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Effects of Subacute Administration of Physostigmine on Dopamine Metabolism in Rat Striatum

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ABSTRACT

Rats were treated with physostigmine, using 0.75 mg/kg acutely, with 0.75 mg/kg daily for 7 dats, or with 0.15 mg/kg/h continuously for 7 days. Striatal dopamine (DA), dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) levels and tyrosine hydroxylase (TH) activities were studied.

After acute treatment striatal DOPAC and HVA concentrations were significantly increased without changes in DA level 1 h, but not 24 h. And also the ratios of DOPAC/DA and HVA/DA were increased, suggesting an increased turnover of DA. however TH activities were decreased 24 h, but not 1 h after acute administration. After both daily and continuous treatment with physostigmine for 7 days, neither DA nor its metabolites were changed. However their ratios were decreased, suggesting a decreased turnover of DA. The TH activities were only decreased in the daily treated group, but not in the continously treated one. These results indicate that dopamine metabolisms are changed after acute and subacute administration with physostigmine. Further it suggest that the subacute stimulation of cholinergic activity may induce the dopamine metablism and activity to be decreased.

Key Words: Physostigmine, Sabacute, Dopamine and metabolites, Tyrosine hydroxylase

INTRODUCTION

Physostigmine has the short biological half-life and it easily penetrates the blood brain barrier (Somani and Khaliique, 1986). The clinical uses and mechanism of action of physostigmine have been reported to improve memory function in patients with Alzheimer's disease (Barthus *et al.*, 1983; Thal *et al.*, 1983). The toxic effects with overdosage of other drugs, such as tricyclic antidepressant (Nattel *et al.*, 1979) and benzodiazepine (Larson *et al.*, 1977) were reported to be reversed by physostigmine. Also it has potential use as a prophylactic agent against organophosphate intoxication (Gordon *et al.*, 1978).

However, it has been reported that the intermittent or the continuous infusion of physostigmine induced some toxicities (Lim *et al.*, 1989) and tolerance to physostigmine (Bhat*et al.*, 1990; Lim *et al.*, 1992).

It has been reported that cholinergic drugs influence other transmitter pathways in the striatum-basal ganglia system (Fuxe *et al.*, 1977), which is rich in monoamine like dopamine as well as in acetylcholine, indicating the existence of cholinergic dopaminergic interaction (Ho *et al.*, 1986). Thus, cholinergic agonists and antagonists increase and decrease the turnover or metabolism of dopamine in the striatum (Corrodi *et al.*, 1967; Javoy *et al.*, 1975; Westerink and Korf, 1976). Also, it has been reported that acute and subacute exposure to organophosphate such as diisopropyl-fluoro-phosphate induced behavioral supersen-

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sitivity to dopamine agonist, apomorphine, (Davis and Rosenverg, 1981) and altered the striatal dopamine levels and dopamine turnovers (Fernando *et al.*, 1984) and the densities in striatal dopamine receptors (Sivam *et al.*, 1983). In contrast to organophosphates, physostigmine reversibly inhibits acetylcholinesterase (AChE) and enzymes inhibited would be reactivated rapidly. Recently, we (1992) have reported that the response to dopamine antagonist, SCH 23390, was markedly sensitized even after both the intermittent and the continuous inhibition of AChE activity with physostigmine.

We therefore investigated the involvement of dopaminergic system further. In the presesnt study, the changes in the striatal dopamine and its metabolites and the striatal tyrosine activity are determined after the acute and the subacute, intermittent and continuous, administration of physostigmine.

MATERIALS AND METHODS

Materials

Monochloloroacetic acid was obtained form Ishisu Pharmaceutical Co. (Osaka, Japan). Acetonitrile (HPLC grade) were purchased form Tedia Co. (Ohio, USA). All other reagents such as physostigmine, ethylenediamine-tetraacetic acid (EDTA), sodium octyl sulfate, dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), brocresine, catalase, DL-6-methyl-5, 6, 7, 8-tetrahydropterin ($6MPH_4$) and 2-(N-morpolino)-ethanesulfonic acid (MES) were obtained from Sigma Chemical Co. (St. Louis, MO). Alumina (WN-3) was purchased from Sigma and washed with acid according to the method of Anton and Sayre (1962).

Treatment protocol

Male Sprague-Dawley rats (SNU animal house, Seoul, Korea) weighing 200-250 g were used throughout the study. The animals were housed four to a cage with free access to food and water in a temperature-regulated room 12/12 hours light-dark cycle.

The rats were divided into three groups. Two groups of the rats were subcutaneously injected with physostigmine of 0.75 mg/kg either acutely or daily for 7 days. The acutely treated rats were sacrificed 30 min, 1 h, 2 h or 24 h after the physostigmine administration. The daily treated rats were decapitated either 24 h following the last injection or 30 min after the additional administration of physostigmine in the 7 days treated group. The doses for physostigmine of 0.75 mg/kg, s. c., were based upon our preliminary study (Lim *et al.*, 1992), which the mortalities did not occur during daily administration.

The other group of the rats was implanted with mini-osmotic pumps (Model 2001, Alza Corp., Palo Alto, CA) delivered physostigmine at a rate of 0.15 mg/kg/h for 7 days. The pumps were implanted under the skin on the backs of the animals after ether anesthesia as described previously (Lim *et al.*, 1989). The dose chosen for continous infusion elicited 65% inhibition of acetylcholinesterase activity as well as minimal toxicity (Bhat *et al.*, 1990; Lim *et al.*, 1992). The each control groups received similar treatments of saline vehicle.

Determination of DA and its metabolites

Levels of DA, 3,4 -dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were assayed using the method described by Mayer and Shoup (1983) with minor modification. The striata were dissected out according to the procedure of Glowinski and Iversen (1966). Immediately following decapitation and dissection, tissue samples were homogenized in 2 ml of ice-cold 0.05 M perchloric acid (PCA). Following centrifugation (20 min, 15,000 g at 4°C) the supernatants were diluted 1: 10 with ice-cold PCA. An aliquot of 100 ul was injected into a high performance liguid chromatography electrochemical detection (HPLC-ECD) system (Waters Systems) to determine DA, DOPAC and HVA. The column employed was a Spheri-5 RP-18, 5 mM, 100×4.6 mm, from Bioanalytical Systems. An electrochemical detector (M460, Waters Systems) with a glassy carbon electrode, at a sensitivity of 10 nA, was used to monitor the column eluate. The applied potential was 700 mV vs Ag/AgCl-3 M NaCl. Peaks were integrated using a Hewlett Packard M7458 integrator. The mobile phase was 10% acetonitrile/monochloroacetate buffer, pH 3.0 with 0.7 mM EDTA and 0.86 mM sodium octyl sulfate. The flow rate was maintained at 0.8 ml/min. The determinations of DA, DOPAC and HVA content were performed

by direct comparison of peak heights between samples and an external standard. The external standards were checked by HPLC once every day prior to the start of sample assays.

Determination of tyrosine hydroxylase (TH) activity

TH activity in the striata was assayed using the procediure of Horwitz and Perlman (1984) with a minor modification. The accumulation of DOPA was measured in the presence of brocresine, an inhibitor of DOPA decarboxylase (Erny *et al.*, 1981). The dissected striata were homogenized in 2 ml of an ice-cold solution containing 10 mM sodium phosphate, 5 mM sodium pyrophosphate, 5 mM EDTA, and 0.2% Triton X-100, pH 6.7. Following centrifugation (5 min, 18,000 g at 4°C), 100 ul of supernatant were added to the 100 ul reaction solution consist of 160 uM L-tyrosine, 300 uM brocresine, 0.4 mM $6MPH_4$, 10,000 units of catalase, 200 uM $FeSo_4$, 200 mM 2-mercaptoethanol and 200 mM MES (pH 6.8). Reactions were carried out for 10 min at 37°C and were terminated by addition of 300 ul of 0.28 M trichloroacetic acid containing 90 pmol of epinephrine. After centrifugation, the supernatant was added to 25 mg of acid-washed alumina and the pH was adjusted to 8.6~8.7 with 3 M Tris containing 10 mM EDTA and 0.1 mM Na_2SO_3. The alumina was washed four times with water, and DOPA was eluted with 200 ul of 100 mM PCA. The eluent was assayed using HPLC-ECD as described above except that acetonitrile was deleted in the mobile solution and the flow rate was 1.2 ml/min. Epinephrine was used as an internal standard to correct for the recovery of DOPA, which shows 85~90% recovery rates. TH activity was estimated after substration of the DOPA produced in enzyme-free incubations and is expressed as pmol DOPA produced/protein /min.

Determination of protein concentration

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

Statistics

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

RESULTS

Effects of acute administration of physostigmine on striatal DA, DOPAC and HVA levels were summarized in table 1. Concentrations of striatal DA were not affected by acute treatment with physostigmine. However, The significant increases in DOPAC concentrations were found 30 min and 1 h following acute treatment. The increased rates were 38.6 and 31.3%, respectively. The significant changes in the HVA concentrations were also found 1 and 2 h after the exposure to physostigmine. The increased rates were 53.8 and 46.2%, respectively. The concentrations of both DOPAC and HVA were returned and comparable with the level of control 24 h after physostigmine administration.

The changes in the ratio of DOPAC/DA and HVA/DA after acute administration of physostig-

Table 1. Effects of acute administration of physostigmine on the level of dopamine and dopamine metabolites in the rat striatum

Treatment	DOPAC	DA	HVA
Control	67.18±3.92	533.5±25.8	34.62±3.37
30 min after	93.08±3.05**	492.2±18.6	41.33±3.45
1 hr	88.20±2.65**	552.9±29.3	53.25±1.72**
2 hr	82.10±6.38	594.5±27.5	50.60±2.20**
24 hr	65.55±5.93	526.3±14.9	32.68±3.77

1) Rats were sacrificed the indicated time after 0.75 mg/kg of physostigmine administration.
2) Units: pmol/mg protein
3) The values are the mean±S. E. of four or five determinations.
4) **$p<0.01$ compared with corresponding control vaues.

mine were similarly increased as the changes in the DOPAC and HVA concentrations except the earlier increased, 30 min, ratio in the HVA/DA (Table 2).

Effects of subacute, daily and continuous, administration of physostigmine on DA and its metabolites levels were summarized in table 3. Neither daily nor continuous treatment with physostigmine affected the concentration of striatal DA, DOPAC and HVA except the significant increase of DOPAC level 30 min after the additional physostigmine administration in daily treated rats.

Interestingly the ratios of DOPAC/DA and HVA/DA in both daily and continuously treated groups were significantly decreased without the changes in the ratio of HVA/DA in the continuously treated rats. However, the ratios of DOPAC/DA and HVA/DA were significantly increased 30 min after the additional treatment in the 7-days treated rats as the acute treatment (Table 4).

Effects of acute and subacute administration of physostigmine on striatal TH activities were summarized in table 5. The significant decreases in the activities of TH were found 2 and 24 h after acute physostigmine tratment. In daily treated rats, the

Table 2. Effects of acute administration of physostigmine on the ratio of DOPAC/DA and HVA/DA in the rat striatum

Treatment	DOPAC/DA	HVA/DA
Contol	0.127±0.006	0.064±0.004
30 min after	0.181±0.012**	0.093±0.007*
1 hr	0.163±0.005**	0.102±0.006**
2 hr	0.135±0.010	0.088±0.003**
24 hr	0.125±0.004	0.062±0.003

1) Rats were sacrificed the indicated time after 0.75 mg/kg of physostigmine administration.

2) The values are the mean±S. E. of four or five determinations.

3) *p<0.05, **p<0.01 compared with corresponding conrtrol values.

Table 4. Effects of subacute administration of physostigmine on the ratio of DOPAC/DA and HVA DA in the rat striatum

Treatment	DOPAC/DA	HVA/DA
Control[a]	0.129±0.006	0.068±0.006
24 hr[c]	0.100±0.005*	0.043±0.005*
30 min[d]	0.165±0.007**	0.093±0.005*
Control[b]	0.150±0.004	0.073±0.003
Implanted[b]	0.108±0.005**	0.070±0.007

1) [a]Rats were daily treated with 0.75 mg/kg, s.c., of physostigmine and [b]continuosusly infused with 0.15 mg/kg/hr, s.c., of physostigmine via mini-osmotic pump for 7days. Animals were sacrificed [c]24hr after 7th injections and [d]30min after 8th injections of physostigmine.

2) The values are the mean±S. E. of four or five determinations.

3) *p<0.05, **p<0.01 compared with corresponding control values.

Table 3. Effects of subacute administration of physostigmine on the level of dopamine and dopamine metabolites in the rat striatum

Treatment	DOPAC	DA	HVA
Control[a]	79.45±1.95	582.6±19.2	41.81±3.43
24 hr[c]	71.87±4.82	730.8±38.4*	31.23±4.75
30 min[d]	95.38±3.87*	563.2±22.8	56.20±4.95
Control[b]	81.88±5.32	544.2±23.2	39.85±2.25
Implanted[b]	69.15±4.83	635.8±35.0	52.88±0.60**

1) [a]Rats were daily treated with 0.75 mg/kg, s. c,, of physostigmine and [b] continuosly infused with 0.15 mg/kg/hr, s. c., of physostigmine via mini-osmotic pump for 7 days. Animals were sacrificed [c] after 7th injections and [d] after 8th injections of physostigmine.

2) Units: pmol/mg protein

3) The values are the mena±S. E. of four of five determinations.

4) *p<0.05, **p<0.01 compared with corresponding control values.

Table 5. Effects of acute and subacute administration of physostigmine on the activities of thyrosine hydroxylase in the rat striatum

Treatment	Acute	Subacute	
		Daily[a]	Continuous[b]
Control	18.45±0.22	20.38±0.87	18.34±0.56
30 min after	19.09±0.70	–	–
1 hr	18.84±0.78	–	–
2 hr	16.77±0.54*	–	–
24 hr	14.43±0.86**	17.79±0.38*	21.08±0.98

1) The acutely treated rats were sacrificed the indicated time after 0.75 mg/kg of physostigmine administration. The subacutely treated rats were sacrificed [a]24hr after 7th administration of physostigmine and [b]7days after the implantation of mini-osmotic pump as the dose of 0.15 mg/kg/h of physostigmine.

2) Units; pmol DOPA produced/mg protein/min.

3) The values are the mean±S. E. of four or five determinations.

4) *$p<0.05$, **$p<0.01$ compared with corresponding control values.

TH activities were significantly decreased 24 h after 7-days treatments. However, those in the physostigmine-infused rats were not affected.

DISCUSSION

The present results demonstrate that the administration of cholinesterase inhibitor, physostigmine, change the striatal dopaminergic activities. The levels of dopamine metabolites and the ratio to dopamine are increased after acute administration with physostigmine. However, after subacute administration, the ratio to dopamine are decreased. The activities of TH are decreased after daily administration with physostigmine.

The results on the acute effects of physostigmine are consistent with demonstration that the central cholinominetics such as, oxotremorine or pilocarpine, increased the turnover of brain DA following acute administration (Haubrich and Reid, 1972; Javoy *et al.*, 1975). The striatal increases in the turnover of dopamine observed after acute treatments with physostigmine return to control levels after cessation of treatments. Thus the neurochemical imbalance produced as a result of acute inhibition of AChE may be partially counteracted by the acute increase in dopaminergic activity. However, Fernando *et al.* (1984) have reported that the acute treatment with organophosphate increased DOPAC levels and decreased DA concentration. Since TH activities are not initially affected and then decreased without the change in DA levels, the changes in a turnover of dopamine might be due to the utilization process of DA. It has been reported that TH activities might be affected by the release of DA (Galloway *et al.*, 1986). the DA nerve activities (Quik and Sourkes, 1977) and the released DA (wolf *et al.*, 1986). Also it has been reported that the changes of DOPAC without altering in DA concentration might be intraneuronal changes in the cytoplasmic pool (Wood and Altar, 1988) and eigthy percent of HVA is reportedly formed from DOPAC as a results of the action of presynaptic monoamine oxidase on DA recovered form the synaptic cleft (Westerink and Spaan, 1982).

Although the relationships between changes in DA levels and TH activities are remained to be intensively elluciated, the increments in the concentrations of DOPAC and HVA without changing in DA levels as the present study imply the changes in the either/both release or/and uptake of dopamine in DA nerve endings.

This might be supported by the fact that the release of DA in stiratal synaptosomes is potentiated by the acetylcholine (Kito *et al.*, 1986; Raiteri *et al.*, 1984), which is accumulated by the AChE inhibition. In the subacute situation the ratios of DOPAC/DA and HVA/DA are found to be decreased with the levels of the DA and its metabolites unchanged. It has been reported that the changes in DA turnover after the subacute treatments with AChE inhibitors, organophosphates,

are either increased (Freed *et al.*, 1976) or decreased (Fernando *et al.*, 1984), and the levels of DA are decreased. Since drugs can have complex effects on DA and its metabolites levels, the determination in the alteration of DA turnover (Sharman, 1981) would be required by physostigmine treatment. The decrease in the turnover of dopamine suggest that the sensitivities in the striatal dopaminergic nerves to dopaminergic agents may be changed after long-term treatment with reversible AChE inhibitors. The recent our results (1992) supported the finding of the decreases in DA activity after subacute treatment. However, the activities in TH between two different treatments are differently affected with the decreased DA turnover. This may be due to the different treatments, that is; the intermittant inhibition and the continuous inhibition of AChE.

It has been reported that the continuous-infusion with physostigmine to guinea pigs reduced the muscarinic receptor density (Lim *et al.*, 1989) and the subacute treatment organophosphate to rats increased the dopamine receptors (Sivam*et al.*, 1983). Thus the reduced dopaminergic activities after the subacute treatment with physostigmine may partially support the increased DA receptors.

It has been suggested the dopaminergic and cholinergic mechanisms interact in a delicate way to maintain the normal function of striatum (Anden *et al.*, 1966). Although the direct effects of physostigmine on DA nerve remain to be studied, the present results suggest that the acute and subacute stimulation of cholinergic nerve with physostigmine may induce the changes in dopaminergic nerve activities to balance these two nerve systems.

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= 국문초록 =

쥐의 선조체에 있어서 Physostigmine의 아급성 투여가 Dopamine 대사에 미치는 영향

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임 동 구 · 최 수 형

Physostigmine을 급성(0.75 mg/kg), 7일간 매일 1회(0.75 mg/kg) 그리고 7일간 연속(0.15 mg/kg /h) 투여한 쥐의 선조체에 있어서 dopamine(DA) 및 대사체와 tyrosine hydroxylase(TH)활성도의 변화를 검색하였다. 급성 투여 1시간 후 선조체의 DA 농도는 변화가 없었으나 dihydroxyphenylacetic acid(DOPAC)과 homovanillic acid(HVA)농도는 증가하였다. 또한 DA의 turnover의 증가를 제시하는 DOPAC/DA와 HVA/DA의 비율도 증가하였다. 그러나 TH활성도는 24시간 후 감소를 나타내었다. Physostigmine을 매일 및 연속 투여군에서는 DA과 대사체의 농도에는 변화가 없었으나, DA의 turnover의 감소를 제시하는 DA과 대사체의 비율은 감소하였다. 그러나 TH활성도는 매일 투여군에서만 감소를 나타내었다.

이러한 결과는 physostigmine을 급성 및 아급성으로 투여시 dopamine대사의 변화가 있음을 제시한다. 또한 콜린 신경계의 아급성 자극은 dopamine 대사 및 활성도를 감소 시킬 가능성을 시사해 주었다.