionsky et al., 2021).

Overall, the relationship between GPCR and autophagy signalling is complex and multifaceted. GPCRs can regulate autophagy by activating downstream signalling pathways (summarized in Figure 1). The

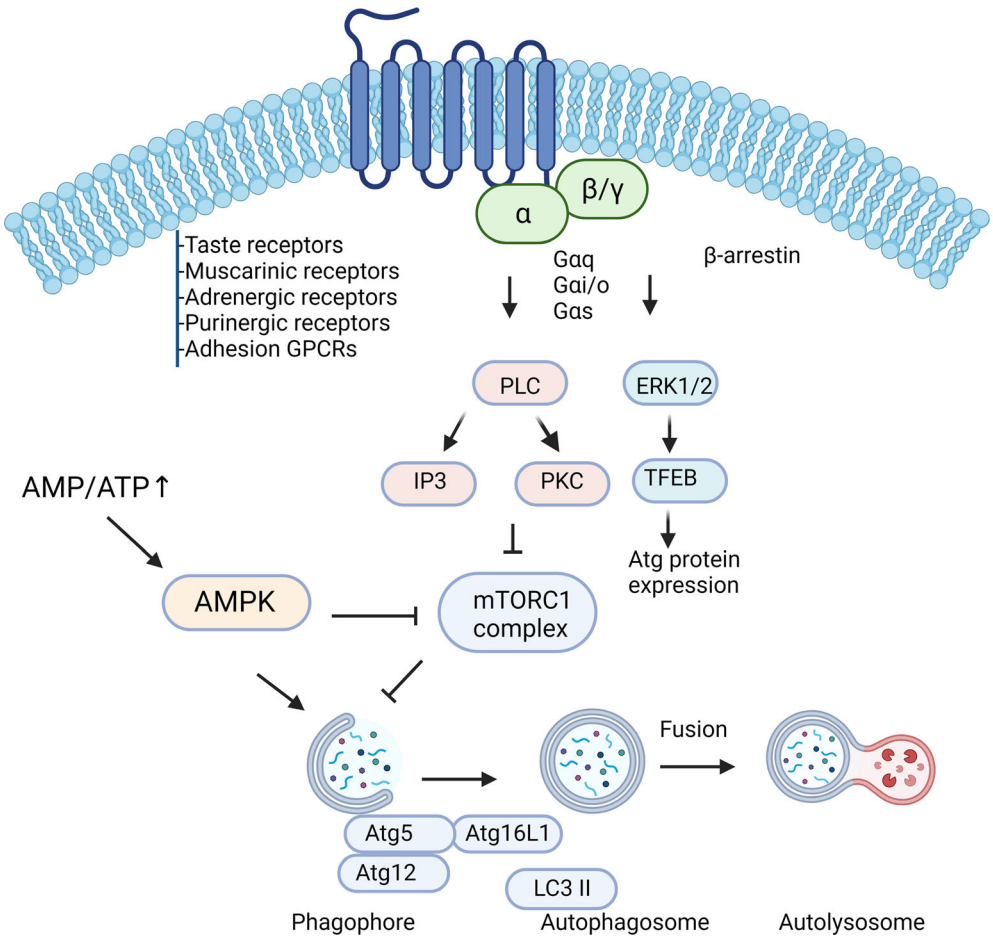

FIGURE 1 The link between G Protein-coupled receptors (GPCRs) and autophagy signalling. Upon ligand binding to GPCRs, G protein α and $\beta\Upsilon$ subunits of heterotrimeric G proteins dissociate to activate various downstream signalling pathways, including PLC, PKC and ERK1/2. The second messengers such as IP_3 and cAMP in turn modulate autophagy through the critical autophagy regulators, the mTORC1 complex and AMPK. Autophagy is also regulated through the ratio of AMP/ATP, which is sensed by AMPK.

stimulatory or inhibitory outcome may depend on the receptor type or cellular context. On the other hand, GPCRs are amenable to regulation of autophagy. Thus, both GPCR and autophagy play important roles in health and disease (Figure 2). Further research is needed to fully understand the mechanisms underlying this relationship, especially under physiological and pathological settings.

In this review, we summarize the role of GPCRs in autophagy regulation, highlighting their integration at the physiological and pathological levels. Understanding these mechanisms may lead to novel therapeutic strategies for the treatment of a variety of disorders.

2 | MUSCARINIC RECEPTORS AND AUTOPHAGY

Muscarinic acetylcholine receptors (mAChRs) are GPCRs that play important signalling roles in a variety of physiological functions (Wess, 2004). These receptors are widely distributed in the central and peripheral nervous systems (Caulfield & Birdsall, 1998). The **mAChR family** comprises five subtypes (M_1 to M_5) that exhibit a high degree of sequence identity and sequence similarity in the TM region. However, response to neurotransmitters is more selective across mAChR subtypes. **M_1**, **M_3** and **M_5** mAChRs are preferentially coupled to Gq/11 and stimulate **phospholipase C**, which catalyses the formation of diacylglycerol and inositol triphosphate (**IP_3**) from phosphatidylinositol 4,5 biphosphate (**PIP_2**), resulting in the initiation of the IP_3 cascade. This pathway causes intracellular Ca^{2+} mobilization and activation of **protein kinase C**. Even numbered **M_2** and **M_4** mAChRs are coupled to the pertussis toxin-sensitive Gi/o family of G proteins and inhibit **adenylyl cyclase** activity, activate **K_{IR} potassium channels** and inhibit **Ca_V2 channels** (Caulfield & Birdsall, 1998). Classically, M_1, M_3 and M_5 mAChRs increase neural excitability, whereas M_2 and M_4 produce inhibition (Brown, 2019).

Muscarinic receptor signalling in the regulation of autophagy has been demonstrated in different cell types and disease conditions (Wauson et al., 2014). In *Caenorhabditis elegans*, starvation activates **MAPK** in the pharyngeal muscles through a muscarinic receptor coupled to Gαq and novel PKC (You et al., 2006). Based on their findings, You and colleagues suggested that muscarinic signal-induced autophagy could contribute to the ability of *C. elegans* to survive starvation, by leading to increased food intake. They added that muscarinic acetylcholine (ACh) signalling was important for the induction of physiological levels of autophagy. In another study, the same group of investigators highlighted the dual role that autophagy can play in survival. Grb-2 mutant worms are hypersensitive to starvation, during which overactivation of muscarinic signalling causes excessive autophagy in the pharyngeal muscles, whereas inhibition of muscarinic signalling can decrease autophagy. Thus, these authors suggested that physiological levels of autophagy are pro-survival, whereas insufficient or excessive levels are pro-death (Kang & Avery, 2008).

Autophagy plays key roles in cardiac homeostasis and the malfunction of autophagy is associated with some cardiovascular disorders (Sridhar et al., 2012). Recent studies have indicated that, particularly the M_2 subtype can modulate autophagy in cardiac cells. Autoantibodies against **beta-1 adrenoreceptors** (β_1-AR) and M_2 mAChRs have been detected in the sera of a group of patients with dilated cardiomyopathy (Fu et al., 1993; Matsui et al., 1995).

It is known that, following ischemia, restoration of blood supply to ischemic tissue can cause myocardium injury and contribute to mortality in patients with myocardial infarction (Yellon &

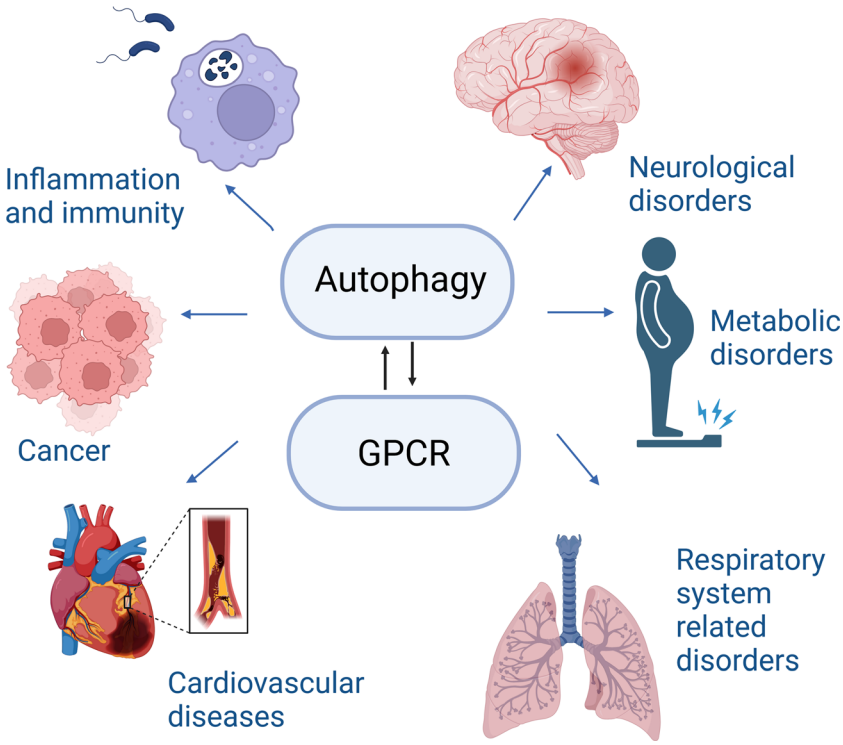

FIGURE 2 The input of G Protein-coupled receptors (GPCRs) and autophagy on disease. The tight association and crosstalk between GPCRs and autophagy is essential in health and is implicated in the pathophysiology of many disorders.

Hausenloy, 2007). The action of autophagy in ischemic injury may depend upon the severity and duration of ischemic insult and reoxygenation (Loos, 2011). H9c2 cells, which have been shown to retain several electrical and hormonal characteristics similar to adult cardiomyocytes, offer an in vitro model to analyse cardiac function, including hypertrophy or heart failure. The possible role of autophagy in **ACh**-elicited protection against hypoxia-reoxygenation (HR) injury was investigated in H9c2 cells (Zhao et al., 2013). Briefly, cells were incubated in a hypoxic incubator with an ischemia mimetic solution for 8 h after which they were transferred to a normoxic incubator for reoxygenation and treated with ACh. Under these conditions, ACh treatment during reoxygenation facilitated autophagy and increased survival of H9c2 cells. Based on their data, Zhao and colleagues proposed that the cytoprotective effects of ACh is elicited through the muscarinic receptor activated-AMP kinase (**AMPK**)-mammalian target of rapamycin (**mTOR**) pathway (Zhao et al., 2013). In a more recent study, Intachai et al. (2022) demonstrated that ACh exerted cytoprotection against HR–induced autophagy and mitochondrial impairment through the activation of both muscarinic and ionotropic nicotinic receptors. This result was obtained by using ACh or the nicotinic **ACh** agonist, **GTS-21**, in H9c2 cells. Furthermore, co-treatment with the muscarinic antagonist **atropine** reduced or even reversed the beneficial effects of ACh and GTS-21. In this study, ACh, when applied before or during hypoxia, elicited cardioprotection against HR via improving mitochondrial fusion and biogenesis and reducing apoptosis and autophagic cell death (Intachai et al., 2022). A recent study showed that the release of ACh from the vagus nerve provides cardioprotection via inhibition of **doxorubicin**-induced autophagic cell death in Wistar rats (Prathumsap et al., 2023). In conclusion, ACh can exert cytoprotective effects on autophagy modulation through muscarinic and nicotinic receptor stimulation.

mAChRs also have been implicated in the regulation of autophagy in cancer cells. Recently, investigators have reported the expression of muscarinic receptor subtypes in non-neuronal cells, including haematopoietic cells and immune cells (Shah et al., 2009). The M_1 mAChR, the mainly expressed receptor subtype in the parasympathetic nervous system, has been shown to regulate cancer progression in a number of tumours, especially breast and pancreatic cancers (Español et al., 2007; Kamiya et al., 2021). In a recent study, Wang et al. (2022) demonstrated the abundant expression of M_1 mAChR both in nude mice with subcutaneous tumours and in prostate cancer cells. The overexpression of M_1 mAChR was correlated with activation of the Atg5 AMPK/mTOR autophagic signalling pathway, resulting in autophagy-mediated cell migration and invasion. In conclusion, the authors' findings indicated that the M_1 mAChR is highly expressed in prostate cancer cells and autophagy enhances migration and invasion ability of tumour cells (Wang et al., 2022).

Studies have demonstrated that the M_1 mAChR can regulate PI3K/**Akt**, MAPK/**ERK**, Wnt, Hedgehog and other signalling pathways (Yin et al., 2018), including AMPK and mTOR pathways (Sridhar et al., 2012).

Neuronal autophagy plays a major role in brain function, whereas impaired autophagy is implicated in the pathogenesis of numerous degenerative disorders (Hernandez et al., 2012; Nikoletopoulou et al., 2015). mAChRs have been reported to regulate autophagy in neurons. Activation of the M_1 subtype has been shown to enhance autophagy and promote the clearance of aggregates in Alzheimer's disease and Parkinson's disease. The downstream signalling pathways involved most likely include the PI3K/Akt/mTOR pathway.

Muscarinic receptors emerge as important therapeutic targets for various diseases. The mechanisms by which mAChRs regulate autophagy is complex and opens possibilities for therapy, therefore merits further investigation.

3 | ADRENERGIC RECEPTORS AND AUTOPHAGY

β-adrenoceptors (β-ARs) mediate a number of intracellular events when stimulated with catecholamines or other ligands. Catecholamines act both as neurotransmitters and hormones throughout the autonomic nervous system. In the heart, catecholamine acts by activation of β-ARs, principally the β_1-AR and **β_2-AR** subtypes. Both subtypes couple to Gs and Gi proteins. Gs activates adenylyl cyclase and promotes intracellular **cAMP** accumulation; conversely, Gi exerts an opposing effect on cAMP accumulation. Gi also activates the PI3K–Akt signalling pathway (Santos & Spadari-Bratfisch, 2006; Spadari et al., 2018). In the heart, basal autophagy contributes to the maintenance of cellular energy and, as such, can protect the heart from dysfunction. It can also be detrimental, depending on its level. When strongly up-regulated, autophagy can lead to programmed cell death. Therefore, proper regulation of autophagy is important for the maintenance of homeostasis in the heart. Dysregulation of autophagy has been associated with various cardiovascular disorders, including ischemic disease (Gustafsson & Gottlieb, 2009) and myocardial infarction (Nishida et al., 2009). In cardiac myocytes, β-adrenoceptor stimulation has been reported to inhibit autophagy (Bahro & Pfeifer, 1987).

On the other hand, activation of the β_2-AR triggers autophagy and increases collagen degradation in cardiac fibroblasts, and this response could contribute to rescuing the harmful effects of high adrenergic stimulation upon cardiac fibrosis (Aránguiz-Urroz et al., 2011). Thus, the autophagic response upon β_2-AR stimulation may depend upon the cellular type involved as well as several other factors.

Changes in mitochondrial structure and function are important in maintaining cardiac function. Deficiencies in the regulation of cardiac energy metabolism via mitophagy may lead to various heart diseases. Previously, β_1-AR antibodies (β_1-AAB) have been detected in the sera of patients with dilated cardiomyopathy, chronic Chagas disease, and heart failure caused by ischemic cardiomyopathy (Jahns et al., 2004; Labovsky et al., 2007; Pei et al., 2012). The mitochondrial membrane potential, $\Delta\Psi m$, is an important indicator of mitochondrial function. In a passively β_1-AAB-immunized rat model, Wang and colleagues showed that β_1-AABs caused cardiac dysfunction, reduced $\Delta\Psi m$ and decreased cardiac autophagy and that activation of autophagy by **rapamycin**, an mTOR inhibitor, restored cardiac function and myocardial autophagic flux in cardiac myocytes (Wang et al., 2013). A

subsequent study provided evidence that endoplasmic reticulum stress contributed to the β_1-induced reduction of autophagy of myocardial tissues and H9c2 cardiomyocytes (Wang et al., 2019). In a subsequent study, the same group of investigators reported that the β_1-adrenoceptor caused a decrease in AMPK phosphorylation and inhibited myocardial autophagic flux, both in vivo and in vitro (Sun et al., 2021).

In the liver, adrenergic signalling is important in regulation of hepatic metabolism and function. Autophagy has been shown to be involved in normal hepatic function. Dysregulation of autophagy has been shown in pathological conditions such as non-alcoholic fatty liver disease and alcoholic fatty liver disease. The potential role of β-AR signalling in hepatic autophagy has been addressed in HepG2 hepatoma cells and primary hepatocytes and in vivo (Farah et al., 2014). **Clenbuterol** and **epinephrine** stimulated autophagy and autophagic flux in vivo. On the other hand, the β-AR blocker **propranolol** induced a late block in autophagy in the presence and absence of clenbuterol, lending support to the view that β-ARs can modulate hepatic autophagy.

Epidemiological data indicate that chronic stress has adverse effects on the incidence and progression of cancer. The stomach is a critical target organ for stress hormones and is frequently subject to stress-related injury. Zhi and colleagues investigated the effect chronic stress on the growth and survival of gastric cancer and the role of autophagy in mice subjected to chronic stress (Zhi et al., 2019). The stress hormone **norepinephrine** significantly enhanced the proliferation of gastric cancer cells. They demonstrated that the β_2-AR was responsible for catecholamine release and also that autophagy was induced under these conditions. This study showed the tumour-promoting role of norepinephrine-induced autophagy under conditions of chronic stress.

Recently, several studies have demonstrated that blocking β-AR signalling could inhibit multiple processes associated with tumour progression (Coelho et al., 2015). A recent study in multiple myeloma patients used the selective β_1-AR-blocker **bisoprolol**, the selective β_2-AR blocker **ICI-118,551** and the non-selective β-blocker propranolol to investigate their anti-tumour effects (Satilmis et al., 2023). The effects on downstream signalling pathways and mechanisms including autophagy, apoptosis, glycolysis and metabolic respiration also were assessed in this study. Based on several multiple myeloma patient cohorts, which included gene expression profiles of bone marrow plasma cells, the authors concluded that β_2-AR expression is associated with poor survival outcome in multiple myeloma. The authors concluded that blockade of the β_2-AR modulated multiple myeloma cancer cell metabolism by reducing mitochondrial respiration and glycolytic activity, thereby increasing apoptosis and autophagy. These authors also pointed to the therapeutic implications of targeting β2-AR as an adjunct therapy for multiple myeloma.

Autophagy, as well GPCRs, play integral roles in pathogenesis of neurodegenerative disorders (Klionsky et al., 2021; Sushma & Mondal, 2019). Alzheimer's disease is characterized by accumulation of **amyloid β** (Aβ) aggregates and neurofibrillary tangles consisting of hyperphosphorylated **tau** in the brain of affected individuals. Aggregates, like Aβ and tau, accelerate the depolymerization of microtubules, which in turn impact autophagic flux (Chong et al., 2018). The microtubule-associated protein tau plays a significant role in stabilizing microtubules. On the other hand, hyperphosphorylation of tau is one of the characteristic hallmarks of Alzheimer's disease pathogenesis.

β-arrestins are involved in termination of GPCR signalling, serve as multiprotein scaffolds, and also can activate signalling cascades independently of G protein activation (DeWire et al., 2007). A study in brains of patients with frontotemporal lobar degeneration reported that β-arrestins are essential for β_2-AR and **mGluR$_2$**-mediated increase in pathogenic tau. Woo and colleagues have shown that β-arrestin-2 levels are increased in frontotemporal lobar degeneration (FTLD) patients (Woo et al., 2020) and also that β-arrestin-1 and β-arrestin-2 promoted aggregation of pathogenic tau by blocking autophagy (Woo et al., 2022). Based on their data in patients and animal models of FTLD, these investigators suggest that β-arrestin-1 and β-arrestin-2 mediate GPCR stimulation effects on taupathy.

In contrast, a more recent study reports that activation of β_2-AR signalling by the agonist clenbuterol, may ameliorate Aβ-induced tau hyperphosphorylation and mitophagy defects in mice by activating the β_2-AR/Akt/PTEN-induced putative kinase 1 (**PINK1**) signalling pathway (Chai et al., 2022).

4 | TASTE RECEPTORS AND AUTOPHAGY

Nutrients, including glucose, amino acids, lipids and nutrient metabolites act by activating GPCRs and promoting the release of gut and pancreatic hormones. Along with its well-known role in the absorption of nutrients, the small intestine also has an important effect on nutrient sensing. GPCR-coupled nutrition sensors are expressed across the intestinal epithelium and react to nutrients contained in the lumen, in addition to taste receptors found on the tongue (Burman & Kaji, 2021). Taste receptors are critical for sensing chemicals in food. Five basic tastes: sweet, bitter, salty, sour, and umami are found in the human body. The recognition of sweet, umami and bitter tastes is achieved by GPCRs. These receptors are referred to as **taste receptor type 1** (T1R) and **taste receptor type 2** (T2R). The T1R family consists of three members within the Glutamate/family C GPCR group that recognize sweet and umami receptors, whereas the T2R family consists of a larger group of GPCRs that mediate bitter taste. Lipid sensing through free fatty acids (FFA) also is mediated by the taste receptor GPCR family (Cygankiewicz et al., 2014; Foster et al., 2014).

In response to nutrient availability, taste receptors activate intracellular signalling pathways, which in turn control a variety of cellular activities, including autophagy and cellular growth. In the last two decades, the molecular mechanism of taste receptor signalling has been delineated. The heteromeric form of taste receptor type 1 (T1R; genes are designated TAS1 in humans) mediates the sense of sweet (**T1R2**–**T1R3**) and umami (**T1R1**–T1R3) tastes (Li, 2009).

Although there are differences in the structure and function of T1R and T2R, the canonical signal transduction pathways of these receptors demonstrate some common features. Both receptors are associated

with a specific G protein α subunit referred to as gustducin ($G\alpha_{t3}$, GNAT3) and Gβ3 and Gγ13, as well as a phospholipase C, **PLCβ2**. Upon binding of ligand to the receptor, the βγ subunits separate from the α-subunit and trigger PLCβ2, which leads to an increase in intracellular Ca^{2+} levels and subsequent opening of transient receptor potential channel M5 to depolarize taste receptor cells (Foster et al., 2014).

Autophagy modulation that occurs in response to nutritional fluctuations is highly complex and different signalling networks may be involved during this process. The mTOR complex 1 (mTORC1) and AMPK signalling cascades are the master regulators of intracellular nutrient and energy levels during autophagy induction (Füllgrabe et al., 2014).

Given the fact that autophagy and GPCR signalling networks overlap with the same protein complexes (PI3K, ERK1/2, PKA, *etc.*), crosstalk between these signalling pathways is expected. On the other hand, little is known about the upstream pathways of nutrient sensing. Several recent studies indicate that the Gαq subunit is a key regulator of mTORC1 signalling over autophagy in response to fluctuations in different types of nutrients (Cabezudo et al., 2021).

Recent evidence has revealed that taste receptors are expressed in many different tissues, including the heart, brain and immune systems. Bitter taste receptors have a wide variety of ligands and are expressed in different tissues, including the heart, respiratory system, *etc*. (Welcome et al., 2023). Hamdard and colleagues indicated that a bitter taste agonist modulated downstream signalling effectors, apoptosis-, autophagy- and antioxidant-related gene expression levels in the heart and kidney (Hamdard et al., 2019). Type II taste receptor subtypes, TASR2, including **T2R10**, **T2R14** and **T2R31** are highly expressed in human airway smooth muscle cells (Deshpande et al., 2010). Pan and colleagues demonstrated that the autophagy modulator **chloroquine** and **quinine** act as T2R agonists and display antimitogenic effects on ASM cells. The same authors demonstrated that chloroquine and quinine promoted microtubule-associated protein 1 light chain 3(LC3)-BII accumulation which is a key autophagy marker in the cytoplasm and autophagy inhibitors reversed this effect. Thus, they suggested that autophagy plays a critical role during the T2R agonist-mediated antimitogenic effect and that targeting this pathway may be a new therapeutic approach for the treatment of asthma (Pan et al., 2017).

4.1 | Amino acid receptors signalling and autophagy

It is well known that amino acids activate mTORC1, in addition to umami taste sensing, but upstream pathways of amino acid sensing still need to be explored, T1R1/T1R3 participates in early amino acid sensing pathways that result in mTORC1 activation. Human T1R1/T1R3 can only detect **glutamate** and **aspartate**, but murine T1R1/T1R3 can detect up to 18 amino acids (Zheng et al., 2016). A decrease in the expression of T1R1/T1R3 prevents activation of mTORC1 by amino acids, leads to impairment in the movement of mTORC1 to lysosomes and induces autophagy (Wauson et al., 2012). Another promiscuous amino acid sensing receptor, **GPRC6A**, is expressed in the gastrointestinal tract and shares 28% homology with the taste receptorT1R1. GPRC6A is involved in a variety of cellular functions, including the regulation of glucose metabolism and energy homeostasis (Meyerhof et al., 2009). A recent study showed that the expression level of autophagy marker, LC3-I/II in skeletal muscle of GPRC6A KO mice was significantly higher than those of WT mice under starvation conditions. In addition, GPRC6A acts as an AA receptor upstream of mTORC1, participating in the regulation of mTORC1 activation and autophagy for the maintenance of proper growth and development of the body (He et al., 2022). These reports raise the possibility that GPRC6A acts as an amino acid sensor to regulate mTORC1.

4.2 | Fat taste receptor signalling and autophagy

An increasing number of suggests that short or long-chain fatty acids promote protective autophagy through their appropriate GPCRs. In the intestinal lumen, commensal bacteria ferment dietary fibre and indigestible starches to create short-chain fatty acids (SCFAs). These fatty acids have substantial effects on health and disease development. According to research, over 90% of all intestinal SCFAs are composed of **acetate**, **propionate** and **butyrate** (Niccolai et al., 2019). Butyrate is a well-studied SCFA and exerts a protective role against many diseases such as diabetes and kidney disease. A recent study revealed that butyrate reduces muscle atrophy associated with autophagy and oxidative stress by improving gut barrier function and PI3K/Akt/mTOR signalling via free fatty acid receptors (FFA) 2 (**FFA2**, GPR43) (Tang et al., 2022).

Docosahexaenoic acid (DHA), an omega-3 long-chain polyunsaturated fatty acid, repaired oxidative stress-impaired autophagic flux in hepatocytes. The **GPR120**/ERK cascade signalling pathway is involved in mitophagy, a specific type of autophagy (Chen et al., 2021). Another study reported that DHA led to the recruitment of β-arrestin-2 to FFA4 (GPR120) and caused receptor internalization and reduction in the inflammasome activation by enhancing autophagy in macrophages (Williams-Bey et al., 2014).

In humans, FFA4 is expressed in all types of taste papillae; **FFAR-3** (GPR41) and FFAR-2 (GPR43) are located in circumvallate and foliate papillae; and FFA1 (GPR40) **FFA1** is found mainly in the circumvallate papillae (Cygankiewicz et al., 2014).

One of the important short fatty acid receptors, FFA3 is a crucial SCFA receptor class member exerting significant effects on both health and sickness. FFA3 is a nutrient sensor of gut microbiota-generated nutrients and is known as a Gαi/o-coupled receptor expressed in enteroendocrine cells where it regulates gut hormone secretion. Double deletion of FFA3 and FFA2 can induce **insulin** secretion in islet cells (Priyadarshini et al., 2020). SCFAs can also induce autophagy in colon cancer (Tang et al., 2011). A recent study showed that autophagy was induced in both WT and FFAR3 KO islets. As a consequence, these data suggest that FFA3 receptor signalling may modulate autophagy through GPCR signalling pathways (Priyadarshini et al., 2020).

The combination of **retinoic acid** and ω-3 polyunsaturated fatty acids (ω-3 PUFAs), membrane receptors of GPR40 (FFA1) and GPR120 (FFA4) respectively, triggered cell death and autophagy induction in vitro and in vivo. In addition, the co-activation of GPR40 and **RAR** in lipid rafts, but not activation of GPR120, **RARβ** or **RARγ** leads to the activation of Gαq-p38 during autophagy induction (Zhu et al., 2017).

Palmitic acid (PA) is the most abundant saturated fatty acid recognized by FFA1 (GPR40) and FFA4 (GPR120). PA plays an important role in the control of body weight and insulin resistance (Suckow et al., 2014). It was shown that PA impairs autophagic flux and reduces insulin sensitivity through FFA1 in hypothalamic neuronal cells (Hernández-Cáceres et al., 2019). New research demonstrated that, in addition to FFA1, PA can induce **GPR110** and stimulate the activation of the mTOR and SREBP-1c pathways for the activation of milk protein and fat synthesis in the mammary gland cells (Zhang et al., 2023).

Several studies have demonstrated that activation of sweet taste receptors T1R2-T1R3 by natural sugars and artificial sweeteners leads to the secretion of glucagon-like peptides (GLP) 1 and 2 (**GLP-1** and **GLP-2**) as well as **glucose-dependent insulinotropic peptide** (GIP). GLP-1 and GIP enhance insulin secretion; while GLP-2 increases intestinal growth and glucose absorption (Morrow et al., 2021). On the other hand, GPR40, **GPR119** and GPR120 can activate the GLP-1 secretion in the intestinal and pancreatic cells (Reimann & Gribble, 2016). Different GLP-1 agonists act through GPCRs and are used in the treatment of diabetes, obesity and cardiovascular diseases (Ussher & Drucker, 2023). The most beneficial characteristic of **GLP1R** activation is that it exclusively causes the release of insulin in the presence of an elevated blood glucose level. Furthermore, accumulating evidence indicates that GLP-1-GLP1R signalling induces autophagy and that, in this way, taste receptors can have an indirect or systematic effect on the human body (Chen et al., 2017; Wu et al., 2019).

5 | PURINERGIC RECEPTORS AND AUTOPHAGY

Purinergic signalling is the process through which extracellular purines, such as **adenosine** and **adenosine 5′-triphosphate** (ATP), activate purinergic receptors (Burnstock, 2014, 2018). These cell surface receptors can be classified into two main families based on agonist selectivity: **P1 adenosine receptors** (GPCR, class A) and adenine nucleotide P2 purinergic receptors. The P2 purinergic receptors are further categorized into two subtypes: **P2X receptors**, which are **ligand-gated ion channels**, and **P2Y receptors** that are GPCRs (class A). The interaction of all three families of purinergic receptors with autophagy has been suggested (Apolloni et al., 2016; Cho et al., 2023; Fabbrizio et al., 2017; Jiang et al., 2021; Takenouchi et al., 2009; Wauson et al., 2014b; Zhang et al., 2021); however, for the purposes of this review, only the adenosine receptors are covered.

Purine nucleotides can activate purinergic receptors on nearby cells when they are released into the extracellular space as a result of biological processes, physical stress or injury (Burnstock, 2018). Thus, purinergic signalling has implications for pathological conditions including neurological, cardiovascular and cancer diseases (Burnstock, 2017; Burnstock & Boeynaems, 2014; de Araújo et al., 2021; Di Virgilio, 2012; Gombault et al., 2012; Pacheco et al., 2014; Wang et al., 2023; Wiprich & Bonan, 2021). Multiple studies demonstrate that adenosine receptors regulate autophagy under similar pathogenic circumstances. In an ischemia model, agonist stimulation of the **adenosine A_{2B} receptor** (A_{2B}R) reduced Beclin-1 expression and autophagy after reperfusion, resulting in cardioprotection (Ke et al., 2015). Experiments with **adenosine A_{2A} receptor** (A_{2A}R) knockout mice and rats exposed to traumatic brain injury revealed that A_{2A}R knockout protects against ischemia by restoring autophagic flux (Zeng et al., 2018). A_{2A}R stimulation by a liposome-associated agonist, on the other hand, has been shown to increase FoxO1 and FoxO3 activation and nuclear localization, as well as autophagic flux, thereby improving chondrocyte metabolic functions (Friedman et al., 2021). Activation of A_{2A}R in an **LPS**-induced systemic inflammatory response syndrome model in murine neutrophils was demonstrated to decrease LPS-induced autophagy and thereby apoptosis (Liu et al., 2016). The observed regulation of autophagy by activated A_{2A}R was independent of **PKA**- and PKC-pathways but rather through the inhibition of the ROS-**JNK** pathway and by promoting GPCR βγ-subunit–Akt signalling. A_{2A}R activation also has been shown to repair autophagic flux abnormalities in Niemann-Pick type C-like oligodendrocyte model cells (De Nuccio et al., 2019). In summary, studies suggest that adenosine receptors are closely linked with the regulation of autophagy and autophagic flux, and future research will reveal the therapeutic potential of adenosine receptor agonists in exploiting this pathway.

6 | ADHESION GPCRS AND AUTOPHAGY

Adhesion GPCRs (ADGRs) are members of a distinct subclass of GPCRs which has a characteristic domain organization composed of an adhesive extracellular N-terminal fragment, a GPCR autoproteolysis-inducing domain and a C-terminal fragment with a 7-TM domain for G protein coupling, and a C-terminal tail (Seufert et al., 2023). Autocleavage of ADGRs was reported to release a short sequence of peptide, proposed to act as a bound agonist, that activates the receptor (Liebscher et al., 2022; Liebscher & Schöneberg, 2016). Recently, the largest known member of ADGRs (McGee et al., 2006) very large G protein-coupled receptor-1 (**VLGR1/ADGRV1**), was reported to interact with proteins involved in the autophagy process and regulate autophagy at internal membranes (Linnert, Güler, et al., 2023). Notably, mutations in VLGR1/ADGRV1 cause Usher syndrome (USH) (Linnert, Knapp, et al., 2023), a form of hereditary deaf-blindness, and have been associated with epilepsy (Dahawi et al., 2021; Myers et al., 2018; Zhou et al., 2022). In their study, Linnert and colleagues utilized affinity proteomics to search for VLGR1/ADGRV1 interaction partners and this search led to the discovery of many autophagy

related proteins. Increased autophagy in VLGR1/ADGRV1-deficient hTERT-RPE1 cells and USH2C patient-derived fibroblasts further suggested a connection between VLGR1/ADGRV1 and autophagy (Linnert, Güler, et al., 2023).

Results with VLGR1/ADGRV1 by Linnert and colleagues are unsurprising, given the existing evidence demonstrating a link between cellular adhesions and autophagy (Güler et al., 2023; Kenific et al., 2016; Ravasio et al., 2022; Sharifi et al., 2016; Vlahakis & Debnath, 2017). For example, inhibition of autophagy was shown to reduce tumour cell migration accompanied by the accumulation of large focal adhesions. It was proposed that autophagy promotes the degradation of focal adhesion protein paxillin, which was shown to interact with LC3, and thus the turnover of these complexes (Sharifi et al., 2016). Furthermore, selective autophagy by the **autophagy cargo receptor** NBR1 was observed to regulate the turnover of **integrin**-mediated focal adhesions during cell migration (Kenific et al., 2016). In the opposite direction, autophagy was found to be induced upon loss of integrin-mediated cell attachments to the surrounding extracellular matrix (Fung et al., 2008). Interestingly, recent work done with Vlgr1-deficient astrocytes derived from Vlgr1/del7TM mouse brains revealed reduced turnover kinetics for paxillin in VLGR1-deficient focal adhesions (Güler et al., 2023). The latter might be linked to the previously observed enhancement of autophagy in Vlgr1-deficient hTERT-RPE1 cells but this effect has yet to be demonstrated (Linnert, Güler, et al., 2023). Overall, these findings suggest that there is an interplay between adhesion G-protein coupled receptors, focal adhesion turnover, migration and autophagy and the impairments in the cross-regulation between these processes may have implications for many pathologies.

7 | CONCLUSIONS

The tight association and crosstalk between GPCRs and autophagy have been demonstrated in many recent publications. However, there is still a degree of controversy on the beneficial versus deleterious effects of GPCR-autophagy signalling pathways. Given the vital roles played by GPCRs and autophagy in health and disease, establishing the links between the two processes deserves further research.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in https://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander et al., 2023).

AUTHOR CONTRIBUTIONS

The manuscript was conceptualized designed and written by D. Ö. A., Z. A. D. and B. K. All authors have read, reviewed and edited the manuscript. D. Ö. A. and Z. A. D. should be considered joint first authors. B. K. is the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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