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A high isoflavone diet decreases 5′ adenosine monophosphate–activated protein kinase activation and does not correct selenium-induced elevations in fasting blood glucose in mice☆

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ABSTRACT

Selenium (Se) has been implicated as a micronutrient that decreases adenosine monophosphate–activated protein kinase (AMPK) signaling and may increase diabetes risk by reducing insulin sensitivity. Soy isoflavones (IF) are estrogen-like compounds that have been shown to attenuate insulin resistance, hyperglycemia, adiposity, and increased AMPK activation. We hypothesized that a high IF (HIF) diet would prevent the poor metabolic profile associated with high Se intake. The purpose of this study was to examine changes in basal glucose metabolism and AMPK signaling in response to an HIF diet and/or supplemental Se in a mouse model. Male FVB mice were divided into groups receiving either a control diet with minimal IF (low IF) or an HIF diet. Each dietary group was further subdivided into groups receiving either water or Se at a dose of 3 mg Se/kg body weight daily, as Se-methylselenocysteine (SMSC). After 5 months, mice receiving SMSC had elevated fasting glucose ($P < .05$) and a tendency for glucose intolerance ($P = .08$). The increase in dietary IF did not result in improved fasting blood glucose. Interestingly, after 6 months, HIF-fed mice had decreased basal AMPK activation in liver and skeletal muscle tissue ($P < .05$). Basal glucose metabolism was changed by SMSC supplementation as evidenced by increased fasting blood glucose and glucose intolerance. High dietary IF levels did not protect against aberrant blood glucose. In FVB mice, decreased basal AMPK activation is not the mechanism through which Se exerts its effect. These results suggest that more research must be done to elucidate the role of Se and IF in glucose metabolism.

Abbreviations: AMPK, Adenosine monophosphate–activated protein kinase; LKB1, Liver kinase B1; ACC, Acetyl-CoA carboxylase; Se, Selenium; GLUT4, Glucose transporter type 4; IR, Insulin resistance; Cyt C, Cytochrome c; UCP3, Uncoupling protein 3; SMSC, Se-methylselenocysteine; WQ, White quadriceps; RQ, Red quadriceps; TA, Tibialis anterior; HIF, High isoflavone; LIF, Low isoflavone; SeP, Selenoprotein P; GTT, Glucose tolerance test.

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1. Introduction

Adenosine monophosphate–activated protein kinase (AMPK) has been characterized as a master regulator of the cellular energy state, and it is known to regulate both lipid and glucose metabolism. Adenosine monophosphate–activated protein kinase is activated in response to changes in high-energy phosphate concentrations through its AMP- and adenosine diphosphate–sensing domains. In general terms, activation of AMPK results in the inhibition of adenosine triphosphate consuming processes such as lipogenesis and protein synthesis and the activation of processes important for adenosine triphosphate synthesis such as β oxidation and glucose uptake (See review [1]).

Current efforts are underway to find effective activators of AMPK as a treatment for diseases associated with insulin resistance (IR), such as type II diabetes. The commonly prescribed diabetes drug metformin, for example, is a well characterized activator of AMPK [2]. In addition to pharmacologic agents, certain dietary factors may potentiate or inhibit AMPK signaling. Understanding the impact of different nutrients or dietary supplements on AMPK signaling and glucose control is important for long-term maintenance of healthy glucose and lipid metabolism.

Selenium (Se) is an essential micronutrient, which plays an important role in redox reactions, especially in enzymes such as glutathione peroxidase and thioredoxin reductase [3]. Research on Se supplementation has supported its chemopreventive efficacy to be substantial for prostate cancer [4–9]. Interestingly, supplementation of inorganic Se compounds has also been shown to alter glucose metabolism [10] in preclinical models. The effects of Se on glucose metabolism depend on the form of dose administered. For example, 2 inorganic forms of Se, selenate and selenite, affect glucose management in opposite ways. Selenate decreases IR [10,11] and in some ways can be considered an insulin mimetic [12]. Alternatively, selenite seems to interfere with insulin signaling [13], contributing to increased IR. Although effects of high doses of inorganic forms of Se are clearly demonstrated in these and similar studies, the relevance to human glucose metabolism is uncertain.

Inorganic Se compounds account for only a small fraction of total Se naturally occurring in foods. Far more abundant are organic compounds such as selenomethionine and Se-methylselenocysteine (SMSC). In the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a high dose of selenomethionine was given to subjects, most of whom began the study with high Se status [14]. Such supplementation resulted in a minimal but statistically significant increase in risk of type II diabetes [14]. The choice of SMSC for use in this study is based on (*a*) its significant contribution to total Se in foods, particularly in those foods of high total Se content; (*b*) its high biological availability; (*c*) its demonstrated ability to induce selenoenzyme activity and increase other markers of Se status; (*d*) chemopreventive efficacy, which is superior to that of selenomethionine; (*e*) its low toxicity in comparison with other Se forms; (*f*) its noninvolvement in protein synthesis, unlike selenomethionine, which is incorporated nonspecifically into proteins in place of methionine and thus diverted from Se metabolic pathways; and (*g*) the paucity of data concerning effects on glucose metabolism of this Se form, which is demonstrably relevant and significant in human nutrition. Elucidating the mechanisms through which supplemental Se affects glucose metabolism, particularly forms of Se that are commonly found in food, is an important step in understanding the associated risk of Se supplementation. Recent work by Misu et al [15] has shown that Se-induced changes in glucose metabolism may occur by reducing basal activation of AMPK. If Se is to be useful as an anticancer supplement without increasing the risk of metabolic diseases associated with IR, it may be necessary to couple it with other factors that limit these potential complications.

Isoflavones (IF) are estrogen-like compounds found primarily in soy. Increased dietary IF cause favorable adaptations in glucose metabolism [16]. Interestingly, there is growing evidence that these changes may be facilitated via increased AMPK activation [17]. Isoflavones are also reported to cause a reduction in body fat that is likely mediated by increased energy metabolism [18]. Thus, increasing IF consumption may be an effective approach to help prevent or limit the potentially negative impact of Se supplementation on glucose management. Therefore, due to differences in metabolic responses to increased IF and Se, we hypothesized that (1) a chronic increase in SMSC consumption would lead to impaired glucose control, (2) a high IF (HIF) diet would improve glucose control, and (3) if HIF diet was consumed with high SMSC, the negative effects on glucose management associated with Se supplementation would be attenuated. Furthermore, we sought to determine if supplemental SMSC alone, increased IF consumption, or the combination of the 2 approaches had an impact on basal AMPK activation in skeletal muscle and liver tissue.

2. Methods and materials

2.1. *Animal care*

All experimental procedures used were approved by the Institutional Animal Care Committee of Brigham Young University. Male FVB mice were assigned to 1 of 2 experimental diets (Table 1) and given either supplemental SMSC or water for 6 months. Mice were housed in a temperature and light controlled room (12 hours 0600-1800, light) and were given free access to food and deionized water. Body weights were recorded 3 times per week.

2.2. *Diets*

Custom diets were designed to provide either minimal IF content (low IF [LIF]) as the control diet or a diet that provided a high concentration of IF (HIF) (500 mg/kg of genistein + daidzein aglycone equivalents) from soybean meal. The soybean meal used in TD.10126 (HIF) was tested for IF, and the sum of genistein + daidzein was 2700 mg/kg (aglycone form). The same lot of soybean meal was used for multiple production of the diet during the course of the experiment. Soybean meal and corn gluten meal in the respective diets contributed equivalent amounts of protein. Specific amino acids were supplemented to provide a balanced amino acid pattern and