Abstract Skeletal muscle is the principal site of whole-body glucose, lipid, and energy metabolism, and several adaptive responses to physical exercise (muscle-contracting stimuli) by skeletal muscle contribute to whole-body health-promoting effects. Acute and/or repeated activation of skeletal muscle 5′AMP-activated protein kinase (AMPK) by physical exercise controls several metabolic adaptations. Thus, skeletal muscle AMPK is likely to be a “central molecule” that mediates anti-obesity/antidiabetes effects in response to physical exercise. Meanwhile, recent reports suggest that functional foods and their natural components (so-called phytochemicals) have anti-obesity/antidiabetes properties that stimulate skeletal muscle AMPK activity in a similar manner to physical exercise. For example, caffeine is a plant alkaloid that activates skeletal muscle AMPK and the activation mechanisms are exercise-like in terms of the association between α isoform-specific AMPK activation and the energy status. Furthermore, berberine, a component of natural medicines, resveratrol, a polyphenol found in red wine and other plant products, and caffeic acid, a coffee polyphenol, all stimulate AMPK activation in skeletal muscle accompanied by energy deprivation. In this study, we review our recent findings and related studies of the activation of AMPK by physical exercise and phytochemicals.

Keywords: alkaloid, Ca2+, diabetes, energy deprivation, glucose transport, polyphenol

Introduction

Habitual physical exercise has beneficial effects on glucose, lipid, and energy metabolism, and it reduces the risk of metabolic disorders such as type 2 diabetes mellitus (T2DM). Skeletal muscle is the principal site of whole-body glucose, lipid, and energy metabolism, and several adaptive responses to physical exercise (muscle-contracting stimuli) by skeletal muscle contribute to whole-body health-promoting effects. Much evidence suggests that the acute and/or repeated activation of skeletal muscle 5′AMP-activated protein kinase (AMPK) by physical exercise is involved with several metabolic adaptations, including enhanced insulin-independent glucose transport1–3, insulin sensitivity4–9, glucose transporter 4 (GLUT4) expression8,10,11, fatty acid oxidation12–14 via the inhibition of acetyl-CoA carboxylase (ACC), modulation of glycogen synthesis15–17 and mitochondrial biogenesis via peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α)18,19 and SIRT120, and alterations in the distribution of muscle fiber types21. These skeletal muscle adaptations might allow AMPK to serve as a metabolic stimulator, which may reduce the risk of metabolic disorders. In addition, recent reports suggest that functional foods and their natural components (so-called phytochemicals) have anti-obesity/antidiabetes properties, which stimulate the activity of skeletal muscle AMPK in a similar manner to physical exercise. In this study, we review the activation mechanisms of AMPK in response to physical exercise in the following sections, before we present the evidence for AMPK activation by phytochemicals.

Structure of AMPK and its activation mechanisms

AMPK is a heterotrimeric kinase, which comprises a catalytic α subunit and two regulatory subunits, β and γ. Two distinct α isoforms (α1 and α2) exist in skeletal muscle, and we refer to α1-containing AMPK as AMPKa1 and α2-containing AMPK as AMPKa2. As its name suggests, AMPK is activated directly by AMP. The binding of AMP to the Bateman domains of the γ subunit of AMPK leads to allosteric activation of AMPK. Furthermore, ATP inhibits the binding of AMP to the γ subunit, so AMPK...
is activated in response to changes in the AMP/ATP ratio and/or the creatine/creatine phosphate ratio, as well as the AMP levels. In addition to allosteric activation, AMPK is activated by the phosphorylation of a specific site at Thr172 via upstream kinases, including LKB1 and Ca²⁺/calmodulin-dependent protein kinase kinase (CaMKK). The LKB1 complex is constitutively active and is not activated directly by AMP, but the binding of AMP to AMPK causes a structural change that facilitates the phosphorylation of AMPK by the LKB1 complex. CaMKK can trigger the activation of AMPK in response to increased intracellular Ca²⁺. The binding of AMP to AMPK promotes phosphorylation and prevents the dephosphorylation of Thr172, which increases the AMPK activity by 10-fold via an allosteric effect; whereas the phosphorylation of Thr172 by upstream kinases increases the activity by 100-fold. Therefore, it is considered that the phosphorylation of Thr172 is more important for AMPK activation than the allosteric effect.

**AMPK activation by metabolic changes during physical exercise**

From a metabolic viewpoint, contracted skeletal muscle cells are exposed to various metabolic stimuli, such as changes in the energy substrates (AMP, ATP, creatine phosphate, and glycogen), variable Ca²⁺ levels, and the production of oxidative stress. AMPK is considered to be activated by these metabolic stimuli (Fig. 1).

**Energy deprivation.** Skeletal muscle is a highly dynamic tissue, which can increase the turnover of ATP by >100-fold in response to physical exercise. In these conditions, the levels of ATP and creatine phosphate are reduced, whereas the AMP and creatine levels are increased. Given the sensitivity of AMPK to cellular energy deprivation, it is not surprising that rapid AMPK activation occurs during physical exercise.

As described above, the LKB1-associated phosphorylation of AMPK is crucial for AMPK activation in energy-deficient conditions. Physical exercise-induced energy deprivation (increases in ratios of AMP/ATP and/or creatine/creatine phosphate) facilitates the phosphorylation of AMPK by LKB1, thereby resulting in acute AMPK activation. The activation of AMPKα2 by muscle contraction was abolished completely in muscle-specific LKB1-knockout mice. Therefore, it is accepted that LKB1 activates AMPK (especially AMPKα2) via energy-dependent mechanisms during physical exercise.

**Ca²⁺ release.** Skeletal muscle contraction is triggered by muscle fiber membrane depolarization. Ca²⁺ is released from the sarcoplasmic reticulum during depolarization, and an increase in cytosolic Ca²⁺ concentration facilitates actin–myosin interaction, thereby causing muscle contraction. CaMKK is a major kinase, which is activated by an

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**Fig. 1** Mechanisms of skeletal muscle AMPK activation by physical exercise (muscle contraction).
increase in intracellular Ca\(^{2+}\) concentration\(^{51}\). The Ca\(^{2+}\)/calmodulin complex binds directly to CaMKK, thereby activating CaMKK by targeting its autoinhibitory domains. CaMKK is expressed in skeletal muscle and it is known to be involved in the regulation of contraction-induced substrate metabolism as an AMPK kinase. In isolated mice skeletal muscle, it was reported that the CaMKK inhibitor, STO-609, suppressed the AMPK activation induced by muscle contraction\(^{60}\). CaMKK-induced AMPK activation occurs via an AMP-independent mechanism\(^{34,36}\), so it is considered that, in contrast to LKB1, CaMKK enhances the activity of AMPK in an energy-independent manner during physical exercise.

**Oxidative stress.** Skeletal muscle cells produce reactive oxygen species and reactive nitrogen species continuously\(^{37,38}\). Muscle contraction increases the production of oxidants, thereby leading to a shift in the prooxidant–antioxidant balance toward oxidants, i.e., oxidative stress\(^{39,40}\).

It was reported that muscle contraction-induced AMPK activation, especially AMPK\(\alpha_1\), was inhibited by antioxidant N-acetyl-L-cysteine\(^{41}\), which suggests that the oxidative stress generated during muscle contraction is an important regulator of AMPK. However, there is no increase in AMP concentration in skeletal muscle during exposure to oxidative stress, which means that oxidative stress is expected to enhance AMPK activation via energy-independent mechanisms during physical exercise.

**AMPK activation by phytochemicals**

At present, AMPK is considered to be a target for T2DM treatment based on studies that demonstrated its modulation by several therapeutic agents, including metformin and thiazolidinediones\(^{42}\). Furthermore, recent studies have suggested that chronic treatment with phytochemicals, such as caffeine\(^{43,44}\), berberine\(^{45,46}\), and resveratrol\(^{47,49}\), can have anti-obesity/antidiabetes effects. These beneficial effects may be related partly to AMPK-associated enhancement of glucose, lipid, and energy metabolism in skeletal muscle. In the following section, we describe the exercise-like actions on skeletal muscle AMPK activation of some phytochemicals, including alkaloids (Table 1), polyphenols (Table 2), and others (Table 3).

**Alkaloids.** Alkaloids are a group of naturally occurring phytochemicals, which mostly contain basic nitrogen atoms, and they are known to have high biological activity. Caffeine (1,3,7-trimethylxanthine) is a xanthine alkaloid found in natural products such as kola nuts, coffee, tea, and cocoa beans. It is generally accepted that the long-term consumption of coffee reduces the risk of obesity and T2DM, and it is suggested that its component caffeine is involved in these benefits\(^{50}\). Caffeine is used widely in muscle research as a Ca\(^{2+}\) release agent and many studies have investigated the effects of caffeine on skeletal muscle AMPK activation. With some exceptions\(^{51,52}\), these studies have shown that caffeine increases the activity of AMPK (phosphorylation of AMPK Thr\(^{172}\))\(^{53-60}\) and its associated metabolic functions include the enhancement of insulin-independent glucose transport\(^{53-59}\), phosphorylation of ACC\(^{53,55,56,58}\), which is a downstream target of AMPK, and fatty acid oxidation\(^{54,56,58}\) in rodent skeletal muscles. In addition, we recently demonstrated that a low dose of caffeine preferentially activated AMPK\(\alpha_1\) via an energy-independent mechanism, while a high dose of caffeine activated AMPK\(\alpha_2\) in the presence of energy deprivation\(^{71}\). Toyoda et al.\(^{67}\) also reported that AMPK\(\alpha_1\) could be activated in the absence of apparent energy deprivation during low-intensity muscle contraction, whereas AMPK\(\alpha_2\) could be activated by an energy-dependent mechanism during high-intensity muscle contraction. Thus, caffeine may have exercise-like effects in stimulating skeletal muscle AMPK and its associated glucose, lipid, and energy metabolism, thereby producing possible anti-obesity/antidiabetes effects.

Given the role of caffeine as a Ca\(^{2+}\) releaser, caffeine-induced AMPK activation may occur via a CaMKK-dependent mechanism. For example, it was reported that caffeine-induced AMPK activation was blocked by a CaMKK inhibitor in rodent skeletal muscle\(^{53}\) and that caffeine enhanced the phosphorylation of Ca\(^{2+}/\)calmodulin-dependent protein kinase (CaMK) I, which is a downstream target of CaMK\(^{50,51}\). However, it was shown that CaMKI phosphorylation did not occur with caffeine stimulation in rat skeletal muscle\(^{57}\). Thus, we consider that CaMK might not be a crucial upstream kinase of AMPK activation during the response to caffeine. Other enzymes such as phosphatases may also be involved in the regulation of caffeine-induced AMPK activation in an energy-independent manner. However, given that caffeine activates AMPK (especially AMPK\(\alpha_2\)) via energy-dependent mechanisms, it is possible that LKB1 is associated with caffeine-induced AMPK activation in an energy-deficient state.

Another alkaloid, berberine, is isolated from medicinal plants such as the Chinese herb, Coptis chinensis, which has been used for thousands of years in Asia to treat T2DM, and it has beneficial effects on hyperglycemia in patients with T2DM\(^{45,46}\). Previously, we showed that berberine enhanced the activity of AMPK (\(\alpha_1\) and \(\alpha_2\)) and insulin-independent glucose transport in rat skeletal muscles when it was accompanied by energy deprivation\(^{62}\). We did not examine the long-term effects of berberine on muscle metabolism, but Kim et al.\(^{63}\) showed that berberine treatment once each day for 3 weeks increased the phosphorylation of AMPK and ACC in the skeletal muscles of diabetic mice. Berberine has an effect similar to metformin and thiazolidinediones because it inhibits respiratory complex I\(^{54}\), which leads to energy deprivation, thereby resulting in AMPK activation. Therefore, the
Table 1. Alkaloids and skeletal muscle AMPK activation

<table>
<thead>
<tr>
<th>Materials</th>
<th>Metabolic changes</th>
<th>Treatment</th>
<th>Species</th>
<th>Condition</th>
<th>Muscle</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>p-AMPK → insulin-independent glucose transport↑</td>
<td>in vitro: 3.5 mM, 15 min</td>
<td>rat</td>
<td>normal</td>
<td>epitrochlearis</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>p-AMPK → AMPKα1 activity↑/p-ACC↑</td>
<td>in vitro: 3 mM, 15 min</td>
<td>rat/ mouse</td>
<td>normal</td>
<td>soleus</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>AMPKα2 activity↑/fatty acid uptake↑/ insulin-independent glucose transport↑</td>
<td>in vitro: 3 mM, 20 min</td>
<td>rat</td>
<td>normal</td>
<td>gastrocnemius-soleus-plantaris complex</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>p-AMPK→AMPK activity (α1, α2)↑/p-ACC↑/ insulin-independent glucose transport↑</td>
<td>in vitro: 3–15 mM, 15–60 min</td>
<td>rat</td>
<td>normal</td>
<td>epitrochlearis/soleus</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>AMPKα2 activity↑/p-ACC↑/fatty acid uptake↑</td>
<td>in vitro: 3 mM, 20 min</td>
<td>rat</td>
<td>normal</td>
<td>gastrocnemius-soleus-plantaris complex</td>
<td>56</td>
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<tr>
<td></td>
<td>p-AMPK↑/AMPK activity (α1, α2)↑/p-ACC↑/ CaMKK activity↑</td>
<td>in vitro: 1–3 mM, 15 min</td>
<td>rat</td>
<td>normal</td>
<td>epitrochlearis</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>AMPKα2 activity↑/p-ACC↑/fatty acid uptake↑/p-CaMKI (CaMKK activity)↑</td>
<td>in vitro: 3 mM, 20 min</td>
<td>mouse</td>
<td>normal</td>
<td>gastrocnemius-soleus-plantaris complex</td>
<td>58</td>
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<tr>
<td>Berberine</td>
<td>p-AMPK↑/p-ACC↑/ insulin-independent glucose transport↑/ insulin-dependent glucose transport↓</td>
<td>in vivo: 1 g/l, 15 days</td>
<td>rat</td>
<td>normal</td>
<td>not described</td>
<td>52</td>
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<tr>
<td></td>
<td>p-AMPK↑/energy status↓</td>
<td>in vitro: 1 mM, 5–16 h</td>
<td>rat</td>
<td>normal</td>
<td>epitrochlearis</td>
<td>60</td>
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<tr>
<td></td>
<td>p-AMPK↑/p-ACC↑/ plasma insulin↓/GLUT4↑</td>
<td>in vivo: 150 mg/day, 30 days</td>
<td>human</td>
<td>obesity</td>
<td>vastus lateralis</td>
<td>49</td>
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<tr>
<td></td>
<td>p-AMPK↑/SIRT1↑/PGC-1α↑/ plasma glucose↓/plasma insulin↓</td>
<td>in vivo: 2–4 g/kg containing diet, 12 weeks</td>
<td>mouse</td>
<td>diabetes</td>
<td>soleus</td>
<td>67</td>
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<td>p-AMPK↑/SIRT1↑/ serum glucose↓/ serum insulin↓</td>
<td>in vivo: 75 mg/day, 12 weeks</td>
<td>human</td>
<td>normal</td>
<td>vastus lateralis</td>
<td>68</td>
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<tr>
<td>Azuki bean polyphenols</td>
<td>p-AMPK↑/p-ACC↑/ insulin-independent glucose transport↑/ glut4↑</td>
<td>in vivo: 0.1–0.6 mM, 15–60 min</td>
<td>rat</td>
<td>normal</td>
<td>epitrochlearis</td>
<td>73</td>
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<tr>
<td>Chlorogenic acid</td>
<td>p-AMPK↑/p-ACC↑</td>
<td>in vivo: 0.01–1 nM, 5–60 min</td>
<td>rat</td>
<td>normal</td>
<td>epitrochlearis</td>
<td>73</td>
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<td>p-AMPK↑/p-ACC↑/GLUT4↑/CaMKK↑/ insulin-dependent glucose transport↑/ insulin-independent glucose transport↓/ serum glucose↓</td>
<td>in vivo: 250 mg/kg/day, 2 weeks</td>
<td>mouse</td>
<td>diabetes</td>
<td>soleus/gastrocnemius</td>
<td>72</td>
</tr>
</tbody>
</table>

p-AMPK: AMPK Thr172 phosphorylation, p-ACC: ACC Ser79 phosphorylation, CaMKK: CaMKK Thr177 phosphorylation, ↑: increase, ↓: decrease, →: no change

Table 2. Polyphenols and skeletal muscle AMPK activation

<table>
<thead>
<tr>
<th>Materials</th>
<th>Metabolic changes</th>
<th>Treatment</th>
<th>Species</th>
<th>Condition</th>
<th>Muscle</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resveratrol</td>
<td>p-AMPK↑/SIRT1↑/PGC-1α↑/ plasma glucose↓/plasma insulin↓</td>
<td>in vivo: 150 mg/day, 30 days</td>
<td>human</td>
<td>obesity</td>
<td>vastus lateralis</td>
<td>49</td>
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<tr>
<td></td>
<td>p-AMPK↑/SIRT1↑/ serum glucose↓/ serum insulin↓</td>
<td>in vivo: 2–4 g/kg containing diet, 12 weeks</td>
<td>mouse</td>
<td>diabetes</td>
<td>soleus</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>p-AMPK↑/PGC-1α↑/GLUT4↑</td>
<td>in vivo: 3 g/kg/day, 12 weeks</td>
<td>human</td>
<td>diabetes</td>
<td>vastus lateralis</td>
<td>47</td>
</tr>
<tr>
<td>Chlorogenic acid</td>
<td>p-AMPK↑/p-ACC↑</td>
<td>in vivo: 0.01–1 nM, 5–60 min</td>
<td>rat</td>
<td>normal</td>
<td>epitrochlearis</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>p-AMPK↑/p-ACC↑/GLUT4↑/CaMKK↑/ insulin-dependent glucose transport↑/ insulin-independent glucose transport↓/ serum glucose↓</td>
<td>in vivo: 250 mg/kg/day, 2 weeks</td>
<td>mouse</td>
<td>diabetes</td>
<td>soleus/gastrocnemius</td>
<td>72</td>
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<tr>
<td>Material</td>
<td>Treatment</td>
<td>Species</td>
<td>Condition</td>
<td>Muscle</td>
<td>Reference</td>
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<tr>
<td>Morus alba leaf extract</td>
<td>p-AMPK /AMPK activity (α1, α2) / insulin-independent glucose transport / energy status in vivo: 4.28-14.3 mg/ml, 15-60 min</td>
<td>rat</td>
<td>normal</td>
<td>epirochlearis</td>
<td>74</td>
<td></td>
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<tr>
<td>Nootkatone</td>
<td>p-AMPK /ACC /p-LKB1 / AMPK activity (α1, α2) / insulin-dependent glucose transport / energy status in vivo: 200 mg/kg, 30-120 min</td>
<td>mouse</td>
<td>normal</td>
<td>soleus/gastrocnemius</td>
<td>90</td>
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<td>Bilberry extract</td>
<td>p-AMPK /GLUT4 /serum glucose / whole body insulin sensitivity in vivo: 2.7% containing diet, 5 weeks</td>
<td>mouse</td>
<td>diabetes</td>
<td>not described</td>
<td>76</td>
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<tr>
<td>Thujone</td>
<td>p-AMPK /ACC /p-LKB1 / AMPK activity (α1, α2) / insulin-dependent glucose transport / energy status in vivo: 0.01 mg/ml, 6 h</td>
<td>rat</td>
<td>normal/insulin resistance state</td>
<td>soleus</td>
<td>91</td>
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<td>Coptidis Rhizoma water extract</td>
<td>p-AMPK /AMPK activity (α1, α2) / insulin-dependent glucose transport / energy status in vivo: 0.1-0.7 mg/ml, 15-60 min</td>
<td>rat</td>
<td>normal</td>
<td>epirochlearis/s soleus</td>
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<td>Malva verticillata seed extract</td>
<td>p-AMPK /ACC /plasma glucose in vivo: 20-40 mg/kg/day, 4 weeks</td>
<td>mouse</td>
<td>diabetes</td>
<td>soleus</td>
<td>77</td>
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<td>Nigella sativa</td>
<td>p-ACC /GLUT4 /plasma glucose in vivo: 200 mg/kg, 15-60 min</td>
<td>meriones shaw</td>
<td>normal</td>
<td>soleus</td>
<td>78</td>
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<tr>
<td>Cacao liquor procyanidin extract</td>
<td>p-AMPK /GLUT4 /plasma glucose in vivo: 0.5-2.0% containing diet, 13 weeks</td>
<td>mouse</td>
<td>obesity</td>
<td>not described</td>
<td>79</td>
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<tr>
<td>Brazilian propolis extract</td>
<td>p-AMPK in vivo: 250 mg/kg, 60 min</td>
<td>rat</td>
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<td>soleus</td>
<td>81</td>
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<tr>
<td>Black soybean seed coat extract</td>
<td>p-AMPK /serum glucose / in vivo: 2.2% containing diet, 6 weeks</td>
<td>mouse</td>
<td>diabetes</td>
<td>not described</td>
<td>80</td>
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</table>

Table 3. Other phytochemicals and skeletal muscle AMPK activation
inhibition of complex I might be a potential target for the prevention of obesity and T2DM by stimulating skeletal muscle AMPK, although the AMPK activation mechanism differs from that during exercise.

**Polyphenols.** Polyphenols are a group of natural chemical substances with more than one phenol unit or building block per molecule, which are well known for their antioxidant properties. Resveratrol is a polyphenolic compound found in grapes and some other plants. It has many beneficial properties such as anticancer, antioxidation, anti-inflammation, and anti-obesity/antidiabetes effects. Chen et al. reported that chronic resveratrol treatment of diabetic mice for 12 weeks increased AMPK phosphorylation and improved the whole-body insulin sensitivity. A human study detected no effects of resveratrol treatment for 12 weeks on the phosphorylation of skeletal muscle AMPK and whole-body glucose tolerance in normal subjects, although several studies of obese/diabetes subjects reported the beneficial effects of resveratrol supplementation, i.e., enhanced AMPK phosphorylation in skeletal muscle, SIRT1 expression, and PGC-1α expression, and improved blood metabolic profiles. We also showed similar results with in vitro resveratrol stimulation enhanced AMPK phosphorylation with energy deprivation in rat skeletal muscles (unpublished data). These results suggest that resveratrol promotes metabolic functions via exercise-like effects including AMPK activation. By contrast, recent reports suggest that resveratrol has no effects on mitochondrial biogenesis, despite AMPK activation and energy deprivation in skeletal muscle cells. Therefore, we consider that further studies will be required to elucidate the precise contributions of resveratrol to glucose, lipid, and energy metabolism in skeletal muscle, as well as the whole body.

Another polyphenol, chlorogenic acid, which occurs in many types of fruits and in high concentration in coffee, has antihyperglycemic properties. A recent study using diabetic mice demonstrated that chlorogenic acid increased the phosphorylation of AMPK, ACC, and CaMKK in skeletal muscle, thereby contributing to improvements in whole-body glucose and lipid metabolism. By contrast, we previously showed that chlorogenic acid had no effects on the phosphorylation of AMPK and ACC in rat skeletal muscle. Chlorogenic acid is hydrolyzed into caffeic acid by the intestinal microflora, so we speculate that the activating effects of chlorogenic acid demonstrated during in vivo studies might depend on caffeic acid, which is derived from chlorogenic acid. Thus, caffeic acid rather than chlorogenic acid might be a polyphenol with potential health-promoting effects via skeletal muscle AMPK activation.

**Others.** Some extracts from plants (e.g., leaves, seeds, and stems) and substances collected by insects have known bioactivities, and they have been used to treat various health problems such as obesity and T2DM since ancient times. Substances with stimulatory effects on skeletal muscle AMPK include extracts from Morus alba leaf, Coptidis Rhizoma, bilberry, Malva verticillata seed, Nigella sativa, cacao liquor, and black soybean, as well as plant substances collected by honeybees, i.e., propolis. These plant extracts and...
propolis contain many compounds such as alkaloids and polyphenols, so their beneficial effects may be attributable to the combined actions of each compound. Indeed, Coptidis Rhizoma contains berberine, and we showed that Coptidis Rhizoma-induced AMPK activation and energy deprivation in skeletal muscle may be attributable partly to berberine.\(^{75}\) Given that there are vast numbers of plant compounds, many novel phytochemicals with activating effects on AMPK that are beneficial for skeletal muscle and whole-body glucose, lipid, and energy metabolism will probably be found in the future.

Can phytochemicals replace exercise?

Physical exercise is a powerful tool that promotes good health and reduces the risk of several diseases, including obesity and T2DM. Skeletal muscle AMPK, which is activated by physical exercise, is a candidate therapeutic target molecule in these conditions. If skeletal muscle AMPK could be activated by alternative approaches other than physical exercise, it would benefit people who are unable to engage in physical exercise because of severe musculoskeletal or cardiovascular conditions, as well as “couch potatoes.” Thus, repeated AMPK activation by phytochemicals may be a more convenient therapeutic tool for achieving long-term metabolic benefits in skeletal muscle and preventing the development of obesity and T2DM (Fig. 2). However, physical exercise has profound beneficial effects on most of the organs in the body. The AMPK-activating effects of the phytochemicals considered in this review are focused mainly on those in skeletal muscle. It must be remembered that phytochemicals cannot provide all of the benefits of physical exercise.

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