Effect of Fensuccinal on Experimental Insulin Resistance

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The effects of new antioxidant fensuccinal on dexamethasone-induced insulin resistance in rats were studied. Oral administration of fensuccinal in a dose of 25 mg/kg for 2 weeks prevented basal hyperinsulinemia and insulin insensitivity of peripheral tissues. Fensuccinal also attenuated oxidative stress by decreasing the concentrations of primary and secondary lipid peroxidation products in liver homogenates. The ability of fensuccinal to prevent dexamethasone-induced insulin resistance is probably due to its antioxidant properties.

Key Words: *insulin resistance; dexamethasone; fensuccinal; antioxidant*

Insulin resistance and hyperinsulinemia are typical of non-insulin-dependent diabetes, obesity, hyperlipidemia, atherosclerosis, and aging [9]. Recently the existence of a vicious cycle including insulin resistance and oxidative stress was hypothesized. According to this hypothesis, hyperinsulinemia increases the content of free radicals due to activation of the sympathetic nervous system and accumulation of nonesterified fatty acids in the plasma [5]. Free radicals impair the mechanisms of insulin action by changing physicochemical properties of plasma membranes and increasing intracellular Ca^{2+} concentration [12].

Our previous experiments showed that fensuccinal, a low toxic derivative of succinic acid, which is now under clinical testing, produces considerable antioxidant effects in animals with various forms of insulin deficiency [6,7]. Here we studied the effects of fensuccinal on dexamethasone-induced insulin resistance.

MATERIALS AND METHODS

Experiments were performed on 24 male Wistar rats weighing 200-250 g. Insulin resistance was induced by subcutaneous injections of 0.125 mg/kg dexamethasone for 14 days [11]. During this period, the rats were perorally treated (through a tube) with 25 mg/kg fensuccinal or placebo (control). Blood glucose homeostasis was evaluated by the basal level of glucose in the blood and its content during the intraperitoneal glucose tolerance test. The blood was taken from the caudal vein after 4-h food deprivation and 30, 60, and 120 min after administration of 3 g/kg glucose. Blood glucose concentration was measured by the glucose oxidase method using an Eksan-G analyzer. The integral glycemia was measured by summation of all values recorded during the glucose tolerance test [4]. Insulin sensitivity was determined by calculating the percent of a decrease in the basal blood glucose level 30 min after intraperitoneal injection of 1 U/kg insulin [3]. The basal blood insulin level was estimated by the radioimmunological method using Belaris kits. The intensity of lipid peroxidation (LPO) was determined by the contents of conjugated dienes (CD) [2] and malonic dialdehyde (MDA) [1] in liver homogenates. Protein concentration was measured by the method of Lowry [8].

The results were analyzed by Student's *t* test.

RESULTS

Fourteen days after dexamethasone administration to control rats, the basal blood insulin level considerably increased, while insulin sensitivity decreased (Table 1). It is known that dexamethasone stimulates production of amyloid polypeptide amylin. This hormone

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TABLE 1. Effects of Fensuccinal on Blood Glucose Homeostasis and LPO in the Liver of Rats Injected with Dexamethasone ($X \pm Sx$, n=8)

Parameter	Intact	Dexamethasone	
		+placebo (control)	+fensuccinal
Basal blood glucose, pmol/ml	81.4±9.7	130.1±10.5*	92.0±8.6+
Insulin sensitivity coefficient, %	41.4±5.0	21.2±3.7*	38.4±2.9
Integrated glucose level, mmol/l	21.6±1.2	44.1±1.1*	29.5±3.7+
MDA, nmol/mg protein	43.5±3.9	59.0±4.3*	35.1±3.7+
CD, nmol/mg protein	89.6±3.4	141.1±10.5*	97.2±5.4+

Note. p<0.05: *compared to intact rats, +compared to the control.

synthesized by pancreatic β-cells is the major component of islet amyloid in patients with non-insulin-dependent diabetes. Physiological role of amylin is poorly understood, but amylin-induced suppression of insulin action in the liver and muscles indicates its important role in the pathogenesis of insulin resistance [10].

Treatment with fensuccinal for 2 weeks prevented insulin resistance induced by dexamethasone in rats: the basal insulin level decreased and the coefficient of insulin sensitivity increased (Table 1). In addition, the slope of glucose-response curves plotted during the intraperitoneal glucose tolerance test 30, 60, and 120 min after glucose administration to fensuccinal-treated rats was much lower than in the control (Fig. 1).

Fensuccinal prevented the decrease in glucose tolerance induced by dexamethasone: the integral blood glucose level in experimental rats approached that in intact animals (Table 1).

Dexamethasone elevated the contents of primary (CD) and secondary (MDA) LPO products in liver homogenates (Table 1), which is consistent with the hypothesis on the relationship between insulin resistance and oxidative stress [5]. At the same time, 2-week treatment with fensuccinal decreased production of MDA and CD in rat liver homogenates compared to the control.

Hence, our findings suggest that low-toxic antioxidant fensuccinal prevents the development of dexamethasone-induced insulin resistance in rats. These data indicate that fensuccinal should be clinically tested as a potent drug for correction of insulin resistance, including non-insulin-dependent diabetes.

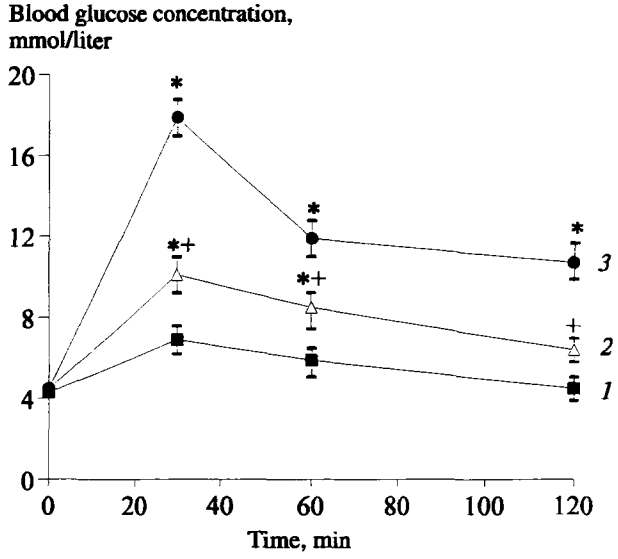

Fig. 1. Blood glucose concentration in rats injected with dexamethasone during glucose tolerance test (3 g/kg intraperitoneally): intact control (*1*), dexamethasone+fensuccinal (*2*), and dexamethasone+placebo (*3*). p<0.05: *compared to intact rats, +compared to the control.

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