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**REVIEWS** | *Intracellular Signal for Skeletal Muscle Adaptation*

# cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration

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**Berdeaux R, Stewart R.** cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. *Am J Physiol Endocrinol Metab* 303: E1–E17, 2012. First published February 21, 2012; doi:10.1152/ajpendo.00555.2011.—Among organ systems, skeletal muscle is perhaps the most structurally specialized. The remarkable subcellular architecture of this tissue allows it to empower movement with instructions from motor neurons. Despite this high degree of specialization, skeletal muscle also has intrinsic signaling mechanisms that allow adaptation to long-term changes in demand and regeneration after acute damage. The second messenger adenosine 3′,5′-monophosphate (cAMP) not only elicits acute changes within myofibers during exercise but also contributes to myofiber size and metabolic phenotype in the long term. Strikingly, sustained activation of cAMP signaling leads to pronounced hypertrophic responses in skeletal myofibers through largely elusive molecular mechanisms. These pathways can promote hypertrophy and combat atrophy in animal models of disorders including muscular dystrophy, age-related atrophy, denervation injury, disuse atrophy, cancer cachexia, and sepsis. cAMP also participates in muscle development and regeneration mediated by muscle precursor cells; thus, downstream signaling pathways may potentially be harnessed to promote muscle regeneration in patients with acute damage or muscular dystrophy. In this review, we summarize studies implicating cAMP signaling in skeletal muscle adaptation. We also highlight ligands that induce cAMP signaling and downstream effectors that are promising pharmacological targets.

cyclic AMP; skeletal muscle; cell signaling; muscle regeneration; atrophy; protein kinase A

ORIGINALLY DISCOVERED by Sutherland and Rall in liver homogenates in 1958 (218), adenosine 3′,5′-monophosphate (cyclic AMP, or cAMP) has since been intensively studied and is one of the best-characterized signaling molecules. In skeletal muscle, acute cAMP signaling has been implicated in regulation of glycogenolysis (213), contractility (32, 83, 84, 88, 138, 234), sarcoplasmic calcium dynamics (58, 147, 184, 204), and recovery from sustained contractile activity (44, 162). The net result of acute cAMP action on the order of minutes in skeletal muscle can generally be described as increased contractile force and rapid recovery of ion balance, especially during prolonged contractions. These acute changes are most pertinent to muscle contraction and energy utilization during exercise, when epinephrine is rapidly released into the circulation (92) and cAMP accumulates in muscle (72).

Many studies have shown, however, that cAMP-inducing agents or genetic modification of proteins involved in cAMP signaling can also have adaptive effects on skeletal muscle by increasing myofiber size and promoting fiber-type transitions to glycolytic fibers (9, 18, 42, 43, 57, 63, 86, 91, 101, 121, 128, 154, 155, 163, 190, 193, 194, 215). The prohypertrophic actions of β-adrenergic receptor (β-AR) agonists and corticotropin-releasing factor receptor 2 (CRFR2) agonists have recently been harnessed to improve muscle function and ameliorate atrophy in several rodent models, including disuse (99, 101, 245), denervation (98, 100–102, 127, 154, 253), aging (195, 254), and muscular dystrophy (90, 103, 185, 254, 256). β-AR agonists have also shown some promise in promoting muscle function in patients with muscular dystrophy (64, 125, 126, 211, 235). Despite many physiological studies, the molecular mechanisms underlying these effects in skeletal muscle are still being elucidated.

In addition to functional adaptation, skeletal muscle has an extraordinary ability to repair and regenerate (93). Resident muscle precursor cells, or satellite cells, become activated in damaged muscle (93). They then proliferate, migrate, and fuse with existing myofibers and with each other to restore normal muscle structure and function. cAMP signaling participates in muscle precursor cell differentiation (39), migration (80), and fusion (48, 249). All of these cellular events are required for efficient regeneration of adult skeletal muscle (93). In adult muscle, stimulation of cAMP production can slow degeneration or promote regeneration in rodent models of necrotic muscle injury (15, 80, 196) and Duchenne's muscular dystrophy (86, 90, 103, 254).

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In this review, we explore cAMP-dependent physiological adaptation in skeletal muscle fibers and muscle precursor cells. We first discuss the components of cAMP signaling machinery that function in this tissue. We then review the known molecular mechanisms by which sustained treatment with ligands capable of inducing cAMP promotes hypertrophy and alters muscle fiber types. Finally, we examine how cAMP signaling affects muscle development and how these same pathways participate in regeneration. For this discussion, we define "adaptation" as cellular events that normally occur on the order of days to weeks and that change phenotypes in individual myofibers or whole muscles.

*Glossary*

| | |
|---|---|
| Akt | Protein kinase B, PKB |
| AKAP | A-kinase anchoring protein |
| AVP | $Arg^8$-vasopressin |
| β-AR | β-Adrenergic receptor |
| cAMP | Adenosine 3′,5′-monophosphate |
| CGRP | Calcitonin gene-related peptide |
| COXIV | Cytochrome *c* oxidase, subunit IV |
| CREB | cAMP response element-binding protein |
| CRF | Corticotropin-releasing factor |
| CRFR2 | Corticotropin-releasing factor receptor 2 |
| CXCR4 | CXC chemokine receptor 4 |
| *dy/dy* | Laminin-deficient mouse with muscular dystrophy |
| Epac | Exchange protein activated by cAMP |
| ERK1/2 | Extracellular signal-regulated kinases 1 and 2 |
| Forskolin | Direct AC agonist |
| FoxO | Forkhead box transcription factors, class O |
| Fzd7 | Frizzled 7 |
| GPCR | G protein-coupled receptor |
| IGF-I | Insulin-like growth factor I |
| IL-6 | Interleukin-6 |
| LTCC | L-type calcium channel |
| MAFbx | Muscle atrophy F-box, Atrogin 1 |
| *mdx* | Dystrophin-deficient mouse strain |
| MuRF1 | Muscle RING finger 1 |
| MyHC | Myosin heavy chain |
| nAChR | Nicotinic acetylcholine receptor |
| NMJ | Neuromuscular junction |
| Nor1 | Neuron-derived orphan receptor 1, also Nr4a3 |
| Nur77 | Nuclear receptor family member 77, also Nr4a1 |
| PI 3-kinase | Phosphatidylinositol 3-kinase |
| MAP kinase | Mitogen-activated protein kinase |
| PGC1-α | PPARγ coactivator 1α |
| PKA | cAMP-dependent protein kinase, protein kinase A |
| PKC | Protein kinase C |
| RhoGDI | RhoGTPase guanine nucleotide dissociation inhibitor |
| RyR | Ryanodine receptor |
| SR | Sarcoplasmic reticulum |
| SERCA | Sarco/endoplasmic reticulum $Ca^{2+}$-ATPase |

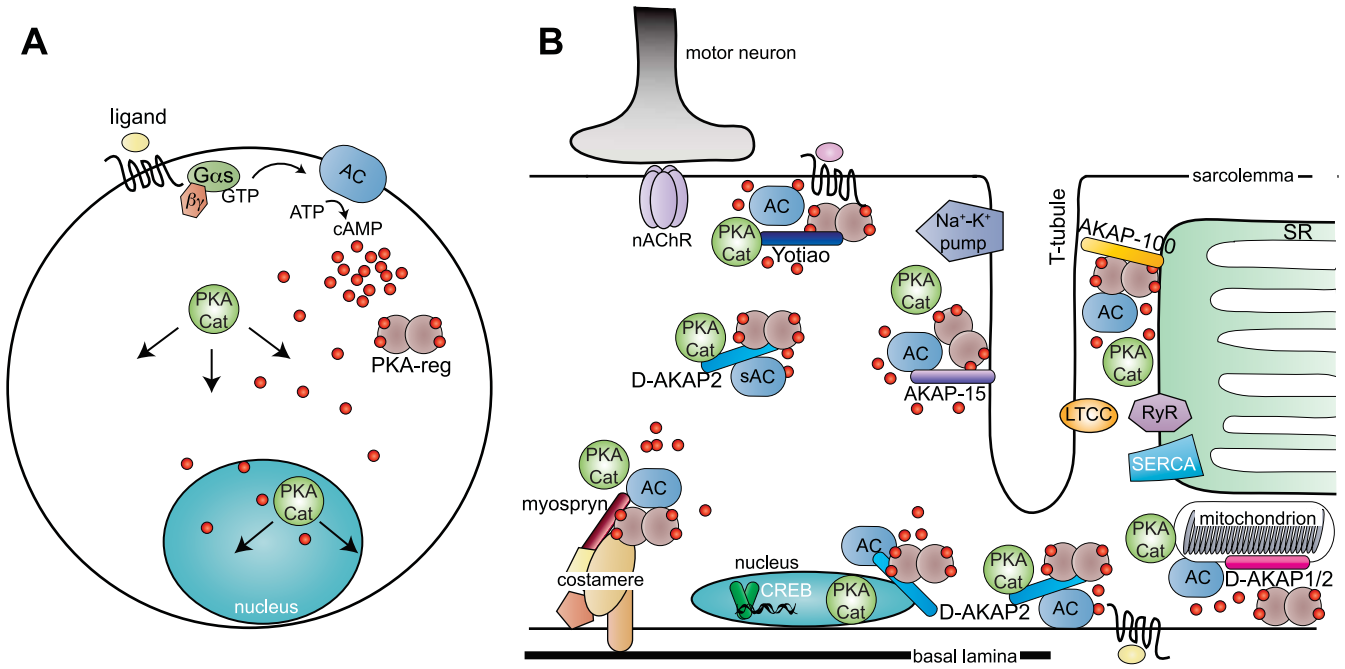


Fig. 1. Models of cAMP signaling in muscle cells. *A*: classic view of cAMP production at the plasma membrane with diffusion into the cytoplasm. A ligand binds to a G protein-coupled receptor (GPCR), which activates $G\alpha_s$. $G\alpha_s$ activates adenylyl cyclase (AC), which produces cAMP. cAMP binds to PKA regulatory subunits (PKA-reg), allowing dissociation of PKA catalytic subunits (PKA-cat), which diffuse into the cytoplasm and nucleus and phosphorylate target proteins. *B*: in a differentiated myofiber, cAMP production and PKA activity are localized to different subcellular compartments by anchoring proteins (AKAPs), including Yotiao (NMJ), AKAP-15 (T-tubules), AKAP-100 (SR), myospryn (costameres), D-AKAP2 (sarcoplasm, nucleus, sarcolemma, mitochondria), and D-AKAP1 (mitochondria). Protein complexes at the neuromuscular junction, on T-tubules, the SR, mitochondrion, and nucleus are shown. PKA-reg (in *A*, sienna) are not labeled in *B*. Several PKA substrates are shown including the $Na^+$-$K^+$ pump, L-type calcium channel (LTCC), and ryanodine receptor (RyR). PKA also modulates activity of the SERCA calcium pump and stability of nicotinic acetylcholine receptors (nAChR).

## A cAMP SIGNALING PRIMER

In the archetypic view of cAMP signaling, activation of G protein-coupled receptors (GPCRs) on the cell surface results in activation of heterotrimeric G proteins, including those containing the stimulatory subunit $G\alpha_s$ (Fig. 1*A*) (111). $G\alpha_s$, in turn, stimulates membrane-bound adenylyl cyclase (AC), which converts ATP to cAMP. Production of soluble, diffusible cAMP is a means of signal amplification and was thought to activate the distant effectors, PKA (cAMP-dependent protein kinase) and Epac (exchange protein activated by cAMP) (112). We now understand that cAMP production and signaling are highly localized (53) and heterogeneous among cell types depending on the complement of GPCRs, G proteins, and AC isoforms expressed. This is particularly pertinent in skeletal muscle, which expresses many GPCRs and has intrinsic subcellular organization that not only accomplishes contraction but also provides a framework for spatially localized cell signaling (Fig. 1*B*).

*Ligand-receptor pairs in skeletal muscle cells.* Although many circulating or locally secreted peptides and molecules can elicit cAMP production in diverse cell types, we have an incomplete picture of the physiologically relevant ligands that activate cAMP signaling in skeletal muscle. A partial list of GPCRs expressed in skeletal muscle has been catalogued (114), and many more have subsequently been found in myoblasts undergoing differentiation (79, 80). It is important to note that many GPCRs in skeletal muscle signal through $G\alpha_q$, which activates phospholipase C and calcium signaling pathways (reviewed in Ref. 112). $G\alpha_s$ and $G\alpha_i$ are the primary regulators of cAMP production. The ligands and receptors known to directly induce cAMP accumulation in muscle precursor cells, myocytes, or myofibers are listed in Table 1. In the text of the review, we focus on the actions of cAMP and in some cases point out the physiologically relevant receptor or ligand.

Among GPCR-ligand pairs, catecholamines and β-adrenergic receptors (β-ARs) have enjoyed the vast majority of experimental attention as cAMP inducers in skeletal muscle, owing most likely to the strong activation of β-AR signaling during exercise, the dramatic inotropic effects of β-AR agonists in cardiac muscle, and the pharmacological importance of β-agonists in heart failure and asthma (reviewed in Ref. 194). Two subtypes of β-ARs are detectable in skeletal muscle ($\beta_1$ and $\beta_2$), although $\beta_2$ is the predominant isoform expressed in muscle tissue (122, 142). $\beta_2$-AR is primarily activated by the catecholamine epinephrine, which is released by the adrenal medulla (82). β-ARs signal through $G\alpha_s$ to activate AC and induce cAMP. In addition, after PKA phosphorylation, $\beta_2$-AR switches to activate pertussis toxin-sensitive $G\alpha_i$ (49); $\beta_2$-AR coupling to $G\alpha_i$ has been demonstrated to occur in soleus (76) and heart (243) but has not been reported in fast-twitch fibers or isolated differentiated myotubes. $\beta_2$-AR can also activate $G\beta\gamma$-dependent signaling to PI 3-kinase, Akt (also called protein kinase B, PKB) and MAP kinases (151). We will discuss how these signaling mechanisms could have profound effects on muscle phenotype in subsequent sections (see *Hypertrophy*). Molecular mechanisms of β-AR regulation have been thoroughly reviewed elsewhere (129, 160, 194).

The corticotropin-releasing factor receptor 2 (CRFR2) is also highly expressed in skeletal muscle (38), and activation of this receptor by a family of ligands called urocortins (Ucn1–3) stimulates cAMP production in differentiated myotubes (133) and isolated muscle tissue (99, 101). Ucn2 is also strongly expressed in skeletal muscle (36), suggesting that it can serve as an autocrine signaling molecule. Although CRFR2 is capable of stimulating cAMP production, it is important to note that CRFR2 can also activate MAP kinase signaling (38). During $C_2C_{12}$ cell differentiation, *Crfr2* mRNA is induced via a MEF2 binding site in the proximal promoter (133). This is thought to account for the selective activity of Ucn3 on CREB (cAMP response element binding protein) reporters in differentiated myotubes (133). *Ucn2* knockout mice are more insulin sensitive and protected from high-fat diet-induced obesity; this is due, at least in part, to enhanced muscle insulin sensitivity (37).

Table 1. *$G\alpha_s$-coupled receptors expressed in skeletal muscle*

| Receptor | Ligand | Cell Type | Effect | Citation |
|---|---|---|---|---|
| β-Adrenergic receptors ($\beta_1$, $\beta_2$, $\beta_3$) | Epinephrine norepinephrine (clenbuterol) (fenoterol) (salmeterol) (isoproterenol) | Myofiber | Glycogen breakdown | (213) |
| | | | Transcription | (131, 164) |
| | | | Excitation-contraction coupling | (172) |
| | | | Metabolic adaptation | (115) |
| | | | Hypertrophy | (121, 151) |
| CGRP receptor | Calcitonin gene-related peptide | Myofiber | nAchR synthesis | (173, 222) |
| | | | Recovery after strenuous contraction | (162) |
| CRFR1 | Corticotropin-releasing factor | Myoblast | Activate cAMP reporter gene, functional effect unknown | (133) |
| CRFR2 | Urocortin 2 | Myofiber | Inhibit insulin action | (37) |
| | Urocortin 3 | | Reduce atrophy | (99, 101) |
| | (sauvagine) | | Reduce degeneration (*mdx*) | (86, 103, 185) |
| | (PD-873637) | | | |
| MOR23 | Unknown (lyral) | Myocyte | Adhesion, migration, fusion during myogenesis and regeneration | (80) |
| Frizzled (?) | Wnt1, Wnt3a, Wnt7a | Muscle precursor cells | Differentiation (proliferation) | (39) |
| Frizzled7 (Frz7) | Wnt7a | Myofiber | Hypertrophy | (237) |
| IL-6 receptor | IL-6 | Myofiber | Induce cAMP (indirectly?), activate AMPK | (118) |
| Adenosine | $A_{2A}$, $A_{2B}$ | Myoblast, Myofiber | Activate CREB, protect during ischemia | (152, 258) |
| Prostaglandin $E_1$ | $EP_1$, $EP_2$, $EP_3$ | Myoblast | Promote fusion | (249) |

Known endogenous ligands (agonists), differentiation state (cell type), and a rough description of functional effects are presented. Additional citations can be found in the relevant section of the text by function. A partial list of β-adrenergic agonists is given.

Thus, Ucn2-CRFR2 signaling normally inhibits insulin action in muscle, though the molecular mechanism is unknown. These findings complicate interpretations of muscle phenotypes resulting from chronic delivery of CRFR2 agonists (86, 99–101, 103, 185) (see *Hypertrophy* and *Injury and regeneration*).

Additional ligands capable of inducing or inhibiting cAMP signaling in muscle cells include calcitonin gene-related peptide (CGRP) (173, 222, 223), corticotropin-releasing factor (CRF) (124, 179), interleukin-6 (IL-6) (118), adenosine (152), prostaglandin $E_1$ (247), $Arg^8$-vasopressin (AVP) (167), and numerous chemokine receptors such as CXCR4 (CXC chemokine receptor 4) (79) and Wnts (39). There are undoubtedly additional ligands that induce or repress cAMP signaling in skeletal muscle. Indeed, numerous $G\alpha_s$-coupled GPCRs of the odorant family are transcriptionally regulated during myogenesis and after skeletal muscle injury (80). Intramuscular cAMP can also be stimulated by chronic stimulation of the motor nerve by an implanted nerve cuff in rabbits and rats (131, 244). This does not require β-AR activity (132) but could involve direct activation of adenylyl cyclases by $Ca^{2+}$-activated PKC isoforms (5, 113, 116, 171) or liberated Gβγ subunits (41, 225) (see *Muscle ACs*). By contrast, in human skeletal myotubes, LPA (lysophosphatidic acid) stimulates pertussis toxin-sensitive inhibitory G proteins ($G\alpha_i$), which antagonize cAMP responses induced by direct AC activators (163). Although many signaling pathways may indirectly modulate intramuscular cAMP signaling via similar pathways or indirect modulation of AC activity, we will limit our discussion to ligands that directly regulate cAMP production.

*G protein subunits.* Heterotrimeric G proteins consist of a GTP-binding α-subunit (Gα) and a heterodimer of β- and γ-subunits (Gβγ). Of the four classes of Gα subunits ($\alpha_s$, $\alpha_i$, $\alpha_q$, and $\alpha_{12/13}$), only $G\alpha_s$ and $G\alpha_i$ signal directly to ACs (95). Upon activation of a GPCR, Gα subunits bind GTP. This releases bound Gβγ subunits and renders Gα competent to interact with downstream effectors. $G\alpha_s$-GTP stimulates ACs, whereas $G\alpha_i$ inhibits these enzymes (95). Developing mouse muscle expresses $G\alpha_s$ and two $G\alpha_i$ isoforms ($G\alpha_{i2}$ and $G\alpha_{i3}$); all are downregulated after birth but strongly upregulated in denervated gastrocnemius muscle (220). In skeletal muscle, pertussis toxin-sensitive G proteins containing $G\alpha_i$ signal via PKC-dependent pathways (135, 163) as well as through released Gβγ in differentiating skeletal muscle cells (61). A very exciting recent study showed that expression of $G\alpha_{i2}$ is sufficient to promote myofiber hypertrophy, oxidative fiber-type switching, myogenic differentiation, and muscle regeneration in mice (163). Although all of the effector pathways are not yet elucidated, PKC mediates $G\alpha_{i2}$-induced hypertrophy and myoblast fusion. It is still unclear how $G\alpha_{i2}$ promotes regeneration of skeletal muscle, but the authors presented evidence of enhanced satellite cell activation and differentiation (163). $G\alpha_i$ also participates in synapse elimination in neonatal rat muscle by an undefined signaling mechanism that could involve PKC (135). $G\alpha_{i2}$ does not seem to act primarily by modulating cAMP production in muscle, as phenotypes observed after $G\alpha_{i2}$ overexpression do not precisely phenocopy $G\alpha_s$ deletion. For example, myofiber size is smaller in $G\alpha_s$ knockout mice than in littermate controls (42); if $G\alpha_{i2}$ promoted hypertrophy by antagonizing $G\alpha_s$ signaling, then $G\alpha_s$ knockout mice would be expected to have larger myofibers. On the other hand, $G\alpha_s$ knockout mice do have more slow-twitch fibers than controls (42). This is consistent with enhanced slow fiber phenotypes after $G\alpha_{i2}$ overexpression (163). However, there is currently no experimental evidence that $G\alpha_{i2}$ induces slow fiber transitions by inhibiting $G\alpha_s$. Thus, it will be important to fully delineate the rest of the downstream signaling pathways underlying the $G\alpha_{i2}$-induced phenotypes and to use additional methods to directly increase or reduce intracellular cAMP in myofibers to determine which observed ligand-induced phenotypes truly involve modulation of intracellular cAMP.

*Muscle ACs.* Mammalian genomes have a large repertoire of transmembrane ACs (AC1–9) and a soluble AC (sAC), which catalyze the conversion of ATP to cAMP (reviewed in Ref. 198). The most abundant forms in adult skeletal muscle are AC2, AC7, and AC9 (87, 220, 232), at least in rodents and rabbits (Table 2). sAC is also detectable (70). AC2 and AC9 are reportedly enriched in fast-twitch myofibers in model organisms (87, 232), and AC2 expression becomes downregulated with chronic motor nerve stimulation in rabbits, coincident with adaptation to a slow-twitch phenotype (232). In addition, AC6 and AC7 are expressed in developing mouse skeletal muscle, although AC6 expression declines dramatically in the postnatal period (220). There is surprisingly little known about AC regulation specifically in skeletal myofibers. Experiments in other cell types and in vitro show that AC isoforms exhibit unique responses to upstream activators and phosphorylation (Table 2). For example, although AC2, AC6, and AC7 are strongly activated by the direct cyclase agonist forskolin or by $G\alpha_s$ (87), AC9 is comparatively poorly sensitive to forskolin (85, 182). In addition to forskolin, PKC (113, 116, 171) and Gβγ (41, 225) can activate AC2 and AC7. Thus, other signaling pathways or GPCRs can potentially activate

Table 2. *Expression and regulation of adenylyl cyclase isoforms in skeletal muscle*

| Property | AC2 | AC6 | AC7 | AC9 | sAC |
|---|---|---|---|---|---|
| Detectable adult expression | Yes (87, 220, 232) | No | Yes (87, 220, 232) | Yes (87, 220, 232) | Yes (70) |
| Developmental expression (220) | − | ++++ | ++++ | ++ | ND |
| Relative adult expression (220) | + | − | ++ | ++++ | ND |
| Expression after denervation (220) | Decrease | Increase | Dramatic increase | Decrease | ND |
| FSK activated | Yes (87) | Yes (87) | Yes (87) | No (85)<br>Weak (182) | No (87) |
| $Ca^{2+}$ or PKC sensitive | Activated (113) | Inhibited (134) | Activated (171) | No (85, 182)<br>Inhibited (6, 7) | Activated (146) |
| Gβγ sensitive | Activated (41) | Inhibited (13)<br>Activated (68) | Activated (246) | No (182) | Not reported |

Activation properties noted. In rows 2–4, expressions of AC2, AC6, AC7, and AC9 were compared in the same samples (220), and expression is relative between them. ND, not determined.

intracellular cAMP production by indirect mechanisms. AC6, on the other hand, is inhibited by PKC or PKA phosphorylation (198). Mouse strains with targeted deletion of AC6 (224), AC7 (97), AC9 (139), and sAC (59) have been generated, and none were reported to have obvious skeletal muscle phenotypes, although histological and functional characterizations were not shown.

*cAMP effectors.* The major effector of cAMP signaling in skeletal muscle is PKA, which was identified biochemically in rabbit skeletal muscle extracts (52). PKA was later shown to mediate the effects of cAMP on muscle glycogen breakdown by both direct inactivation of glycogen synthetase and indirect stimulation of glycogen phosphorylase (213). Inactive PKA is a tetramer of two dimers comprised of regulatory (R) and catalytic (C) subunits (reviewed in Ref. 24) (Fig. 1*A*). cAMP binding to PKA regulatory subunits permits release of catalytic subunits, which are then free to catalyze phosphorylation of target proteins. There are multiple isoforms of regulatory (RIα, RIβ, RIIα, and RIIβ) and catalytic (Cα, Cβ, and Cγ) subunits. The α-isoforms are ubiquitously expressed, but β- and γ-isoforms are restricted to brain, testis, and adipose (24). PKA catalyzes phosphorylation on serine and threonine residues in numerous proteins. In skeletal muscle, these include metabolic enzymes (213), ion channels (204, 205), transcription factors (74), and structural proteins (187) (Fig. 2).

In isolated primary myoblasts, PKA activity increases prior to fusion (189), after which it declines, in part due to stabilization of RI-α subunits (148), which can act as a sink for extra catalytic subunits synthesized during differentiation (149). In concert, intracellular cAMP levels also peak prior to myoblast fusion (250) and are highly regulated during limb muscle development (251) (see *cAMP dynamics during myogenesis).* In mouse embryonic skeletal muscle, both RIα and Cα are highly expressed, with strong mRNA and protein localization to neuromuscular junctions (NMJ) (110), where cAMP signaling is thought to control nicotinic acetylcholine receptor (nAChR) subunit expression during development and after denervation (104, 110) (see *Injury and regeneration).* In keeping with this notion, RIα mRNA is localized to the NMJ from late embryonic development through adulthood and is strongly induced after denervation injury, particularly in slow-twitch soleus muscle (104). In later fetal development, Cα mRNA becomes uniformly distributed throughout the muscle tissue, and both RIα and Cα proteins are abundant and uniformly distributed in the myofibers, at least when viewed in cross-sections (110).

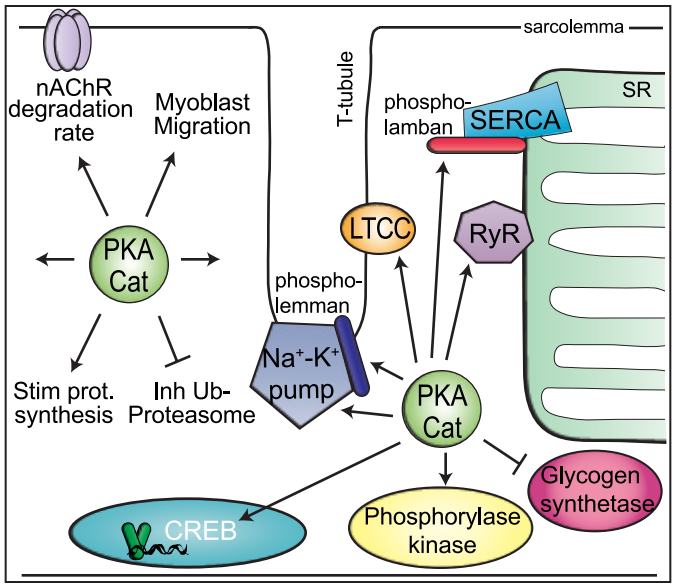


Fig. 2. PKA targets in myofibers. Some specific substrates include the $Na^+$-$K^+$ pump, phospholemman, LTCC, RyR1, phospholamban (slow-twitch fibers only), glycogen synthetase, phosphorylase kinase, and CREB. Other general cellular processes for which specific targets are not clearly identified are also depicted: nAChR degradation, protein synthesis, the ubiquitin-proteasome pathway, and migration (undifferentiated myoblasts only). This is a partial depiction of PKA substrates.

No skeletal muscle phenotypes have been reported in any of the PKA knockout models to date, although some of these mutations result in embryonic or perinatal lethality (4, 30, 108, 210). In skeletal muscle of PKA-RIIα-deficient mice, analysis of L-type calcium channel (LTCC) regulation suggests that PKA-RIα can functionally compensate for loss of PKA-RIIα (30). This functional compensation has been overcome by overexpression of a dominant-negative RIα mutant incapable of binding cAMP (39, 241), which traps PKA catalytic subunits in inactive complexes. This mutant blocks somitogenesis in developing mouse embryos (39). Tissue-specific expression of dominant-negative RIα in mouse embryonic fibroblasts or in liver tissue is sufficient to reduce PKA activity and block activation of a CREB reporter (241), suggesting that this new animal model will be a useful genetic tool for studying cAMP-PKA signaling in skeletal muscle.

Epac1 and Epac2 are also directly activated by cAMP, whereupon they catalyze guanine nucleotide exchange and activate small Ras-like GTPases Rap1 and Rap2 (51). Of the two isoforms, Epac1 is modestly or poorly expressed in muscle tissue (51, 117), whereas Epac2 is restricted to brain and kidney (50, 51). The physiological effects of Epac1 in skeletal muscle have recently been studied using the Epac-selective agonist 8-pCPT-2′-*O*-Me-cAMP (12, 26). These two studies indicate that Epac may mediate cross-talk between β-ARs and the PI 3-kinase-Akt pathway, but no genetic loss-of-function studies have tested Epac function in skeletal muscle or myocytes. Additionally, skeletal muscle phenotypes were not discussed in the recent report of *Epac1* knockout mice (219), so it is unknown whether this protein plays a key role in muscle in vivo. Given the paucity of data regarding Epac action in skeletal muscle, we will focus on cAMP effects mediated by PKA.

*Restricting cAMP action: PDEs and AKAPs.* Although initially envisioned as an event that occurs in diffuse regions of the cytosol and in the nucleus (Fig. 1*A*), cAMP-PKA signaling is spatially restricted by A-kinase anchoring proteins (AKAPs), especially in highly structured cell types like skeletal myofibers (53) (Fig. 1*B*). AKAPs organize PKA and its substrates into macromolecular complexes at specific subcellular locales (Fig. 1*B*). The prominent AKAP isoforms expressed in skeletal muscle include AKAP15 (AKAP7) (78), AKAP-100/mAKAP (AKAP6) (159), Yotiao (AKAP9) (144), D-AKAP1 (AKAP1) (107) and D-AKAP2 (AKAP10) (29, 106), and myospryn (CMYA5) (187), which localize PKA to sites of excitation-contraction coupling, the SR, the NMJ, mitochondria, the nucleus, and costameres, respectively (Table 3). Of the AKAPs listed above, only *mAkap* (161), *D-Akap1 (Akap1)* (174) and

Table 3. *AKAPs expressed in skeletal muscle and localization*

| AKAP | Localization | Citation |
|---|---|---|
| AKAP15 | T-tubules | (78) |
| AKAP-100 (m-AKAP) | Sarcoplasmic reticulum | (159) |
| Yotiao (AKAP9) | Neuromuscular junction | (144) |
| D-AKAP1 | Mitochondria | (107) |
| D-AKAP2 | Mitochondria, cytosol, nucleus | (29, 106) |
| Myospryn | Costameres | (187) |

*D-Akap2* (*Akap10*) (230) have been deleted in mice, but skeletal muscle phenotypes were not reported in any of these knockout models. It is notable that cAMP microdomains are disrupted (188) and PKA activity is reduced (186) in dystrophic skeletal muscle from a mouse model of Duchenne's muscular dystrophy (*mdx*). This could partly result from disrupted expression and localization of myospryn, which interacts with dystrophin in costameres in normal muscle (186). Myospryn misregulation correlates with reduced PKA activity and RIIα mislocalization in dystrophic myofibers (186), although it is not known whether altered PKA signaling contributes to the dystrophic phenotype. For more discussion of AKAP-PKA complexes, the reader is referred to an excellent recent review (53).

Termination of cAMP signals is accomplished by cAMP phosphodiesterases (PDEs), which have been purified from skeletal muscle (218). Subsequent to the initial discovery, no less than eleven different PDE classes, many with multiple isoforms encoded by distinct genes, have been identified. Among cAMP-specific PDEs, PDE4 isoforms are highly expressed in skeletal muscle (8, 207) and account for the majority of PDE activity in mouse limb muscle (21). PDE7B and PDE11A are also expressed in skeletal muscle (60, 69, 96, 202). Pharmacological inhibition of PDEs reduces proteolysis and atrophy in rodent muscle ex vivo (170) and in vivo after denervation or casting (98) or in rodent models of diabetes (11) and sepsis (145). These data suggest that selective upregulation of cAMP signaling in skeletal muscle may be a strategy to prevent muscle atrophy in patients with aging-related atrophy, disuse atrophy, cancer cachexia, or sepsis. Interestingly, elevated PDE activity is observed in skeletal muscle of dystrophic mice (20, 21, 143). Although these findings do not imply that reduced cAMP abundance in dystrophic muscle causes the dystrophic phenotype, it would be interesting to test whether chronic PDE inhibition can improve muscle regeneration or function in dystrophic muscle in a manner analogous to $\beta_2$-AR and CRFR2 agonists (90, 103, 185, 254, 256). Studies with prolonged PDE inhibitor treatment should be evaluated with caution, as mice lacking *Pde4d* display exercise intolerance and evidence of myofiber damage after downhill running (17). As no thorough histological and functional investigation of skeletal muscle phenotypes in any of the PDE knockout lines has been reported, we have little additional genetic information about the functions of specific PDE isoforms in skeletal muscle in vivo.

## cAMP IN FUNCTIONAL ADAPTATION OF SKELETAL MUSCLE

Adaptive functions of sustained GPCR signaling have been identified using chronic treatment with agonists and antagonists in humans and model organisms (9, 18, 43, 57, 63, 86, 91, 101, 115, 121, 154, 155, 197) as well as by targeted genetic approaches in mice (42, 163, 164). These and other studies have revealed striking myofiber hypertrophy and fiber-type transitions to faster fiber types with prolonged activation of β-AR signaling in particular. Although there is evidence supporting cAMP-dependent signaling as a mediator of long-term adaptive responses to β-AR agonists and possibly other GPCR ligands (42, 98), additional downstream effector pathways mediated by $G\alpha_i$/PKC (163) and Akt (127) are also clearly involved. These alternate pathways may or may not respond to initial or sustained cAMP production. In this section, we provide an overview of the effects of sustained activation of cAMP-coupled GPCRs in skeletal muscle, focusing on myofiber hypertrophy and fiber-type transitions. For an additional discussion, the reader is referred to a comprehensive review by Lynch and Ryall (151).

*Hypertrophy.* Myofiber hypertrophy is a form of muscle adaptation that occurs in response to resistance exercise (226). There is great interest in understanding molecular mechanisms underlying this adaptive response, because skeletal muscle atrophy accompanies and exacerbates many pathological states, including disuse, denervation injury, cancer, AIDS, and aging (reviewed in Ref. 71). Increased muscle mass and myofiber cross-sectional area in adult skeletal muscles are brought about by shifts in the relative rates of protein synthesis and degradation; the net result is enhanced muscle strength (71). It has been appreciated for many years that systemic treatment with $\beta_2$-AR agonists such as clenbuterol (Table 1) induces skeletal muscle hypertrophy in rodents, large mammals, and humans (reviewed in Ref. 151) (Fig. 3). Additionally, β-adrenergic agonists blunt muscle atrophy after denervation (253), muscular dystrophy (192), or nutritional deficiency (73). At the cellular level, clenbuterol has been shown to stimulate total protein synthesis (57, 154) and translational efficiency (155) as well as reduce proteolysis in rabbit, rat, and chick skeletal muscles (18, 63, 190). These effects are probably mediated by cAMP, as PDE inhibitors reduce atrophy in skeletal muscle (98) and a cell-permeable cAMP analog (db-cAMP) or PDE inhibitors reduce proteolysis in muscle studied ex vivo (11, 170). Moreover, in cell culture models of hyperthermia-induced proteolysis, formoterol (a $\beta_2$-AR agonist) reduced proteolysis by a mechanism dependent on AC activity (3). In

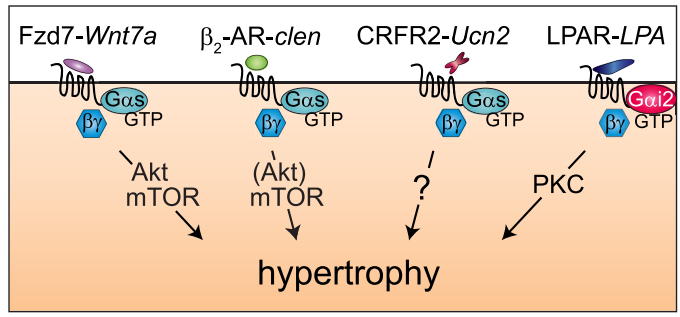


Fig. 3. GPCRs that induce myofiber hypertrophy. Four GPCRs (Fzd7, $\beta_2$-AR, CRFR2, and LPA receptor) have been shown to stimulate hypertrophy in myotubes and/or myofibers. Cognate ligands are italicized. A partial view of the known signaling mediators is shown. CRFR2 stimulates myofiber growth by an uncharacterized effector pathway. $\beta_2$-AR also induces fiber type transitions to fast-twitch fibers (not shown).

addition, activation of the GPCR Fzd7 (Frizzled 7) by Wnt7a was also shown to induce hypertrophy in rodent myotubes via a pathway involving $G\alpha_s$ (237). On the contrary, mice lacking $G\alpha_s$, which stimulates cAMP production, have smaller myofibers than littermate controls (42).

In pathological settings, ligands for two GPCRs, $\beta_2$-AR and CRFR2, reduce atrophy or help sustain muscle function and strength in rodent models after denervation (100, 101, 123, 127, 154, 253, 255), unloading (99, 101, 123, 127) or aging (35). $\beta_2$-AR agonists have also been shown to reduce muscle atrophy in animals with cancer cachexia (31, 33, 46). In addition, agonists for $\beta_2$-AR or CRF receptors improve muscle function in dystrophin-deficient *mdx* (86, 90, 103, 185, 192, 254, 256) and laminin-deficient *dy/dy* (94) mice. However, efficacy of $\beta_2$-AR agonists on muscle size and force generation vary with the type and dose of agonist, as well as the muscle studied. Small scale clinical trials in muscular dystrophy patients revealed limited promise of the $\beta_2$-AR agonist albuterol (64, 125, 126, 235), which appeared to improve muscle function with varying effects on muscle strength (211). These studies have been extensively analyzed by Lynch and Ryall (151).

Although genetic and pharmacological studies confirmed that the anabolic effects of clenbuterol in rodents are mediated by $\beta_2$-ARs (43, 102), the precise molecular mechanisms by which $\beta_2$-AR signaling induces hypertrophy are still not fully elucidated. Both $\beta_2$-AR and CRFR2 are expressed in muscle cells and are capable of stimulating cAMP production (54, 124, 179). The phenotype of smaller myofibers in $G\alpha_s$ knockout mice provides genetic evidence that cAMP signaling does have a role in myofiber hypertrophy (42) (Fig. 3). Moreover, activation of a noncanonical signaling pathway by Wnt7a-Fzd7 is also sufficient to drive muscle fiber hypertrophy in vitro (237). The authors found that Fzd7 physically interacts with $G\alpha_s$, and $G\alpha_s$ is required for Fzd7-induced PI 3-kinase activation and hypertrophy (237). However, the recent study by Minetti et al. (163) demonstrates that the inhibitory G protein $G\alpha_{i2}$ is also sufficient to promote myofiber hypertrophy in vitro and in vivo (Fig. 3). In other cell types, $\beta_2$-AR and CRFR2 have been shown to activate additional effector pathways such as $G\alpha_q$-PLC, $G\alpha_i$-PKC, $G\beta\gamma$, or β-arrestin-Akt (25, 76, 77, 89, 243), which could mediate anabolic effects of these receptors (Fig. 4). An additional possibility is that after initial activation of $G\alpha_s$, PKA phosphorylation of the $\beta_2$-AR causes it to couple to $G\alpha_i$. This mechanism occurs in cardiac muscle (243) and soleus (76), and it will be interesting to determine whether this regulatory mechanism is a general feature of all skeletal muscle types. Nonetheless, dynamic coupling to G proteins by chronically stimulated receptors could account for observations that inhibition of $G\alpha_s$ or activation of $G\alpha_i$ leads to opposite changes in myofiber size.

Many studies have established that IGF-I strongly activates muscle hypertrophy by stimulating the PI 3-kinase-Akt pathway (10, 166) (Fig. 4). Akt, in turn, activates the downstream kinase mTOR, which stimulates p70 S6 kinase and other effectors, ultimately culminating in enhanced protein synthesis (23, 191). In addition, Akt represses FoxO (F box, class O) transcription factors, which drive expression of muscle-specific ring finger E3 ubiquitin ligases *MuRF1* (*Muscle RING Finger 1*) and *MAFbx* (*Muscle Atrophy F-box*, also called *Atrogin-1*) when Akt signaling tone is reduced (22, 201, 217). The potent

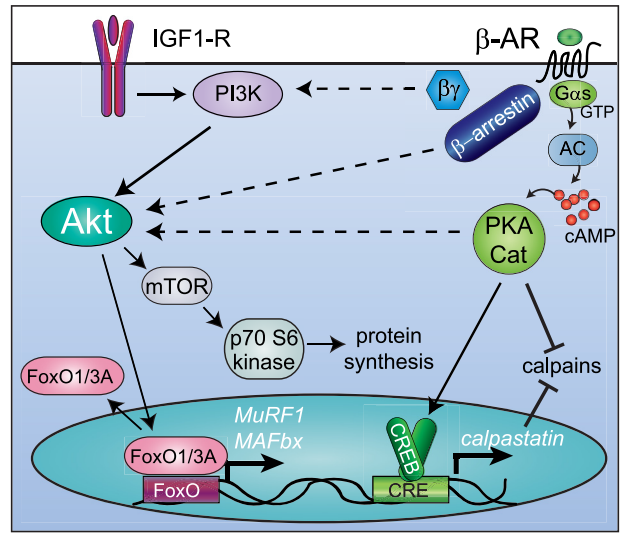


Fig. 4. Possible mechanisms of Akt activation by β-AR signaling. IGF-I activates Akt, which stimulates protein synthesis via activating mTOR and inhibits muscle-specific ubiquitin ligase expression via repressive phosphorylation of FoxO transcription factors. $\beta_2$-AR signaling leads to muscle hypertrophy, which is accompanied by activation of Akt, activation of protein synthesis, and inhibition of proteolysis. PKA signaling induces *calpastatin* transcription and inhibits calpains by an unknown mechanism. $\beta_2$-AR signaling also activates Akt by an unknown mechanism, possibly mediated by $G\beta\gamma$ subunits, β-arrestin, or PKA (dashed arrows). Not shown: Wnt7a-Fzd7-$G\alpha_s$ activates PI 3-kinase directly.

effects of IGF-I-Akt signaling on muscle hypertrophy prompted several investigators to address the role of Akt signaling in muscle responses to clenbuterol (Figs. 3 and 4). Kline et al. (127) showed that clenbuterol activates Akt in skeletal muscle, and the mTOR inhibitor rapamycin partly blocks anabolic effects of clenbuterol. In agreement with these findings, $\beta_2$-AR agonists promoted muscle protein synthesis after 7 days with concomitant activation of Akt (130) (Fig. 4). Clenbuterol treatment has also been associated with a transient increase of activated p70 S6 kinase (212). Signaling from $\beta_2$-AR to Akt appears to be direct and not mediated by an autocrine pathway, as adrenergic signaling does not induce IGF-I protein expression in skeletal muscle (127, 245). It has been proposed that, similar to cardiac muscle, the signaling mechanism from $\beta_2$-AR to Akt could be mediated by $G\beta\gamma$ (127). Consistent with this model, myotube hypertrophy induced by ectopically expressed $G\alpha_{i2}$ was blocked by rapamycin or PKC inhibitors, but not by PI 3-kinase inhibitors, suggesting that G protein signaling to Akt is direct (163) (Fig. 4). Alternatively, the recent data from von Maltzahn et al. (237) clearly implicate direct activation of PI 3-kinase by $G\alpha_s$ or released $G\beta\gamma$ as a mechanism for Akt activation by Fzd7, a $G\alpha_s$-coupled receptor. Another intriguing possibility is that Akt could be activated by β-arrestin upon $\beta_2$-AR activation, as recently observed in fibroblasts (89). This hypothesis has not been tested in skeletal muscle. The same signaling mechanism may apply to other GPCRs. However, it is important to note that, although CRFR2 agonists induce muscle hypertrophy and blunt muscle atrophy (99–101), they actually inhibit insulin-Akt signaling (37). Therefore, multiple molecular mechanisms may mediate antiatrophic effects of GPCRs in skeletal muscle. Ultimate determination of how $G\alpha_s$-coupled receptors activate Akt will

provide mechanistic insight into the commonly observed effects of $\beta_2$-AR agonists and other GPCR ligands on muscle hypertrophy and may uncover new targets for therapeutic promotion of muscle growth.

In addition to promoting muscle growth and protein synthesis, cAMP signaling inhibits proteolysis by both calpains and the ubiquitin proteasome system. Calpains are calcium-activated proteases, which are inhibited by the protein calpastatin (reviewed in Ref. 168). β-AR agonists reduce calpain activity in skeletal muscle tissue in animal models (9, 63, 169). This occurs in part by cAMP-induced expression of the inhibitor calpastatin (Fig. 4) via CREB binding sites in the bovine (45), porcine (206), and human (257) *calpastatin* gene promoters. cAMP might also regulate calpastatin expression by posttranslational mechanisms, as CREB binding sites have not been annotated in the rodent promoters (257). In addition, calpastatin activity was elevated in porcine and rat skeletal muscle after continuous infusion with β-AR agonists even though the *calpastatin* mRNA was not uniformly induced (130, 176). Animal models support modulation of the calpain system as a useful therapeutic strategy: *mdx* mice have aberrantly high levels of calpain activity (228), whereas muscle-specific overexpression of calpastatin reduces atrophy in disuse models (199, 229) and reduces necrosis in *mdx* muscle (214), but perhaps does not improve overall regeneration (27).

The other major proteolytic system in skeletal muscle is the ubiquitin-proteasome system. Two E3 ubiquitin ligases, *MuRF1* and *MAFbx/Atrogin-1*, undergo massive transcriptional induction in skeletal muscle after denervation injury (22). Mice lacking *MuRF1* or *MAFbx/Atrogin-1* are resistant to muscle atrophy, demonstrating the crucial role of the ubiquitin-proteasome pathway in this pathology (22). *MuRF1* and *MAFbx/Atrogin-1* mRNAs are induced by FoxO transcription factors FoxO1 and FoxO3a, which are normally sequestered in the cytoplasm by Akt phosphorylation (201, 217) (Fig. 4). The $\beta_2$-AR agonist clenbuterol reduces amounts of high-molecular-weight ubiquitin conjugates and proteasome activity in fast-twitch skeletal muscles undergoing atrophy from hindlimb unloading (245), suggesting the possibility that β-AR activation also suppresses FoxO activity. Consistently, clenbuterol potently suppresses both *MuRF1* and *MAFbx/Atrogin-1* transcription in normal muscle and attenuates expression of these genes in atrophying muscle in rats (127). In addition, cAMP signaling activates Akt and represses ubiquitin-proteasome pathway activity in $C_2C_{12}$ cells and rat skeletal muscle (73). It is tempting to speculate that FoxO transcription factors might mediate the activity of β-AR on *Murf1* and *Mafbx/Atrogin-1*; indeed, FoxO3A phosphorylation correlates with clenbuterol-induced Akt phosphorylation in vivo in muscle from fasted animals (73). FoxO1 phosphorylation has not been explored in this model, and much uncertainty remains regarding the mechanisms by which $\beta_2$-AR agonists modulate ubiquitin-mediated protein degradation in skeletal muscle.

Four GPCRs, $\beta_2$-AR, CRFR2, the LPA receptor, and Fzd7, have been shown to induce hypertrophy in skeletal muscle or isolated myotubes. The field is closer to understanding mechanisms underlying GPCR-induced hypertrophy, and it will be of great scientific and clinical interest to determine whether these receptors utilize common effector pathways. It is clear that CRFR2 signaling can block pathological muscle atrophy. However, genetic and pharmacological studies indicate that Ucn2 inhibits Akt signaling (37); so alternate downstream effector pathways likely mediate the anabolic effects of this ligand-receptor pair. Given the promising anabolic effects of CRFR2 agonists on mouse models, it will be important for future studies to rigorously interrogate the signaling pathway mediating these effects. It will also be exciting to determine whether chronic stimulation of other GPCRs expressed in skeletal muscle have the same hypertrophic effects in normal muscle and anti-atrophic effects in aging or diseased muscle.

*Metabolic adaptation.* In the postnatal period, skeletal myofibers develop distinct phenotypic characteristics that enable classification into one of several fiber types, including slow oxidative (type 1), fast oxidative (type IIa), and fast glycolytic (type IIb or type IIx) (reviewed in Ref 203). Despite this initial specialization, phenotypes of individual muscle fibers are plastic in adult mammals. Cross-innervation studies in model organisms demonstrated that the pattern of motor neuron firing (tonic or phasic) dictates muscle fiber phenotypes and that fast and slow fibers can be interconverted by altering the pattern of innervation by denervation or by endurance exercise (203). At the molecular level, changes to a slow fiber phenotype are mediated by several signal transduction pathways, which drive mitochondrial proliferation and activate transcription of slow myosin isoforms, myoglobin, and enzymes involved in oxidative metabolism (203). Schiaffino et al. (203) provide a comprehensive discussion of muscle fiber type plasticity.

Several observations associate cAMP signaling with oxidative adaptation to exercise. First, epinephrine is released into circulation during exercise (67), and intramuscular cAMP increases within minutes of treadmill running (72). Second, β-AR density is highest in oxidative muscles and correlates with oxidative capacity in mixed or intermediate fiber types (62, 156, 240); AC activity is also increased by endurance training in rats (28). Third, in cultured muscle cells, agents that induce intracellular cAMP activate oxidative enzymes, some at the level of expression (66, 136). Additionally, β-AR signaling or cAMP-sensitive transcription factors have been reported to regulate genes involved in oxidative metabolism, including *Pgc1α* (*PPARγ coactivator 1α*) (2, 164, 242), *cytochrome c* (65), *CoxIV* (*cytochrome c oxidase IV*) (75), and orphan nuclear receptors *Nor1* (*neuron-derived orphan receptor 1*, or *Nr4a3*) and *Nur77* (*nuclear receptor family member 77*, or *Nr4a1*) (157, 178). Overexpression of cAMP-activated CREB coactivators is also sufficient to induce mitochondrial proliferation in cultured myotubes (242). In rats, the β-adrenergic antagonist propranolol blunted activation of mitochondrial enzyme activity after endurance treadmill training (115), but a histological examination of fiber types was not shown in that study. In additional studies, propranolol substantially reduced normal increases in mitochondrial enzyme activity of rat muscles (91), although the effects varied among fiber types (227). In addition, Kraus et al. (131) showed that chronic electrical stimulation of fast-twitch muscles elicited an increase in cAMP with concomitant induction of mRNAs encoding myoglobin and proteins involved in oxidative metabolism. These correlations could imply that β-AR-cAMP signaling during exercise participates in oxidative metabolic adaptation of skeletal muscle.

However, compelling genetic and pharmacological data from mice and humans suggest that this is not likely the case. In humans, mitochondrial enzyme activity increases with en-

durance exercise despite treatment with the beta-blocker propranolol, and no significant change in fiber-type percentage or cross-sectional area was reported in this study (221). Moreover, *Pgc1α* expression was still induced, albeit to a lesser extent, by treadmill training in mice lacking all β-ARs (164). It is also notable that, although the CREB binding site is required for *Pgc1α* promoter activation in response to electrical stimulation (2), the CREB family protein ATF2 binds this site and mediates *Pgc1α* transcription in this setting (1). Additionally, mice with muscle-specific deletion of $G\alpha_s$ or overexpression of $G\alpha_{i2}$ (both leading to reduced cAMP accumulation in muscle) exhibit fiber-type switching toward a higher proportion of oxidative fibers (42, 163). Genetic inhibition of CREB activity in differentiated muscle leads to defects in myofiber survival but not alterations in muscle fiber type (19). Finally, a large body of data from humans and model organisms shows that chronic stimulation of $\beta_2$-AR signaling causes shifts toward faster, not slower, myofiber phenotypes (14, 47, 55, 150, 180, 183, 252).

The molecular mechanism by which $\beta_2$-AR agonists induce fast fiber-type transitions is not known. Shi et al. (208) found that isoproterenol treatment of $C_2C_{12}$ myoblasts stimulates promoters of *MyHC-IIb* (myosin heavy chain IIb) and *Serca1* (sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPase) genes, which are expressed in fast myofibers. In addition, clenbuterol activated a *MyHC-IIb* reporter in mouse gastrocnemius muscle (208). As ERK1/2 (extracellular signal-regulated protein kinase) activation by clenbuterol was greater in fast muscles than in slow muscles, the authors propose that ERK signaling downstream of the $\beta_2$-AR mediates fast fiber-type transitions in clenbuterol-treated animals (208). It will be interesting to further test this mechanism using additional loss-of-function approaches. Lynch and Ryall (151) noted that overexpression of Eya1/Six1 induces expression of fast-type *MyHC-IIb* myosin in soleus (81) and proposed this as a possible unexplored mechanism to explain the fiber-type transitions observed with sustained clenbuterol treatment. The observations that mice with targeted deletion of $G\alpha_s$ (42) or overexpression of $G\alpha_{i2}$ (163) have more slow-twitch fibers are consistent with promotion of fast fiber-type switching by cAMP effectors. Interestingly, both AC2 and AC7 mRNAs are enriched in fast myofibers (87, 232), so it is possible that these fibers have more sustained cAMP production in a chronic treatment setting. However, in rats, AC and PKA activity are both higher in slow-twitch soleus than in fast-twitch extensor digitorum longus muscles (28, 104, 240), and AC activity increases more after exercise training in oxidative muscles (28). Finally, although CREB stimulates genes involved in oxidative metabolism (242), it is possible that cAMP-induced transcriptional responses are dampened by autoregulatory feedback loops after prolonged β-AR activation (236). This notion is supported by microarray data showing that acute β-AR agonist treatment induces genes involved in oxidative metabolism, whereas prolonged treatment is associated with repression of genes involved in myostatin signaling (177).

In summary, ligands capable of inducing cAMP signaling exert hypertrophic effects on skeletal muscle and, in some cases, induce fast fiber-type transitions. Receptor and AC isoform expression is not well correlated with measured AC and PKA activities among fiber types. Thus, expression patterns do not simply account for the observed changes to faster fiber types with prolonged adrenergic agonist treatment. The recent finding that inhibitory $G\alpha_{i2}$ induces hypertrophy as well as oxidative fiber-type transitions (163) underscores the importance of further investigation into whether and how different signaling mediators, possibly independently of cAMP, contribute to the phenotypes observed with prolonged activation of GPCRs in skeletal muscle.

## cAMP IN MUSCLE DEVELOPMENT AND REGENERATION

cAMP signaling is dynamically regulated during embryonic muscle development, ex vivo myogenesis, and muscle regeneration (16, 34, 39, 120, 137, 251). In adult skeletal muscle, resident muscle stem cells, or satellite cells, become activated after acute injury or in response to hypertrophic stimuli (93). These cells then proliferate, differentiate, and fuse with each other and existing fibers. Satellite cells are absolutely crucial for skeletal muscle regeneration and are thought to contribute to ongoing productive hypertrophy (239), although this is still under debate (158). Regeneration is an adaptive response of muscle, so understanding of cAMP signaling pathways in satellite cells and their progeny is important to understanding the overall adaptive capacity of skeletal muscle. Several proteins involved in cAMP signaling, including receptors, G proteins, and cAMP-activated transcription factors, have been found to promote muscle regeneration (80, 163, 216) and functional recovery after injury (15, 196). Ligands for these GPCRs also improve muscle function and slow disease progression in dystrophic *mdx* mice (86, 90, 103, 185, 192, 254, 256). In conjunction with the anti-atrophy effects described in the preceding section (see *Hypertrophy*), GPCR signaling in muscle precursor cells is a potential area for development of novel therapeutic agents that could promote regeneration and limit atrophy in patients with muscular dystrophy, denervation atrophy, age-related sarcopenia, or muscle wasting due to cancer. In the final section of this review, we will trace the actions of cAMP in myogenesis and explore the recent studies on cAMP signaling during satellite cell-mediated skeletal muscle regeneration.

*cAMP dynamics during myogenesis.* Skeletal muscle formation during embryogenesis, or myogenesis, is a complex process involving proliferation and determination of precursor cells, myoblast migration, cell-cell fusion, and myogenic differentiation to ultimately form multinucleated, contractile myotubes (93). Numerous cell surface receptors and interwoven transcriptional networks act cooperatively during myogenesis. Early work implicated cAMP signaling in myogenesis, as AC activity, cAMP, and PKA activity all increase at specific times during embryonic muscle development and differentiation of myoblasts in culture (137, 153, 189, 238, 250, 251). Moreover, transient treatment with catecholamines (48) or prostaglandin $E_1$ (249), which stimulate intracellular cAMP production, enhances fusion of primary chick myoblasts. However, this increase in cAMP production must be tightly regulated. Intracellular cAMP and PKA activity normally decline after myoblast fusion (137, 238, 251), and sustained cAMP signaling achieved by pharmacologic methods or by ectopic expression of $G\alpha_s$ markedly inhibits myoblast fusion and differentiation (105, 119, 140, 233, 248). Thus, therapeutic approaches to stimulate myoblast fusion must be designed with caution to allow dynamic cAMP regulation in vivo.

*Migration and fusion.* It is not known why sustained cAMP-PKA signaling inhibits myoblast fusion, nor is it understood how transient cAMP signaling exerts a priming effect on this process (249). However, recent groundbreaking work by Pavlath and colleagues provided clues that the odorant family GPCR MOR23 stimulates cAMP signaling and regulates myoblast cell migration, adhesion, and fusion during myogenesis via cAMP-mediated pathways (80). In vivo, silencing MOR23 blunted muscle regeneration after myotoxic injury and left many branched, unfused myofibers (80). Dynamic cytoskeletal rearrangements are required for cell migration and fusion (40), suggesting that unrecognized PKA effectors regulate the cytoskeleton in myoblasts. This idea is supported by findings that cAMP signaling promotes fusion in a mouse satellite cell-derived line and that a fraction of PKA-RII subunits localizes to lamellipodia of bipolar myotubes (165). Interestingly, excessive PKA signaling in mouse embryos lacking RIα also results in defective cell migration (4). Together, these findings support a model in which dynamic PKA activity at the leading edge of migrating cells is important for migration and fusion. In fibroblasts, PKA phosphorylates the small GTPase RhoA, blocking interaction between RhoA and the Rho guanine dissociation inhibitor (RhoGDI) protein, rendering RhoA active (231). Additional experimental effort will be required to determine whether PKA regulation of Rho or other cytoskeletal modulators regulates myoblast migration and fusion.

*Myogenic differentiation.* In addition to blocking myoblast fusion, sustained cAMP signaling potently inhibits myogenic differentiation, in part by inhibiting myogenic transcription factors (56, 105, 140, 200). However, cAMP-PKA dynamically regulates CREB-dependent transcription during vertebrate muscle development, during which phosphorylated CREB is localized to differentiating regions of the dermomyotome in mouse (39) and *Xenopus* (120). Although additional PKA effectors likely participate in myogenesis, loss-of-function studies have established a key role for CREB in myogenic differentiation and myofiber survival (Fig. 5). Through an elegant series of experiments, Chen et al. (39) showed that mouse embryos lacking *Creb* exhibit smaller somites and drastically reduced expression of the myogenic determination factors *Pax3* and *Myf5*. The small somite size in *Creb* mutant embryos resulted from reduced proliferation, although the CREB transcriptional targets mediating muscle precursor cell proliferation are unknown. Using embryo explants, the authors discovered a noncanonical Wnt signaling pathway, mediated by cAMP and PKA, which drives CREB phosphorylation on $Ser^{133}$ and is necessary for myogenesis, possibly via direct transcriptional induction of *Pax3* or *Myf5* (39) (Fig. 5). Consistently, we found that myoblasts from knock-in mice expressing a CREB gain-of-function mutant (CREB-Y134F) exhibit enhanced proliferation in culture. Furthermore, differentiating CREB-YF myocytes expressed more Myf5 protein than wild-type controls (216). Although the *Myf5* promoter contains several conserved CREB binding sites (39), chromatin immunoprecipitation assays have not been performed to demonstrate that CREB directly transactivates this gene. CREB phosphorylation is also induced during early stages of differentiation in cultured $C_1C_{12}$ cells (153) but declines during late differentiation (209), when it induces *RB* and *follistatin* mRNAs in conjunction with MyoD (109, 153). CREB has furthermore been implicated in transcription of the mRNA encoding the mitochondrial protein cytochrome *c* in differentiating myotubes (65).

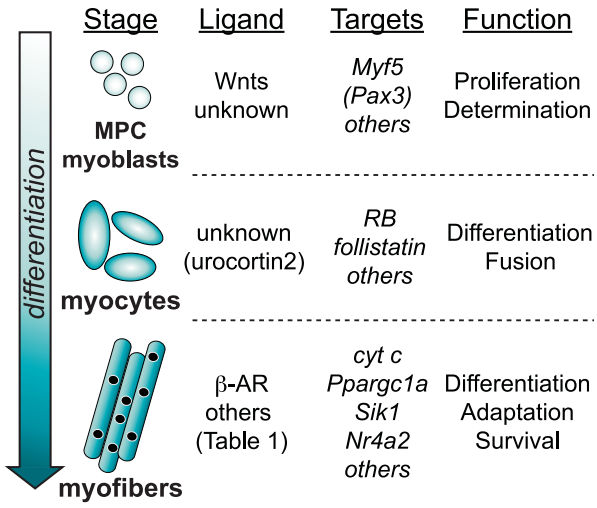


Fig. 5. Roles of CREB in muscle cells at different stages of differentiation. During development or after injury, myogenic precursor cells (MPCs) differentiate into myoblasts, myocytes, and myofibers. The known ligands that stimulate CREB, known CREB target genes, and CREB functions at each developmental stage are listed.

cAMP signaling during myogenesis is dynamic, and ectopically sustained cAMP signaling inhibits bHLH myogenic transcription factors and MEF2D (56, 105, 140, 200). If high amounts of cAMP are needed to activate CREB but also inhibit myogenic differentiation, it seems paradoxical that CREB could participate in differentiation. A possible model to rectify these results holds that cAMP-CREB transcription exerts a priming effect on the myogenic program by induction of *Myf5* and probably other early target genes (Fig. 5). Additionally, cAMP levels decline in myocytes during later stages of differentiation, when CREB participates in regulation of *cytochrome c* (65), so it is also possible that during differentiation CREB is regulated by a cAMP-independent kinase such as p38 MAP kinase, which activates CREB during mesoderm patterning in *Xenopus* embryos (120). Finally, many CREB-regulated promoters are subject to combinatorial control; CREB interacts with MyoD on both the *RB* and *follistatin* promoters (109, 153), suggesting that CREB promoter occupancy may be permissive for these genes, not limiting. Nonetheless, CREB activity is required for myogenic differentiation in vitro (153) and in vivo (39), so a thorough understanding of the upstream activating signals and the mechanisms by which sets of target genes are selected at different stages of differentiation will contribute to the mechanistic understanding of this complex process.

*Injury and regeneration.* Satellite cell-mediated regeneration is studied in model organisms by injection of toxins or the anesthetic bupivacaine, which cause myofiber necrosis, or by studying regenerative capacity in genetic models of muscular dystrophy, particularly the *mdx* mouse (93). Modulation of cAMP signaling using pharmacological agents (86, 90, 103, 196, 254) or genetic means (80, 163, 216) can improve muscle regeneration in these models. β-AR density increases threefold after necrotizing muscle injury, with concomitant increases in intramuscular cAMP relative to normal muscle (16). Other GPCRs are also upregulated after muscle damage, including

the odorant receptor MOR23, which contributes to myogenesis and fusion during regeneration (80). Similarly to β-AR, MOR23 is coupled to $G\alpha_s$, suggesting that one or both of these receptors stimulates cAMP production in cells in the injured region. CRFR2 agonists also not only limit atrophy but also appear to modulate degeneration, inflammation, and fibrosis in *mdx* muscle by unknown mechanisms (103). Paradoxically, intramuscular injection of forskolin or a PDE inhibitor after myotoxic injury reduces expression of a MEF2 reporter during regeneration, probably due to direct inhibition of MEF2D by PKA (56). This finding indicates that, as in development, dynamic cAMP signaling is required during regeneration.

In addition to its actions during muscle development, CREB also exerts positive effects on muscle survival and regeneration in mouse skeletal muscle. We previously showed that mice expressing dominant-negative CREB (A-CREB) in skeletal myofibers exhibit muscle degeneration, due at least in part to reduced expression of salt-inducible kinase-1 (*Sik1)* (19). SIK1 phosphorylates and inhibits HDAC5, thereby activating MEF2 (19). In muscle A-CREB mice, compromised sarcolemmal integrity is probably secondary to reduced expression of *desmin* (a MEF2 target gene) or M-line structural abnormalities due to reduced *Mef2c* expression; mutations in either *desmin* or *Mef2c* result in similar myopathic phenotypes (141, 181). On the other hand, knock-in mice expressing activated CREB(Y134F) have enhanced proliferation after muscle injury and improved regeneration on an *mdx* background (216). It is not known which transcriptional targets of CREB mediate its effects on muscle repair. We favor a model in which, after injury, CREB induces genes in muscle precursor cells to drive proliferation and subsequently contributes to myoblast fusion via *follistatin* (109). Finally, CREB may further promote differentiation via transcriptional induction of *Myf5* (39) and *RB* (153) (Fig. 5). In support of this model, amounts of phospho-CREB are elevated in both Pax7-positive satellite cells and nascent myofibers within regenerating *mdx* muscle (216). However, the endogenous ligands that activate CREB in myocytes and regenerating myofibers are poorly characterized. In the embryo, Wnt1, Wnt3a, or Wnt7a is capable of activating CREB via a noncanonical cAMP pathway (39). *Wnt1* and *Wnt3a* mRNAs have also been detected in mature myofibers (175). Wnt7a was recently demonstrated to activate Fzd7 and $G\alpha_s$-mediated signaling in differentiated myotubes (237). It is therefore tempting to speculate that local Wnt signaling activates CREB in regenerating areas. Indeed, adult muscle crushed ex vivo releases ligands that induce cAMP signaling (80) and activate CREB (216) in isolated muscle precursor cells. It is not known whether Wnts or other cAMP-inducing ligands, such as Ucn2 (36), are responsible for this activity.

It will be exciting to determine how cAMP-PKA signaling contributes to normal muscle regeneration. This likely involves promotion of muscle precursor cell proliferation (39, 216), migration and fusion (80, 249), and possibly terminal steps in differentiation (65, 153, 216). Detailed investigation of signaling pathways downstream from PKA in regenerating muscle may uncover novel, skeletal muscle-specific regulatory mechanisms that could be targeted specifically to promote muscle regeneration.

## CONCLUDING REMARKS

In the five decades since cAMP was discovered, its numerous roles in skeletal myofibers have been steadily identified. Although well studied and promising for treatment of muscle atrophy in patients, the potential detrimental effects of long-term β-AR agonist treatment on the cardiovascular system must be taken into account for human therapeutic use (194). It will therefore be important in the future to further study physiological effects and downstream signaling pathways elicited by other, less-studied ligands that induce cAMP in skeletal muscle and myoblasts. At least one of these, Ucn2, has similar beneficial effects to clenbuterol on denervated and dystrophic skeletal muscle. It remains to be seen how other ligand-receptor systems may be exploited for therapeutic benefit in this tissue. A potentially more promising avenue is identification of skeletal muscle-specific cAMP effector pathways that can be selectively targeted to promote hypertrophy and muscle regeneration after injury. Such targets could be used in patients with a wide variety of pathological conditions, such as muscular dystrophy or atrophy due to aging, immobilization, cachexia, and nerve or muscle damage.

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## AUTHOR CONTRIBUTIONS

Author contributions: R.B. prepared figures; R.B. and R.S. drafted manuscript; R.B. and R.S. edited and revised manuscript; R.B. and R.S. approved final version of manuscript.

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