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An *in vivo* Study of Dopamine Metabolism in Hyperglycemic Rat Striatum

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The changes in the levels of the extracellular dopamine metabolites and the responses to various dopamine agents were studied by using microdialysis in hyperglycemic rat striatum. The hyperglycemia were induced by the administration of streptozotocin (40 mg/kg, i.p. for 3 days.). The basal levels of striatal dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were significantly decreased in hyperglycemic rat striatum. After the administration of D-1 and D-2 receptor antagonists, SCH-23390 and (-)sulpiride, to rats 14 days after the last administration of STZ, the increased rates in DOPAC levels were higher in hyper- than in normoglycemic rats. However after the administration of dopamine autoreceptor agonist, 3(-)PPP, the levels of the extracellular HVA were increased in normoglycemic rats, but those were not altered in hyperglycemic rats. The results indicate that the striatal dopamine activities were decreased in the hyperglycemic rats and suggest that the release of dopamine may be decreased in hyperglycemic rats. Furthermore it suggest that the increase in the levels of the extracellular dopamine metabolites by dopamine antagonists might be due to the increased sensitivities of the dopamine receptors in hyperglycemic state.

Key words: Hyperglycemia, Extracellular DOPAC and HVA, Microdialysis, Dopamine antagonists

INTRODUCTION

Chronic diabetes increases stroke risk and damage, and the prevalence of seizure (McCall, 1992), but their pathophysiological basis for CNS abnormalities are largely unknown.

It has been reported that various neuronal activities were altered in the diabetes mellitus (Bitar and DeSouza, 1990; Lim *et al.*, 1994; Shimomura, 1990) The 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 also been reported that various parameters of central dopaminergic nervous systems were altered in diabetes mellitus. The dopamine synthesis rate and the accumulation of dopamine metabolites were decreased in the striatum of diabetic rats (Lim *et al.*, 1994; Trulson and Himmel, 1983). It has been reported that the changes in the characteristics of dopamine (DA) receptor subtypes were differently affected after inducing the hyperglycemia (Lim *et al.*, 1994; Lozovsky *et al.*, 1981: Salkovic and Lackovic, 1992; Trulson and Himmel, 1983).

It has been reported that the release of DA was regulated, in part, by the presynaptic autoreceptors (Nowak *et al.*, 1983; Tepper *et al.*, 1985). Although it has been reported that DA autoreceptor was D-2 DA receptor type (Filloux *et al*, 1987), Saller and Salama (1986) have reported that D-1 and D-2 DA receptors were significantly interacted (Starr, 1988). It has been reported that behavioral responses of diabetic rats to drugs acting on dopaminergic neuronal systems were changed (Chu *et al.*, 1986; Shimomura *et al.*, 1988). Recently it has been reported that the levels of dopamine in synaptpsome were increased in the hyperglycemic rats (Lim and Lee, 1995). Furthermore, it has been reported that acute administration of glucose suppress completely the discharge rate of dopamine containing substantia nigra neuron (McCaleb and Myers, 1979; Saller and Chiodo, 1980). These reports have been suggested that the dopaminergic neurotrasmission may be decreased in the hyperglycemic state. However little is known about the release of dopamine and its metabolites in the central nervous system in hyperglycemic state.

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It has been developed to measure the concentrarion of DA and its metabolites in the extracellular space of brain regions deep inside the intact brain (Ewing *et al.*, 1983; Millar *et al.*, 1985). The technique of brain dialysis permited direct *in vivo* sampling of neurotransmitters and their metabolites in the brain extracelluar fluid and might use for the determination of release of the neurotransmitters (DiChiara, 1990). Since various parameters of dopaminergic nervous systems were changed in the hyperglycemic state, this microdialysis methods may illucidate the *in vivo* release of DA and its metabolites in this disease.

Therefore we undertook a systematic investigation of the extracellular levels of dopamine metabolites and *in vivo* effect of D_1 and D_2 selective drugs by microdialysis in STZ-induced diabetic rats.

MATERIALS and METHODS

Animals and materials

Male Sprague-Dawley rats (Ge Yong animal house, Daejeon, Korea) weighing 200-250 g were used throughout the study. The animals were housed four to a 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.

R(+)-SCH-23390 HCl, S(-)sulpiride, and S(-)-3-(3-hydroxy phenyl)-N-propylpiperidine HCl (S(-)-3-PPP HCl) were purchased from Research Biochemical Inc. (Wayland, MA). Microdialysis probes were purchased from Eicom Co. (Tokyo, Japan) All other chemicals were obtained from Sigma Chemical Co. (St. Louis, MO).

Animal treatment

Diabetic rats were induced by injecting streptozotocin (STZ, 40 mg/kg, i.p.) dissolved in 0.1 M citrate buffer (pH 4.5) as the previous report (Lim *et al.*, 1994). Control rats received injections of the buffer only. Hyperglycemia was verified by the measurement of 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.

Animal surgery

All surgical procedures were performed on male Sprague-Dawley rats with initial weights 250-300 g. Rats were anesthetized with Equithsin and mounted in a David Kopf stereotaxic apparatus. The skull was exposed and a guide cannula (EICOM) was implanted according to Paxino and Watson (1986) through the dural surface into the right striatum with respect to bregma at the following coordinates: A +1.0, L -2.4, V -2.5. Skull screws and dental cement were used for fixation of guide cannula. A stainless steel obturator was inserted into the guide cannula. Penicilline 30,000 I.U. was administered to protect from infection after surgery. Before the injection of STZ to make hyperglycemic state, the rats were allowed to recover from surgery for 4 days, housed singly in their cages. After that, rats were injected with STZ to make hyperglycemic srate.

Microdialysis

Microdialysis probes (EICOM, 3 mm length) were manually inserted through the guide cannula. The probes were connected to a syringe pump (model KASP 005/150 MT, KEUN-A Co., LTD) and perfused with artificial cerebrospinal fluid (CSF) composed of 0.13 M NaCl, 1.77 mM $CaCl_2$, 2.65 mM KCl, 0.98 mM $MgCl_2$ and 0.25 mM ascorbic acid, pH 7.3. The flow rate was 2 µl/min. Following the 70 min of the equilibration period, dialysates were collected at 20 min intervals in polyethylene tubes containing 40 µl of 0.1 M PCA to protect the oxidation of dopamine and its free acid metabolites, DOPAC and HVA. Three samples were used for baseline determinations. Then, the following drugs were administered subcutaneously into rats 14 days after the last administration of STZ or buffer and striatal perfusates were collected for an additional 80 min.: SCH-23390 (0.5 mg/kg, s.c.) as a D_1 receptor antagonist, (-)sulpiride (10 mg/kg, s.c.) as a D_2 receptor antagonist, and (-)3-PPP (10 mg/kg, s.c.) as an autoreceptor agonist. Because of the high variation of individual rat, the extracellular levels of dopamine metabolites after the drug administration were expressed as the percent of each baseline level in normoglycemia and 14 days after the STZ treatment. Repeated probe insertion in the same brain site appears to be acceptable for performing chronic microdialysis studies in the same subject, provided neurochemical and morphological changes are taken into the consideration (Georgieva *et al.*, 1993). The probe recovery rates of dopamine, DOPAC, and HVA were 9.2%, 11.8% and 10.2%, respectively. In our preliminary study, the levels of dopamine metabolites were stable in dialysates from the striatum over 70 min following the implantation of dialysis probe.

Determiantion of the levels of DA metabolites (DOPAC, HVA)

Dialysates were injected in a volume of 25 µl onto a reversed phase HPLC-EC system on the experimental day, and the contents of DOPAC and HVA were determined. The concentrations of 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined according to

the method described by Mayer and Shoup with a minor modification (1983). Separations were achieved using a C18 reverse phase analytical column (5 μm spheres, 10×4.6 mm, Biophase ODS, Bioanalytical Systems, Inc.) and a mobile phase flow rate of 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 metabolites were determined by direct comparison of sample peak heights to those of an external standard containing three neurochemicals. However, in our preliminary study, the level of dopamine was not detected because of the detection limitation of dopamine in our HPLC-EC systems (0.1 pmol/25 μl.). It has been reported that the level of dopamine is 100 times as low as the level of DOPAC (Kito *et al.*, 1986; Sharp *et al.*, 1986; Zetterstrom *et al.*, 1986).

Statistics

The statistical significance of differences were determined using Student's t-tests.

RESULTS

Fig. 1 shows the changes in the levels of dopamine metabolites in striatal dialysates in hyperglycemic state. The extracellular DOPAC level was dramatically decreased in hyperglycemic state (0.255±0.066 pmol/min and 0.558±0.039 pmol/min, 1 day and 14 days after the treatment, respectively), when compared with control level (0.862±0.049 pmol/min) The extracellular HVA level was decreased significantly 1 day after the treatment (0.237±0.133 pmol/min), but no change was observed 14 days after the treatment (0.455±0.164 pmol/min), when compared to control level (0.480±0.031 pmol/min).

The changes in the levels of extracellular striatal DA metabolites after the administration of SCH-23390 at 14 days after the last administration of STZ were shown in Fig. 2. Neither the DOPAC level nor the HVA level was changed significantly after the administration of SCH-23390 in normo- and hyperglycemic states. But the DOPAC level was showing the increasing tendency in hyperglycemic state (+22.8% 80 min after drug injection) compared to normoglycemic state. And also at 40 min after the ad-

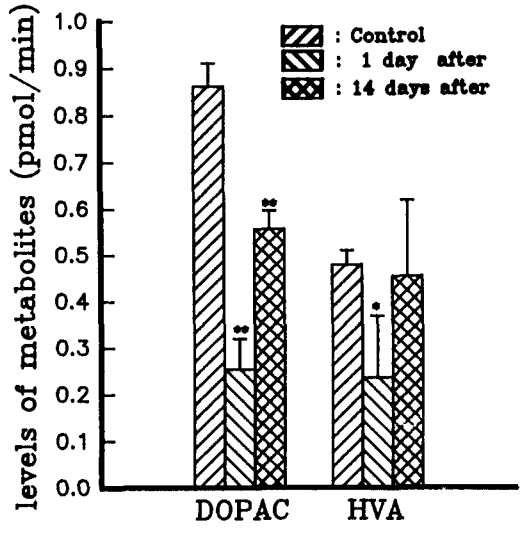

Fig. 1. Changes in the levels of dopamine metabolites in striatal dialysates in hyperglycemic state. Rats were determined at the indicated time after the last administration of STZ by microdialysis method. The dialysates over 70 min following the implantation of dialysis probe were determined three times by 20 min interval. Each value represents the mean±S.E.M. of three or eight determinations. *p<0.05, **p<0.01 compared to the respective control values.

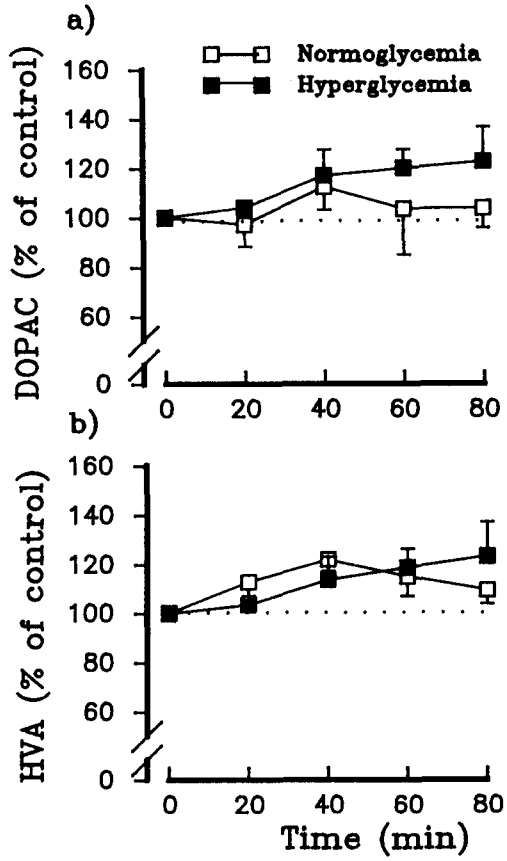

Fig. 2. Time course changes of DOPAC[a)] and HVA[b)] in striatal dialysates after injection of 0.5 mg/kg SCH-23390. Drug is administered 14 days after the last administration of STZ or buffer. Each curve represents data obtained from three to six rats with time points being mean±S.E.M. The 100% value indicates the average of the 3 stable measurements before drug injection.

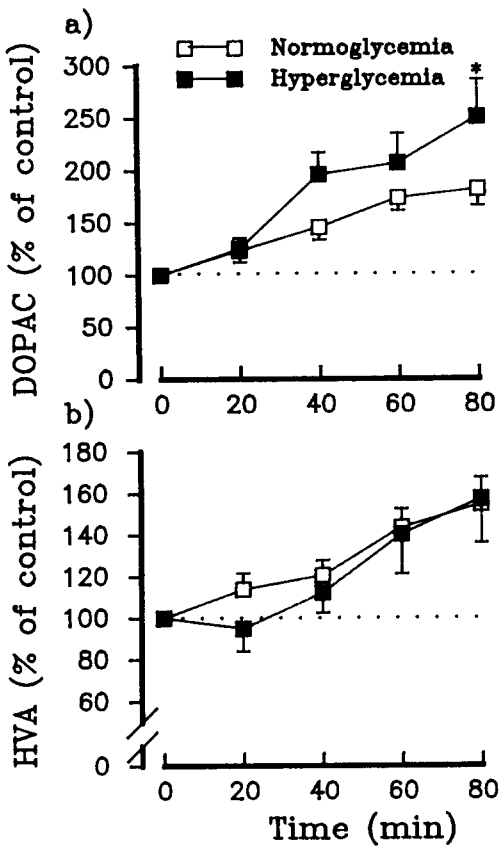

Fig. 3. Time course changes of DOPAC[a] and HVA[b] in striatal dialysates after injection of 10 mg/kg (-)sulpiride. The legend is same as Fig. 2. *p<0.05 compared to the respective control value.

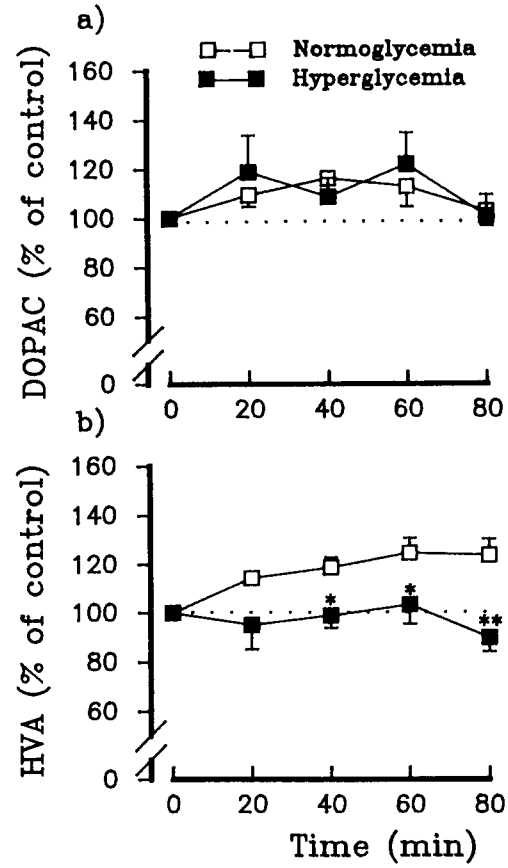

Fig. 4. Time course changes of DOPAC[a] and HVA[b] in striatal dialysates after injection of 10 mg/kg 3(-)PPP. The legend is same as Fig. 2. *p<0.05, **p<0.01 compared to the respective control values.

ministration of SCH-23390 in normoglycemia, the levels of either DOPAC or HVA were reached high and then returned to the baselines. However in hyperglycemia, the levels of DOPAC and HVA were continuousely increased till 80 min after the adminstration of SCH-23390.

The changes in the levels of extracellula striatal DA metabolites after the administration of (-)sulpiride at 14 days after the last administration of STZ were shown in Fig. 3. The levels of both striatal DOPAC and HVA were increased by the adminstration of (-)sulpiride in both normo- and hyperglycemic rats. However, at 80 min after the sulpiride adminstration, the level of striatal DOPAC in hyperglycemia (+150.7%) was higher than those in normoglycemia (+81.7%) significantly (Fig. 3a). But the increased levels of striatal HVA in normoglycemia (+54.7%) and in hyperglycemia (+57.4%) after the adminstration of (-)sulpiride were similar (Fig. 3b).

The changes in the levels of DA metabolites after the administration of (-)3-PPP at 14 days after the last administration of STZ were shown in Fig. 4. The administration of (-)3-PPP (10 mg/kg) in normo- and hyperglycemia affected the similar increase in the level of DOPAC. However, the level of HVA in normoglycemia was increased (+24.6%) after the adminstration of (-)3-PPP, while that in hyperglycemia did not changed. Furthermore, the level of HVA was decreased 80 min after drug adminstration in hyperglycemic rats.

DISCUSSION

The present results demonstrate that central dopaminergic neuronal activities are altered in the STZ-induced diabetic mellitus. We found that there are the decreased extracellular level of striatal dopamine metabolites in diabetic mellitus. However the increments in the extracellular levels of dopamine metabolites were augumented after the administration of dopamine antagonists in diabetic rats.

It has been reported that the accumulation of dopamine metabolites (DOPAC, HVA) and dopamine turnover rate was decreased in STZ-induced diabetic rat striatum (Bellush and Reid, 1991; Lim *et al.*, 1994; Shimomura et al., 1988; Trulson and Himmel, 1983). Recently Lim and Lee (1995) reported that the do-

pamine uptake and monoamine oxidase activities are decreased in the hyperglycemic rats. Since the brain dialysate shows the levels of neurotransmitter and its metabolites in the extracellular fluid (DiChiara, 1990), the present results indicate that the extracellular levels of dopamine metabolites (DOPAC, HVA) were significantly decreased. Furthermore it has been reported that acute administraion of glucose suppress the discharge rate of dopaminergic neurons in substantia nigra (McCaleb and Myers, 1979; Saller and Chiodo, 1980). Recently Wilke *et al.* (1993) reported that diabetes also decreased the secretion of epinephrine from adrenomedullary chromaffin cells in response to stimulation of their innervating neurons. Since striatal tissue levels of DOPAC have been shown to increase following electrical stimulation of the nigrostriatal pathway and to decrease after cessation of impulse flow, it has been proposed that DOPAC is a useful index of central dopamine release (Roth *et al.*, 1976). Although it needs to further illuciate in the extracellular dopamine level, the decreases in the extracellular levels of metabolites might be due to the decreased release and metabolism.

It has been reported that the dopamine receptor subtypes were altered after inducing the hyperglycemia; that is, the decreased density (Salkovic and Lackovic, 1992) or the increased affinity of D1 (Lim *et al.*, 1994) and the increased density of D_2 receptors (Lozovsky *et al.*, 1981: Trulson and Himmel, 1983), respectively. Recent pharmacological studies using D_1 and D_2 selective agonists and antagonists indicate that the dopamine autoreceptor regulates dopamine release from nigro-striatal dopamine neurons (Stoof and Kebabian, 1984). Although the dopamine autoreceptor is D-2 type and D-2 agents, such as sulpiride and apomorphine, control the dopamine release (May and Wightman, 1989; Nowak *et al.*, 1983). However, it has been suggested that the level of dopamine metabolism might be influenced by the D_1 receptor (Zetterstrom *et al.*, 1986). Indeed the increase and the decrease of dopamine in dialysate by D-1 antagonist, SCH 23390, and agonist, SKF 38393, are reported, respectively (Imperato *et al.*, 1987; Zetterstrom *et al.*, 1986). The present results reveal that dopamine release was changed after the adminstration of D_1 and D_2 selective drugs in hyperglycemic rat striatum. The adminstration of SCH-23390 and (-)sulpiride increased the DOPAC level about 2 times higher in hyperglycemic rat than in normoglycemic rat. Thus the higher concentrations of extracellular dopamine metabolites in hyperglycemic rats might be due to the increased D_1 receptor affinity and D_2 receptor density in hyperglycemic state as previously reported (Lim *et al.*, 1994). Therefore, the present results suggest that the changes in dopamine receptor might affect the release of dopamine. However, (-)3-PPP showed a very low rate of change in HVA level in hyperglycemia, while increased the HVA level in normoglycemia. (-)3-PPP appears to be a dopamine autoreceptor agonist whose intrinsic activity is variable (Hjorth *et al.*, 1983). It has been reported that (-)3-PPP exhibits a different actions on dopamine synthesis rate, which is incresased in the normal rats and decreased in the reserpine-treated rats (Hjorth *et al.*, 1983; Magnusson *et al.*, 1983). Also it has been reported that (-)3-PPP increases the electrically evoked release of dopamine (Arbillar and Langer, 1984) and decreases striatal extracellular HVA at low dose (O'Neill and Fillenz, 1985). Those imply that the actions of (-)3-PPP depend on the relative concentration of drug and endogenous dopamine (Clarke *et al.*, 1984). Although the changes in the characteristics of the autoreceptor is needed in the hyperglycemic state, the decrease in extracellular HVA level in hyperglycemia might be due to the decreased release and metabolism of dopamine. Furthermore the present result suggest that dopamine autoreceptors may be also altered in the hyperglycemic state.

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