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Editorial

Resveratrol: is selectivity opening the key to therapeutic effects?

The rapid increase in obesity-related diseases such as diabetes, cardiovascular disease, and cancer is becoming a significant biomedical and socioeconomic burden. Defining the biological and pathophysiological basis of these metabolic disorders as well as novel appropriate therapies is a priority for current research. Better therapeutic agents are needed to help ameliorate the current epidemic. Resveratrol, a natural plant-derived polyphenolic compound that is abundant in berries, grapes, wines, and peanuts, and its synthetic activators are among the promising new therapeutic agents that have been proposed and are currently being researched as a potential treatment of metabolic diseases such as obesity and type 2 diabetes mellitus [1,2].

Since the interesting finding that red wine has a potential cardioprotective effects has been released, many studies have demonstrated resveratrol's therapeutic impacts in various diseases, including obesity and aging-related illnesses [2-4]. In addition, its positive influence in longevity was postulated in species ranging from lower organisms to rodents [2,5]. The mechanism whereby resveratrol exerts its diverse beneficial effects has not been fully addressed. It has been shown that resveratrol's metabolic effect(s) could be mediated via SIRT1, the mammalian Sir2 ortholog and one of the nicotinamide adenine dinucleotide–dependent histone deacetylase, which is widely expressed in metabolically active tissues regulating insulin sensitivity. The SIRT1 pathway is also activated by caloric restriction, which may lead to an extension of life span. Because of these observations, resveratrol has been proposed to be an agent that functions to mimic effects of caloric restriction [6].

The insulin-signaling pathway is tightly linked to the homeostatic regulation of life span in animal models [7] in which SIRT1 may be the main underlying mechanism [6]. To unveil how SIRT1 and its activators improve insulin sensitivity, studies exploring resveratrol's function on insulin signaling are indispensable; but data to date have not always been consistent. In this issue, Kang et al [8] demonstrate that resveratrol administration enhanced insulin signaling in insulin-resistant conditions but not in normal conditions. In vitro experiments showed that resveratrol's ability to suppress inflammatory signaling was greatly increased when adipocytes were exposed to inflammatory conditioned media. The studies were further extended to investigate the in vivo therapeutic effects of resveratrol in the insulin-resistant state, with particular emphasis on the metabolic action of insulin. Kang et al found that, in diet-induced obese mice, relatively low doses of resveratrol improved glucose metabolism and insulin sensitivity, which are mainly associated with improved insulin signaling in the liver and white adipose tissue, as well as decreased fat content in the liver. These results are in line with previous findings indicating beneficial effects of resveratrol in insulin-resistant animals made by a high-fat or high-calorie diet [5,9-11]. In contrast, an inhibitory action of insulin on key steps of signaling, including insulin receptor substrate–1 and Akt phosphorylation, was seen in normal adipocytes treated with resveratrol [8]. A study by Pearson et al [12] also showed that resveratrol therapy had no effects on survival rate or maximal life span under the condition of a standard normal diet. Collectively, these and other studies suggest that resveratrol may affect divergent actions on cellular events involved in insulin signaling and that responses may be dependent on the metabolic milieu.

An energy sensor, adenosine monophosphate–activated protein kinase (AMPK), has been identified as one of SIRT1′s targets [13]. Um et al [14] demonstrated that resveratrol had no effect on insulin sensitivity, glucose tolerance, or mitochondrial biogenesis in AMPK-deficient mice, suggesting a role for AMPK in resveratrol-mediated metabolic action [13,15]. Interestingly, the study by Kang et al [8] found the tissue-specific regulation of AMPK by resveratrol in insulin-resistant obese mice: AMPKα phosphorylation was increased in the skeletal muscle but decreased in the liver. Support for this comes from the recent finding that resveratrol's action to induce the expression of inducible nitric oxide synthase in insulin-sensitive tissues is differently regulated, presumably via AMPK signaling [16]. Although a precise mechanism responsible for this action is unclear at this time, it seems likely that AMPK is a critical player of resveratrol-mediated selective cellular events in a certain metabolic state. Similarly, SIRT1 activation is also modulated in a tissue-specific manner when calorie intake is limited [17]. However, whether SIRT1 induced by calorie restriction is required for activation of AMPK signaling is unknown. Furthermore, the current work by Kang et al raises the important question of whether tissue-specific changes in AMPK signaling are due to a SIRT1-dependent or -independent mechanism in obese, insulin-resistant mice treated with resveratrol.

It should be noted that insulin's ability to stimulate PI3K and MAPK signaling is diminished by treatment with

resveratrol, independent of SIRT1 [18,19]. Centeno-Baez et al [16] also indicated that resveratrol-induced AMPK activation is not associated with SIRT1 activation. However, the previous findings by Sun et al [10] revealed that SIRT activation by resveratrol can cause a significant improvement in insulin resistance by suppressing expression of protein tyrosine phosphatase 1B, a major negative regulator of insulin action. Possibly, this discrepancy could be due to the fact that certain signaling cascades can be stimulated with a high dose of resveratrol, but not a low dose. Further research is needed to delineate whether resveratrol-mediated metabolic changes in diet-induced obese mice are due to changes in SIRT1 activity directly and in a dose-dependent manner.

In-depth mechanistic and interventional studies are needed to further elucidate resveratrol's role in metabolic-related disorders including obesity, type 2 diabetes mellitus, and the metabolic syndrome. Importantly, initial evaluation of clinical feasibility reveals that resveratrol is relatively safe and well absorbed in humans, although its low bioavailability is of concern [4,20]. It is thus of essence to establish whether the currently available data of resveratrol action can be translated into advances in human physiology and therapeutics. Finally, understanding the molecular mechanisms for the selectivity of resveratrol action to regulate insulin-mediated metabolism could determine whether this candidate could have any potential therapeutic applications in humans in the not-so-distant future.

Conflict of Interest

Nothing is disclosed.

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