PROCEEDING

Control of oxidative stress and metabolic homeostasis by the suppression of postprandial hyperglycemia

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Abstract : Repeated mental stress may lead to chronic alterations in cortisol and catecholamine concentrations and to insulin resistance. Furthermore, chronically elevated cortisol concentrations may favour the development of abdominal obesity and of the metabolic syndrome. Oxidative stress impairs glucose uptake in muscle and fat and correlates with BMI. Obese subjects with type 2 diabetes, especially soon after the onset of diabetes, usually exhibit postprandial hyperglycemia with delayed hyperinsulinemia. It is recognized that insulin resistance causes postprandial hyperglycemia ; however, it is also possible that impairment of early insulin secretion in response to an oral glucose load is the reason why postprandial hyperglycemia occurs. Since even modest increases in postprandial glucose values can be a risk factor for cardiovascular disease. Therefore, the effects of palatinose based functional food which reduces postprandial hyperglycemia and hyperinsulinemia were investigated in rats. This novel food definitely reduced visceral fat accumulation and improved insulin sensitivity. Therefore, it is suggested that functional food which suppresses postprandial glucose level is beneficial for both stress and metabolic controls. J. Med. Invest. 52 Suppl. : 259-265, November, 2005

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STRESS AND APPETITE

Eating is thought to be suppressed during stress due to anorectic effects of corticotrophin releasing hormone, and increased during recovery from stress due to appetite stimulating effects of residual cortisol (1). Cortisol clearly plays an important role in energy regulation, increasing available energy through gluconeogenesis and lipolysis. Glucocorticoids lead to hyperphagia and weight gain, and are necessary for the expression of their obesity (2).

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Several studies have shown that people under chronic stress tend to gain weight over time, which may be due to both stress- related endocrine changes, as well as coping behaviors (3). It was hypothesized that high cortisol reactivity in response to stress may lead to eating after stress, given the relations between cortisol with both psychological stress and mechanisms affecting hunger. High cortisol reactors consumed more energy on the stress day compared to low reactors, high reactors ate significantly more sweet food across days. Increases in negative mood in response to the stressors were also significantly related to greater food consumption. Thus, psychophysiological response to stress influences subsequent eating behavior. In the current study of college undergraduate women (4), dieting was related to eating less during a control day, whereas cortisol reactivity predicted eating

more on a stress day. Multiple comparisons of food type consumed by reactivity group revealed further differences of the sweet food consumed after stress, the high reactors consumed significantly more high fat food.

STRESS AND IMPAIRED CARBOHYDRATE AND LIPID METABOLISM

Responses to mental stress involves activation of the sympathetic nervous system and secretion of epinephrine from the adrenal medulla and activation of the hypothalamo-pituitary adrenal axis, the latter resulting in the secretion of glucocorticoids from the adrenal cortex. The combined effects of these neuroendocrine alterations are the mobilization of lipids from the adipose tissue and of glucose from hepatic glycogen to ensure ample energy availability together with the development of an acute state of insulin resistance, which diverts glucose away from skeletal muscle to ensure glucose supply to the brain.

Mental stress significantly enhances plasma catecholamine and cortisol concentrations, but does not acutely impair insulin sensitivity (5). Repeated mental stress may lead to chronic alterations in cortisol and catecholamine concentrations and to insulin resistance. Furthermore, chronically elevated cortisol concentrations may favour the development of abdominal obesity and of the metabolic syndrome (6, 7) (Fig. 1). Repeated mental stress particularly in obese patients can contribute to increased blood pressure and to increased plasma glucose concentrations.

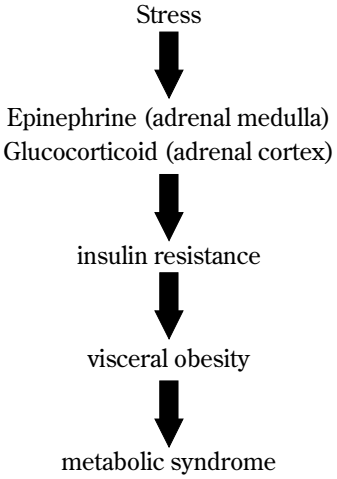

Fig. 1 Mental stress leads to insulin resistance and to the metabolic syndrome.

STRESS AND INFLAMMATION

It has been recognized that low-grade, chronic inflammation is present in individuals at risk of developing atherosclerotic disorders (8). Obese insulin-resistant individuals show increased tumor necrosis fantor-α(TNF-α) and interleukin (IL) concentrations in plasma, adipose tissue and skeletal muscle (9-11). TNF-α and other pro-inflammatory cytokines acutely reduced insulin sensitivity (12-14). Dietary factors can modulate the expression of these cytokines in insulin-sensitive tissue. In particular, a high-fat diet appears to reduce insulin sensitivity by activating inflammatory responses in adipose tissue through the stimulation of the inhibitor of nuclear factor kappa B (NF-kB) (15).

Several studies demonstrated that psychological stress stimulates the production of pro-inflammatory cytokines. In elderly individuals, the chronic stress of looking after a dementing spouse led to increased plasma IL-6 concentrations. Raised plasma concentrations of pro-inflammatory cytokines were recorded in individuals expecting an academic examination (16). Both chronic psychological stress and acute mental stress have been demonstrated to increase pro-inflammatory cytokines (17, 18). The pathways responsible for the stimulation of cytokine release involve activation of the sympathetic nervous system (19). In humans, mental stress acutely activated NF-kB, a nuclear factor acting upstream of the inflammatory cascade, in peripheral blood mononuclear cells (20).

OXIDATIVE STRESS AND INSULIN RESISTANCE

Obese subjects with type 2 diabetes, especially soon after the onset of diabetes, usually exhibit postprandial hyperglycemia with delayed hyperinsulinemia. It is recognized that insulin resistance causes postprandial hyperglycemia (21, 22) ; however, it is also possible that impairment of early insulin secretion in response to an oral glucose load is the reason why postprandial hyperglycemia occurs (23). Since even modest increases in postprandial glucose values can be a risk factor for cardiovascular disease (24), patients with diabetes would probably benefit from early and effective mealtime treatment. The meal-induced activation of homeostasis in patients with type 2 diabetes can be reduced by decreasing postprandial hyperglycemia (25).

Oxidative stress is widely invoked as a pathogenic mechanism for atherosclerosis. Among the sequelae of hyperglycemia, oxidative stress has been suggested as a potential mechanism for accelerated atherosclerosis (26-28). Hyperglycemia can increase oxidative stress through several pathways. A major mechanism appears to be the hyperglycemia-induced intracellular reactive oxygen species (ROS), produced by the proton electromechanical gradient generated by the mitochondria electron transport chain and resulting in increased production of superoxide (26). Oxidative stress impairs glucose uptake in muscle and fat (29-30) and decreases insulin secretion from pancreatic β cells (31).

It has been demonstrated in nondiabetic human subjects that fat accumulation closely correlated with the markers of systemic oxidative stress and that plasma adiponectin levels correlated inversely with systemic oxidative stress (32). Those are in good agreement with data suggesting that systemic oxidative stress correlates with BMI (33, 34). It is suggested that increased ROS secretion into peripheral blood from accumulated fat in obesity is also involved in induction of insulin resistance in skeletal muscle and adipose tissue, impaired insulin secretion by β cells.

Therefore, strategies to reduce postprandial hyperglycemia and hyperinsulinemia represent an important approach to improving glycemic control in patients with type 2 diabetes mellitus and may even prevent the deterioration of glucose metabolism in impaired glucose tolerance and the subsequent progression to diabetes.

PREPARATION OF PALATINOSE BASED FUNCTIONAL FOOD

Palatinose (isomaltulose), which is present in honey, has shown promise as a noncariogenic caloric sweetener (35, 36). A previous study clearly demonstrated that the increase in plasma glucose (PG) and insulin (IRI) after palatinose ingestion was significantly smaller than that after sucrose (37). Furthermore, palatinose has been shown to be an insulin-sparing caloric sweeteer with a lower glycemic index than sucrose in type 2 diabetic patients and streptozotocin-diabetic animals (38, 39). The difference may be due to a difference in digestibility because palatinose is digested to glucose and fructose by the intestinal isomaltase, and the hydrolysis of palatinose by a homogenate of human intestinal mucosa was one-fourth that of sucrose (40). However, palatinose was completely cleaved and absorbed (41).

The novel enteral liquid formula designated as Inslow was prepared by the replacement of dextrin in the standard balanced formula (SBF) with 55.7% palatinose among carbohydrate (Table 1) (41). Inslow contains palatinose, branched dextrin, xylitol, and other carbohydrates containing dietary fiber and mixed carbohydrates from raw material as the principal carbohydrates, and the percentages of protein, fat, and carbohydrate in the formula are 20%, 29.7%, and 50.3%, respectively. The commercially available SBF that was used for comparison contains dextrin and sucrose as the principal carbohydrates, and the percentages of protein, fat, and carbohydrate are 16%, 25%, and 59%, re-

Table 1 Composition of Inslow and standard balanced formula (SBF)

	Inslow		Standard balanced formula(SBF)
○ Energy	1 kcal/ml		1 kcal/ml
○ Protein	20.0%		6.0%
○ Fat	29.7%		25.0%
SFA	9.5%		9.0%
MUFA	68.5%		45.0%
PUFA	16.8%		40.0%
○ Carbohydrate	50.3%		59.0%
Maltodextrin	22.8%	Sucrose	2.8%
Xylitol	8.9%	Dextrin	97.2%
Paratinose	68.3%		

Abbreviations : SFA, saturated fatty acid ; MUFA, monounsaturated fatty acid ; PUFA, polyunsaturated fatty acid

spectively. Spray-dried powder versions of Inslow and SBF were prepared for use in the long term study.

CONTROL OF METABOLIC HOMEOSTASIS BY THE SUPPRESSION OF POSTPRANDIAL HYPERGLYCEMIA

The effect of Inslow on carbohydrate and lipid metabolism in Sprague-Dawley rats were compared with those of SBF (42). After a bolus intragastric injection of each formula equivalent to 0.9 g/kg carbohydrate, the peak levels of PG and IRI in the femoral vein of the Inslow group were significantly smaller than those of SBF group (Fig. 2). The values of total incremental area (area under the curve : AUC) of PG and IRI from the basal level for 120 min after INSLOW ingestion were significantly smaller than that after SBF ingestion (Fig. 3).

From 20 to 27 weeks of age, daily food intake and body weight did not differ significantly among the Inslow and SBF groups ; however, body weight gain in the Inslow group was lower than in SBF group. After ingestion of Inslow or SBF for two months, fasting PG levels were not different among the two groups, but the IRI level in the Inslow group was significantly lower than that in the SBF group. The TG level markedly decreased by 34% in the Inslow group and increased by 23% in the SBF group. The TG level of the Inslow group was significantly lower than that of the SBF group. The concentrations of serum free fatty acid (FFA) and total cholesterol did not differ among the two groups.

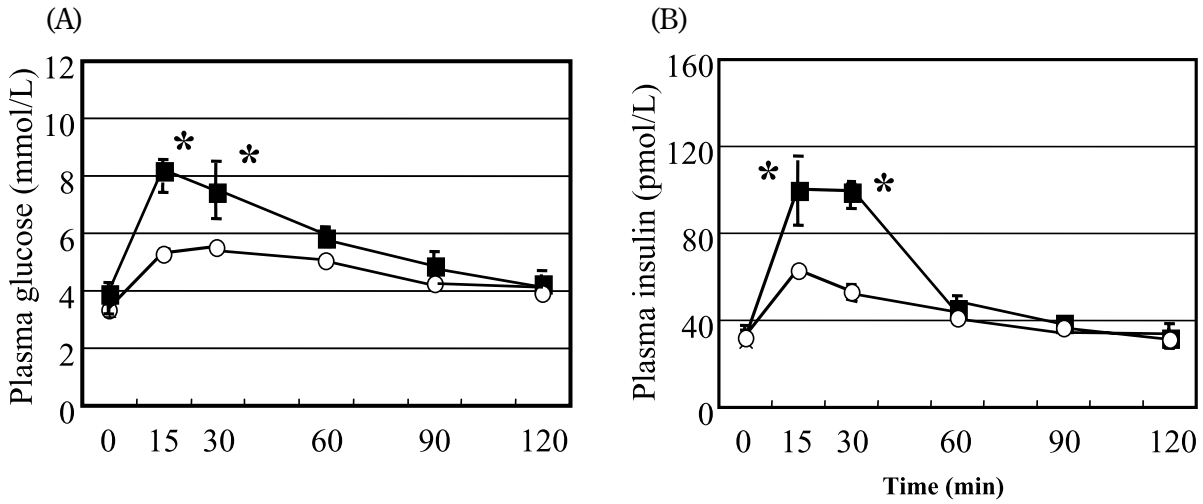

Fig. 2 Changes in plasma glucose (PG) (A) and plasma insulin (IRI) (B) in the femoral vein after oral administration of Inslow (white circles) and SBF (black squares). Values are means ± SE for n=10. * : p<0.001 (vs. Inslow)

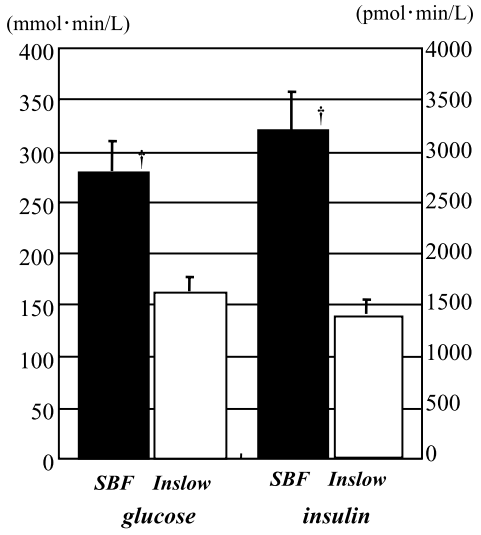

Fig. 3 Area under the curve (AUC) after 120 min of PG and IRI in the femoral vein during oral administration of Inslow (white bar) or SBF (black bar). Values are means ± SE for n=10. † : p<0.01 (vs. Inslow)

The weights of epididymal, mesenteric, and retroperitoneal adipose tissues were significantly lower in the Inslow group than in the SBF group. The weights of liver and pancreas in the Inslow group were higher than in the SBF group. The concentration of TG in the liver in the Inslow group was significantly lower than that in the SBF group.

Insulin sensitivity in the Inslow and SBF groups was evaluated by the hyperinsulinemic euglycemic clamp test with oral glucose load. The glucose infusion rate (GIR), which reflected the insulin sensitivity in peripheral tissues, of the Inslow group was significantly higher than that of the SBF group

(Fig. 4). The rate of hepatic glucose uptake (HGU), which might reflect insulin sensitivity in the liver, was significantly higher in the Inslow group than in the SBF group (Fig. 4).

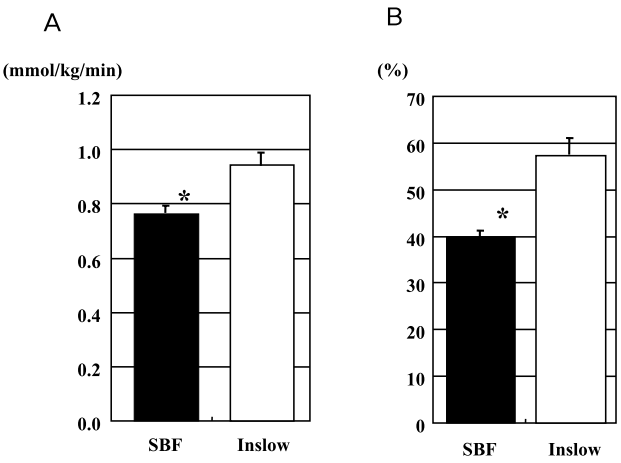

Fig. 4 Glucose infusion rate (A) and hepatic glucose uptake (B) during hyperinsulinemic euglycemic clamp with oral glucose load in Inslow (white bar) and SBF (black bar) groups. Values are means ± SE for n=10. * : $p<0.05$ (vs. Inslow)

CONCLUSION

Postprandial glucose and insulin levels affects body weight and body fat even though the intake was same amount of energy. The effects of Inslow could be due to the suppression of the excess calories exposed in adipocytes which was controlled by insulin. In addition, increased ROS production observed by postprandial hyperglycemia leads to increased oxidative stress in blood and other organs.

Both metabolic and epidemiologic evidence suggest that replacing high-glycemic-index forms of carbohydrate with low-glycemic-index carbohydrates could reduce the risk of type 2 diabetes (43). Differences in the pattern of postprandial glucose response offer a potential explanation for the conflicting results on insulin sensitivity, with possibility that increases in insulin exposure may affect insulin sensitivity through down-regulation of insulin action (44). Therefore, it is suggested that Inslow which suppresses postprandial glucose level is beneficial for both stress and metabolic controls.

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