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Changes in the Distribution of Dopamine and it's Metabolites in Streptozotocin-induced Diabetic Rat Striatum

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Changes in the distribution of dopamine and its metabolites, activities of monoamine oxidase, and dopamine uptake were studied in hyperglycemic rat striatum. The hyperglycemia was induced by the administration of streptozotocin (STZ, 40 mg/kg, i.p. for 3 days.). The levels of dihydroxyphenylacetic acid (DOPAC) and homovanillic acid were significantly decreased without change in dopamine level in the synatic cleft 14 days after STZ treatmment. In the synaptosome, the dopamine level, however, was significanly increased after the treatment. But the DOPAC level in the synaptosome was decreased 14 days after the treatment. The affinity of dopamine uptake was significantly decreased without changes in the velocity 14 days after the treatment. However the response to uptake inhibitor was unchanged. The striatal monoamine oxidase activities were also decreased in the hyperglycemic state. These results indicate that various parameters of striatal dopamine activities were decreased in the hyperglycemic rats. Furthermore, it suggests that the increase in dopamine level of synaptosome might be due to the decrease in the release of dopamine in hyperglycemic state.

Key words : Hyperglycemia, Dopamine distribution, Monoamine oxidase activity, Dopamine uptake

INTRODUCTION

In diabetes mellitus, neuropathy, retinopathy and nephropathy are serious complications. Although the pathophysiological basis for CNS abnormalities are largely unknown, chronic diabete increases stroke risk, and the prevalence of seizure (McCall, 1992).

It has been reported that various neuronal activities were altered in the diabetes mellitus (Bitar and DeSouza, 1990; Lim *et al.*, 1994; Shimomura, 1990) Decreases in the rate of synthesis and metabolism of norepinephrine (Bitar and DeSouza, 1990; Bitar *et al.*, 1986) and in the metabolism of tryptophan and serotonin (Crandall *et al.*, 1981; Trulson and Mackenzie, 1980) were observed in the STZ-treated animals. It has been also reported that amphetamine- or apormorphine- induced stereotypy is attenuated in diabetic rats (Rowland *et al.*, 1985), and hyperglycemia suppressed ambulatory activity, especially in the dark cycle (Shimomura *et al.*, 1988). These studies indicate that the neurotransmissions within the brain, especially monoamines, are abnormal in untreated diabetic animals.

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It has been reported that metabolism of dopamine in the brain was changed in diabetes mellitus. Dopaminergic neuronal activities were decreased in the striatum of diabetic rats (Lim *et al.*, 1994; Trulson and Himmel, 1983). Furthermore, behavioral responses of diabetic rats to drugs acting on the dopaminergic neuronal systems are increased, and these results are consistent with a hypersensitivity seen after decreased dopaminergic neurotransmission (Saller and Kopin, 1981). These reports have been suggested that the dopaminergic neurotrasmission may be decreased in the hyperglycemic state.

It is well documented that the total neuronal dopamine constitute the different dopamine pools, such as vesicular, cytosol and synaptic sites (Schoemaker and Nickolson, 1983; Westerink, 1985). It has been reported that synaptic concentration of dopamine is regulated largely by the uptake of neurotransmitter (Schoemaker and Nickolson, 1983) and catabolic enzymes (Stenstrom *et al.*, 1987). Although Bitar *et al.* (1986) reported that the maximum velocity of tyrosine hydroxylase was reduced in diabetic rats, recently it has been reported that tyrosine hydroxylase activities were not altered (Lim *et al.*, 1994). This suggests that the changes in other metabolic pathways may be responsible for the decrease of the dopamine metabolism in diabetic rats. However little is known

about the distribution of dopamine and its metabolites, and its termination in the central dopaminergic nervous system in hyperglycemic state.

Therefore, we undertook a systematic investigation of the levels of dopamine and its metabolites in synaptosome and in the synaptic cleft, activities of monoamine oxidase, and the characteristics of the dopamine uptake site in STZ-induced diabetic rats.

MATERIALS AND METHODS

Animals and materials

Four male Sprague-Dawley rats weighing 200-250 g were housed per cage at 22±2°C on a 12 h light/12 h dark schedule (8:00 a.m.-8:00 p.m.). Rats were freely accessible on food and water.

(1-(2-(bis(4-fluorphenyl)-methoxy)-ethyl)-4-(3-phenylpropyl)-piperazine (GBR-12909) was purchased from Research Biochemical Inc. (Wayland, MA). The tritium labeled ligand, [^{3}H]dopamine (specific activity, 24.5 Ci/mmol), was obtained from New England Nuclear (Boston, MA). All other chemicals were obtained from Sigma Chemical Co. (St. Louis, MO).

Animal treatment

Diabetic rats were induced by injecting STZ (40 mg/kg, i.p.) dissolved in 0.1 M citrate buffer (pH 4.5) as previously reported (Lim *et al.*, 1994). Control rats received injections of the buffer only. Hyperglycemia was verified by measuring blood glucose levels by the glucose hexokinase method using a commercial kit purchased from Sigma (St. Louis, MO), and blood glucose levels of STZ-treated rats were more than 350 mg/dl.

Determination of concentrations of DA and its metabolites in synaptosome and the synaptic cleft

Rats were sacrificed by decapitation, and the striatum was dissected out rapidly according to the method of Glowinski and Iverson (1966). The striatum was homogenated gently by moving up and down for 7 times in 2 ml of 0.32 M sucrose (containing 1 mM pargyline) using a glass homogenizer. One hundred microliter of homogenate was taken from each sample for protein content. The remaining homogenate was then centrifuged at 100,000 g for 1 hr at 4°C to separate a synaptosomal fraction. The supernatant, containing the dopamine and its metabolites in synaptic cleft, was diluted with 0.1 M PCA for injection into the HPLC. The pellet was then homogenated in 1 ml of 0.05 M PCA with a teflon pestle and centrifuged at 15,000 g for 20 min at 4°C. This supernatant was diluted with 0.05 M PCA for injection into the HPLC. The concentrations of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined according to the method described by Mayer and Shoup (1983) with a minor modification. Separations were achieved using a C18 reverse phase analytical column (5 μm spheres, 100×4.6 mm, Biophase ODS, Bioanalytical Systems, Inc. West Lafayette, IN) and a mobile phase flow rate was 0.8 ml/min. The LC column was coupled to an electrochemical detector (M460, Waters Systems) equipped with a glassy carbon electrode set at a potential of 700 mV vs Ag/AgCl-3M NaCl reference electrode. The mobile phase was 10% acetonitrile/monochloroacetate buffer, pH 3.0 with 0.7 mM EDTA and 0.86 mM sodium octyl sulfate. The concentrations of dopamine and its metabolites were determined by direct comparison of sample peak heights to those of an external standard containing three neurochemicals.

Determination of [^{3}H]dopamine uptake

[^{3}H]dopamine uptake was determined following the method of Lim *et al.* (1990) with a minor modification. Striata was homogenated gently by hand in 4 ml of 0.32 M sucrose using a glass homogenizer. The homogenate was centrifuged at 1,000 g for 10 min and the supernatant was recentrifuged at 12,000 g for 15 min. The pellet was reconstituted to between 1.5 and 2 mg protein/ml using a solution which consisted of 118 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 0.6 mM ascorbic acid, 11 mM glucose, 0.03 mM Na_2EDTA and 0.125 mM pargyline, and gassed with 95% oxygen-5% carbon dioxide to give a pH of 7.4.

One-tenth milliliter of the preparation was added to 0.9 ml of solutions containing various concentrations of [^{3}H]dopamine (0.05-2 μM). All procedures prior to and after incubation were carried out at 0-4°C. Dopamine uptake was increased by transferring incubation tubes to a shaking incubator, agitating the tubes at 37°C for 2.5 min, and then rapidly cooling to 4°C, while the paired samples were kept in an iced bath. The incubation mixtures were then centrifuged at 12,000 g for 15 min. The pellets were superficially washed twice with 0.5 ml of ice-cold buffer and solubilized with tissue solubilizer (Solvable™). Radioactivity of each sample was determined at liquid scintillation spectrometry. Specific uptake by the synaptosomes was calculated by substracting activity of paired samples from activity of incubation samples. The uptake experiments were completed within 4 hrs of sacrifice. The displacement experiment of dopamine uptake was carried out with various concentration of 10^{-10}-5×10^{-8} M GBR-12909, a specific uptake inhibitor for dopamine.

Determination of monoamine oxidase (MAO) activity

Rats were sacrificed by decapitation, sample tissues were dissected out rapidly according to Glowinski and Iverson (1966). MAO activities were determinated by a slight modification of the method of Suzuki *et al.* (1979).

The striatum was homogenated 1.8 ml of 0.1 M phosphate buffer. One hundred microliter of homogenate was taken from each sample for protein content. The remaining homogenate was used as an enzyme source. The assay mixture consisted of 0.1 M sodium phosphate buffer (pH 7.4), enzyme solution (0.08 to 1.41 mg of protein), peroxidase solution (0.2 mg), homovanillic acid solution (0.5 mg), serotonin as a substrate (10, 20 or 200 μM), and water, 0.5 ml of each, to give a final volume of 3.0 ml. After incubation at 37°C for 60 min, the enzyme reaction was terminated by adding 0.1 ml of pargyline solution (0.2 mg), and the mixture was centrifuged at 18, 000 g for 20 min at 4°C. The supernatant fraction was subjected to fluorescence measurement with excitation at 315 nm and with emission at 425 nm. Blank assays differed from controls only in that the substrate solution was added with pargyline after incubation. Standards were taken by adding 0.5 ml of hydrogen peroxide solution (4.42 to 22.1 nmoles) to the assay mixture instead of the enzyme solution. MAO activity is expressed as H_2O_2 nmol/hr/mg protein. Although dopamine is also substrate for MAO, serotonin is known as more specific substrate for MAO-A form (Suzuki *et al.*, 1979). In our preliminary studies, the affinity constant (K_m) and maximal initial velocity of reaction (V_{max}) values of MAO with high affinity to 5-HT were 7.93 μM and 240.51 H_2O_2 nmol/hr/mg protein, respectively. Those of MAO with low affinity were 278.14 μM and 3459.5 H_2O_2 nmol/hr/mg protein, respectively. Therefore, the concentrations of 10 and 20 μM serotonin were chosen as the substrate of high affinity form and 200 μM was as that of low affinity form of MAO.

Determination of protein concentration

The protein content of tissue homogenates was determined by the method of Lowry *et al.* (1951) using bovine serum albumine as a standard.

Statistics

The statistical significance of differences were determined using Student's t-tests. The kinetic parameters of dopamine uptake, K_m and V_{max} were estimated by the double reciprocal plot method. The potencies (IC_{50}) of GBR-12909 in inhibiting dopamine uptake were determined by anlayses of competition curves using the computer program, Ligand (Munson and Rodbard, 1980).

RESULTS

Effects of hyperglycemia on the distribution of DA and its metabolites

Table I shows the changes in the distribution of dopamine and its metabolites in the synaptic cleft and the axoplasm in the hyperglycemic rat striatum. The levels of DOPAC in the synaptic cleft were decreased significantly by 21.7% and 16.9% 1 day and 14 days after the treatment, respectively. And the level of HVA was also decreased by 18.5% 14 days after the treatment. But no change was observed in the level of dopamine. On the other hand, in synaptosome the level of dopamine was significantly increased 1 day (27.8%) and 14 days after (48.6%) the treatment. But the level of DOPAC was decreased markedly by 53. 1% 14 days after the treatment. There was little HVA in synaptosome.

Effects of hyperglycemia on the DA uptake and the characteristics of DA uptake sites

Table II shows the changes in the K_m and V_{max} for dopamine uptake and IC_{50} of the *in vitro* effect of GBR-12909 on dopamine uptake in rat striatum. The K_m values were increased significantly (38.2%) 14

Table I. The distribution of dopamine and its metabolites in hyperglycemic rat striatum

		Control	1 day	14 days
Synaptic cleft	DA	355.2±20.0	326.8±10.1	311.1±18.1
	DOPAC	77.7±3.4	60.8±2.4**	64.6±2.9*
	HVA	64.8±2.0	66.2±3.4	52.8±2.8*
Synaptosome	DA	275.2±13.9	351.6±13.2**	408.9±23.1**
	DOPAC	6.4±0.4	6.1±0.5	3.0±0.2**

Rats were sacrificed at the indicated time after the last administration of STZ. The concentration units of dopamine and its metabolites are pmol/mg protein. Each value represents the mean±S.E.M. of four or five determinations. *$p<0.05$, **$p<0.01$ compared to the respective control values

Table II. The changes in the characteristics of dopamine uptake and IC_{50} of GBR-12909 in hyperglycemic rat striatum

	K_m (μM)	V_{max} (μM/mg protein/2.5 min)	IC_{50} (nmol)
Control	0.199±0.026	0.014±0.001	13.489±1.551
1 day	0.287±0.028	0.020±0.003	12.737±1.326
14 days	0.275±0.012*	0.016±0.001	13.879±1.876

Rats were sacrificed at the indicated time after the last administration of STZ. Each value represents the mean±S.E.M. of four or five determinations, each performed in duplicates. *$p<0.05$ compared to the respective control value

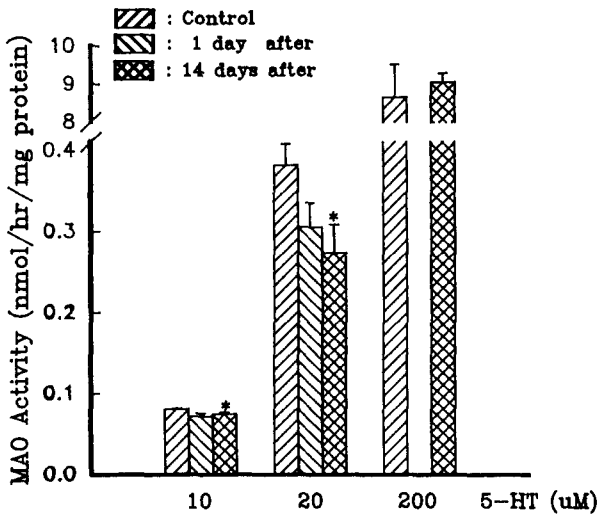

Fig. 1 Changes in striatal MAO activities after the administration of STZ. Rats were sacrificed at the indicated time after the last administration of STZ. Values represent the mean±S.E.M. of four determinations, each performed in duplicate. *p<0.05 compared to the respective control value.

days after STZ-treatment in rat striatum, but no change was observed 1 day after the treatment. In contrast, the V_{max} values were not changed 1 day and 14 days after the treatment. The potencies of the specific dopamine uptake inhibitor, GBR-12909, in hyperglycemic rat striatum were not altered, when compared to the control.

Effects of hyperglycemia on the MAO activities in rat striatum

Changes in the activities of MAO in the hyperglycermic rat striatum are shown in Fig. 1. The activity of MAO was significantly decreased in low substrate concentrations. In low substrate concentrations (5-HT, 10 μM and 20 μM), the activity was decreased significantly 14 days after the treatment compaired with that of control (0.081±0.001 vs. 0.075±0.002, 0.382±0.026 vs. 0.274±0.035 H_2O_2 nmol/hr/mg protein in 10 μM and 20 μM of 5-HT, respectively). In contrast, no change was observed 1 day after the treatment. In high substrate concentration (200 μM), there was no change in the activity of MAO, either.

DISCUSSION

The present results demonstrate that central dopaminergic neuronal activities are altered in the STZ-induced diabetic mellitus. We found that there are the altered striatal DA distribution, the decreased activities of MAO, and the decreased DA uptake.

It has been reported that levels of DA metabolites and ratios of DA to its metabolites were decreased in STZ-induced diabetic rat striatum (Bellush and Reid, 1991; Lim *et al.*, 1994; Shimomura *et al.*, 1988; Trulson and Himmel, 1983). The present results are also consistent with those reports. Furthermore, DA metabolites, DOPAC and HVA, were decreased in both synatosome and the synaptic cleft. It has been reported that the changes of DOPAC might be intraneuronal changes in the cytosolic pool (Wood and Altar, 1988) and eighty percent of HVA is reportedly formed from DOPAC as a result of action of presynaptic MAO on DA recovered from the synaptic cleft (Westerink and Spaan, 1982). Thus, decreases in the metabolites levels in both synaptosome and the synaptic cleft might be due to the decrease in the uptake of cleft DA. However, DA was increased markedly in synaptosome without change in the synaptic cleft in the hyperglycemic state. It has been reported that several DA pools in the dopaminergic nervous systems existed (Westerink, 1985). And it has also been reported the releasable pool of DA was smaller and more dynamic than the total neuronal stores of DA within the striatum (Wood *et al.*, 1988). Although the role of multiple vesicular and/or cytosolic DA pools is needed to be further defined, the increase in synaptosomal DA pools as the present results imply the decreases in the release of DA. Thus the present results suggest that both/either the release and/or the uptake of DA might be decreased in the hyperglycemic rat striatum. The decreased dopamine and its metabolites in the diabetic state might be related to the decrease in ambulatory activity and the change in behavioral responses to dopamine agents (Lim *et al.*, 1994; Rowland *et al.*, 1985; Shimomura *et al.*, 1988).

The local inactivation in the catecholaminergic nervous systems is not significantly blocked when activities of catechol-O-methyl transferase or MAO are inhibited, and it is believed to involve mainly reuptake of the transmitter by sympathetic neurons (Cooper *et al.*, 1986). It has been reported that glucose facillitate the uptake of DA into striatal synaptosomal preparations (Dorris, 1978). However, recently Shimosawa *et al.* (1992) reported that insulin enhances norephinephrine reuptake in peripheral sympathetic nerve endings. The present results reveal that the affinity of DA uptake in DA transport site was significantly decreased in hyperglycemic state without change in the DA uptake velocity. This result may support the decreases in the levels of DA metabolites. In addition, the response of DA uptake sites to dopamine uptake inhibitor was not altered. Altar and Marshall (1988) have reported that striatal DA uptake is unaltered in the adult rats despite significant loss of striatal DA. This suggests that the dynamics of preservation of DA uptake in the striatum are very ac-

tive. Thus the present results suggest that the decrease in the affinity of dopamine uptake in dopamine transport site might be due to the decreases in the release of dopamine in order to maintain the neuronal balance.

It is known that MAO occurs in 2 forms termed A and B, and 5-HT used in the present study is a specific substrate of MAO-A (Suzuki *et al.*, 1979). Also it has been reported that MAO activitthe rat striatum is predominantly localized within the intraneuron and intrasynaptosomal deamination of DA is brought about mainly by MAO-A (Stenstrom *et al.*, 1987; Westerink and Spaan, 1982) The present results reveal that the significant reduction was occurred in the MAO activity in the low concentrations of substrate. This results indicate that the activities of MAO-A is decreased in the hyperglycemic state and suggests that the DA metabolism might be decreased in the hyperglycemia. Although various parameters of dopaminergic activity are decreased in STZ-induced hyperglycemic rats, further work in insulin independent diabetes is needed.

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