Effect of prolonged treatment with tyramine on glucose tolerance in streptozotocin-induced diabetic rats


Institut National de la Santé et de la Recherche Médicale, U586, CHU Rangueil and Laboratoire Pharmacochimie des Substances Naturelles et Pharmacophores Redox, IRD-UMR-152, Université Paul Sabatier, 31043 Toulouse, France

(Received on June 24, 2003)

The biogenic amine tyramine has been reported to stimulate in vitro glucose transport in adipocytes, cardiomyocytes and skeletal muscle, and to improve in vivo glucose utilization in rats. These effects were dependent on amine oxidation, since they were blocked by inhibitors of monoamine oxidase (MAO) and semicarbazide-sensitive amine oxidase (SSAO). We thus tested in this work whether a prolonged treatment with tyramine could improve glucose tolerance in streptozotocin-induced diabetic rats. First, tyramine content of standard rodent chow was determined by HPLC and daily tyramine intake of control rats was estimated to be around 26 μmol/kg body weight. Then, tyramine was administered during 3 weeks in streptozotocin-induced diabetic rats at 29 μmol/kg by daily i.p. injection alone or together with vanadate 0.02 μmol/kg. In another group of diabetic rats, tyramine was subcutaneously delivered at 116 μmol/kg/day by osmotic minipumps. All tyramine treatments resulted in a decrease of the hyperglycemic responses to an i.p. glucose load. Adipocytes isolated from either untreated or treated diabetic rats were sensitive to the stimulation of glucose uptake by tyramine. However, diabetic animals receiving tyramine for three weeks did not recover from their hyperglycemia, hypoinsulinemia and glucosuria. These results show that the improvement of glucose tolerance induced by prolonged tyramine administration occurs in an insulin-depleted model and probably results from peripheral insulin-like actions of the oxidation of MAO/SSAO substrates, such as the stimulation of glucose uptake into adipocytes.

Key words: Semicarbazide-sensitive amine oxidase, Monoamine oxidase, Diabetes, Insulin, Rats.

Correspondence to C. Carpéné (e-mail: carpene@toulouse.inserm.fr).
Amine oxidation is occurring in many tissues where it has been considered as a way to scavenge exogenous or biogenic amines and to terminate the action of several neurotransmitters (7). Two families of amine oxidases are involved in amine oxidation: the FAD-dependent monoamine oxidases (MAO) and the copper-containing amine oxidase family, essentially represented by semicarbazide-sensitive amine oxidases (SSAO). We have recently reported that adipose and muscular tissues, which are sensitive to insulin, regarding to the stimulation of glucose uptake, express substantial amount of MAO and SSAO (10). In keeping with this, several amines such as tyramine or benzylamine markedly stimulate glucose transport in adipocytes via their oxidation by MAO or SSAO (2, 9). In fact, this stimulation of glucose transport takes place in a manner that partially resembles that of insulin, leading to the translocation of the insulin-sensitive glucose transporter GLUT4 to the cell surface (16). Other insulin-like effects, have been reported for tyramine, which is a substrate for both MAO and SSAO: stimulation of adipose differentiation (5, 8), inhibition of lipolysis (15), and, most importantly, in vivo acute improvement of glucose tolerance in conscious rats (10).

The present work aimed at investigating whether prolonged administration of tyramine could improve the impaired glucose disposal of diabetic rats. Therefore, we have studied the capacity of chronically administered tyramine to modify the hyperglycemic response induced by glucose load in rats previously rendered hyperglycemic and insulin-deficient by streptozotocin injection. First of all, we have estimated the amount of alimentary tyramine daily ingested by laboratory rats, by determining the amount of amines in the standard chow with an high-performance liquid chromatographic (HPLC) method. Then, a dose approximatively equivalent to the estimated daily oral intake of tyramine, was daily i.p. injected during 3 weeks to streptozotocin-induced diabetic rats. Other groups of diabetic rats received vanadate at a dose ineffective on its own (0.02 μmol/kg), alone and in combination with tyramine, since vanadate has been reported to improve the insulin-like effect of amine oxidase substrates (16) and the antidiabetic action of chronically administered benzylamine (1). A higher dose of tyramine (116 μmol/kg/day) was also chronically administered during three weeks via mini-osmotic pumps implanted in the dorsal region of streptozotocin diabetic rats.

We report here that the hyperglycemia provoked by i.p. glucose load was reduced in tyramine-treated rats, when compared to untreated diabetic rats, producing an overall increased glucose utilization. Accordingly, tyramine and other amine oxidase substrates were able, in the presence of vanadate, to stimulate in vitro glucose uptake into adipocytes of diabetic rats. Although the prolonged treatments with tyramine did not completely correct the troubles induced by streptozotocin, such as reduced body weight gain, hyperglycemia and hypoinsulinemia, we propose that the improvement of glucose disposal by MAO/SSAO substrates may be useful for the treatment of glucose intolerance.

Materials and Methods

Chemicals.—Tyramine and amines used as standards for HPLC calibration, collagenase, cytochalasin B, fatty-acid-free bovine serum albumin, dansyl chloride, and other reagents were obtained from Sigma-Aldrich (Saint Quentin Fallavier,