

Acute and Chronic Kudzu Improves Plasma Glucose Tolerance in Non-Diabetic CD-1 Mice

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Abstract: Previous studies demonstrate that kudzu root extract and its major isoflavone (puerarin) improve glucose metabolism in animal models of insulin resistance and type 2 diabetes; however, these beneficial effects have not been investigated in normal glycemic mice. The present study investigates the effect of acute and chronic kudzu root extract supplementation on glucose tolerance in normoglycemic CD-1 mice. Male, adult CD-1 mice were fed a phytoestrogen-free diet containing 0.2% or 0.0% kudzu root extract for 6 weeks. Thereafter, they were acutely administered kudzu root extract (75 mg/kg BW; oral) or vehicle followed by a glucose challenge (2 g/kg BW; oral). In control fed mice, the acute glucose challenge increased blood glucose ~300% after 30 minutes, and acute kudzu root extract administration significantly blunted this response by ~50%. In mice chronically fed a kudzu-supplemented diet, glucose tolerance was improved, and acute treatment caused no additional improvement. Irrespective of treatment, all mice were normoglycemic at the start of each glucose challenge. Administration of insulin resulted in a larger decrease in blood glucose in chronic kudzu-supplemented compared to control mice. Co-administration of phloridzin (a specific inhibitor of SGLT-mediated glucose uptake), improved glucose tolerance in acutely kudzu-treated mice but had no significant effect on glucose tolerance in chronically treated mice. These results indicate that both acute and chronic administration of kudzu root extract improves glucose tolerance in a normal glycemic mouse strain and that the effects of chronic kudzu feeding may be mediated, in part, by enhanced insulin sensitivity (chronic) and inhibition of sodium dependent glucose transport.

Keywords: Kudzu, Cd-1 mice, Puerarin, Glucose metabolism, Insulin sensitivity.

INTRODUCTION

The use of botanical supplements has a long history in traditional medicine, and their usage has grown substantially over recent decades in the United States and worldwide for prevention and treatment of disease [1, 2]. While this increased usage reflects the publics' search for effective non-pharmaceutical therapies, research is only beginning to explore the efficacy and underlying mechanisms of the most commonly used plant supplements. One such botanical is kudzu root (*Radix puerariae*) extract, which has been used for centuries in traditional Chinese herbal medicine as an anti-alcohol abuse agent [3, 4], for the prevention and treatment of cardiovascular disease and stroke, and as an antipyretic, anti-diarrheic and anti-emetic agent [2, 4].

Studies by several groups including ours indicate that acute administration of puerarin, the most abundant isoflavone in kudzu root extract, improves glycemic control in rodent models of diabetes. In streptozotocin-treated diabetic rats, puerarin induces a dose-dependent decrease in fasting glucose levels and decreases the plasma glucose response to an

intravenous glucose challenge [5]. Similar results have been reported with ob/ob mice and support the suggestion that puerarin may act, at least in part, by inhibiting intestinal sodium-dependent glucose transporters [6]. In addition to improving glycemic control, puerarin prevents hyperglycemic-related damage to the kidney [7, 8], heart [9], retina [10] and vascular smooth muscle [11]. Puerarin also reduces diabetic-related increases in oxidative stress [12], improves lipoprotein profiles [13-15], and may reduce arterial pressure through increased endothelial production of nitric oxide [13, 14] or via direct hyperpolarization of vascular smooth muscle [16]. These findings support the idea that puerarin may be beneficial to individuals with diabetes and/or metabolic syndrome.

While isoflavones like puerarin may be efficacious in an isolated form, botanical supplements such as kudzu root extract often contain multiple bioactive compounds that may have synergistic or antagonistic effects [1]. Indeed, Meezan *et al.* [6] demonstrate that acute pretreatment with the daidzin, the second most prevalent isoflavonoid in kudzu root extract, significantly impairs glucose tolerance in ob/ob mice. Thus, the daidzin found in whole kudzu extract could decrease or negate the beneficial metabolic effects of puerarin, reducing the efficacy of kudzu extract for improving glycemic control. Further, botanical

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supplements like kudzu root extract are most often used for the prevention of chronic disease. We previously investigated the effects of long-term consumption of kudzu root extract on glucose and lipid metabolism in ob/ob mice and in spontaneously hypertensive rats, both models of insulin resistance [15, 17]. However, it is unclear whether the protective effects of kudzu extract extend to non-diseased animals. Thus, the present study explored whether the beneficial effects of kudzu root extract could be observed in animal models in which glucose metabolism and blood pressure were "normal," in this case, the CD-1 mouse.

MATERIALS AND METHODS

8-week-old, male CD-1 mice (Harlan Sprague Dawley, Indianapolis, IN) were housed in a climate-controlled room with a 12:12 light:dark cycle. Mice were allowed *ad libitum* access to tap water and AIN93M diet (polyphenol-free) with or without the addition of 0.2% kudzu root extract for six weeks. All experimental procedures were conducted in accordance with Institutional Animal Care and Use Committee of the University of Alabama, Birmingham, and National Institutes of Health guidelines.

Dietary Preparation

The kudzu-supplemented diet was prepared by adding kudzu root extract (0.2% w/w; AMAX NutraSource, Inc, Eugene, OR) to powdered diet, mixed completely and subsequently pelleted (TestDiet, Richmond, IN 47374). The kudzu diets were formulated to reflect a puerarin concentration of 500 µg/gram diet (~ 0.05% of the extract by weight) based on our previous studies [15].

Plasma Isoflavone Analysis

Isoflavone analysis was performed on a group of mice chronically fed either an isoflavone-free (control; n=11) or kudzu-supplemented (n=10) diet, using our previously published method [18]. Briefly, each serum sample (200 µL) was subjected to enzymatic hydrolysis of the isoflavone glucuronides and sulfates for the total isoflavone determination and extracted into diethyl ether. After concentrating samples to dryness, they were dissolved in methanol-water (80:20, v/v) prior to LC-MS/MS analysis. Sample preparation and quantification of puerarin in biological samples were performed as described previously [19].

Experimental Procedures

Chronic Kudzu and Arterial Pressure

To investigate whether dietary kudzu root extract alters cardiovascular function, blood pressure and heart rate were measured in mice fed either control (n=6) or kudzu-supplemented (n=6) diets using tail cuff plethysmography (MC 4000, Hatteras instruments, Inc., Cary, NC) at 1-week and 4-weeks after initiation of the diets. To ensure accuracy of recordings, mice were placed in the tail cuff restrainer for 5 consecutive days to acclimate them to the instrumentation. On the day of testing animals were placed in the training room for at least 30 minutes prior to measurement. Five preliminary recording cycles were then taken, which warms the mouse to improve blood flow to the tail while also acclimating the mouse to the chamber. Ten recording cycles were taken and the data averaged together.

Kudzu and Glycemic Control

A separate group of mice was maintained on the above diets for six weeks (n=6 for each diet) and body weights recorded. Mice were fasted overnight and blood glucose measurements performed the following morning. Mice were lightly anesthetized (isoflurane) and a micro sample of tail blood (one drop; < 2 µL) was taken for measurement of baseline blood glucose concentration using a blood glucose monitoring system (Prestige Smart System, CVS). Mice then received an oral gavage of either kudzu root extract (75 mg/kg BW) or vehicle (10% alcohol in saline), followed by an oral glucose gavage (2 grams glucose per kg BW). Blood glucose was measured at 15, 30, 45, 60, 90 and 120 minutes after the glucose challenge under light anesthesia. The following week the protocol was repeated so that mice previously receiving kudzu extract were given a vehicle gavage and vice versa.

To determine whether chronic dietary kudzu extract improves glucose handling by enhancing insulin sensitivity, control and kudzu-fed mice were fasted overnight and given a bolus injection of insulin (0.75 U/kg, i.p.; bovine insulin, Sigma, St Louis, MO) on a subsequent day and blood glucose measured at 15, 30, 45, 60, 90 and 120 minutes after insulin administration. To test the hypothesis that chronic kudzu root extract improves glucose tolerance by blocking intestinal sodium-dependent glucose co-transporters (SGLT), a separate group of control and kudzu-fed mice were pre-treated with the SGLT-specific blocker phloridzin (0.2 mg/kg BW; oral gavage)

followed by vehicle or kudzu, after which mice received a glucose challenge, as described above.

Statistics

All experimental data were evaluated by one-way analysis of variance followed by a Student-Newman-Keuls post hoc test to determine the source of main effects and interactions (Kaleidagraph 4.0, Synergy Software). The significance criterion for all experiments was $P < 0.05$.

RESULTS

In mice maintained on a kudzu-supplemented diet for six weeks ($n=6$), chronic dietary kudzu root extract significantly increased plasma isoflavone concentrations above levels observed in the isoflavone-free control diet ($n=6$; Table 1). There were no differences in body weight between the chronic kudzu vs. control groups (99 ± 4 mg/dl vs. 92 ± 4 mg/dl; n.s., respectively). Similarly, long term dietary kudzu root extract had no effect on mean arterial pressure (kudzu diet: 109 ± 3).

In the mice fed the control diet (non-supplemented with kudzu root extract; $n=6$), there was no difference in baseline blood glucose concentrations between animals receiving vehicle or kudzu root extract (62.5 ± 5.1 mg/dl vs. 73.1 ± 9 mg/dl, respectively). In vehicle-treated mice on the control diet, the oral glucose challenge increased blood glucose concentration to nearly 300% of baseline at 30 minutes following the glucose administration, and the glucose concentration decreased to only 200% of baseline at 120 minutes post-glucose gavage (Figure 1). Acute kudzu root extract pretreatment of the control diet mice significantly improved glucose tolerance; plasma

glucose levels were significantly lower than those of vehicle treated mice at every time point following the glucose administration (Figure 1).

To explore whether insulin sensitivity was altered by the kudzu root diet, a bolus of insulin was injected into the control and kudzu root diet mice and plasma glucose monitored. Treatment with insulin significantly decreased blood glucose levels in both groups, but by 90 minutes blood glucose levels were significantly lower in the kudzu fed compared to control diet group (Figure 2). There was no difference in baseline glucose levels between mice fed a kudzu diet vs. the control diet group (81.0 ± 5.3 mg/dl vs. 70.1 ± 4.8 mg/dl, respectively).

A second mechanism by which kudzu could improve glucose handling is by altering intestinal uptake of glucose via inhibition of SLGT-mediated glucose uptake. To test this hypothesis, a second series of CD-1 mice were acutely pretreated with either phloridzin (a potent inhibitor of intestinal SLGT-mediated glucose uptake) or vehicle prior to gavage of with either kudzu root extract or vehicle and glucose tolerance was tested. In mice fed the control diet, phloridzin significantly improved glucose tolerance beyond that of kudzu root extract alone (Figure 3), particularly at 60 and 90 minutes ($p < 0.05$; Figure 3) following the glucose gavage. In contrast, phloridzin did not cause any significant change in glucose tolerance in CD-1 mice that had been maintained on a kudzu root extract diet for six weeks (Figure 3).

DISCUSSION

Many recent studies suggest that botanical products have benefits in relation to cardiovascular and

Table 1: Plasma Isoflavone Concentrations in Cd-1 Mice Fed an Isoflavone-Free (Control; $n=11$) or Kudzu-Supplemented Diet ($n=10$) for One Month

| Isoflavone | Control Diet (nM) | Kudzu Diet (nM) |
|-------------|--------------------|---------------------|
| Equol | ND* | 6631.8 ± 471.23 |
| Genistein | $15.03 \pm 3.06^*$ | 141.39 ± 47.80 |
| Puerarin | $16 \pm 0.014^*$ | 82 ± 0.012 |
| O-DMA | $4.23 \pm 1.25^*$ | 1658.9 ± 377.8 |
| DHD | ND* | 224.89 ± 34.32 |
| Glycitein | ND* | 75.94 ± 16.41 |
| Enterodiol | $5.08 \pm 2.95^*$ | 37.95 ± 14.18 |
| Biochanin-A | $0.21 \pm 0.19^*$ | 4.41 ± 0.57 |

P-value < 0.05 vs. mice fed the kudzu diet; ND (Not detectable); O-DMA (O-desmethylangolensin); DHD (dihydrodaidzein). mm Hg; control diet: 106 ± 3 mm Hg) or heart rate (kudzu diet: 670 ± 23 bpm; control diet: 677 ± 23 bpm).

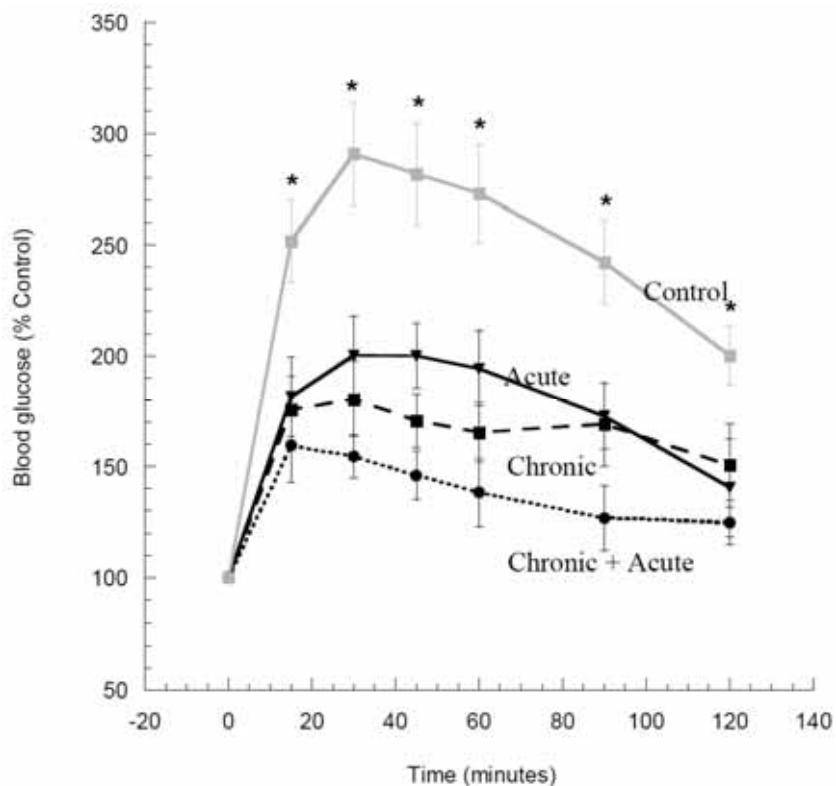


Figure 1: A summary of acute (gavage) and chronic (diet-fed) effects of kudzu root extract on glucose tolerance in CD-1 mice. Acute kudzu root extract (solid black line) significantly improves plasma glucose tolerance vs. vehicle-treated mice (solid gray line; Control). Chronic dietary kudzu root extract (dashed line) also improves glucose tolerance, and the effect is similar to that in acute treated mice. Acute kudzu root extract gavage does not significantly improve glucose tolerance in kudzu-fed mice (dotted line). n=6 for each group; *P-value < 0.05 Control vs. all other groups.

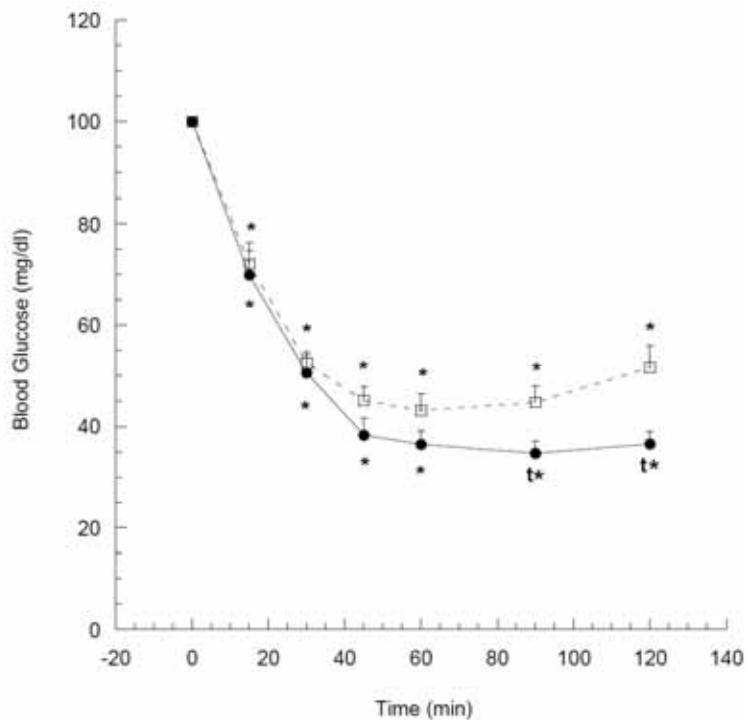


Figure 2: Treatment with insulin (0.75 U/kg) lowers blood glucose to a greater degree in mice chronically fed a diet containing kudzu root extract (n=6; solid line) compared to control-fed animals (n=6; dashed line). * P-value < 0.05 vs. within group baseline; ^tP-value < 0.05 vs. vehicle group.

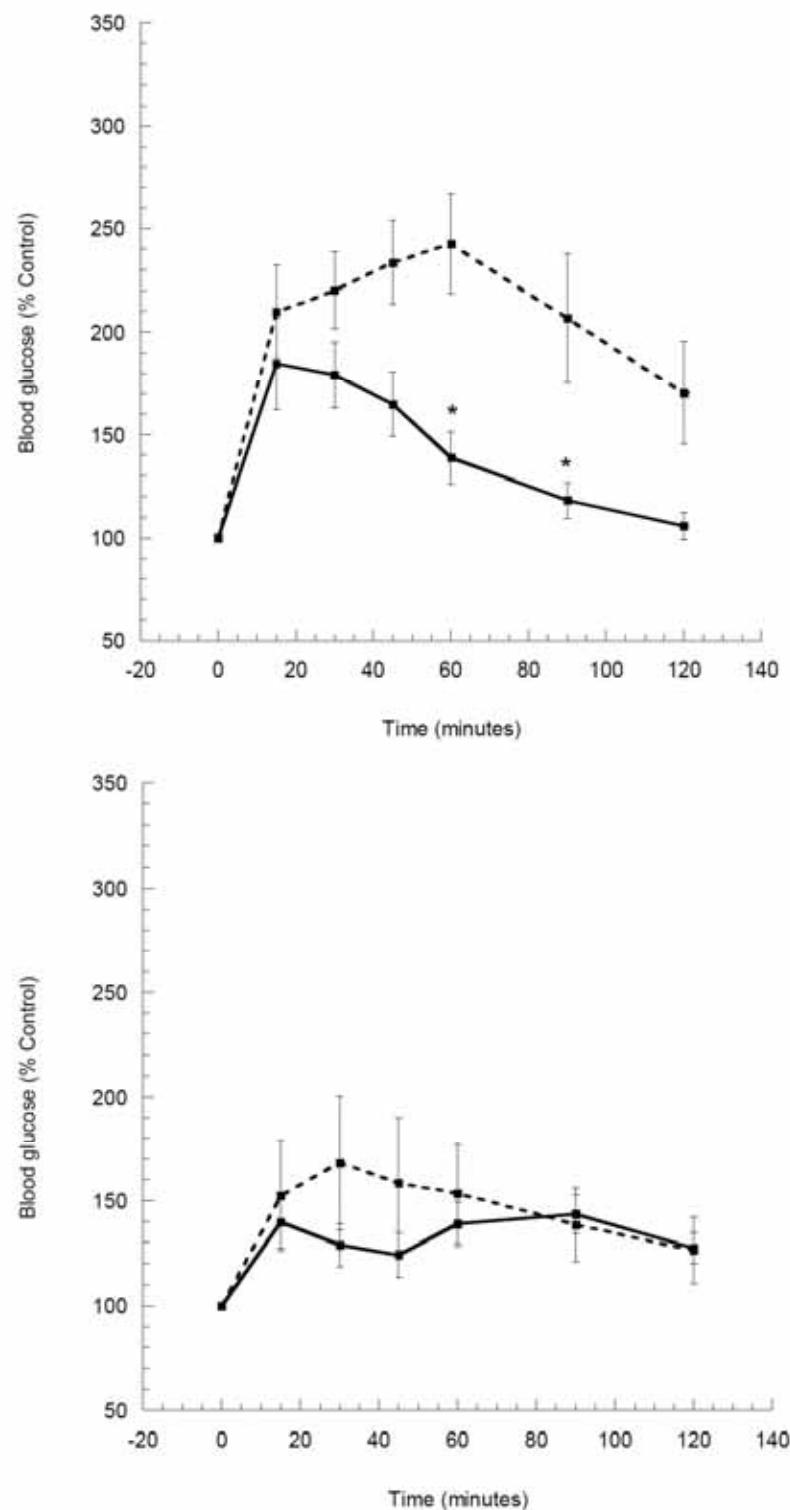


Figure 3: In control diet mice acutely treated with kudzu root extract (n=6; top panel), phloridzin (a potent inhibitor of intestinal sodium-dependent glucose uptake) greatly decreases blood glucose to a glucose challenge. In contrast, in mice maintained on kudzu-supplemented diet (n=6; lower panel), the phloridzin pretreatment has no significant effect. The solid line indicates the response of mice pre-treated with phloridzin. * P-value < 0.05 compared to non-phloridzin group.

metabolic health, and our past studies have demonstrated that kudzu root extract can normalize glucose metabolism in two rodent models of disease characterized by glucose intolerance (i.e. hypertension

and obesity) [15, 17]. The present study examined the hypotheses that either acute kudzu root extract administration or chronic kudzu root dietary supplementation can improve glucose tolerance in non-

diabetic mice. The study also explored potential mechanisms by which kudzu root extract improves glucose tolerance, including enhanced insulin sensitivity and inhibition of sodium-linked glucose transport (SGLT). The results also indicate that the effect acute kudzu root extract administration does not improve glycemic control in dietary kudzu root supplemented mice. Finally, while chronic kudzu extract exerts a positive effect on the plasma glucose responses to a glucose challenge, it does not alter baseline glucose levels in these non-diabetic mice, thus, the effect of kudzu root extract does not appear to act by inducing hypoglycemia in non-diabetic mice.

The observation that acute intake of whole kudzu extract improves glucose tolerance in non-diabetic mice extends previous observations in diabetic rat and mouse models [15, 17]. The current experiments utilized whole kudzu root extract, while previous studies used either whole kudzu root extract or its major isoflavone component, puerarin [5, 6]. While puerarin is the most common isoflavonoid in kudzu root extract, several others isoflavones are present in the extract, including daidzin and genistin (see Table 1), and these (especially daidzin) could have synergistic or antagonistic effects on puerarin-induced changes in glucose tolerance [6]. In a previous study in ob/ob mice, daidzein by itself worsened glucose tolerance while puerarin improved it [6]. The present observation that whole kudzu root extract improves glucose tolerance to about the same extent as previously observed following acute puerarin administration [6] suggests that daidzin or other isoflavonoids do not negate the hypoglycemic effects of kudzu root extract on glucose handling in "normal" (i.e. non-disease model) mice.

In the present study, CD-1 mice fed a kudzu-supplemented diet for six weeks displayed improved glucose tolerance to about the same extent as mice on a non-kudzu diet that received an acute bolus of kudzu root extract. Interestingly, while acute kudzu mice improved glucose tolerance in control diet mice, it did not improve glucose tolerance in chronic kudzu root extract fed mice. These results suggest a similar efficacy for acute vs. chronic kudzu intake and indicate that there is not an additive effect of acute and chronic administration on glucose handling (at least not in normal glycemic mice); however, it is also possible that either treatment lowered the glucose tolerance to a limiting level. Together this might indicate that acute vs. chronic kudzu root treatment act *via* a common mechanism; however, our results suggest that there

may be some differences in the underlying mechanisms.

There are several mechanisms by which kudzu extract may enhance glucose handling, including increasing insulin receptor levels [20], insulin expression [20], and activation of antidiabetic TGF β 1/Smad2 pathways [21]. Work in our laboratory has focused on the contribution of SGLT receptors located in the small intestinal brush border [6] and proximal convoluted tubules of the kidney, which are targets of other hypoglycemic botanical compounds e.g. quercetin [22]. To test whether kudzu extract enhances glucose tolerance by inhibiting SGLT-mediated glucose uptake, mice were pretreated with phloridzin, a specific blocker of SGLT receptors [2], prior to kudzu gavage. Phloridzin pretreatment significantly reduced glucose tolerance below the level reached with puerarin alone. In contrast to the acute studies, phloridzin had no additional effect on glucose uptake in mice maintained on the kudzu diet. Thus, different mechanisms likely underlie at least some of the beneficial effects of acute vs. chronic kudzu feeding e.g. insulin sensitization.

Another mechanism by which kudzu isoflavones may lower plasma glucose concentration is through enhancing the cellular response to insulin. In mice receiving chronic dietary kudzu (compared to those fed the control diet), administration of insulin resulted in a greater decrease in blood glucose (approximately 10%). These results suggest that chronic administration of kudzu root extract lowers blood glucose, in part, by enhancing insulin sensitivity, even in mice that appear to be normally insulin sensitive. This supports our previous findings in stroke-prone hypertensive rats [15] and research in STZ-induced diabetic rats [5], along with observations that puerarin increases glucose uptake in isolated muscle tissue through an increase in GLUT4 transporters [23].

It should be noted that the current experiments utilized CD-1 mice, which have normal glycemic control, and thus the effects would be expected to be smaller compared to those observed in diabetic models. In animals with compromised glucose or cardiovascular function, the effect of combined acute and chronic kudzu may be more potent or synergistic. Hsu *et al.* [5] have observed a stronger effect of puerarin on diabetic vs. normoglycemic rats. Similarly, in stroke-prone hypertensive rats (a model metabolic syndrome), chronic dietary kudzu root extract lowers arterial pressure, baseline glucose and circulating

cholesterol [15]. It will be of interest to determine the effects of kudzu root extract on arterial pressure in other animal models of disease.

PERSPECTIVES

The increasing prevalence of impaired glucose regulation, type-2 diabetes and metabolic syndrome worldwide, especially in older adults, increases the urgency to find methods for improving glucose regulation, especially for non- or pre-diabetic individuals in whom the treatment may delay the onset of insulin resistance and diabetes. The present study suggests that in non-diabetic mice, isoflavanoids contained in kudzu root extract exert a positive effect on glucose tolerance by lowering plasma glucose levels following an oral glucose challenge. Further, this effect is observed after both acute and chronic kudzu treatment, although the underlying mechanisms may differ. Kudzu root extract does not appear to have any adverse effects in rodents, even at 10X the doses used in this study (unpublished data), and no adverse effects have been reported in humans who take kudzu root extract supplements. Unlike traditional diabetes therapy, kudzu root extract is not associated with weight gain or other adverse effects of traditional diabetes therapy, and it has no apparent adverse effects on cardiovascular health. Thus, the identification of effective and inexpensive supplements such as kudzu root extract may provide new, complementary agents that will reduce the adverse effects of impaired glucose and insulin regulation in humans.

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