Role of the cAMP Pathway in Glucose and Lipid Metabolism

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Abstract

3′–5′-Cyclic adenosine monophosphate (cyclic AMP or cAMP) was first described in 1957 as an intracellular second messenger mediating the effects of glucagon and epinephrine on hepatic glycogenolysis (Berthet et al., J Biol Chem 224(1):463–475, 1957). Since this initial characterization, cAMP has been firmly established as a versatile molecular signal involved in both central and peripheral regulation of energy homeostasis and nutrient partitioning. Many of these effects appear to be mediated at the transcriptional level, in part through the activation of the transcription factor CREB and its coactivators. Here we review current understanding of the mechanisms by which the cAMP signaling pathway triggers metabolic programs in insulin-responsive tissues.

Keywords

CBP (CREB Binding Protein) • CREB (cAMP Response Element Binding protein) • CRTC (cAMP Regulated Transcriptional Coactivator)

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1 Introduction

In mammals, cAMP is produced from ATP by a family of enzymes called adenylate cyclases (ACs). There are nine transmembrane members of this family (tmACs Type I–IX) and one *soluble* isoform (AC10 or sAC) (Kamenetsky et al. 2006). The soluble AC is conserved across species, from prokaryotes and fungi, to humans (Buck et al. 1999). This enzyme is localized to the cytosol, the nucleus, and the mitochondria where it is activated by increases in bicarbonate from cellular respiration (Zippin et al. 2004; Acin-Perez et al. 2009). The nine transmembrane ACs are expressed at different levels in various cell types (Defer et al. 2000) where they are confined to discrete functional domains together with upstream regulators and downstream targets of cAMP signaling. The most extensively characterized regulators of tmAC activity are heterotrimeric G proteins composed of β and γ subunits (Chen et al. 1995) and either stimulatory ($G_{\alpha s}$) or inhibitory ($G_{\alpha i}$) subunits that convert extracellular stimuli engaging G-protein-coupled receptors (GPCRs) into intracellular signals through modulation of tmAC activity. Other signal transducers that regulate tmAC activity include calmodulin (Valverde et al. 1979), protein kinase A (PKA) (Iwami et al. 1995), protein kinase C (PKC) (Yoshimasa et al. 1987), as well as regulator of G-protein signaling 2 (RGS2) (Sinnarajah et al. 2001). These regulators affect specific tmAC types, allowing versatile feedback loops that are cell-type specific and that integrate cAMP signaling with calcium, $G_{\alpha q}$, and growth factor signals.

Precise regulation of cAMP turnover, clustering of ACs with downstream targets in microdomains, and inhibitory feedback mechanisms all serve the purpose of compartmentalizing the cAMP signal both spatially and temporally. Separation of discrete cAMP signals is the functional basis for the coexistence and fidelity of multiple signaling pathways using cAMP as a second messenger in the same cell (Hayes et al. 1980; Di Benedetto et al. 2008; Zaccolo 2011; Houslay 2010). It is important to note that under physiological conditions, diffusion of cAMP beyond these defined microdomains is insignificant (Zaccolo and Pozzan 2002). Indeed, protein microdomains are instrumental in maintaining distinct cAMP signaling compartments, and the scaffolding proteins known as A-kinase anchor proteins (AKAPs) play a key role in the formation of these microdomains (Dessauer 2009; Smith et al. 2013). Through direct physical interactions, AKAPs station cAMP-effector proteins optimally relative to ACs and phosphodiesterases (PDEs) allowing exposure to cAMP concentrations within their dynamic range.

The physiological outcome of signals eliciting a cellular cAMP response depends on the subcellular localization of the effectors relative to the source of cAMP and to potential downstream targets. Three classes of cAMP-effector proteins have been established to date: PKA (Walsh et al. 1968), exchange proteins directly activated by cAMP (EPACs) (de Rooij et al. 1998), and hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channels (DiFrancesco and Tortora 1991). These effectors bind cAMP allosterically, leading to direct effects on downstream targets or permitting them to serve as integrators of the cAMP signal with other secondary messenger systems and signaling pathways. In addition to the

three established cAMP-effector mechanisms, PDE10A isozymes (Handa et al. 2008) and Popeye domain-containing (Popdc) proteins (Froese et al. 2012) have been identified as cAMP-binding proteins. The importance of PDE10A and Popdc proteins as cAMP effectors is yet to be determined.

While cAMP synthesis is determined by the activities of ACs, the superfamily of PDEs is the predominant cAMP-lowering mechanism in mammalian cells. These cyclic nucleotide-hydrolyzing enzymes are classified into multiple families (PDE1–11) with distinct expression patterns and specificities. Eight of these families can hydrolyze cAMP to AMP (PDEs 4, 7, and 8 are specific to cAMP), while the others are selective for 3′–5′-cyclic guanosine monophosphate (cGMP). Each family consists of several isozymes with distinct subcellular distributions and means of regulation (for a comprehensive review, see Francis et al. 2011). Dynamic changes in PDE expression, localization, oligomerization, and relative cGMP levels in the case of dual-specificity PDEs are all crucial determinants of total cAMP hydrolytic activity. The magnitude of the cAMP signal and fine-tuning of its kinetics by the PDEs is also coordinated by interactions with regulatory proteins and posttranslational modifications of the PDEs, such as phosphorylation by PKA itself (Francis et al. 2011; Keravis and Lugnier 2010). The amplitude, propagation, and duration of the cAMP signal are not only restricted by localization of PDE activities but are also regulated by a negative feedback mechanism in which cAMP itself activates PDE3 and PDE4 isozymes (Sette et al. 1994; Gettys et al. 1987). As will be discussed later in this chapter, PDEs are widely targeted by pharmacological agents to correct cAMP signaling in human disease.

2 cAMP in Metabolic Control

Cyclic AMP signaling has enormous impact on metabolic pathways both at the cellular and systemic levels. In the following sections, we will focus on inducers, regulators, and effectors of cAMP signals in important metabolic tissues. Mechanisms will be discussed in the context of nutrient homeostasis and the metabolic syndrome, a state of severe metabolic imbalance signified by perturbations in cAMP signaling in multiple tissues.

Most tissues are under the control of the sympathetic nervous system (SNS). Through the coordinated release of epinephrine from the adrenal glands into the circulation and the release of synaptic norepinephrine, the SNS activates membrane-bound adrenergic receptors on target cells. Of these, α2-adrenergic receptors inhibit and β-adrenergic receptors (β1, β2, and β3) stimulate cAMP production through G_i and $G_{\alpha s}$ activation, respectively (Insel 1996). The SNS has classically been associated with stress responses (Seematter et al. 2004), but synaptic tone is also involved in regulating basal metabolic rate, glucose disposal, and lipid partitioning (Monroe et al. 2001; Boyda et al. 2013; Arner et al. 1990). In this light, it is interesting to note that a growing body of literature links metabolic disorders like obesity and diabetes to dysregulation of adrenergic receptor signaling (Boyda et al. 2013; Yasuda et al. 2006; Ziegler et al. 2012).

2.1 Liver

Cyclic AMP signaling was first discovered in the liver as a critical mediator of glucose metabolism. Mammals use highly interconnected hormonal signaling mechanisms that include the opposing actions of glucagon and insulin to maintain glucose homeostasis. Decreases in circulating glucose concentrations during fasting trigger the release of pancreatic glucagon, which stimulates gluconeogenesis and provides substrate supply to glucose-dependent tissues like the brain and red blood cell compartments. During feeding, increases in circulating insulin downregulate hepatic gluconeogenesis in part through activation of the Ser/Thr kinase Akt. Increases in insulin resistance promote hyperglycemia, in part due to a failure of insulin to suppress hepatic glucose production. Indeed, lowering hepatic glucose production represents a major objective for treatment of type II diabetic individuals. A potential regulatory target in this process is the transcription factor CREB (Altarejos and Montminy 2011a) and its associated coactivators the CREB-binding protein (CBP) and cAMP-regulated transcriptional coactivators (CRTCs).

Triggering of the glucagon receptor on hepatocytes activates adenylate cyclase, leading to production of cAMP and increases in PKA activity. Following its PKA-mediated phosphorylation, CREB interacts with CREB-binding protein (CBP) (Chrivia et al. 1993a; Eckner et al. 1994) and initiates transcription of key gluconeogenic enzymes such as pyruvate carboxylase (PC), phosphoenolpyruvate carboxykinase (PEPCK-C) (Herzig et al. 2001; Quinn and Granner 1990; Wynshaw-Boris et al. 1986), and glucose-6-phosphatase (Lin et al. 1997). The induction of gluconeogenic genes by CREB is further augmented by the CREB-regulated transcription coactivator 2 (CRTC2), which is dephosphorylated in response to glucagon, where it migrates to the nucleus and associates with CREB over relevant promoters (Koo et al. 2005; Chrivia et al. 1993b). Under feeding conditions, CRTC2 is phosphorylated by salt-inducible kinases (SIKs) and sequestered in the cytoplasm via an association with 14-3-3 proteins. Exposure to glucagon promotes the PKA-mediated phosphorylation and inhibition of SIKs, leading to the dephosphorylation of CRTC2.

The CREB/CRTC2 pathway appears to be active primarily during short-term fasting; with prolonged fasting, forkhead box protein O1 (FOXO1) activity appears critical in maintaining expression of gluconeogenic genes (Liu et al. 2008). The physiological relevance of CREB and CRTC2 in hepatic glucose production is demonstrated in vivo with a mouse model expressing dominant-negative CREB inhibitor A-CREB (Ahn et al. 1998) and in cultured hepatocytes with a knockout of CRTC2 (Wang et al. 2010).

In addition to these transcriptional effects, PKA modulates gluconeogenesis by altering substrate flux. PKA phosphorylates the bifunctional enzyme fructose-2,6-bisphosphatase/phosphofructokinase-2, favoring the phosphatase activity and therefore decreasing production of the metabolic intermediate fructose 2,6-bisphosphate. This metabolite is a powerful allosteric activator of phosphofructokinase-1 (PFK-1), the first rate-limiting enzyme in glycolysis. By depleting the activator, PKA inhibits glycolytic flux through PFK-1, enhancing

glucose production and liver glucose output (El-Maghrabi et al. 1982; Richards et al. 1982).

Liver glycogenolysis is another means by which glucose homeostasis is maintained during fasting and exercise or in response to stress as manifested by increased catecholamine signaling. Following its activation by glucagon and epinephrine, PKA phosphorylates and activates phosphorylase kinase, which in turn stimulates glycogen phosphorylase, allowing for glucose release from liver glycogen stores (Studer and Borle 1982; Studer et al. 1984).

In addition to its regulation by fasting and feeding signals, hepatic glucose production is also modulated by the circadian clock. Like other tissues, the liver clock is governed by E-box transcription factors called brain and muscle ARNT-like (BMAL) and circadian locomotor output cycles kaput (CLOCK), which trigger expression of cryptochrome (CRY) and period (PER) proteins. In turn, CRY and PER repress transcription of CLOCK and BMAL, providing feedback regulation. Although they are regarded primarily as transcriptional repressors, CRY1 and CRY2 appear to inhibit expression of the gluconeogenic program during the night-to-day transition by binding to the cytoplasmic $G_s\alpha$ subunit of the heterotrimeric G protein. Conversely, decreases in CRY1 and CRY2 levels during the day-to-night transition enhance hepatic glucose production due to increases in cAMP signaling (Zhang et al. 2010). CREB and CRTC2 have been reported to promote the expression of BMAL1, suggesting that this pathway may modulate the core clock (Sun et al. 2015).

2.2 White Adipose Tissue

White adipose tissue (WAT) in mammals serves as an insulation, a storage depot of energy in the form of triglycerides, and an endocrine organ. The characteristics of fat depots throughout the body are largely dictated by their location; they are under complex endocrine, nutritional, neuronal, and immunological control (Rosen and Spiegelman 2014). Many of these regulatory signals are mediated by cAMP, which is known to have a significant role in both adipogenesis and lipid partitioning in white adipose tissue. Mature adipocytes arise from fibroblastic precursors through a dynamic differentiation process that requires extensive chromatin remodeling (Park et al. 2012; Siersbaek et al. 2014; Tang and Lane 2012). The cAMP signaling pathways are among the most well-characterized mechanisms controlling adipocyte differentiation. PDE inhibitors and synthetic cAMP analogs are commonly employed to switch on the adipogenic program in vitro (Russell and Ho 1976). An early increase in preadipocyte cAMP levels stimulates PKA, which in turn phosphorylates and activates the nuclear basic leucine zipper transcription factor cAMP-response element-binding (CREB) protein and members of the ATF family (Zhang et al. 2004; Fox et al. 2006a). These transcriptional activators have been linked to the induction of critical regulators of adipogenesis, including peroxisome proliferator-activated receptor-γ (PPAR-γ) and CCAAT/enhancer-binding protein (C/EBP) α and β (Fox et al. 2006a; Niehof et al. 1997; Birsoy et al. 2008).

Expression of constitutively active CREB is sufficient to promote adipogenesis in 3T3-L1 cells (Fox et al. 2006b), highlighting the importance of the cAMP pathway in adipocyte differentiation. Activation of EPAC1 also appears important for a subset of cAMP effects (Petersen et al. 2008) possibly in synergy with the effects of PKA. Adipogenesis is impaired in mice lacking $G_{\alpha s}$ expression in adipose tissue (Chen et al. 2010), providing strong evidence that cAMP is crucial to adipogenesis in vivo. Embryonic fibroblasts isolated from these mice have significantly reduced adipogenic potential in vitro even when PDE activity is inhibited. The nature of the signals stimulating cAMP production during adipogenesis in vivo remains to be elucidated, however.

In addition to its effects on differentiation, cAMP signaling also regulates lipid metabolism in WAT. During instances of high energy demand, such as fasting, triglycerides stored in adipocyte lipid droplets are hydrolyzed to fatty acids and glycerol in a process known as lipolysis (Frayn 2002). For decades, it has been suggested that adipokinetic factors released from the pituitary (e.g., growth hormone), adrenal (e.g., glucocorticoids), and pancreas (e.g., glucagon) can stimulate lipolysis from WAT (Hollenberg et al. 1961; White and Engel 1958). Although some of these factors have been shown to induce lipid breakdown from adipocytes in vitro, the significance of their lipolytic actions in vivo is likely to be of limited importance (Coppack et al. 1994). Rather, lipolytic signals come primarily from sympathetic innervation of the adipose depots (Adler et al. 2012; Dodt et al. 1999; Nishizawa and Bray 1978). In humans, catecholamines are the primary hormones involved in triggering lipolysis in WAT. β-Adrenergic stimuli increase cAMP levels and promote lipid breakdown. However, stimulation of receptors coupled to inhibitory G_i proteins, such as EP3 receptor by prostaglandin E_2 (PGE_2), will lead to inhibition of adenylate cyclase activity, hindering cAMP synthesis and decreasing lipolysis (Kolditz and Langin 2010; Richelsen and Pedersen 1985; Cummings et al. 1996). By releasing PGE2, adipose tissue macrophages may contribute to catecholamine resistance in certain depots.

Studies of several genetically modified animal models point to an important role for cAMP in lipolysis in vivo. A direct lipolytic function for PKA and cAMP signaling in WAT is further supported by numerous studies documenting PKA phosphorylation and activation of several key regulators of lipolysis in response to elevated cAMP levels. These include the hormone-sensitive lipase (HSL) (Anthonsen et al. 1998), adipocyte-specific triglyceride lipase (ATGL) (Pagnon et al. 2012), and lipid droplet-associated protein perilipin (Brasaemle et al. 2009).

Another genetic mouse model showing increased cAMP-induced lipolysis is the PDE3B knockout mouse. In addition to an increased lipolytic response to adrenergic stimuli in vivo, the well-known anti-lipolytic effect of insulin (Olefsky 1977) is not observed in isolated PDE3B null adipocytes (Choi et al. 2006). This dual phenotype can be explained by the distinct localization of PDE3B in separate microdomains. In wild-type adipocytes, specific pools of PDE3B are phosphorylated and activated by PKA in response to β-adrenergic stimulation, whereas insulin receptor signaling will promote AKT-mediated phosphorylation and activation of other PDE3B pools (Ahmad et al. 2009). PKA maintains temporal

autoregulation of the cAMP signal while promoting lipolysis by allowing PDE3B fine-tuning of the cAMP signal to a concentration range that is ideal to sustain activity, whereas AKT blocks lipolysis by dissociating it from lipolytic signals at least in part by activating discrete pools of PDE3B. Significantly, PDE3B mutant mice show hepatic lipid accumulation and insulin resistance, suggesting that the increase in lipolysis is not accompanied by an increase in fatty acid oxidation and may reflect the redundancy between PDE family members or the diminished importance of PDE3B in the regulation of fatty acid oxidation in non-adipose tissues such as the liver.

2.3 Brown Adipose Tissue

Brown adipose tissue (BAT) is an oxidative tissue specialized in dissipating energy as heat, crucial for maintaining optimal body temperature when exposed to changes in the environment (Rosen and Spiegelman 2014). BAT was initially characterized as an interscapular fat pad in newborn rodents but has since been identified in both infants (Lidell et al. 2013) and adult humans (Virtanen et al. 2009; Cypess et al. 2009; van Marken Lichtenbelt et al. 2009; Huttunen et al. 1981). Unlike WAT, BAT expresses uncoupling protein 1 (UCP1, also known as thermogenin) allowing uncoupling of mitochondrial oxidative phosphorylation and thermogenesis (Cannon et al. 1982; Heaton et al. 1978; Enerback et al. 1997). Cold exposure induces the oxidative and thermogenic capacity of BAT (Cameron and Smith 1964) through SNS activation and adrenergic stimulation of cAMP production (Thomas and Palmiter 1997). Cyclic AMP immediately activates PKA (Skala and Knight 1977) leading to increased lipolysis and activation of UCP1 (Fedorenko et al. 2012). In an adaptive response to prolonged cold exposure, cAMP also contributes to increased UCP1 levels (Mattsson et al. 2011), mitochondrial biogenesis (Bogacka et al. 2005), and expanded BAT mass. These adaptive effects are believed to require transcriptional changes although the exact mechanisms, and the relative importance of these pathways, are still debated. Transcriptional activators that have been found to play prominent roles in BAT adaptation to cold exposure include CREB (Rim and Kozak 2002), PPAR gamma-coactivator 1-alpha (PGC1a), IRF4 (Kong et al. 2014), and PRDM16 (Kajimura et al. 2009; Seale et al. 2007). In particular, PGC1a, which is itself induced by cAMP, is required for commitment of preadipocytes to differentiate into brown adipocytes (Puigserver et al. 1998) and appears to be decreased in the adipose tissue of obese patients (Semple et al. 2004).

In order to sustain thermogenesis, the BAT must fuel ATP synthesis by oxidizing substrate. Cyclic AMP signaling, via adrenergic stimuli from sympathetic innervation, will lead to the increased synthesis of both lipoprotein lipase and GLUT1 (Shimizu et al. 1998). This allows increased release of fatty acids and uptake of glucose for oxidation. Importantly, the enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which plays a significant role in glycolysis and lipid metabolism, is also upregulated by norepinephrine and cAMP analogs (Barroso et al. 1999). Bone morphogenic protein 8 (BMP8) was found to enhance

thermogenesis in a manner dependent upon on the CREB pathway, and loss of BMP8 was associated with decreased metabolic rate and thermogenesis (Whittle et al. 2012).

Importantly, the thyroid hormone triiodothyronine (T3) (Silva and Larsen 1983; de Jesus et al. 2001) also has a significant effect on obligatory thermogenesis and BAT function. T3 is required for maintaining BAT lipolysis and for sustaining the basic metabolic rate by promoting uncoupling of oxidative phosphorylation (Mullur et al. 2014). T3 levels in the BAT are carefully regulated by conversion of T4 to T3 by deiodinases. In the BAT, adrenergic signaling as well as activation of the bile acid receptor TGR5 leads to cAMP increases, which promote 5′-deiodinase type 2 activity, increasing local T3 levels (Silva 2006; Arrojo et al. 2013).

Induction of cAMP signaling can also trigger "browning" of white adipose tissue to a more oxidative tissue phenotype (Dempersmier et al. 2015). The possibility of inducing BAT characteristics in WAT by modulating cAMP signaling points to cAMP agonists as potential targets for drug development for the treatment of obesity. Indeed, administration of β3-adrenergic agonist to mice with a knockout of phosphodiesterase 3B (PDE3B) increases cAMP accumulation in epididymal WAT, leading to browning of these WAT depots (Guirguis et al. 2013). Furthermore, bone morphogenic protein 7 (BMP7), which is upregulated by cAMP (Ishibashi et al. 1993), also promotes brown adipose characteristics in human adipogenic stem cells (Okla et al. 2015).

2.4 Pancreas

The cAMP pathway contributes importantly to pancreatic β-cell growth and insulin secretion (Furman et al. 2010; Altarejos and Montminy 2011b; Dalle et al. 2011). The incretin hormone glucagon-like peptide-1 (GLP-1) increases cAMP levels by acting through its GPCR, leading to CREB activation, increased glucose-stimulated insulin secretion and β-cell expansion (Wang et al. 1997; Tourrel et al. 2001). Another incretin, glucose-dependent insulinotropic peptide (GIP), also increases cAMP signaling via interaction with its GPCR (Yabe and Seino 2011). However, receptors for this hormone are downregulated in response to high glucose, making it a less attractive target for the treatment of diabetes compared to GLP-1 signaling (Puddu et al. 2015). Insulin-like growth factor 1 (IGF-1), which is produced in the liver, has been shown to be important for proper development, growth, and proliferation of β-cells. Its actions are mediated through insulin response substrate 2 (IRS2), which is known to play a role in the protection of β-cells against apoptosis and in promoting their growth by activating the pro-growth kinase Akt (George et al. 2002; Withers et al. 1999). Cyclic AMP signaling via CREB also activates IRS2 and in this manner will enhance IGF-1 signaling (Jhala et al. 2003). Notably, activation of the IGF-1 pathway also increases the activity of PDE3B, which degrades cAMP (Zhao et al. 1997); cAMP itself activates PDE3B via PKA (Heimann et al. 2010), creating a negative feedback loop and also modulating

cAMP levels to ensure proper cAMP signaling and to prevent uncontrolled insulin secretion (Härndahl et al. 2002).

Other signals in addition to GLP-1 appear capable of stimulating islet function. Cyclic AMP levels are also elevated in response to γ-aminobutyric acid (GABA), for example, which prevents apoptosis and increases β-cell mass (Purwana et al. 2014). Indeed, acetylcholine, like glucose, induces membrane depolarization and calcium influx, this stimulating insulin secretion. This effect is dependent on protein kinase C (PKC) and phospholipase C coupled to muscarinic receptors (Love et al. 1998; Niwa et al. 1998). Acetylcholine was also found to activate adenylate cyclase activity and to increase cAMP production in diabetic rat islets, leading to CREB activation and enhanced cell viability (Screaton et al. 2004; Eckert et al. 1996). Whether this effect occurs via increases in Ca^{2+} or PKC activity or is due to signaling variations in the diabetic islets remains to be fully elucidated.

In addition to PDE3B, several additional mechanisms limit accumulation of cAMP in β-cells. Increases in intracellular Ca^{2+} in response to glucose elevations activate PDE1, increasing degradation of cAMP. Neuropeptide Y (NPY) (Morgan et al. 1998), PGE_2 (Kimple et al. 2013), and adrenaline (Metz 1988) all signal through GPCRs coupled to G_i, inhibiting adenylate cyclase activity and negatively regulating cAMP accumulation.

Insulin secretion from β-cells is tightly regulated by increases in extracellular glucose concentrations. Glucose transport and phosphorylation allow for its subsequent oxidation; the production of ATP stimulates insulin granule release. The primary transporter involved in facilitated diffusion of glucose in human β-cells is GLUT1. This transporter is not hormonally regulated, suggesting that cellular amounts of this protein have a predominant effect on the efficiency of glucose transport (Thorens et al. 2000). The GLUT1 promoter region has been reported to contain a CREB-binding site that mediates induction of this gene by cAMP (Murakami et al. 1992). However, increased GLUT1 expression may not necessarily affect insulin response (Ishihara et al. 1994); increases in hexokinase I enhance insulin secretion in response to glucose. Cyclic AMP has been shown to increase hexokinase I expression and may in this manner contribute to heightened insulin detection (Yokomori et al. 1992; Borboni et al. 1999).

CREB has been demonstrated to protect β-cells from cytokine-mediated apoptosis and glucotoxicity (Jhala et al. 2003; Jambal et al. 2003; Costes et al. 2009). Overexpression of A-CREB led to diminished replication and increased apoptosis of β-cells, causing hyperglycemia in mice (Jhala et al. 2003). Additionally, it has been shown that the CREB coactivator CRTC2 is necessary for glucose-mediated insulin release (Eberhard et al. 2013; Blanchet et al. 2015). These data collectively underscore the centrality of cAMP signaling through CREB in β-cell survival and endurance. Cyclic AMP is also thought to augment insulin secretion by promoting the PKA-mediated phosphorylation of the SUR1 subunit of the ATP-sensitive potassium channel, thereby inhibiting channel activity and enhancing depolarization (Light et al. 2002); by PKA-dependent phosphorylation of voltage-sensitive calcium channels, increasing Ca^{2+} influx (Leiser and Fleischer 1996; Gerhardstein

et al. 1999); and by directly regulating exocytosis of insulin-containing vesicles (Ammälä et al. 1993; Ding and Gromada 1997).

Though most effects of cAMP in β-cells appear to proceed via a PKA-dependent mechanism, a subset of these effects may be mediated by EPACs (Kang et al. 2006; Henquin and Nenquin 2014; Yoshida et al. 2014). The pancreatic β-cell expresses both EPAC1 and EPAC2, which are directly activated by cAMP. Knockdown of EPAC expression in vivo led to abrogation of cAMP-mediated stimulation of glucose-induced insulin secretion from the pancreas and development of metabolic syndrome in vivo (Kashima et al. 2001; Kai et al. 2013), highlighting the importance of alternative cAMP-dependant pathways to β-cell function.

Incretin hormones have been found to promote β-cell replication at least in rodent cells by increasing the expression of the cell cycle regulators cyclins D1 (Kim et al. 2006) and A2 (Song et al. 2008). cAMP also stimulates the expression of Bcl-2 and Bcl-xL (Hui et al. 2003; Kim et al. 2008), which protect β-cells from apoptosis. cAMP may also terminate cell death cascades by inhibiting caspases (Ehses et al. 2003; Welters et al. 2006).

In addition to its effects on insulin secretion, β-cell growth and proliferation, cAMP may also enhance differentiation. GLP-1 appears to increase the expression of pancreatic duodenal homeobox – 1 (PDX-1) (Perfetti et al. 2000), a transcription factor central to the differentiation of pancreatic endocrine, exocrine, and ductal cell populations from endoderm during fetal development (Zhou et al. 2002; Offield et al. 1996). PDX-1 is also necessary for maturation of β-cells and allows selective differentiation of pancreatic endocrine progenitors to form insulin-producing β-cells while suppressing formation of glucagon-producing α-cells (McKinnon and Docherty 2001; Ber et al. 2003; Gao et al. 2014). It has been shown that cAMP, via PKA, is required to maintain GLP-1-mediated PDX-1 increases and PDX-1 translocation to the nucleus. PDX-1 also promotes expression of the GLP-1 receptor, enhancing cAMP production (Wang et al. 2005).

In contrast to PDX-1 expression, the transcription factor MafA is upregulated during the later development of the endocrine pancreas, where it promotes full maturation of β-cells and stimulates insulin biosynthesis (Kaneto et al. 2008; Artner et al. 2010; Hang and Stein 2011). GLP-1 and cAMP agonists were found to increase MafA expression via induction of the CREB pathway, further implicating cAMP in pancreatic development and differentiation (Blanchet et al. 2015).

The role of cAMP in other pancreatic cell types within the islet is not as well understood. GLP-1 has been demonstrated to increase glucagon release from α-cells via the cAMP/PKA pathway (Ding et al. 1997). Inhibiting EPAC-2 activity in α-cells was also found to decrease glucagon gene transcription, suggesting that both pathways (PKA and EPAC) modulate glucagon production (Islam et al. 2009). Though GLP-1 appears to increase glucagon secretion from α-cells in vitro, this effect may be largely inhibited in vivo due to effects of GLP-1 on somatostatin release from pancreatic δ-cells. Indeed, cAMP stimulates somatostatin secretion from δ-cells, thereby inhibiting adenylate cyclase and cAMP synthesis in α-cells via G_i-coupled GPCR (Elliott et al. 2015; Hauge-Evans et al. 2009). Finally,

adrenergic stimulation (e.g., adrenaline action) can increase both glucagon (Dai et al. 2014) and somatostatin (Gromada et al. 1997) release via cAMP elevation.

2.5 Muscle

Skeletal muscle has a specialized architecture that directly relates to its function in movement and to its regulation by neuronal inputs. Muscle contraction is dependent upon proper calcium signaling, and cAMP plays a significant role in regulating this process. Beta-adrenergic signaling elevates muscle cAMP and thereby modulates Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum, acutely increasing contractile force (Saida and Van Breemen 1984; Cairns and Dulhunty 1993). This effect has been postulated to reflect cAMP-regulated phosphorylation of L-type voltage-dependent Ca^{2+} channels (Sculptoreanu et al. 1993). Cyclic AMP is also necessary for PKA-mediated activation of the Na^{+}–K^{+} pump, which is important in membrane hyperpolarization and in the restoration of muscle excitability (Clausen 2003).

Glycogenolysis, which is critical for meeting energy demands of the muscle, is also promoted by cAMP. Acute cAMP effects are especially important during exercise, when energy consumption by the muscle is at its peak and when epinephrine levels are high, leading to increases in muscular cAMP (Ezrailson et al. 1983; Soderling et al. 1970). Significantly, chronic activation of cAMP pathways in the muscle promotes adaptive responses that include increased myofiber size as well as metabolic transition to a more glycolytic fiber type (Chen et al. 2009; Maltin et al. 1989). Activation of β-adrenergic receptors, which stimulate the cAMP pathway, may prove to be an effective mechanism to enhance muscle function and slow atrophy in disease states such as Duchenne's muscular dystrophy (Harcourt et al. 2007; Hinkle et al. 2007; Ryall et al. 2008).

3 Conclusion

Cyclic AMP mediates the effects of glucagon and beta-adrenergic signals in regulating glucose and lipid metabolism. A key feature of type II diabetes (T2D) is the failure of insulin to trigger glucose uptake into the muscle and to suppress glucose production from the liver (Centers for Disease Control and Prevention 2015; Brown and Goldstein 2008; Basit et al. 2004). Suppressing liver gluconeogenesis and glycogenolysis via inhibition of cAMP signaling or CREB-dependent transcription may have salutary effects on blood glucose concentrations.

While lowering cAMP signaling in the liver may prove beneficial, upregulating cAMP in other tissues may also improve glucose and lipid homeostasis. The chronic hyperglycemia associated with insulin resistance is accompanied initially by compensatory increases in pancreatic islet mass and in insulin secretion. However, unremitting insulin resistance eventually causes β-cell failure and apoptosis, ultimately leading to T2D (Poitout and Robertson 2008; Kahn 2003). In some cases,

an innate susceptibility of the β-cell may magnify the risk of developing T2D; a number of studies have concluded that prediabetes and youth-onset T2D in certain ethnic groups are more strongly associated with β-cell dysfunction (Gujral et al. 2014; Staimez et al. 2013; Dowse et al. 1990). Developing therapeutic strategies to protect β-cells from glucolipotoxicity may provide effective treatment for T2D in this setting. The cAMP signaling pathway is important for β-cell viability, proliferation, and glucose responsiveness. Increasing cAMP signaling or CREB activity may further potentiate β-cell function and provide therapeutic benefit to insulin-resistant individuals.

Upregulating the cAMP pathway in brown and white adipose tissues may also have positive effects on fat burning and thereby decrease inflammatory infiltrates that contribute to insulin resistance in obesity. In view of the pleiotropic effects of the cAMP pathway on glucose and lipid metabolism, a major challenge will be to target relevant modulators in specific tissues. Based on the considerable number of phosphodiesterases with distinct pharmacological properties and tissue localization, these regulators may prove particularly useful in this regard. Future studies on region-specific cAMP signaling in different organelles may also provide further insight into the regulatory properties of this second messenger.

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