ELSEVIER

European Journal of Pharmacology 338 (1997) 117–121

ejp

Short communication

Effects of amphetamine challenge on local cerebral glucose utilization after chronic dopamine D_1 and D_2 receptor agonist administration to rats[1]

Yn-Ho Huang [a,*], Shih-Jen Tsai [b,c], Hei-Jen Huang [a], Cho-Boon Sim [b]

[a] *Institute and Department of Anatomy, National Yang-Ming University, Taipei, Taiwan, ROC*
[b] *Department of Psychiatry, Veterans General Hospital, No. 201, Shih-Pai Road, Sec. 2, Taipei 11217, Taiwan, ROC*
[c] *Division of Neuropsychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*

Received 26 June 1997; revised 5 September 1997; accepted 9 September 1997

Abstract

Repeated amphetamine administration can cause an augmentation of regional cerebral metabolic activity. This study analyzed the regional cerebral metabolic changes which occurred in rats after pretreatment with the selective dopamine D_1 and D_2 receptor agonists, (±)SKF 38393 ((±)-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine HCl) and quinpirole (*trans*-(−)-4a*R*-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo(3,4-g)quinoline), as measured by the 2-[^{14}C]deoxyglucose method. The results showed selective metabolic augmentation in rats pretreated with SKF 38393 but not in those pretreated with quinpirole alone or with quinpirole in combination with SKF 38393. These findings demonstrated that dopamine D_1 receptors may play a critical role in the development of metabolic augmentation after repeated stimulant administration. © 1997 Elsevier Science B.V.

Keywords: Amphetamine administration, chronic; Deoxyglucose; Sensitization; SKF 38393; Quinpirole

1. Introduction

Repeated administration of psychomotor stimulants results in behavioral sensitization to subsequent stimulant administration. It has been suggested that repeated administration of amphetamine to experimental animals may provide an insight into the mechanisms underlying amphetamine psychosis and, perhaps, schizophrenia in humans (Robinson and Becker, 1986). Several recent reports have suggested that dopamine D_1 receptors may play a critical role in the development of behavioral sensitization (Vezina and Stewart, 1989; Drew and Glick, 1990; White et al., 1990; Mattingly et al., 1993). However, Ujike et al. (1989) and Weiss et al. (1989) reported that selective dopamine D_2 receptor antagonists block the development of behavioral sensitization to methamphetamine and cocaine. It has been suggested that dopamine D_2 receptor antagonists interfere with the development of conditioning and the development of conditioned stimulus control over the expression of sensitization, rather than with the development of sensitization itself (Reith et al., 1986). In addition, this discrepancy may come from the difference in the behaviors measured (Tirelli and Jodogne, 1993).

The physiological changes which occur in conjunction with chronic stimulant treatment are not entirely clear. We demonstrated earlier that repeated amphetamine administration can cause an augmentation of the rate of local cerebral glucose utilization, especially in the dopaminergic pathways (Huang et al., 1995). The rate of local cerebral glucose utilization can be assessed with the 2-[^{14}C]deoxyglucose method which simultaneously and globally maps the sites of drug action in the brain (Sokoloff et al., 1977). Because of the close coupling between energy metabolism and functional activity, this method may provide an alternative way to explore the underlying mechanisms of stimulant induced sensitization.

In order to examine the relative contribution of

* Corresponding author. Tel.: (886-2) 826-7069; Fax: (886-2) 821-2884; e-mail: ynho@dns.ym.edu.tw

[1] This experiment was performed in the Cerebral Metabolism Laboratory, Institute and Department of Anatomy, National Yang-Ming University, Taiwan, Republic of China.

dopamine D_1 and D_2 receptor-mediated mechanisms to the metabolic augmentation which occurs following chronic amphetamine treatment, the selective dopamine D_1 and D_2 receptor agonists, (±)SKF 38393 ((±)-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine HCl) and quinpirole (*trans*-(−)-4a*R*-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo(3,4-g)quinoline), were administered alone or in combination to rats over a period of 2 weeks. Following a 7 day recovery period, the metabolic response to amphetamine challenge was evaluated.

2. Materials and methods

2.1. Animals

Adult experimentally naive male rats of Sprague–Dawley descent weighing from 300–450 g were used in this study. The animals were housed in group cages with standard controlled temperature and a 12 h light/dark cycle. Food and water were provided ad libitum.

Table 1
Effects of repeated administration of dopamine agonists on local cerebral glucose utilization (mean ± standard error mean, μmol/100 g per min) in rats

Structure	Normal saline ($n = 4$)	SKF 38393 ($n = 6$)	Quinpirole ($n = 6$)	SKF 38393 + Quinpirole ($n = 6$)
Extrapyramidal system				
Caudatoputamen	103 ± 6	106 ± 4	109 ± 3	106 ± 4
Globus pallidus	65 ± 4	61 ± 3	59 ± 3	60 ± 3
Substantia nigra pars compacta	85 ± 5	87 ± 3	89 ± 4	82 ± 6
Substantia nigra pars reticulata	42 ± 3	59 ± 7 [a]	44 ± 2 [b]	53 ± 4
Subthalamic nucleus	74 ± 6	84 ± 3	74 ± 3	79 ± 4
Limbic and related areas				
Anterior pretectal nucleus	104 ± 7	102 ± 3	109 ± 5	99 ± 8
Arcuate nucleus	49 ± 1	57 ± 3	48 ± 1 [b]	52 ± 4
Basomedial amygdala	76 ± 3	76 ± 2	72 ± 2	69 ± 3
Central amygdala	56 ± 4	62 ± 3	54 ± 2	58 ± 3
Hippocampus formation	80 ± 7	84 ± 3	84 ± 3	80 ± 5
Interpeduncular nucleus	119 ± 9	119 ± 4	125 ± 6	112 ± 11
Nucleus accumbens				
Core	78 ± 4	83 ± 3	82 ± 4	86 ± 4
Shell	65 ± 5	69 ± 4	66 ± 2	69 ± 4
Lateral habenular nucleus	97 ± 6	101 ± 4	97 ± 2	94 ± 7
Medial preoptic nucleus	49 ± 6	63 ± 4 [a]	49 ± 2	53 ± 2
Medial septal nucleus	63 ± 4	69 ± 3	72 ± 2	72 ± 3
Nucleus diagonal band of Broca				
Horizontal limb	91 ± 10	80 ± 4	93 ± 2	84 ± 6
Vertical limb	71 ± 5	74 ± 3	74 ± 2	74 ± 4
Paraventricular nucleus	41 ± 3	53 ± 2 [a]	47 ± 1 [b]	48 ± 3
Posterior cingulate cortex	108 ± 9	116 ± 4	122 ± 5	113 ± 9
Ventral tegmental areas	63 ± 5	64 ± 8	63 ± 3	65 ± 7
Ventromedial nucleus	53 ± 2	66 ± 3	60 ± 3	62 ± 4
Neocortex				
Anterior cingulate cortex	91 ± 3	111 ± 4	106 ± 5	105 ± 7
Auditory cortex	139 ± 8	138 ± 5	151 ± 6	138 ± 7
Frontal cortex	99 ± 7	94 ± 7	97 ± 5	87 ± 6
Medial prefrontal cortex	95 ± 1	107 ± 8	109 ± 5	98 ± 6
Motor cortex	94 ± 4	93 ± 4	100 ± 3	92 ± 5
Somatosensory cortex I	109 ± 7	107 ± 3	115 ± 4	109 ± 7
Somatosensory cortex II	128 ± 11	125 ± 3	141 ± 4	127 ± 9
Sensory-motor system				
Lateral geniculate nucleus	81 ± 5	93 ± 4	85 ± 3	90 ± 7
Medial geniculate nucleus	100 ± 6	103 ± 6	104 ± 5	97 ± 6
Mediodorsal nucleus	109 ± 8	106 ± 3	111 ± 2	106 ± 9
Parafasicular nucleus	96 ± 5	112 ± 7	96 ± 3	97 ± 5
Paratenial nucleus	101 ± 11	100 ± 4	101 ± 3	95 ± 5
Superior colliculus	85 ± 5	85 ± 4	81 ± 4	82 ± 6
Ventrobasal nucleus	102 ± 7	101 ± 4	99 ± 4	97 ± 6

[a] $P < 0.05$ compared to normal saline control group.
[b] $P < 0.05$ compared to SKF group.

2.2. Drug administration

SKF 38393 and quinpirole were purchased from Research Biochemicals International (Natick, MA, USA) and D-amphetamine sulfate from Sigma (St. Louis, MO, USA). SKF 38393 was dissolved in distilled water. D-Amphetamine and quinpirole were dissolved in 0.9% saline. SKF 38393 and quinpirole were administered intraperitoneally at 10.0 and 1.0 mg/kg, respectively. The animals were randomly divided into four treatment groups. The groups received either intraperitoneal injections of distilled water–saline (control group), distilled water–quinpirole, SKF 38393–saline and SKF 38393–quinpirole, once daily for 14 days followed by a withdrawal period of 7 days.

The 2-[^{14}C]deoxyglucose method was applied 15 min after the 0.5 mg/kg amphetamine challenge intraperitoneally. A 7 day recovery period was provided in order to avoid the effects of depressed metabolic rates during stimulant withdrawal (Clow and Hammer, 1991). It has been reported that sensitization did not develop fully until after one to two weeks of abstinence (White et al., 1990; Kelland et al., 1991).

2.3. Local cerebral glucose utilization

On the final day of the experiment, the rats were anesthetized with 1% halothane and femoral arterial and venous catheters were inserted. The rats were lightly restrained on wooden blocks. After 3 h of recovery from anesthesia, the rats were challenged with 0.5 mg/kg D-amphetamine intraperitoneally. 15 min following the amphetamine challenge a pulse of 100 μCi/kg of 2-[^{14}C]deoxyglucose (New England Nuclear; specific activity = 58.0 Ci/mmol) was injected through a venous catheter. Arterial blood samples drawn from an arterial catheter at timed intervals over the experimental period were analyzed for the glucose level. 45 min after administration of the tracer, the animals were killed with an intravenous overdose of sodium pentobarbital. The brains were rapidly removed, frozen in isopentane at −50°C, then coated with embedding medium and stored in a freezer at −70°C until sectioning. Coronal sections of the brain (20 μm thick) were made in a cryostat. Every third section was placed on a glass coverslip and dried on a standard slide-warming tray (65°C). Kodak SB-5 X-ray films along with a set of calibrated standards (Amersham, [^{14}C] Micro-Scales RPA 504L) were exposed to the sections for 10 days. The autoradiograms were analyzed by quantitative densitometry, using a computerized-image processing system (MCID, BRS2). Tissue [^{14}C]-concentrations were determined by densitometry of the autoradiograms with reference to the calibrated standards. Rates of glucose utilization were then calculated from the local ^{14}C tissue concentrations, the time course of the plasma glucose and ^{14}C concentrations, according to the operative equation of the method (Sokoloff et al., 1977).

2.4. Statistical analysis

The statistical significance of the local cerebral glucose utilization was evaluated by one-way analysis of variance followed by Duncan's multiple range test.

3. Results

The effect of chronic administration of selective dopamine agonists on local cerebral glucose utilization was examined in 37 cerebral structures and the results are listed in Table 1. Repeated SKF 38393 administration significantly increased local cerebral glucose utilization in the substantia nigra pars reticulata, the medial preoptic nucleus or the paraventricular nucleus, compared with the control group. No regions were significantly affected by chronic treatment with quinpirole alone or in combination with SKF 38393.

4. Discussion

The major finding of this study was that repeated SKF 38393 but not quinpirole alone or in combination with SKF 38393 produced increases in glucose utilization in the substantia nigra pars reticulata, the medial preoptic nucleus and the paraventricular nucleus. Previous reports from studies which used the same regimen demonstrated that the density of dopamine D_2 receptors was decreased following chronic treatment with quinpirole alone or in combination with SKF 38393 whereas SKF 38393 by itself had no effect on this receptor (Subramaniam et al., 1992). In addition, the density of dopamine D_1 receptors was increased following treatment with SKF 38393 where quinpirole by itself had no effect on dopamine D_1 receptors. Our findings are at variance with those of another study that showed no differences in metabolism between saline and SKF 38393 pretreatment groups (Thomas et al., 1996). However, these authors followed a different schedule of SKF 38393 treatment (2 mg/kg at day 1 and challenge with cocaine 30 mg/kg on the next day). The major difference between these two studies was the length of the withdrawal period (1 versus 7 days). It was found that chronic administration of SKF 38393 induced functional desensitization of D_1 dopamine receptors, but 1 week withdrawal was followed by sensitization (White et al., 1990; Kelland et al., 1991).

The substantia nigra pars reticulata is one of the two major output nuclei of the striatum (Gerfen et al., 1990). In situ hybridization histochemical studies have demonstrated that the D_1 dopamine subtype is localized in striatal neurons that project directly to the substantia nigra. There was a previous report that chronic SKF 38393 administration resulted in an increased number of dopamine D_1 receptors

in the substantia nigra (Subramaniam et al., 1992). These results could explain the metabolic augmentation in the substantia nigra pars reticulata which occurs with chronic SKF 38393 administration. Our findings are also consistent with those of Trugman and Wooten (1987) who found that the enhanced local cerebral glucose utilization response to dopamine D_1 stimulation was an index of dopaminergic supersensitivity.

The medial preoptic nucleus and the paraventricular nucleus also showed metabolic augmentation after SKF 38393 pretreatment (Table 1). Increases in local cerebral glucose utilization following chronic SKF 3839 administration may be a direct or an indirect effect, since an entire pathway may be activated, even though the direct action of the drug is exerted only at the origin of the pathway (Porrino et al., 1987). The increased metabolism in the medial preoptic nucleus and the paraventricular nucleus which occurs after chronic SKF 38393 treatment is of clinical significance. The medial preoptic nucleus appears to exert a generally facilitative effect on sexual behavior (Malsbury, 1971). The increased metabolic response in this region found in the present study was compatible with previous clinical findings that increased libido was described by 52% of amphetamine abusers (Ellinwood, 1967). The paraventricular nucleus is ideally situated to modulate activity in limbic forebrain sites that have been implicated in schizophrenia and are affected by antipsychotic drugs (Cohen and Wan, 1996). The metabolic change in this nucleus may be related to the psychosis induced by chronic amphetamine abuse.

In our previous study, metabolic augmentation was found in the nucleus accumbens after chronic amphetamine administration and this did not occur in the present study with SKF 38393 pretreatment (Huang et al., 1995). Willner et al. (1992) suggested that there are differences in the sensitization effects induced by amphetamine and direct dopamine agonists. There are several differences in the manner in which amphetamine and agonists activate the dopamine systems. For example, it appears that amphetamine stimulates receptors other than dopamine receptors and that amphetamine may act both the pre- and postsynaptically. In addition, the D_1 dopamine agonist, SKF 38393, we now used is a partial dopamine D_1 receptor agonist. A full dopamine D_1 receptor agonist (for example SKF 82958), might induce greater metabolic sensitization.

In summary, the findings of this study suggest that SKF 38393 pretreatment, but not pretreatment with quinpirole alone or in combination with SKF 38393, results in an augmented metabolic response to subsequent amphetamine challenge. The regions with an augmented response included dopaminergic and non-dopaminergic nuclei. These results have implications for therapy which employs psychostimulant sensitization and for the interpretation of positron emission tomography of amphetamine psychosis and schizophrenia.

Acknowledgements

This work was supported by Grant DOH86-TD-099 from the Department of Health, Taiwan, R.O.C.

References

Clow, D.W., Hammer Jr., R.P., 1991. Cocaine abstinence following chronic treatment alters cerebral metabolism in dopaminergic reward regions. Neuropsychopharmacology 4, 71–75.

Cohen, B.M., Wan, W., 1996. The thalamus as a site of action of antipsychotic drugs. Am. J. Psychiatry 153, 104–106.

Drew, K.L., Glick, S.D., 1990. Role of D1 and D2 receptor stimulation in sensitization to amphetamine-induced circling behavior and in expression and extinction of the Pavlovian conditioned response. Psychopharmacology 101, 465–471.

Ellinwood, E.H., 1967. Amphetamine psychosis. I. Description of the individuals and process. J. Nerv. Ment. Dis. 141, 273–283.

Gerfen, C.R., Engber, T.M., Mahan, L.C., Susel, Z., Chase, T.N., Monsma Jr., F.J., Sibley, D.R., 1990. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250, 1429–1432.

Huang, Y.-H., Tsai, S.-J., Yu, M.-F., Wang, Y.-C., Yang, Y.-C., Sim, C.-B., 1995. Dose-dependent effects of chronic amphetamine administration in local cerebral glucose utilization in rat. Neuropsychobiology 32, 149–155.

Kelland, M.D., Pitts, D.K., Freeman, A.S., Chiodo, L.A., 1991. Repeated SKF 38393 and nigrostriatal system neuronal responsiveness: Functional down-regulation is followed by up-regulation after withdrawal. Naunyn Schmiedebergs Arch. Pharmacol. 343, 447–457.

Malsbury, C.W., 1971. Facilitation of male rat copulatory behavior by electrical stimulation of the medial preoptic area. Physiol. Behav. 7, 797–805.

Mattingly, B.A., Rowlett, J.K., Lovell, G., 1993. Effects of daily SKF 38393, quinpirole, and SCH 23390 treatments on locomotor activity and subsequent sensitivity to apomorphine. Psychopharmacology 110, 320–326.

Porrino, L.J., Burns, R.S., Crane, A.M., Palombo, E., Kopin, I.J., Sokoloff, L., 1987. Local cerebral metabolic effects of L-dopa therapy in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism in monkeys. Proc. Natl. Acad. Sci. USA 84, 5995–5999.

Reith, M.E.A., Meisler, B.E., Sershen, H., Lajtha, A., 1986. Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Biochem. Pharmacol. 35, 1123–1129.

Robinson, T.E., Becker, J.B., 1986. Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res. Rev. 11, 157–198.

Sokoloff, L., Reivich, M., Kennedy, C., Des Rosiers, M.H., Patlak, C.S., Pettigrew, K.D., Sakurada, O., Shinohara, M., 1977. The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure and normal values in the conscious and anesthetized albino rat. J. Neurochem. 28, 897–916.

Subramaniam, S., Lucki, I., McGonigle, P., 1992. Effects of chronic treatment with selective agonists on the subtypes of dopamine receptors. Brain Res. 571, 313–322.

Thomas Jr., W.L., Cooke, E.S., Hammer Jr., R.P., 1996. Cocaine-induced sensitization of metabolic activity in extrapyramidal circuits involves prior dopamine D1-like receptor stimulation. J. Pharmacol. Exp. Ther. 278, 347–353.

Tirelli, E., Jodogne, C., 1993. Behavioral sensitization and tolerance to the D2 agonist RU 24213: Dissociation between several behavior patterns in mice. Pharmacol. Biochem. Behav. 44, 627–632.

Trugman, J.M., Wooten, G.F., 1987. Selective D1 and D2 dopamine agonists differentially alter basal ganglia glucose utilization in rats with unilateral 6-hydroxydopamine substantia nigra lesion. J. Neurosci. 7, 2927–2935.

Ujike, H., Onoue, R., Akiyama, K., Hamaura, T., Otsuki, S., 1989. Effects of selective D-1 and D-2 dopamine antagonists on development of methamphetamine-induced behavioral sensitization. Psychopharmacology 98, 89–92.

Vezina, P., Stewart, J., 1989. The effect of dopamine receptor blockade on the development of sensitization to the locomotor activating effects of amphetamine and morphine. Brain Res. 499, 108–120.

Weiss, S.R.B., Post, R.M., Pert, A., Woodward, R., Murman, D., 1989. Context-dependent cocaine sensitization: Differential effect of haloperidol on development versus expression. Pharmacol. Biochem. Behav. 34, 655–661.

White, F.J., Hu, X.-T., Brooderson, R.J., 1990. Repeated stimulation of dopamine D1 receptors enhances the effects of dopamine receptor agonists. Eur. J. Pharmacol. 191, 497–499.

Willner, P., Papp, S., Cheeta, S., Muscat, R., 1992. Environmental influences on behavioural sensitization to the dopamine agonist quinpirole. Behav. Pharmacol. 3, 43–50.