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A potential role for mTORC1/2 in β_2 adrenergic regulation of skeletal muscle glucose oxidation in models of intrauterine growth restriction

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ABSTRACT

The epidemic of intrauterine growth restriction (IUGR) continues to be a leading cause of perinatal morbidity and mortality throughout the world. This condition has been linked to the development of metabolic health problems such as obesity, hypertension, glucose intolerance, and type 2 diabetes at all ages. Previous studies have demonstrated that IUGR fetal adaptations impair proper glucose homeostasis in part via changes in insulin responsiveness in key tissues including skeletal muscle and liver, and that these deficits persists into adulthood. Many components of insulin signaling pathways associated with glucose metabolic regulation have been evaluated in IUGR tissues for adaptive changes. Among these are mammalian target of rapamycin complexes 1 and 2 (mTORC1/2) and their associated pathways, which function in mitochondrial control and maintenance. However, recent findings demonstrate that β_2 adrenoceptors (β_2AR) appear to activate an insulin-independent pathway or pathways that modify glucose metabolism via mTORC1/2 complexes. These findings represent a novel potential target for interventions that could improve the treatment and prevention of IUGR-induced metabolic disorders. This review will focus on mechanistic components of β_2AR-mTORC1/2 signaling as well as their role in regulating glucose oxidative metabolism within skeletal muscle.

Keywords: β_2 Agonist, developmental origins of health and disease (DOHaD), glucose intolerance, mammalian Target of Rapamycin Complex

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INTRODUCTION

Intrauterine growth restriction (IUGR) is characterized by developmental adaptations to chronic fetal malnutrition that result in asymmetric growth restriction of skeletal muscle and other non-visceral soft tissues, regardless of birth weight percentile (Yates et al., 2012). Indeed, asymmetric growth demarcates this condition from other non-nutritional causes of small-for-gestational-age newborns (Sharma et al., 2016). Worldwide, IUGR affects approximately 30 million pregnancies each year and the incidence is six-fold greater in developing countries, well above the internationally-recommended level for initiating public health actions (de Onis et al., 1998). Studies in animal models demonstrate that IUGR is a major predisposing factor for a multitude of postnatal metabolic complications related to impaired insulin sensitivity and glucose homeostasis (Camacho et al., 2017). Studies by us and others have demonstrated the ability of β_2 adrenoceptors (β_2AR) to regulate glucose metabolism in skeletal muscle via insulin-independent pathways (Cadaret et al., 2017; Mukaida et al., 2017; Cipolletta et al., 2017). Furthermore, Yates et al. (2011) highlighted the ability of fetal catecholamines to mediate metabolic adaptations in ovine models of IUGR. Together, these findings demonstrate the need for a better understanding of how chronic adrenergic stimulation contributes to the development and progression of IUGR. Recent work in our lab demonstrates that acute β_2 stimulation also acts synergistically with insulin to enhance stimulation of glucose oxidation in mature skeletal muscle (Cadaret et al., 2017). In stark contrast, however, fetal adaptations to chronically increased catecholamines impair skeletal muscle insulin responsiveness and reduce glucose oxidation rates in IUGR fetal and postnatal muscle (Limesand et al., 2007; Brown et al., 2015; Camacho et al., 2017). These results demonstrate that β_2-adrenergic and insulin activity can lead to similar downstream effects on glucose metabolism via distinctly different pathways that ultimately converge downstream. One likely site of convergence is the activation of mTORC1 and mTORC2, which appear to be common downstream targets for both pathways, as illustrated in Figure 1. Both mTORC1 and mTORC2 are potent regulators of glucose uptake when activated by the insulin/PI3K/PDK1 pathway or inhibited by stress-activated AMPK and TSC pathways (Polak & Hall, 2009). Previous findings indicate that mTORC1/2 also influence mitochondrial oxidation rates and are activated by insulin-independent increases in cyclic AMP (cAMP) activity (Cunningham et al.,

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2007; Schieke et al., 2006). Adrenergic regulation of skeletal muscle and its crosstalk with insulin may represent novel therapeutic targets for improving metabolic outcomes in IUGR affected individuals. In this review, we discuss how these findings relate to our recent studies, which demonstrate that β_2 adrenergic stimulation increases both basal and insulin-stimulated glucose oxidation rates in skeletal muscle without concurrently increasing glucose uptake (Cadaret et al., 2017; Merrick et al., 2017).

β_2 adrenergic activation of mTORC2

β_2 adrenoceptors are G protein-coupled receptors that primarily activate adenylyl cyclase to increase production of the second messenger cAMP (Mukaida et al., 2017). Greater concentrations of cAMP produced by β_2 stimulation lead to activation of mTORC2 by phosphokinase A (PKA)-mediated phosphorylation at Ser^{2481} (Sato et al., 2014). In turn, mTORC2 then activates Akt via Ser^{473} phosphorylation (Sato et al., 2014). Not surprisingly, inhibition of mTORC2 activity leads to decreased phosphorylation of Akt and a reduction in the associated downstream effects (Kline et al., 2006; Sarbassov et al., 2005). This pathway is significant because it represents a route of Akt activation that does not require the involvement of PI3K/PDK1, which activates Akt via phosphorylation at Thr^{308} (Sato et al., 2014), and demonstrates one potential mechanism by which β_2 adrenergic-mediated pathways lead to the activation of Akt in an insulin-independent manner. Additional comparative studies demonstrate that inhibition of Akt leads to the loss of both insulin-mediated and β_2 agonist-mediated effects (Mukaida et al. 2017). This further indicates that these pathways differ upstream, presumably at the level of mTORC2, but ultimately converge at Akt activation. Convergence of the β_2/cAMP/mTORC-mediated pathway with the insulin-PI3K pathway in skeletal muscle may explain the additive effects of insulin and β_2 stimulation on glucose oxidation by our lab and others (Cadaret et al., 2017; Scheidegger et al., 1984). These findings also indicate that mTORC1 is a downstream mediator of the effects of β_2 adrenoceptor activation, as it is responsive to both Akt and cAMP (Kline et al., 2006; Kim et al., 2010).

Differential pathways of β_2-stimulated mTORC1 activation

Past studies have shown that Akt and its substrate PRAS40 are important activators of mTORC1 in skeletal muscle (Kline et al., 2006; Oshiro et al., 2007). A subsequent study by Kim et al. (2010) also demonstrated cAMP to be an indirect promoter of mTORC1 activity via its inhibitory action on PDE4D, a known suppressor of mTORC1. These parallel pathways (summarized in Figure 1) represent a multi-faceted capacity for β_2 adrenergic regulation of mTORC1 via Akt (similarly to insulin), as well as via a unique Akt-independent PDE4D-mediated pathway. Ultimately, each of these pathways is capable of upregulating activity of the small GTPase, Rheb, which is a well-characterized activator of mTORC1 (Kim et al., 2010; Oshiro et al., 2007; Polak and Hall, 2009). Indeed, these findings would appear to indicate that the two pathways re-converge upon activating their common hub, Rheb. Moreover, these parallel pathways offer a likely explain for how β_2 adrenergic stimulation acts both with and independently of insulin in regulating skeletal muscle mTORC1 activity and subsequent glucose oxidation.

mTORC1 mediates mitochondrial oxidative function

Studies have demonstrated that mTORC1 is a central metabolic regulator capable of eliciting rapid changes in cellular metabolism (Cunningham et al., 2007; Ramanathan and Schreiber, 2009). Indeed, inhibition of mTORC1 decreases mitochondrial respiration rates in an S6K1/4eBP1-independent manner (Ramanathan & Schreiber, 2009). This non-canonical pathway functions via post-transcriptional co-activation of YY1 and PGC-1α, which are transcription factors integral to the control of mitochondrial oxidative metabolism (Cunningham et al., 2007). It is noteworthy that the effects on mitochondrial function were not due to changes in overall mitochondrial content in either of the above studies, further implicating the acute effects of this pathway. Interestingly, Polak & Hall (2009) have described how tissue-specific loss of mTORC1 results in similar phenotypic traits and metabolic consequences to those observed in IUGR-born animals (Yates et al., 2011; 2012) (Figure 2). Collectively, these results indicate that mTORC1 is a key mediator of the effects of β_2 stimulation that we have observed on both basal and insulin-stimulated glucose oxidation in skeletal muscle and myoblasts (Cadaret et al., 2017; Merrick et al., 2017). More importantly, they also indicate a potential key role for mTORC1 in the metabolic phenotype associated with IUGR-induced adaptations. Indeed, these mTORC1-mediated pathways not only provide a mechanistic model for the role of the β_2 adrenergic system in regulation of glucose homeostasis but may also represent a potential target for improving metabolic outcomes in IUGR-born individuals.

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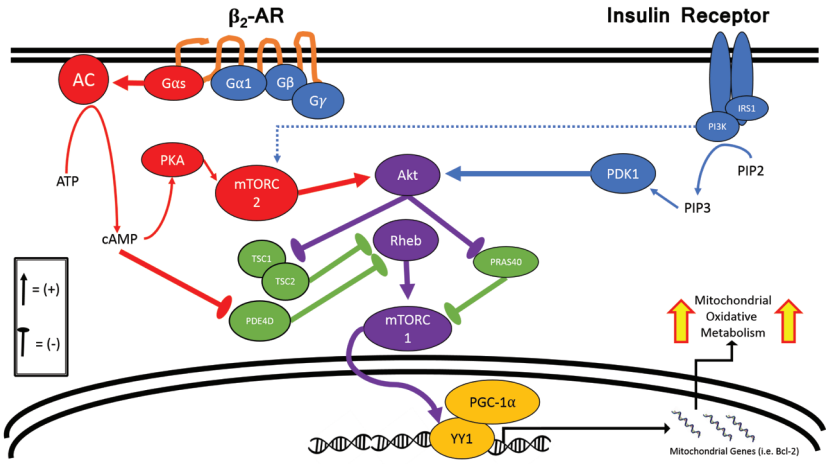

Figure 1 Proposed pathways for insulin-dependent and insulin-independent β_2 adrenergic regulation of skeletal muscle glucose oxidation. G protein-coupled β_2 adrenoceptors (β_2-AR) stimulate adenylyl cyclase (AC) to increase production of cAMP, which sequentially leads to activation of phosphokinase A (PKA), mTORC2, and Akt. Canonical insulin pathways also activate Akt via PI3K/mTORC1 and via PDK1. Akt inhibits PRAS40, which directly increases mTORC1 activity, and inhibits TSC1/2, which indirectly increases mTORC1 activity by increasing its upstream activator, Rheb. Greater cAMP production further increases mTORC1 activity by inhibiting the Rheb suppressor, PDE4D. Upon activation, mTORC1 enters the nucleus, joins co-activators PGC-1α and YY1, and initiates transcription of genes associated with mitochondrial oxidative metabolism

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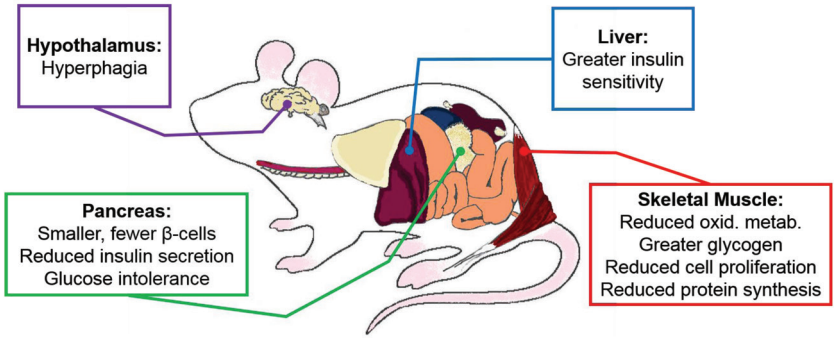

Figure 2 Similar metabolic phenotypes result from IUGR adaptations and from mTORC1 deficiency. The phenotypes listed have been observed in IUGR-born individuals/animals as well as mTORC1 KO mice

CONCLUSIONS

Skeletal muscle glucose oxidation is a major factor in glucose homeostasis and metabolic health. In this review, we describe key roles for mTORC1 and mTORC2 in β_2 adrenergic pathways that appear to regulate skeletal muscle glucose oxidation rates and capacity. Research has shown that adrenergic adaptations appear to be highly involved in glucose oxidation deficits in IUGR skeletal muscle and thus these pathways represent potential therapeutic targets for metabolic disorders associated with IUGR. We recently observed that β_2 adrenergic activity enhances both insulin-stimulated and insulin-independent glucose oxidation in skeletal muscle and myoblasts without parallel effects on glucose uptake. We postulate that this is explained by two parallel β_2 adrenergic pathways for Rheb activation, one involving mTORC2-mediated activation of Akt and the other resulting from cAMP-mediated inhibition of the Rheb suppressor, PDE4B. Strikingly similar metabolic deficiencies between IUGR animal models and mTORC1 knockout models make these separate but complimentary pathways for β_2 adrenergic enhancement of Rheb-mediated mTORC1 activity particularly intriguing as potential therapeutic targets for IUGR-induced metabolic dysfunction.

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