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REVIEW ARTICLE

Adrenoceptor regulation of the mechanistic target of rapamycin in muscle and adipose tissue

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A vital role of adrenoceptors in metabolism and energy balance has been well documented in the heart, skeletal muscle, and adipose tissue. It has been only recently demonstrated, however, that activation of the mechanistic target of rapamycin (mTOR) makes a significant contribution to various metabolic and physiological responses to adrenoceptor agonists. mTOR exists as two distinct complexes named mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) and has been shown to play a critical role in protein synthesis, cell proliferation, hypertrophy, mitochondrial function, and glucose uptake. This review will describe the physiological significance of mTORC1 and 2 as a novel paradigm of adrenoceptor signalling in the heart, skeletal muscle, and adipose tissue. Understanding the detailed signalling cascades of adrenoceptors and how they regulate physiological responses is important for identifying new therapeutic targets and identifying novel therapeutic interventions.

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1 | INTRODUCTION

Adrenoceptors belong to the GPCR family, a conserved family of seven transmembrane receptors that is one of the largest protein classes to be targeted for drug therapy (Sriram & Insel, 2018). These receptors are classified as α- or β-adrenoceptors, based on differences in responses to various catecholamines such as **adrenaline**, **noradrenaline** and **isoprenaline**. The **α-adrenoceptors** have been classified into two major families: α_1 and α_2 and the β-adrenoceptors are subdivided into β_1-, β_2-, and β_3-subtypes . All adrenoceptor subtypes have common primary structures comprising one extracellular N-terminal domain, seven α-helical transmembrane spanning regions, and one intracellular C-terminal tail. Recent studies have shown that α_1- and **β_1-adrenoceptors** in the heart, **β_2-adrenoceptors** in skeletal muscle, and **β_3- adrenoceptors** in brown adipose tissue (BAT) can link to a

Abbreviations: 4E-BP1, 4E binding protein-1; AMPK, 5′AMP-activated protein kinase; AS160, Akt substrate of 160 kDa; BAT, brown adipose tissue; DEPTOR, DEP domain-containing mTOR-interacting protein; eIF4E, eukaryotic translation initiation factor 4E; ERRα, oestrogen-related receptor α; GLUT4, glucose transporter 4; GRK, G protein receptor kinases; hMADS, human multipotent adipose-derived stem; LARP1, La-related protein 1; MLST8, mammalian lethal with SEC13 protein 8; Mst1, macrophage stimulating 1; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; NRVM, neonatal rat ventricular myocytes; PDK1, phosphoinositide-dependent kinase 1; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; Raptor, regulatory-associated protein of mTOR; REPTOR, repressed by TOR; Rictor, rapamycin-insensitive companion of mTOR; S6K1/2, ribosomal protein S6 kinase 1 and 2; SGK1, serum and glucocorticoid-responsive kinase-1; Tel2, telomere maintenance 2; TSC1/2, tuberous sclerosis complex; UCP1, uncoupling protein 1; WAT, white adipose tissue

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protein called **mechanistic target of rapamycin (mTOR)**, which plays a significant role in physiological and metabolic responses.

mTOR is an atypical serine/threonine kinase with a molecular weight of ~289 kDa, belonging to the PI3K-related kinase family. mTOR interacts with other molecular components to form two physically and functionally distinct complexes, namely, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). In mTORC1, the mTOR protein interacts with regulatory-associated protein of mTOR (Raptor; Kim et al., 2002), proline-rich PKB (Akt) substrate of 40 kDa (PRAS40; Sancak et al., 2007), mammalian lethal with SEC13 protein 8 (MLST8; Kim et al., 2003), DEP domain-containing mTOR-interacting protein (DEPTOR; Peterson et al., 2009), Tel two interacting protein 1 (Tti1), and telomere maintenance 2 (Tel2; Kaizuka et al., 2010). On the other hand, mTORC2 comprises mTOR; the scaffold protein rapamycin-insensitive companion of mTOR (Rictor; Sarbassov et al., 2004); mammalian stress-activated protein kinase interacting protein 1 (mSIN1, Jacinto et al., 2006); protein observed with Rictor 1 and 2 (Protor1/2, Pearce et al., 2007); MLST8 (Kim et al., 2003); DEPTOR (Peterson et al., 2009); inhibitor of nuclear factor κ-B kinase (IKK, Xu et al., 2013); Sestrin 3 (Tao, Xiong, Liangpunsakul, & Dong, 2015); exchange factor found in platelets, leukemic, and neuronal tissues (Xpln, Khanna, Fang, Yoon, & Chen, 2013); tuberous sclerosis complex 2 (TSC2; Huang, Dibble, Matsuzaki, & Manning, 2008); and Tel2 and Tti1 (Kaizuka et al., 2010).

While remarkable progress has been made in understanding the role of mTORC1, the contributions of mTORC2 are less well understood. Collectively, many studies have demonstrated that mTORC1 plays a vital role in the regulation of cellular homeostasis, growth and response to stress. mTORC1 activated under nutrient-replete conditions promotes protein synthesis by several complementary mechanisms. First, mTORC1 activates the **ribosomal protein S6 kinase 1** and **ribosomal protein S6 kinase 2** (S6K1/2), which in turn activates the protein translation process (Laplante & Sabatini, 2013; Saxton & Sabatini, 2017). In parallel, mTORC1 inhibits eukaryotic translation initiation factor 4E (eIF4E)-binding protein-1 (4E-BP1) and thus allows the formation of the eIF4F complex that triggers cap-dependent translation (Kennedy & Lamming, 2016; Laplante & Sabatini, 2013; Saxton & Sabatini, 2017). Finally, mTORC1 boosts translation by phosphorylation and consequent inactivation of the target La-related protein 1 (LARP1; Fonseca et al., 2015). When active, LARP1 represses translation of terminal oligopyrimidine mRNAs that encode ribosomal proteins and positive regulators of translation.

mTORC1 modulates cell metabolism, as it increases glycolysis by promoting transcription and translation of hypoxia-induced factor 1α (TNF_{α}, Hudson et al., 2002). It also activates the transcription factor sterol regulatory element-binding proteins 1 and 2 (SREBP1/2), which promote lipogenesis (Kennedy & Lamming, 2016; Laplante & Sabatini, 2013; Saxton & Sabatini, 2017). Further, mTORC1 plays a role in mitochondrial biogenesis through **PPAR-γ**-mediated activation of the transcription factor Ying-Yang 1 (Cunningham et al., 2007; Laplante & Sabatini, 2012). When cells are subjected to stress or nutrient starvation, they undergo a regulated catabolic process termed autophagy. Another well-characterized role of mTORC1 is the inhibition of autophagy under nutrient replete conditions. mTORC1 phosphorylates Unc-51 like autophagy activating kinase (ULK1), preventing its activation via **5′ AMP-activated protein kinase (AMPK)**, which in turn inhibits autophagy (Kim, Kundu, Viollet, & Guan, 2011). The phosphorylation and nuclear translocation of the transcription factor EB (TFEB), which regulates the expression of proteins governing autophagy and lysosomal biogenesis, is inhibited by mTORC1 (Settembre et al., 2012). Recent studies have demonstrated that mTORC1 also contributes to protein turnover via the ubiquitin–proteasome system. Acute inhibition of mTORC1 increases proteasome-dependent proteolysis (Rousseau & Bertolotti, 2016; Zhao et al., 2015a). Interestingly, long-term activation of mTORC1 in mouse embryonic fibroblasts due to deletion of inhibitory Tsc2 also increases proteasome activity (Zhang et al., 2014). This finding was replicated in a mouse model of neuronal Tsc2 deletion and in the liver of a wild-type mice subject to fasting then 6 hr refeeding. The authors suggest that longer term activation of proteasomal pathways by mTORC1 is an adaptive response that supports protein synthesis by replenishing the cellular amino acid pool (Zhang et al., 2014). Two further mTORC1 targets have been identified: (a) The γ isoform of **phosphatidylinositol-5-phosphate 4-kinase (PIP4K2C)** maintains basal mTORC1 signalling during starvation (Mackey, Sarkes, Bettencourt, Asara, & Rameh, 2014); and (b) repressed by TOR (REPTOR) is a downstream effector of TORC1 in *Drosophila melanogaster* (Tiebe et al., 2015). When TORC1 phosphorylates REPTOR, it leads to cytoplasmic retention; in contrast, upon inhibition of TORC1, REPTOR is dephosphorylated, translocates into the nucleus, and activates transcription of target genes involved in energy homeostasis and cellular survival under conditions of nutrient starvation (Tiebe et al., 2015).

Compared to mTORC1, studies and knowledge of mTORC2 regulation and function have lagged behind. One well-characterized role of mTORC2 is its response to growth factors and insulin via **PI3K**-dependent mechanisms (Gan, Wang, Su, & Wu, 2011). mTORC2 directly phosphorylates **Akt** at Ser^{473}, which is facilitated by prior phosphorylation of Thr^{308} by phosphoinositide-dependent kinase 1 (**PDK1**), as part of the insulin cascade (Sarbassov, Guertin, Ali, & Sabatini, 2005). mTORC2 can modulate **PKCα** activity and thereby play a role in remodelling of the actin cytoskeleton (Sarbassov et al., 2004). Similarly, a study by Jacinto et al. (2004) demonstrated that mTORC2 regulates cell polarity and cytoskeletal organization through the regulation of PKCα and Ras homolog gene family member A. mTORC2 has also been demonstrated to regulate other PKC family members, including **PKCδ** (Gan et al., 2012) and **PKCζ** (Li & Gao, 2014). Hydrophobic motif phosphorylation and activation of PKCδ plays a vital role in fibroblast migration and pulmonary fibrosis development (Gan et al., 2012) whereas mTORC2 modulation of PKCζ activity is involved in organization of the actin cytoskeleton (Li & Gao, 2014). Sciarretta et al. (2015) conducted a study showing that mTORC2 negatively regulates the activity of macrophage stimulating 1 (MST1), as disruption of Rictor/mTORC2 leads to a significant activation of MST1. This marked MST1 activation promotes cardiac dilation, cardiac dysfunction, and impaired cardiac growth and adaptation in response to pressure overload.

While mTORC1 and mTORC2 both have distinct functions, there is evidence that these two complexes are interconnected. S6K1, downstream of mTORC1, directly phosphorylates rictor of mTORC2 and promotes a negative regulatory effect on the mTORC2-dependent phosphorylation of Akt-Ser^{473} (Dibble, Asara, & Manning, 2009). mTORC2-activated Akt, in contrast, enhances mTORC1 activity through the inactivation of tuberous sclerosis complex (TSC1/2), a complex that inhibits mTORC1 via GTPase-activating protein activity towards Ras homologue enriched in the brain (Dibble et al., 2012).

We will discuss the manner in which current knowledge of mTOR relates to recent studies demonstrating that adrenoceptor agonists increase activation of mTORC1-mediated cell growth and also mTORC2-mediated glucose uptake and cell survival in vivo and in vitro (Olsen et al., 2014; Sato et al., 2014; Sato et al., 2018). We have focused this review on the interplay between adrenoceptors and mTOR in skeletal and cardiac muscle as well as adipose tissue, in light of our own expertise and the need to assimilate considerable information that is now available for these tissues. However, given the ubiquitous expression of mTOR and its partner proteins, as well as widespread expression of different adrenoceptor subtypes, it is highly likely that adrenoceptor–mTOR pathways are important in additional cell types. For example, there are a number of studies linking activation of hippocampal β-adrenoceptors with mTOR-dependent increases in protein translation (Connor, Wang, & Nguyen, 2011; Gelinas et al., 2007). These mechanisms are critical for long-term potentiation and memory consolidation.

1.1 | Role of β_2-adrenoceptor-mediated mTOR activation in skeletal muscle

Skeletal muscle comprises up to 50% of total body mass, consumes a significant proportion of metabolic fuel, and has a major role in whole-body metabolic homeostasis, being responsible for 75% of insulin-mediated glucose uptake and utilization in the fed state. There is evidence showing that the sympathetic nervous system promotes glucose uptake in active skeletal muscle (e.g., during exercise and fight-or-flight responses), which results primarily from noradrenaline release from adrenergic nerve terminals, acting on β-adrenoceptors at the cell surface (Nonogaki, 2000). Skeletal muscle expresses abundant β-adrenoceptors that are predominantly β_2-adrenoceptors, with 7–10% β_1-adrenoceptors and no detectable β_3-adrenoceptors (Nevzorova, Bengtsson, Evans, & Summers, 2002). Stimulation with the β-adrenoceptor agonist isoprenaline promotes glucose uptake in L6 myoblasts and myotubes, and intact skeletal muscle in vitro and in vivo (Nevzorova, Evans, Bengtsson, & Summers, 2006; Sato et al., 2014). Notably, isoprenaline increases glucose uptake to a greater extent than insulin in vivo in wild-type mice, but not in β_1/β_2-adrenoceptor knockout mice (Sato, Dehvari, Oberg, Dallner, et al., 2014), consistent with another study showing that mice lacking all three β-adrenoceptors display glucose intolerance (Asensio, Jimenez, Kuhne, Rohner-Jeanrenaud, & Muzzin, 2005).

Insulin stimulates skeletal muscle glucose uptake by activating signalling steps that increase the translocation of **glucose transporter 4 (GLUT4)** from intracellular vesicles to the cell surface. Following insulin-mediated increases in PI3K activity, **phosphatidylinositol 3,4,5-trisphosphate (PIP_3)** recruits PDK1 and inactive Akt to the plasma membrane via N-terminal PH domains, facilitating Akt phosphorylation at Thr^{308} by PDK1. In parallel, mTORC2 is phosphorylated via unknown mechanisms. A conformational change in Akt associated with phosphorylation of Thr^{308} enables mTORC2 to phosphorylate Akt at Ser^{473}, leading to full activation. Akt promotes subsequent phosphorylation of the Rab GTPase-activating protein Akt substrate of 160 kDa (AS160) at Thr642, which is critical for insulin-increased GLUT4 translocation (Figure 1). Our previous studies showed that isoprenaline-stimulated glucose uptake in L6 muscle cells was markedly reduced by the PI3K inhibitors **PI-103**, **wortmannin**, and **LY294002** (Sato, Dehvari, Oberg, Dallner, et al., 2014), suggesting that insulin receptor and β_2-adrenoceptor-mediated glucose uptake may share a common signalling pathway. Unlike responses, we observed to insulin; however, there was no Akt phosphorylation at Thr^{308} or Ser^{473}, or AS160 phosphorylation at Thr^{642} upon isoprenaline treatment, nor any increase in PIP_3 levels, and glucose uptake was not inhibited by **Akt inhibitor X** (Nevzorova et al., 2002; Nevzorova et al., 2006; Sato, Dehvari, Oberg, Dallner, et al., 2014). Earlier studies demonstrated that PI-103 and other widely used PI3K inhibitors including wortmannin and LY294002 have substantial affinity for related kinases including mTOR (Brunn et al., 1996; Knight et al., 2006). It is thus clearly important to consider the involvement of mTOR as well as PI3K when interpreting inhibitory effects of LY294002, wortmannin, or PI-103 on downstream signalling outputs. In light of this, we found that the highly specific mTOR inhibitor **KU0063794** (Sato, Dehvari, Oberg, Dallner, et al., 2014) inhibited both isoprenaline and insulin-stimulated glucose uptake indicating that mTOR is involved in adrenoceptor-stimulated glucose uptake. The combined results show that the pathways shared by insulin and isoprenaline overlap at a more downstream point leading to mTOR activation, and the β_2-adrenoceptor-associated pathway does not include PI3K or Akt. siRNA knockdown of mTORC2 (rictor), but not mTORC1 (raptor), markedly inhibits both insulin-mediated and β_2-adrenoceptor-mediated glucose uptake (Sato, Dehvari, Oberg, Dallner, et al., 2014). In addition, in muscle lacking rictor, insulin-stimulated Akt phosphorylation at Ser^{473} and AS160 at Thr^{642} are dramatically decreased, and muscle-specific rictor knockout mice display glucose intolerance and decreased insulin-stimulated glucose uptake (Kumar et al., 2008). This confirms mTORC2 as a key regulator of glucose uptake in skeletal muscle. Confirming this, we found that KU0063794 also inhibits β_2-adrenoceptor-mediated skeletal muscle glucose uptake ex vivo and in vivo (Sato, Dehvari, Oberg, Dallner, et al., 2014).

The β_2-adrenoceptor couples primarily to $G\alpha_s$ proteins, activating **adenylyl cyclase** to increase intracellular **cAMP** levels, resulting in **PKA** activation. β_2-Adrenoceptor stimulation can also cause cellular effects independently of this classical cAMP–PKA pathway. After agonist stimulation, β_2-adrenoceptors are rapidly phosphorylated by **G protein receptor kinases (GRKs)**, allowing recruitment of β-arrestins (which uncouple the receptor from its Gα protein partners), receptor internalization, and activation of β-arrestin-mediated signalling pathways (Tobin, Butcher, & Kong, 2008). The signalling effectors linking the β_2-adrenoceptor with activation of mTORC2 are still unknown

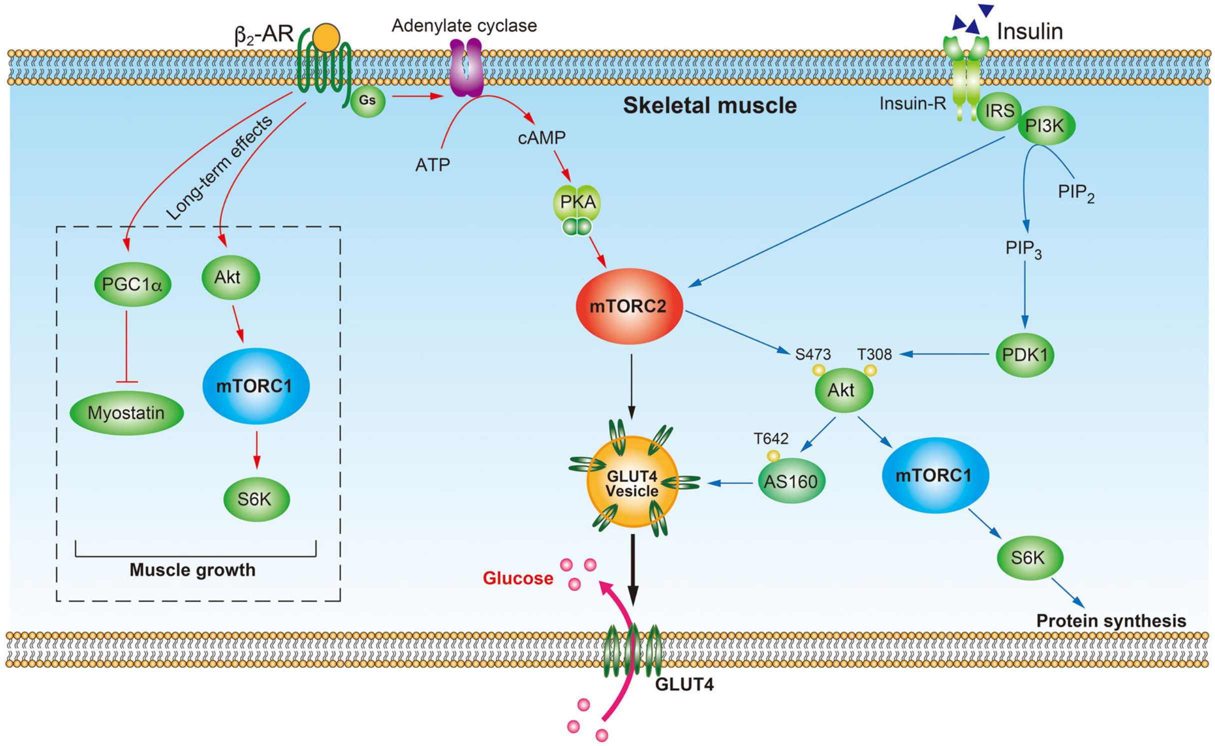

FIGURE 1 Proposed mechanisms for β_2-adrenoceptor-mediated mTOR signalling in skeletal muscle. In skeletal muscle, activation of the β_2-adrenoceptor (β_2-AR) coupled to Gα_s stimulates adenylate cyclase, leading to cAMP accumulation. cAMP activates PKA, which then phosphorylates mTORC2. The phosphorylated mTORC2 and GRK2 stimulates translocation of GLUT4 vesicles from the cytosol to the plasma membrane, leading to increased glucose uptake. The long-term stimulation of β_2-adrenoceptors causes activation of the Akt–mTORC1–S6K pathway and inhibition of myostatin production by PGC1α, which contributes to muscle growth. Insulin binds to the insulin receptor (Insulin-R), resulting in activation of PI3K. PI3K then increases levels of PIP$_3$, which activates PDK1 to phosphorylate Akt at Thr^{308}. PI3K also activates mTORC2, which phosphorylates Akt at Ser^{473}. Fully activated Akt phosphorylates AS160 to promote GLUT4 translocation to the plasma membrane leading to increased glucose uptake. Akt also phosphorylates mTORC1 and thereby promotes protein synthesis

but may be downstream of PKA as the selective PKA inhibitor PKI decreases isoprenaline-induced mTORC2 phosphorylation, and 8-bromo-cAMP increases mTORC2 phosphorylation (Sato, Dehvari, Oberg, Dallner, et al., 2014). Interestingly, β_2-adrenoceptor-stimulated glucose uptake is only partly dependent on cAMP (Nevzorova et al., 2002; Nevzorova et al., 2006; Sato, Dehvari, Oberg, Dallner, et al., 2014), suggesting contributions from alternative effectors that are cAMP-independent. Involvement of **GRK2** in β_2-adrenoceptor-mediated glucose homeostasis has been suggested as one possible mechanism (Dehvari et al., 2012). CHO-K1 cells stably expressing the human GLUT4 carrying an exofacial c-Myc epitope (CHO-GLUT4myc) were transfected with wild type or a truncated β_2-adrenoceptor lacking the entire C-terminal tail, or co-transfected with wild-type β_2-adrenoceptor and βARKct, which sequesters Gβγ subunits required for GRK2 recruitment to the plasma membrane. Cells expressing wild-type β_2-adrenoceptor plus βARKct, or the truncated receptor alone, showed markedly reduced isoprenaline-stimulated glucose uptake compared with cells expressing the wild-type β_2-adrenoceptor only. In addition, CHO-GLUT4myc cells expressing a kinase-dead GRK2 K220R mutant displayed significantly decreased GLUT4 translocation to the cell surface (Dehvari et al., 2012). Collectively, our studies indicate the potential role of GRK2 and PKA as upstream kinases of mTORC2 following activation of β_2-adrenoceptors.

Glucose uptake mediated by β_2-adrenoceptors is blocked by GLUT inhibitors and by pretreatment with GLUT4 siRNA (Sato, Dehvari, Oberg, Dallner, et al., 2014). Type 2 diabetes is closely associated with defects in insulin signalling mechanisms involving insulin receptor substrates (Chakrabarti et al., 2013), PI3K activity, and Akt phosphorylation (Cusi et al., 2000), but β_2-adrenoceptors expressed in skeletal muscle could bypass these defects through mTORC2-mediated regulation of GLUT4 trafficking, providing a compensatory pathway following loss of insulin sensitivity (Sato et al., 2014; Sato, Dehvari, Oberg, Dallner, et al., 2014). This is of particular interest considering that β_2-adrenoceptor expression is unaltered in skeletal muscle from diabetic patients (Frederiksen et al., 2008).

Apart from being important for glucose uptake, β_2-adrenoceptor-stimulated cAMP accumulation can have long-term effects on muscle phenotype (Pearen, Ryall, Lynch, & Muscat, 2009). Chronic stimulation of skeletal muscle β_2-adrenoceptors utilizing agonists such as clenbuterol, **fenoterol**, and **formoterol** can activate anabolic signalling pathways, leading to increased muscle mass and force-producing capacity (Lynch & Ryall, 2008) The anabolic and anti-catabolic processes in response to β_2-adrenoceptor agonists occur via protein translation and synthesis mediated by the Akt–mTOR–S6 kinase signalling axis (Hagg et al., 2016; Figure 1). Chronic stimulation of β_2-adrenoceptors increases the transcription of PPAR-γ coactivator 1-α, which is associated with the suppression of myostatin, and these effects are blocked by **ICI-118,551**, a highly selective β_2-adrenoceptor antagonist (Jesinkey, Korrapati, Rasbach, Beeson, & Schnellmann, 2014). Treatment of mice with formoterol stimulates small but significant increases in the phosphorylation of Akt and mTOR in gastrocnemius muscle after 8 hr, differing in time frame from more acute measurements of Akt/mTOR phosphorylation and glucose uptake (10 min to 2 hr; Sato, Dehvari, Oberg, Dallner, et al., 2014). Dexamethasone-induced muscular atrophy and slow-to-fast myosin heavy chain isoform transition is antagonized by the β_2-adrenoceptor agonist clenbuterol, which stimulates Akt and mTORC1 activity, and **insulin-like growth factor 1** expression (Jesinkey et al., 2014). These findings could potentially provide a new basis for a pharmacological approach to target mTOR for the treatment of conditions involving muscle loss.

1.2 | The role of adrenoceptor-mediated mTOR activation in the heart

1.2.1 | α_1-adrenoceptors and mTOR in the heart

Cardiac function is tightly regulated via both α_1- and β-adrenoceptors, due to release of noradrenaline from sympathetic nerve terminals innervating the heart and by circulating adrenaline released from the adrenal gland in response to danger or stress. The β-adrenoceptors comprise roughly 90% of total cardiac adrenoceptors, and the α_1- adrenoceptors account for the remaining 10%. In heart failure, unlike β_1-adrenoceptors, α_1- adrenoceptors are not down-regulated and may therefore play an enhanced role in regulating cardiac contractility (Skomedal, Borthne, Aass, Geiran, & Osnes, 1997). Although mRNAs for all three α_1-adrenoceptor subtypes are detected in the heart of mice and rats, cardiomyocytes express only the **α_{1A}**- and **α_{1B}**-subtypes (O'Connell et al., 2003) while **α_{1D}-adrenoceptors** are confined to the coronary vasculature (McCloskey et al., 2003; O'Connell et al., 2003). Due to the putative enhanced role in heart failure, α_1- adrenoceptor function and signalling are therefore of particular interest.

A series of knockout mouse studies indicate that neither α_{1A}- nor α_{1B}- adrenoceptors are required for basal contractile function (O'Connell et al., 2003; Vecchione et al., 2002). However, cardiomyocyte-specific overexpression of the α_{1A}- adrenoceptor enhances basal contractile function (Lin et al., 2001) and reduces adverse remodelling following pressure overload (Du et al., 2004; Du et al., 2006). These results are consistent with an in vitro study by Mohl et al. (2011), identifying an α_{1A}- adrenoceptor-mediated signalling pathway that increases calcium entry and cardiomyocyte contractility. In contrast, overexpression of the α_{1B}-adrenoceptor causes depressed contractile function and pathological remodelling in the heart (Lemire et al., 2001; Wang, Du, Autelitano, Milano, & Woodcock, 2000). The capacity of α_{1A}- adrenoceptors to increase contractile function may have important compensatory roles in the failing heart.

In addition to maintaining myocyte contractility, activation of α_1-adrenoceptors promotes glucose uptake (Shi, Papay, & Perez, 2016), receptor-mediated preconditioning, cardiac hypertrophy, and inhibition of cardiomyocyte apoptosis (Jensen, O'Connell, & Simpson, 2011; O'Connell, Jensen, Baker, & Simpson, 2014). α_1-adrenoceptors are expressed in human myocardium and are not down-regulated in heart failure (Jensen, Swigart, De Marco, Hoopes, & Simpson, 2009), and blockade of α_1- adrenoceptors worsens heart failure (Dhaliwal et al., 2009; Jensen et al., 2011). In murine cardiac myocytes that express endogenous α_{1A}- and α_{1B}- adrenoceptors, long-term agonist treatment increases the abundance of α_{1A}- adrenoceptors without desensitization of inotropic effects, while increased stimulation or expression of the α_{1A}- but not the α_{1B}- adrenoceptor in vivo limits global cardiac remodelling and reduces mortality from heart failure (Du et al., 2006; Rorabaugh et al., 2005). In a transgenic rat model that overexpresses the cardiomyocyte α_{1A}-adrenoceptors, animals are protected from heart failure by increased angiogenesis associated with secretion of **VEGF** from cardiomyocytes (Zhao, Zhai, Gygi, & Goldberg, 2015).

In vitro and in vivo studies have indicated that stimulation of α_1-adrenoceptors reduces cardiomyocyte cell death. Hypoxia-, serum starvation-, and isoprenaline-induced apoptosis can be inhibited by exposure of cardiomyocytes to **phenylephrine**, a non-selective α_1-adrenoceptor agonist. This phenylephrine cytoprotective effect was blocked by **phentolamine** and **prazosin** (Iwai-Kanai et al., 1999). Cardiomyocytes from α_{1A}-/α_{1B}-adrenoceptor knockout mice display significantly increased necrosis and apoptosis when subject to toxic stimuli such as doxorubicin or H_2O_2 (Huang et al., 2007; O'Connell et al., 2006), and this sensitivity can be reduced by re-expression of α_{1A}- adrenoceptors but not α_{1B}-adrenoceptors (Huang et al., 2007). The chemotherapeutic agent **doxorubicin** produces cardiotoxic effects in patients and in animal models. In mice, long-term in vivo infusion of the α_{1A}- adrenoceptor agonist **A61603** protects cardiomyocytes against apoptosis and reduces adverse ventricular remodelling and myocardial fibrosis following doxorubicin treatment, thereby improving cardiac function (Chan, Dash, & Simpson, 2008; Montgomery et al., 2017). These protective effects of A61603 are not observed in α_{1A}- adrenoceptor knockout mice. Another study showed that **dabuzalgron**, an orally available, selective α_{1A}- adrenoceptor agonist also increases survival and preserves fractional shortening in wild-type but not in α_{1A}- adrenoceptor knockout mice (Beak et al., 2017). All of these studies indicate that α_1- adrenoceptors could be an important target in the failing heart.

The non-selective α_1- adrenoceptor agonist phenylephrine is a well-known hypertrophic agent in the heart and has been linked to activation of the mTORC1 target S6K1 (Boluyt et al., 1997). Treatment of neonatal rat ventricular myocytes (NRVMs) with phenylephrine stimulated the activity of S6K1, increased protein synthesis, and produced a 50% increase in cardiomyocyte area. Phenylephrine-induced S6K1 activity and hypertrophy were significantly reduced by the mTORC1 inhibitor **rapamycin** and by the PI3K inhibitor LY294002; however, the authors acknowledge that compounds such as LY294002 affect other PI3K-related kinases (Boluyt et al., 1997). As outlined in the skeletal muscle section of this review, PI3K inhibitors including wortmannin and LY294002 have substantial activity at mTOR (Brunn et al., 1996; Knight et al., 2006). Thus, studies in which LY294002 is used as a sole PI3K inhibitor should be regarded with caution. Taken together, these results suggest that phenylephrine activates S6K1 and promotes cardiomyocyte hypertrophy via mTORC1 and possibly PI3K. We have shown recently that treatment of NRVMs with the highly selective α_{1A}-AR agonist A61603 increases phosphorylation of S6 ribosomal protein, a downstream target of mTORC1 and S6K1, and this is inhibited by rapamycin. NRVM hypertrophy observed in response to A61603 was prevented by the mTOR inhibitor KU0063794, which blocks the phosphorylation and activation of both mTORC1 and mTORC2 (Sato et al., 2018). It is thus clear that α_1-adrenoceptors stimulate mTORC1 and that this could be an important player in the ability of α_1-adrenoceptors to protect the heart.

Phenylephrine stimulates activation of S6K1 and phosphorylation of 4E-BP1 in adult cardiomyocytes (Wang & Proud, 2002). The latter protein interacts with eIF4E and represses translation. Phosphorylation of 4E-BP results in its dissociation from eIF4E and activation of mRNA translation. The response to phenylephrine was blocked by MEK inhibitors, and adenoviral expression of constitutively active MEK caused activation of S6K1, phosphorylation of 4E-BP1, and activation of protein synthesis in a rapamycin-sensitive manner. This study provides insight into a signalling pathway involving Ras, MEK, and mTOR (Wang & Proud, 2002). Phenylephrine also activates S6K2 in adult rat ventricular cardiomyocytes. Both MEK1/2 inhibitors and rapamycin abolished phenylephrine-induced activation of S6K2, and the expression of constitutively active **MEK1** activated S6K2. This indicates that MEK/**ERK1/2** in combination with mTOR signalling plays a role in regulating phenylephrine-induced S6K2 activation (Wang, Gout, & Proud, 2001).

Although the classic α_1- adrenoceptor signalling pathway includes Ca^{2+}-dependent PKC, phenylephrine also regulates S6K1/2 and 4E-BP1 (downstream substrates of mTORC1) leading to protein synthesis in a Ca^{2+}-independent PKC manner in adult cardiomyocytes (Wang, Rolfe, & Proud, 2003). The classical Ca^{2+}-dependent PKCα and the Ca^{2+}-independent PKCδ and **PKCε** are readily detected in adult cardiomyocytes (Puceat, Hilal-Dandan, Strulovici, Brunton, & Brown, 1994; Steinberg, Goldberg, & Rybin, 1995). In addition, Ca^{2+}-independent PKC is also required for the phenylephrine-induced ERK1/2 activation demonstrated by the significantly reduced ERK1/2 activation in the presence of the broad-spectrum PKC inhibitor BIM I (Toullec et al., 1991). **Rottlerin** (Gschwendt et al., 1994), a selective inhibitor of PKCδ, almost completely inhibited the phenylephrine-induced ERK1/2 phosphorylation, while Gö6979 (Martiny-Baron et al., 1993), an inhibitor of Ca^{2+}-dependent PKC has no obvious effect on ERK1/2 activation. Furthermore, Rottlerin prevented phenylephrine-induced S6K activation whereas Gö6979 had no apparent effects. Phosphorylation of 4E-BP1 was also inhibited by **rottlerin** in a similar manner (Wang et al., 2003). These data suggest Ca^{2+}-independent PKC isoforms play a vital role in α_1-adrenoceptor-mediated mTOR signalling in adult cardiomyocytes.

While mTORC1 plays an important role in cardiomyocyte hypertrophy, there is convincing evidence that mTORC2 promotes cardiomyocyte development and survival (Gonzalez-Teran et al., 2016; Shende et al., 2016; Xu & Brink, 2016). For example, mice with cardiomyocyte-specific knockdown of rictor and thus disruption of mTORC2 display abnormalities by the age of 6 months, including cardiac dilation, fibrosis, and exacerbated heart failure in response to pressure overload (Sciarretta et al., 2015; Yano et al., 2014). Following ischaemic preconditioning, activation of mTORC2 promotes cardiomyocyte survival in part by suppressing activity of the kinase **Mst1** (large tumour suppressor kinase 2), a key component of the Hippo pathway that promotes apoptosis and inhibits cell growth (Sciarretta et al., 2015; Yano et al., 2014). Importantly, cardiomyocytes that are rictor-deficient or overexpress Mst1 display increased cell death. In the study by Shende et al. (2016), tamoxifen-inducible cardiomyocyte-specific rictor knockdown was used to allow normal cardiac development. Mice in which Cre recombinase expression was induced at 4 or 10 weeks of age displayed normal cardiac size and echocardiography up to 44 weeks after tamoxifen treatment, but transverse aortic constriction and resultant pressure overload caused more pronounced cardiac dysfunction than in wild-type mice, indicating the importance of mTORC2 in the failing heart (Shende et al., 2016; Volkers et al., 2013).

Cardiac α_1-adrenoceptorshave been linked with mTOR in exerting cardioprotective effects. **Serum and glucocorticoid-responsive kinase-1 (SGK1)** is a downstream substrate of mTORC2 (Garcia-Martinez & Alessi, 2008) that regulates cardiomyocyte survival and hypertrophy in response to the non-selective α_1-adrenoceptor agonist phenylephrine, both in vivo and in vitro (Aoyama et al., 2005). Cardiomyocytes infected with an adenoviral vector encoding constitutively active SGK1 show reduced apoptosis after serum- or oxygen-deprivation and increased [^{3}H]-leucine incorporation in response to phenylephrine, while expression of kinase-dead SGK1 increases apoptosis. SGK1 has also been placed downstream of PI3K (Park et al., 1999), although again inhibition of mTOR may have confounded the interpretation of these experiments involving the use of LY294002 as a PI3K inhibitor.

We have demonstrated that noradrenaline and the α_{1A}-adrenoceptor agonist A61603 increase glucose uptake in NRVMs by parallel activation of AMPK and mTORC2 but do not promote phosphorylation of Akt at Thr^{308} or Ser^{473} (Sato et al., 2018). The lack of Akt phosphorylation mirrors similar findings by Wang et al. (2001), who demonstrated using adult cardiomyocytes that phenylephrine does not produce Akt phosphorylation at Ser^{473} and that adenoviral expression of a dominant-negative Akt mutant fails to block activation of S6K2 by phenylephrine. We found that the mTORC1/2 inhibitor KU0063794 partly reduced α_{1A}- adrenoceptor and insulin-stimulated glucose uptake in cardiomyocytes, whereas the mTORC1 inhibitor rapamycin had no effect. A61603 stimulated the phosphorylation of mTOR at Ser^{2448} and Ser^{2481}. Overall, the data suggest that α_{1A}-adrenoceptors stimulate mTORC2 to increase glucose uptake and mTORC1 to promote protein synthesis and hypertrophy in NRVMs (Sato et al., 2018; Figure 2), but the detailed mechanism whereby α_{1A}-adrenoceptors activate mTORC2 is still not known.

1.2.2 | β- adrenoceptors and mTOR in the heart

Both β_1- and β_2-adrenoceptors are expressed in the mammalian heart, although in isolated cardiomyocytes, the β_1-adrenoceptor is

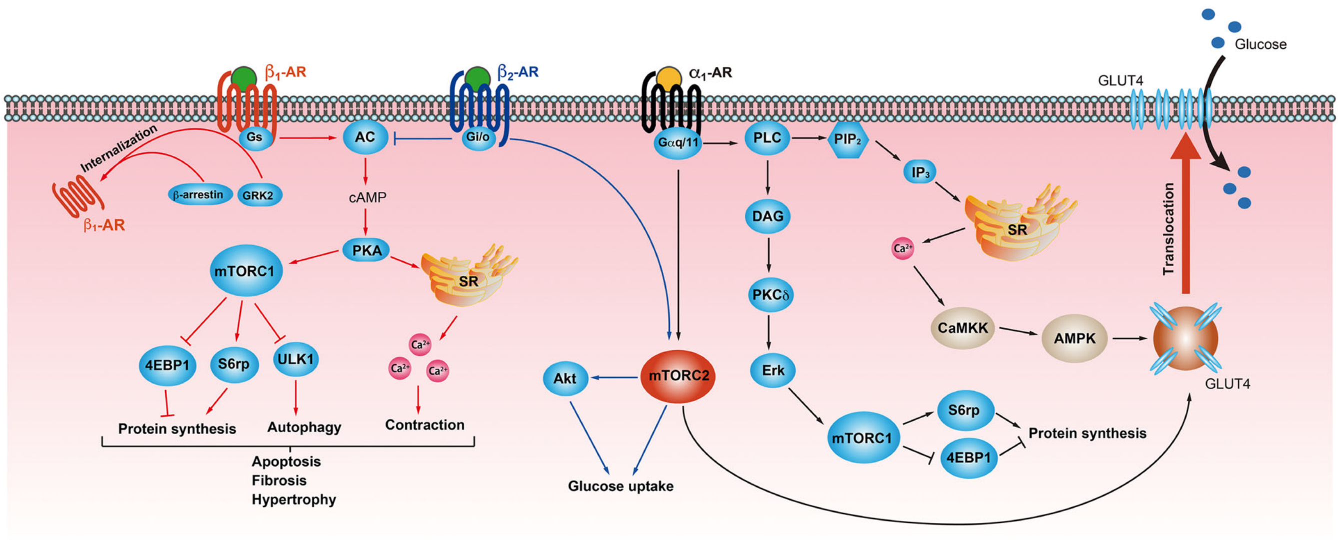

FIGURE 2 Proposed mechanisms for mTOR signalling in the heart, mediated by α_1- and β-adrenoceptors. Activation of α_1-adrenoceptors (α_1-AR) results in increased levels of cytosolic Ca^{2+} through a classical pathway involving $G\alpha_{q/11}$, PLC, phosphatidylinositol bisphosphate (PIP_2), and inositol trisphosphate (IP_3). Release of intracellular Ca^{2+} activates CaMKK and AMPK pathways. α_1-Adrenoceptors also activate mTORC2 via unknown mechanisms. AMPK and mTORC2 both play significant roles in GLUT4 translocation to the plasma membrane, resulting in increased glucose uptake. α_1-Adrenoceptors promote mTORC1 activation via diacyl glycerol (DAG), PKCδ, and Erk1/2, leading to increased activation of S6rp and 4EBP1, which promote protein translation. β_1- and β_2-adrenoceptors (β_1- AR, β_2-AR) both couple to $G\alpha_s$, whereas β_2-adrenoceptors switch coupling to $G\alpha_{i/o}$ in pathological states such as heart failure. Overstimulation of β_1-adrenoceptors increases Ca^{2+} mobilization and mTORC1 activation leading to increased protein synthesis and inhibition of autophagy, resulting in apoptosis, fibrosis, and hypertrophy. In the later stages of heart failure, GRK2 overexpression results in adrenoceptor phosphorylation and interaction with β-arrestin, thereby promoting receptor internalization. Activation of the β_2-adrenoceptor–$G\alpha_{i/o}$ pathway inhibits cAMP production and counteracts the pro-apoptotic effects of excessive β_1- adrenoceptor stimulation. The β_2-adrenoceptors stimulate glucose uptake through mTORC2-Akt activation

the predominant subtype (Buxton & Brunton, 1985). In the human heart, the abundance of β_1-adrenoceptor protein in cardiomyocytes is 68–80 fmol·mg^{-1} protein, and it decreases to 30–41 fmol·mg^{-1} protein in failing hearts (Bristow et al., 1993; Morisco et al., 2008). Both β_1- and β_2- adrenoceptor subtypes are present in large coronary arteries (Young, Vatner, & Vatner, 1990), while the primary subtype found in fibroblasts and on the small vessel endothelium is the β_2-adrenoceptor (Freissmuth, Hausleithner, Nees, Bock, & Schutz, 1986; Zhou & Pu, 2016).

Activation of β-adrenoceptors plays an important role in the regulation of cardiovascular function, including positive inotropic and chronotropic effects (Bristow et al., 1993; Brodde, 1991). Noradrenaline exerts its effects on the heart nearly exclusively via β_1-adrenoceptors (Kaumann, Hall, Murray, Wells, & Brown, 1989). Thus, under normal physiological conditions β_1-adrenoceptors are the predominant cardiac adrenoceptors responsible for regulation of heart rate and contractility. The β_1-adrenoceptors activate the canonical $G\alpha_s$-adenylate cyclase-cAMP-PKA signalling cascade. In cardiomyocytes, the activation of PKA promotes phosphorylation of multiple proteins that increase calcium mobilization primarily from the sarcoplasmic reticulum and, to a lesser extent, from the extracellular milieu, leading to increased rates of contraction and relaxation and to increased force of contraction (Sirenko et al., 2014; Figure 2). In the early stages of heart failure, cardiac output is increased via overstimulation of β_1-adrenoceptors as a compensatory mechanism for the insufficient blood and oxygen supply (Brodde, 1993), but this leads to longer term structural damage, including ventricular remodelling, cardiomyocyte apoptosis and fibrosis, and cardiac hypertrophy (Engelhardt, Hein, Wiesmann, & Lohse, 1999; O'Connor et al., 1999). In addition, recent evidence has shown that β_1-adrenoceptors decrease myocardial autophagy that maintains cellular homeostasis (Wang et al., 2013; Wang et al., 2015). Inhibition of autophagy causes the accumulation of denatured proteins and damaged organelles, contributing to cardiac dysfunction (Magnusson, Wallukat, Waagstein, Hjalmarson, & Hoebeke, 1994), and up-regulation of autophagy by the mTORC1 inhibitor rapamycin can improve impaired cardiac function (Wang et al., 2015). The β_1-adrenoceptor-mediated inhibition of autophagy occurs via PKA phosphorylation of Ser^{12} in the autophagy-related protein LC3 (Kroemer, Zamzami, & Susin, 1997). mTORC1 is overactive in the early stages of heart failure and plays a role in the β_1-adrenoceptor-mediated inhibition of autophagy (Wang et al., 2015; Figure 2).

Cardiac β_1-adrenoceptors become desensitized and down-regulated as heart failure progresses to end-stage dilated cardiomyopathy (Bohm et al., 1988). Desensitization is related in part to an increased abundance and activity of GRK2, the predominant GRK subtype in the heart (Cannavo, Liccardo, & Koch, 2013). Phosphorylation of β_1-adrenoceptors by GRK2 leads to increased interaction with β-arrestin, thereby promoting receptor internalization and degradation (Rockman, Koch, & Lefkowitz, 2002; Figure 2). The β_2-adrenoceptors, on the other hand, are pleiotropic receptors that couple to $G\alpha_s$, $G\alpha_{i/o}$, and $G\beta\gamma$ (Evans, Sato, Sarwar, Hutchinson, & Summers, 2010; Xiao, Cheng, Zhou, Kuschel, & Lakatta, 1999). In the healthy human heart,

β_2-adrenoceptors preferentially couple to $G\alpha_s$ proteins, whereas in pathological states involving high circulating catecholamine levels and high expression levels of cardiac $G\alpha_{i/o}$ proteins during congestive heart failure, the β_2-adrenoceptors switch to $G\alpha_{i/o}$ signalling (Brown & Harding, 1992; Woo, Song, Xiao, & Zhu, 2015). Activation of the β_2-adrenoceptor–$G\alpha_{i/o}$ pathway inhibits cAMP production and protects cardiomyocytes from the pro-apoptotic effects of excessive β_1-adrenoceptor stimulation (Chesley et al., 2000; Zhu et al., 2001). β_2-adrenoceptor-$G\alpha_{i/o}$ signalling also activates Akt, which is known to be activated by PI3K and mTORC2 (Figure 2). The Akt signalling cascade is known to promote protein synthesis and glucose uptake in cardiomyocytes (Chesley et al., 2000).

1.3 | The role of β-adrenoceptors and mTOR in adipose tissue

There are two types of adipose tissue with distinct physiological functions: white adipose tissue (WAT) that stores chemical energy as triacylglycerol; and BAT that releases chemical energy as heat (thermogenesis). BAT is responsible for sympathetically mediated non-shivering thermogenesis in mammals and is activated by members of the adrenoceptor family (Cannon & Nedergaard, 2004). In addition, many groups have described the existence of brown adipocytes in depots thought to be primarily WAT, both in animal models and in humans (Petrovic et al., 2010; Wu et al., 2012). These cells differ from prototypical BAT found in rodents or human infants and have been termed “brite” (brown in white) or “beige” adipocytes (Petrovic et al., 2010; Wu et al., 2012). The appearance of brite adipocytes per se is insufficient to promote increased energy expenditure, as these cells must also be activated by environmental, hormonal, or pharmacological stimuli such as drugs acting at GPCRs (Merlin et al., 2016). The expression of adrenoceptors in brown, white, and brite adipocytes and their contribution to adipocyte function is described in detail in an accompanying review (Evans, Merlin, Bengtsson, & Hutchinson, 2019). We will focus here on the interplay between adrenoceptor signalling and the role of mTOR complexes in adipocyte browning and glucose metabolism.

1.3.1 | β-adrenoceptors and mTOR in WAT

When nutrients are plentiful, insulin is released from the pancreas and stimulates the uptake of glucose and fatty acids by adipose tissue, where they are stored as triacylglycerol forming lipid droplets. Insulin signalling in adipocytes is mediated by the PI3K–Akt–mTOR pathway, producing anabolic effects including cell growth and inhibition of lipolysis (Chakrabarti et al., 2013). During periods of fasting or stress, catecholamines are released by the sympathetic nervous system to activate β-adrenoceptors. Stimulation of the β_3-adrenoceptors in WAT activates adenylyl cyclase, leading to increased cAMP levels and PKA activity. PKA phosphorylates and regulates several important targets in adipocytes, including hormone-sensitive lipase and the lipid droplet-associated perilipins, which collectively promote triglyceride hydrolysis and liberation of free fatty acids (Granneman & Moore, 2008; Figure 3).

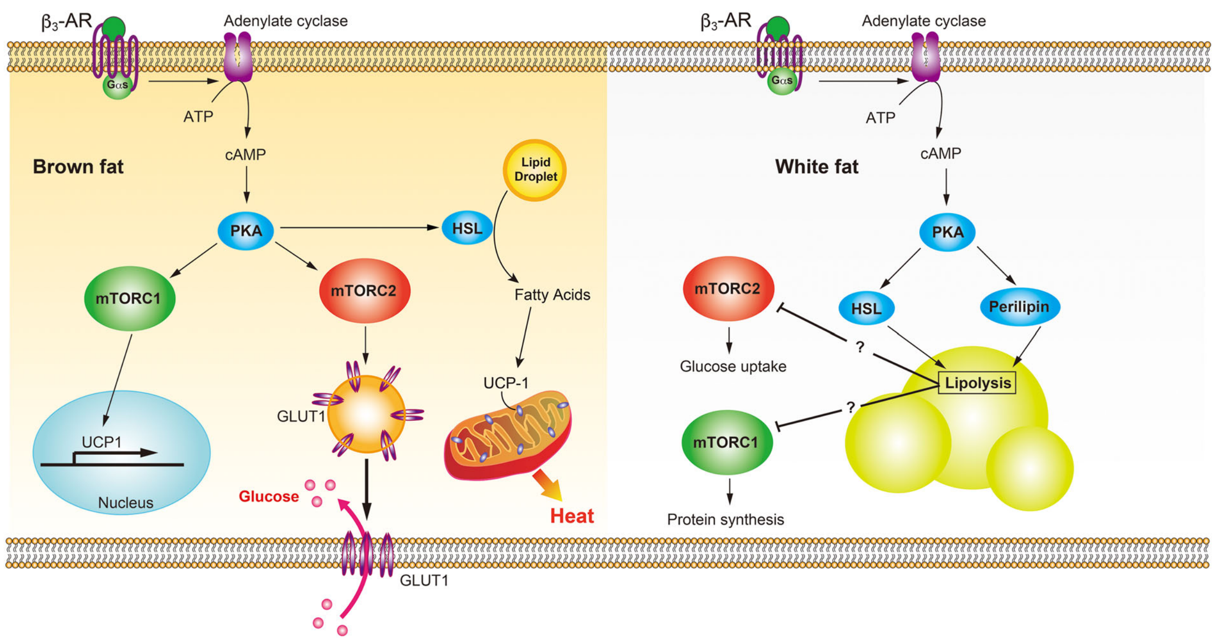

FIGURE 3 mTOR signalling pathways stimulated by β_3-adrenoceptors (β_3-AR) in BAT and WAT. Stimulation of these receptors increases the production of cAMP via $G\alpha_s$-adenylate cyclase and enhances activation of PKA in BAT and WAT. In brown adipocytes, PKA promotes the transcription and translation of UCP1 via mTORC1. The increased abundance and activation of UCP1 in mitochondria by free fatty acids promotes thermogenesis. GLUT1 translocation is increased due to mTORC2 activation, leading to increased glucose uptake. In white adipocytes, β_3-adrenoceptor-mediated PKA activation leads to phosphorylation of hormone-sensitive lipase (HSL) and perilipin. Phosphorylated perilipin undergoes a conformational change and interacts with lipid droplet HSL, which then hydrolyses the stored triglycerides into fatty acids. Lipolytic products may inhibit mTORC1-mediated protein synthesis and mTORC2-mediated glucose uptake in white adipocytes

Two studies have suggested that adrenoceptor-stimulated lipolysis inactivates mTOR in WAT (Mullins et al., 2014; Scott & Lawrence, 1998). Mullins et al. (2014) demonstrated that β-adrenoceptor-mediated lipolysis suppresses glucose uptake because lipolysis causes both mTORC1 and mTORC2 complexes to dissociate (Figure 3). This is in agreement with the proposal that in white adipocytes, cAMP indirectly prevents activation of mTOR, since there is a decrease in **p70S6K**, a downstream target of mTORC1 (Scott & Lawrence, 1998). Conversely, there are new studies indicating that stimulation of β_3-adrenoceptors in WAT does not inhibit mTOR complexes but instead activates mTORC1 through PKA (Liu et al., 2016), resulting in browning of WAT depots. This variance in results might be due to the fact that β-adrenoceptor stimulation interacts differently with mTOR in different WAT depots. Nonetheless, these results suggest that β-adrenoceptor regulation of mTOR could have an important role in WAT function.

1.3.2 | β-adrenoceptors and mTOR in BAT

Binding of noradrenaline to BAT β-adrenoceptors activates intracellular signalling cascades leading to increased expression of **uncoupling protein 1 (UCP1)** and breakdown of triglycerides to free fatty acids that activate UCP1 in the inner mitochondrial membrane (Figure 3). Activated UCP1 collapses the proton gradient that drives ATP synthesis and energy storage; thus, β-adrenoceptor signalling increases mitochondrial respiration and non-shivering thermogenesis (Cannon & Nedergaard, 2004). The metabolic capacity of BAT potentially allows it to influence whole-body energy homeostasis. For instance, BAT has been shown to play an important role in the regulation of glucose homeostasis and insulin secretion (Guerra et al., 2001). Cold exposure of animals increases glucose uptake into BAT due to activation of the sympathetic nervous system (Shibata, Perusse, Vallerand, & Bukowiecki, 1989; Shimizu, Nikami, & Saito, 1991), and this response is mimicked by administration of β-adrenoceptor agonists in vivo (Liu, Perusse, & Bukowiecki, 1994; Olsen et al., 2014). Mouse brown adipocytes cultured in vitro also display increased glucose uptake upon treatment with β-adrenoceptor agonists (Chernogubova, Hutchinson, Nedergaard, & Bengtsson, 2005; Dallner, Chernogubova, Brolinson, & Bengtsson, 2006; Merlin et al., 2018; Olsen et al., 2014). While a role for β_3-adrenoceptor-mediated glucose uptake in rodents is well established, the contribution of these receptors in human adipose tissue is less clear. It has been demonstrated, however, that cold exposure increases ^{18}F-2-deoxyglucose uptake in human BAT depots, and this effect can be mimicked by administration of the β_3-adrenoceptor agonist **mirabegron** that is used clinically for overactive bladder (Baskin et al., 2018; Cypess et al., 2015).

There is strong evidence that glucose uptake in response to β_3-adrenoceptor agonists occurs via a $G\alpha_s$–cAMP–PKA pathway, based on the use of pharmacological inhibitors (Chernogubova, Cannon, & Bengtsson, 2004; Olsen et al., 2014). In addition, 8-bromo-cAMP and upstream activation of $G\alpha_s$ by cholera toxin both increase glucose uptake in primary brown adipocytes (Chernogubova et al., 2004; Olsen et al., 2014). Other mechanisms involved in β_3-adrenoceptor-mediated glucose uptake include localization of the β_3-adrenoceptors in lipid-rich microenvironments in the plasma membrane (Sato et al., 2012), conventional and novel PKC isoforms (Chernogubova et al., 2004), and AMPK (Hutchinson, Chernogubova, Dallner, Cannon, & Bengtsson, 2005; Inokuma et al., 2005). As demonstrated in skeletal muscle, mTORC2 plays a pivotal role in adipocyte glucose uptake stimulated by β-adrenoceptor agonists, as well as insulin.

The contributions of mTORC1 and mTORC2 have been examined in mice with specific ablation of raptor or rictor in all adipocytes, as these cells express Cre recombinase under control of the adiponectin promoter (Kumar et al., 2010; Polak et al., 2008). Ablation of raptor (mTORC1) in adipose tissue increases mitochondrial uncoupling but has no effect on insulin-mediated Akt phosphorylation or glucose tolerance profiles in chow-fed mice (Polak et al., 2008). In contrast, adipocytes isolated from mice with fat-specific ablation of rictor (mTORC2) display reduced insulin-stimulated Akt-Ser^{473} phosphorylation, GLUT4 translocation to the cell surface, and glucose uptake, and these mice have impaired glucose tolerance profiles in vivo (Kumar et al., 2010). These studies indicate that like in skeletal muscle, the mTORC2 complex is involved in glucose homeostasis in adipocytes.

We have demonstrated using brown adipocytes that mTORC2 is involved in β_3-adrenoceptor-mediated glucose uptake (Olsen et al., 2014). Overall inhibition of mTOR by **Torin-1** or KU0063794 reduces glucose uptake, but two lines of evidence demonstrate the involvement of mTORC2 rather than mTORC1: (a) 24-hr, but not 2-hr, rapamycin treatment attenuates β_3-adrenoceptor-mediated glucose uptake (rapamycin acutely inhibits mTORC1, whereas long-term treatment prevents mTORC2 assembly), and (b) siRNA against rictor, but not raptor, reduces glucose uptake by β_3-adrenoceptors (Mohl et al., 2011; Olsen et al., 2014). In brown adipocytes, β_3-adrenoceptor-mediated glucose uptake depends on de novo synthesis and translocation of **GLUT1** (Dallner et al., 2006), which are both cAMP-dependent (Figure 3). mTORC2 is specifically involved in the translocation of newly synthesized GLUT1 to the plasma membrane, but is not required for de novo synthesis of GLUT1 (Olsen et al., 2014). In brown adipocyte cultures, inhibition of PI3K by compound 15e, or of Akt by inhibitor X, reduced insulin- but not isoprenaline-stimulated glucose uptake. Akt was phosphorylated at Thr^{308} and Ser^{473} in response to insulin but not isoprenaline (Olsen et al., 2014).

A recent study has also shown that mice lacking rictor in adipose tissue are hypothermic, show increased susceptibility to cold, and have impairment of cold-induced glucose uptake and glycolysis (Albert et al., 2016). This study indicates that mTORC2 plays a central role in adipose tissue metabolism and translocation of GLUT 1/4 in vitro and in vivo. Interestingly, the GLUT 1/4 content in the plasma membrane of brown adipocytes was not altered by cold exposure in that study. Also in contrast to our previous findings (Olsen et al., 2014), both immortalized mouse brown adipocytes treated with noradrenaline (1 μM) for 5 min and native BAT from wild-type mice treated for 30 min in vivo with noradrenaline (1 $mg \cdot kg^{-1}$) showed phosphorylation of Akt at Ser^{473} , known to be downstream of mTORC2. There is no clear explanation for the disparity with our brown adipocytes;

however, an emerging view is that adipose depots display considerable heterogeneity in cell composition (Shinoda et al., 2015). This would account for differences between in vivo and in vitro data and may also be consistent with phenotypic differences between primary brown adipocyte cultures that are representative of the starting population of stromal vascular pre-adipocytes and immortalized adipocytes that have been selected for the presence of plasmid encoding SV40 T antigen (Klein, Fasshauer, Klein, Benito, & Kahn, 2002) and therefore represent only a small subset of the starting cell population. In addition, noradrenaline may activate the α_2-adrenoceptors present in BAT or brown adipocytes, promoting signalling via a $G\alpha_{i/o}$-Gβγ-PI3K-PDK1-Akt axis. In immortalized human multipotent adipose-derived stem (hMADS) brown adipocytes treated with low concentrations of isoprenaline, glucose uptake is blocked by the mTOR inhibitor KU0063794, as seen in mouse brown adipocyte primary cultures (Olsen et al., 2014). It would be interesting to determine whether hMADS cells display Akt phosphorylation at Ser^{473} in response to isoprenaline treatment.

1.3.3 | mTORC1 mediates browning of brite adipocytes

In addition to BAT, there is increasing evidence for the existence of brown adipocytes in depots thought to be primarily WAT, both in animal models and in humans (Petrovic et al., 2010). These cells differ from prototypical BAT found in rodents or human infants and have been termed "brite" (brown in white) or "beige" adipocytes. Two studies indicate that brite adipocytes contribute significantly to whole-body energy expenditure: Mouse models that have increased brite adipocytes in WAT are protected from diet-induced obesity (Seale et al., 2011), and browning of WAT contributes to non-shivering adaptive thermogenesis in the absence of classical brown adipocytes (Schulz et al., 2013). Our in vitro results show that stimulation of the β_3-adrenoceptors increases glucose uptake in brown and brite adipocytes, but not white adipocytes, in contrast to insulin, which increases glucose uptake in all three adipocyte cultures (Merlin et al., 2018).

Separate studies have shown that the β-adrenoceptor–cAMP–PKA pathway can lead to mTORC1 activation (Figure 3) and is necessary for the induction of adipose tissue browning and BAT development (Liu et al., 2016). In addition, wild-type mice treated with the mTORC1 inhibitor rapamycin or mice with adipocyte-specific deletion of raptor are cold-intolerant and show impaired expression of UCP1 and other mitochondrial components in inguinal WAT, suggesting that there may be a role for mTORC1 even in the early development of inguinal WAT brite adipocytes (Liu et al., 2016; Tran et al., 2016). Several downstream target genes of **PPAR-α** and **oestrogen-related receptor α (ERRα)** are similarly under the control of mTORC1. PPAR-α is a master nuclear receptor for fatty acid β-oxidation and has been shown to participate in UCP1 expression either directly or indirectly through ERRα (Morganstein et al., 2010). Therefore, mTORC1 appears to have an important role in the catabolic process of adipose tissue browning and the dissipation of chemical energy by thermogenesis.

2 | CONCLUSIONS

This review has summarized the evidence for metabolic and survival roles of adrenoceptor-mTOR signalling in the heart, skeletal muscle, and brown/brite adipocytes. The α_{1A}- adrenoceptors mediate glucose uptake and cardioprotection via mTOR in the failing heart. In skeletal muscle, β_2-adrenoceptors facilitate protein synthesis and glucose uptake via mTORC1 and mTORC2 respectively. Type 2 diabetes is associated with defects in insulin signalling components including insulin receptor substrate, PI3K, and Akt, causing impaired glucose uptake. These defects can be bypassed by the β_2-adrenoceptor–mTORC2 pathway in skeletal muscle, which is independent of insulin signalling. Likewise, adipose β-adrenoceptors play a significant role in lipolysis in WAT and increase glucose uptake in BAT, which can contribute significantly to whole-body energy expenditure. mTORC1 also plays a role in browning of brite adipocytes. The capacity of key GPCRs to modulate physiological responses through mTOR activation represents a novel paradigm that holds great potential in the identification of drug targets for treating a range of metabolic disorders.

2.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander, Christopoulos et al., 2017; Alexander, Cidlowski et al., 2017; Alexander, Fabbro et al., 2017; Alexander, Kelly et al. 2017).

CONFLICT OF INTEREST

T.B. owns stocks in the following pharmaceutical companies: Sigrid Therapeutics AB, Atrogi AB, and Glucox Biotechnology AB. D.S.H. owns stocks in Glucox Biotechnology AB and is a scientific advisor for Atrogi AB.

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