Adenosine monophosphate kinase activator α -lipoic acid: A promising therapeutic agent for metabolic syndrome?

As a consequence of overnutrition and sedentary lifestyles, the rate of cardiovascular disease has been rapidly increasing among patients with obesity and type 2 diabetes. Metabolic syndrome, which is closely related to cardiovascular disease, is a cluster of conditions characterized by several metabolic risk factors, typically including abdominal obesity, insulin resistance, dyslipidemia and elevated blood pressure¹. Several organizations have attempted to develop a unifying definition for metabolic syndrome, but a precise, generally accepted, worldwide definition remains to be established. Regardless of which definition is used, this syndrome is increasing at a rapid rate¹. Metabolic syndrome reduces life expectancy and increases the incidence of many health problems, including not only cardiovascular disease, but also other comorbidities, such as type 2 diabetes, non-alcoholic fatty liver disease, sleep apnea, hypogonadism and other reproductive disorders, certain types of cancer, osteoarthritis, and others¹. Lifestyle modification is the main method of prevention and management of metabolic syndrome. However, such lifestyle modifications have proven to be difficult to implement, and the use of weight-reducing drugs for the treatment of obesity has several limitations. Thus, the treatment of metabolic syndrome is complex and difficult.

Exercise has been shown to have many beneficial effects for the management of metabolic syndrome. The mechanisms for these beneficial effects include increased adipose tissue lipolysis and skeletal muscle glucose uptake. These effects have been mainly attributed to the activation of adenosine monophosphate-activated protein kinase (AMPK), a key energy sensor that helps to maintain physiological balance. All living cells must continuously maintain a constant level of adenosine triphosphate (ATP). AMPK is primarily activated by a reduction in cellular energy content (i.e. an increased AMP:ATP ratio), and its primary effect is that it turns off pathways that consume ATP (e.g. anabolic pathways that synthesize fatty acids and cholesterol) while it stimulates metabolic pathways that produce ATP (e.g. catabolic pathways that oxidize glucose and fatty acids). AMPK is activated by the phosphorylation of its threonine residue 172, which is located at the activation site in the catalytic subunit of the AMPK α subunit. There are at least two protein kinases capable of phosphorylating Thr172 *in vivo*, liver kinase B1 (LKB1) and Ca²⁺/calmodulin-dependent kinase kinase, especially the β isoform (CaMKK β). Phosphorylation and activation of AMPK can be reversed by protein phosphatases².

The gene expression and activation of AMPK largely occur in metabolically relevant tissues, such as the liver, skeletal muscle, adipose and hypothalamus. In the liver, AMPK reduces hepatic lipid synthesis, stimulates fat burning and blocks hepatic glucose production. In skeletal muscle, AMPK stimulates glucose uptake by increasing insulin sensitivity and by enhancing the translocation of the glucose transporter, GLUT4. In addition, AMPK activation and exercise can increase glucose uptake in muscle independently from insulin action. Overall, the activation of AMPK in the liver and muscle plays a crucial role in metabolism and shows the potential to ameliorate type 2 diabetes and the metabolic syndrome³.

The AMPK is activated by various physiological and pathological stresses in response to an increased intracellular AMP/ATP ratio, such as exercise, muscle contraction, glucose deprivation, hypoxia or oxidative stress. It is also activated by hormones (through G protein-coupled receptors) and by oral anti-diabetic drugs, such as thiazolidinediones (glitazones) and metformin. Various natural products, including alkaloids, bitter melon extracts, berberine, α -lipoic acid (ALA) and others, have also been found to activate AMPK³.

ALA is a naturally occurring short chain fatty acid with sulfhydryl groups that has potent anti-oxidant activity. ALA occurs as R- and S-enantiomeric structures, but only the R-form is essential to biological systems. R-ALA, a cofactor for four enzyme complexes exclusively located in mitochondria, is essential for energy production, and for the regulation of carbohydrate and protein metabolism. ALA is almost entirely covalently bound to the E2 component of three α -ketodehydrogenase complexes and the glycine cleavage system. ALA is synthesized *in vivo* by ALA synthase, but has stimulated clinical research interest as both a micronutrient and a therapeutic agent⁴.

Experience has shown that ALA is effective in reducing painful neuropathy in patients with type 2 diabetes. This effect has been shown in several clinical trials using i.v. ALA, but other clinical trials using oral administration of ALA have shown no effect. One possible explanation for this difference in efficacy between intravenous and oral ALA might be as a result of differences in the bioavailability or solubility of the medication in the gastrointestinal tract. In addition, recent studies have shown that ALA is very effective in ameliorating various oxidative stress-mediated diseases including diabetes, vascular disease, hypertension and inflammation⁵. ALA treatment can also

Figure 1 | Preventive and therapeutic effects of α -lipoic acid (ALA) against metabolic syndrome through modulation of adenosine monophosphate-activated protein kinase (AMPK) activity. ALA might prevent metabolic syndrome through its pleiotropic beneficial effects on multiple peripheral tissues, including skeletal muscle, liver and adipocytes by activating AMPK. By contrast, ALA reduces food intake by inhibiting hypothalamic orexigenic AMPK activity. However, the mechanisms underlying the differential effect of ALA on activation or inhibition of AMPK activity in the peripheral tissues and hypothalamus should be delineated. ATP, adenosine triphosphate; CaMKK β , Ca²⁺/calmodulin-dependent kinase kinase β ; LKB1, liver kinase B1.

reduce bodyweight by regulating AMP-activated protein kinase (AMPK)⁶.

Recently, we reported that ALA treatment (1800 mg/day ALA treatment for 20 weeks) significantly reduced bodyweight and waist circumference. Thus, ALA is effective for the treatment of obesity⁶. In the subgroup analysis, subjects with diabetes randomized to receive 1800 mg/day ALA also showed a mean 0.38% reduction from baseline in hemoglobin-A1c levels ($P < 0.05$). Blood pressure and fasting plasma glucose and cholesterol levels, however, were not significantly altered by treatment with ALA⁶. A previous clinical trial showed that hemoglobin-A1c levels in diabetic patients were significantly reduced by ALA administration. However, as that study was carried out in patients being treated with oral glucose-lowering medications or insulin, the independent effects of ALA treatment alone were not shown. In this regard, there are insufficient long-term clinical data to establish a glucose-lowering effect of ALA. Because metformin is a first-line therapy for the treatment of diabetes, it is important to evaluate whether ALA or other AMPK activators can be combined with or have synergistic effects with metformin. Thus, ALA administration is effective for the treatment of obesity, although the role of diet and exercise in the treatment of obesity was not investigated separately in that study. If AMPK is a common downstream intracellular mediator or effector of both ALA and exercise, a separate study using ALA treatment alone would be expected to show greater similarity between the effects of ALA and those of exercise.

In summary, AMPK activation has been shown to have many beneficial effects on metabolic disease (see Figure 1). Thus, there is increasing demand for more potent and selective agents that

activate AMPK, and for testing these agents in the treatment of metabolic syndrome. In this regard, the AMPK activator, ALA, might be a promising drug to be used in the treatment of metabolic syndrome. Finally, even though AMPK activation is a fascinating approach to the management of metabolic disease, the glucose-lowering efficacy of this strategy remains to be shown.

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