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Metabolic and Behavioral Response in Rats Treated with Amphetamine Chronically with and without Challenge

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ABSTRACT

Chronic amphetamine (AMPH) treatment may cause behavioral sensitization in animals and can be used as an animal model of psychosis. The aim of the study was to check the behavioral and metabolic response in this animal model.

In rats pretreated with normal saline (NS) or AMPH, with or without AMPH challenge, the [^{14}C]deoxyglucose method was employed to check the metabolic changes in 42 regions. Behavioral testing was performed in rats with the same treatment. The results showed that after challenge with AMPH, glucose utilization was enhanced in most of the regions investigated. However, metabolic enhancement of the AMPH-pretreated group was lower in the caudate nucleus when compared with that of the NS-pretreated group though the stereotypy rating was higher in the former. Dissociation between the metabolic enhancement and behavioral response was noted. Furthermore, more significant differences between the two pretreated conditions of glucose utilization were found with challenge than without challenge. Further evaluation using procedures which include advanced techniques can be applied in further investigation.

Key Words: amphetamine; deoxyglucose; locomotion; sensitization; stereotypy.

I. Introduction

Repeated amphetamine (AMPH) treatments may enhance some of the drug's behavioral effects in animals; this is known as behavioral sensitization or reverse tolerance (Segal and Mandell, 1974; Klawans and Margolin, 1975). This phenomenon has also been found in humans who repeatedly use AMPH; they sometimes develop a psychosis with features resembling those of paranoid schizophrenia (Sato *et al.*, 1992). An understanding of the mechanisms of behavioral sensitization may provide insight into the neurobiological processes responsible for AMPH psychosis and even for schizophrenia.

The neural mechanisms and the loci of the changes responsible for behavioral sensitization are still unknown though diverse methods have been employed and different hypotheses have been extensively reviewed by Robinson and Becker (1986). With a limit on employable methods, most studies have focused on some nuclei of the dopaminergic systems. In rats, locomotion and stereotyped behaviors elicited by AMPH are the result of increased dopaminergic neurotransmission in the mesolimbic and the nigrostriatal dopaminergic systems, respectively (Asher and Aghajanian, 1974; Costall *et al.*, 1977; Kelly *et al.*, 1975). Thus, these two pathways have been most thoroughly examined as possible sites of action of AMPH. The [^{14}C]deoxyglucose method (Sokoloff *et al.*, 1977) can be used to measure the rates of local cerebral glucose utilization (LCGU) simultaneously in all the anatomical and functional components of the entire central nervous system. It has been used to detect functional changes in various physical and pharmacological states (Sokoloff *et al.*, 1977). Therefore, the purpose of the present study

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was to employ this method to detect the metabolic response in rats treated with AMPH chronically with and without challenge. Furthermore, an attempt was made to check the relationship between the behavioral action of AMPH and the metabolic changes in the sensitized state. This result can elucidate the mechanism of the behavioral sensitization.

II. Materials and Methods

1. Animals

Adult male Sprague-Dawley rats, weighing 300-450 g, were used in this experiment. Animals were housed in group cages, and maintained under standard controlled temperatures (22 ± 2°C) and a 12-hr light/dark cycle. Food and water were available *ad libitum*.

2. Administration of d-AMPH

d-AMPH sulfate (Sigma, St. Louis, MO.) was dissolved in normal saline. Two groups of rats (n = 4 or 5) were pretreated with NS or 5.0 mg/kg of *d*-AMPH (i.p.; in a volume of 3.0 ml/kg) once per day for 14 consecutive days. After 7 days of abstinence, the [^{14}C]deoxyglucose method was performed 15 min following 5.0 mg/kg d-AMPH challenge (i.p.). This abstinence period was used because it has been suggested that sensitization occurs only after seven days of abstinence (Gawin and Ellinwood, 1988). We detected the metabolic response 15 min after challenge for this is the time used in previous studies and may record the maximal effect of AMPH (Wechsler *et al.*, 1979; Orzi *et al.*, 1983). Another two groups of rats with the same pretreatment accepted the LCGU test without challenge. To test whether the above-described AMPH paradigm could cause behavioral sensitization, two groups of rats (n = 6) pretreated with the same regimens were used for behavioral testing before and after challenge with 5.0 mg/kg *d*-AMPH (i.p.).

3. Behavioral Testing

Behavioral testing was performed in motor activity cages (Opto Varimex-Minor, Columbus Instruments, OH). The acrylic cage within the monitor measured approximately 42 cm square and 20 cm high; through the cage 30 infrared beams were passed on the horizontal plane, and 15 on each axis. Ambulatory movement was recorded as the distance traveled in centimeters and was calculated from the interruption of alternate beams. One week after pretreatment, the rats were used for behavioral testing. The animals were placed singly in the activity cages and allowed 45 min for accommodation. Behaviors were tested for 15 min in the steady state, and then all rats were challenged with the same dose of *d*-AMPH (5.0 mg/kg, i.p.). Measurement of motor activity began 15 min after injection and continued for a period of 15 min. During the testing period, each rat was also videotaped for rating of stereotyped behaviors. Stereotypy was rated by a single rater who was blind to the pretreatment conditions. Stereotypy involving sniffing and repetitive head movement was rated using a 0-5 score adapted from Ujike *et al.* (1992): 0: asleep or stationary; 1: active with normal exploration; 2: increased rate of sniffing and head movement associated with locomotion and rearing; 3: discontinuous sniffing and stereotyped up-down head movement with periodic locomotor activity; 4: almost continuous and intense stereotyped sniffing and repetitive head movement, but sometimes interrupted by brief locomotion; 5: continuous and intense stereotyped sniffing and repetitive head movement at one location only. All tests were carried out between 0800 and 1500 hr in an isolated environmental room.

4. Local Cerebral Glucose Utilization

One week after abstinence from the AMPH pretreatment, the 2-deoxyglucose method was performed on the four groups of rats. The experimental procedures and analysis of LCGU are described in detail elsewhere (Tsai *et al.*, 1994). Briefly, femoral arterial and venous catheters were implanted under halothane anesthesia. The animals were allowed to recover for at least 3 hr prior to 2-deoxyglucose injection. For each rat, 100 μCi/kg of 2-[^{14}C]deoxyglucose (New England Nuclear; specific activity = 58.0 Ci/mmol) was injected through the venous catheter. Arterial blood samples were taken for glucose analysis. At the end, the animals were sacrificed. Brains were rapidly removed and frozen in isopentane chilled to −50°C. Coronal sections of the brain (20 μm) were cut in a cryostat. Sections were autoradiographed along with a set of calibrated standards on X-ray films. The 2-deoxyglucose autoradiograms were analyzed by quantitative densitometry with a computerized-image processing system. The LCGU was then calculated from the local tissue [^{14}C]-concentration, the concentration of ^{14}C and glucose in arterial plasma and the operative equation of Sokoloff *et al.* (1977). The unit for the rate of LCGU was μmol/100 g/min, which indicates the amount of glucose consumption in 100 g brain tissue per min.

5. Statistical Analysis

Data of LCGU and locomotion are presented as mean ± SEM. Statistical differences in glucose use were analyzed by the two-tailed Student's *t*-test. Because of the three comparisons of interest among the four experimental groups, the Bonferroni correction for the α-level was employed to maintain the overall α-level at 0.05. Locomotor activity and stereotypy rating, with the same pretreated conditions, were compared with the two-tailed Student's *t*-test and a nonparametric Mann-Whitney U test; measures in the same animals before and after challenge were analyzed with the paired *t*-test and Wilcoxon signed-ranks test.

III. Results

1. Behavioral Testing

Table 1 presents the averaged activity and stereotypy rating of NS- and AMPH-pretreated rats before and after AMPH challenge. All the rats showed hyperactivity after being placed in activity cages, but most were asleep or stationary 15 min before AMPH challenge. There was no significant difference between the two groups in the steady state. Challenge with AMPH resulted in stereotyped behaviors in all rats, but the AMPH-pretreated group showed more intense repetitive sniffing and head movement at one location. The stereotypy score but not the locomotor activity in the AMPH-pretreated group was more significantly enhanced after than before challenge; the same was true for the NS-pretreated group.

The behaviors of the four groups of rats in which LCGU was measured were also observed throughout the experiment. Partial restraint of the animals restricted ambulation, but the challenged groups showed stereotyped head movements which were not found in the non-challenged groups.

Table 1. Locomotor Activity (Distance Traveled: cm) and Stereotypy Scores before and after AMPH Challenge Following 14-Day of NS or AMPH Pretreatment

	n	Mean	S.E.M.	Group Median	S.I.Q.R.*
Before Challenge					
NS	6	192	61	0	0
AMPH	6	248	91	0	0
After Challenge					
NS	6	2,438	753	3.0	1.0
AMPH	6	1,810	710	5.0[a,b]	0.6

There were no significant differences in locomotion among groups.
*S.I.Q.R.: Semi-interquartile Range.
[a] $p < 0.05$ for the comparison between NS-pretreated and AMPH-pretreated animals.
[b] $p < 0.05$ for the comparison between non-challenged and challenged animals.

2. Local Cerebral Glucose Utilization

The effects of repeated AMPH treatment in LCGU were examined in forty-two cerebral structures, and the results are summarized in Table 2. Glucose utilization between the two non-challenged groups demonstrated differences in two regions (somatosensory area II and the medial geniculate nucleus). Significant LCGU differences between AMPH-pretreated groups with and without challenge were found in 11 components, mostly in the thalamus and the extrapyramidal systems (*e.g.* the anteroventral nucleus and parafascicular nucleus of thalamus, caudate nucleus, globus pallidus, and subthalamic nucleus). After AMPH challenge, the metabolic response was more pronounced in the NS-pretreated group than in the AMPH-pretreated group especially in the neocortex areas, including the nucleus accumbens and the caudatoputamen (Fig. 1).

IV. Discussion

1. Behavioral Testing

Before AMPH challenge, the rats were asleep or stationary most of the time. Also, no struggling or stereotypy were found in the non-challenged groups tested for LCGU. This finding is consistent with a previous report that no activity abnormalities occurred in sensitized rats in the steady state (Segal and Mandell, 1974). These behaviors are thought to be mediated by the mesolimbic and the nigrostriatal dopaminergic pathways. It is possible that sensitization does not result in a change in the basal rate of dopamine utilization but has an exaggerated response to further challenge (Robinson and Becker, 1986). Behavioral testing after 5.0 mg/kg d-AMPH challenge revealed stereotyped behaviors in both groups, but the AMPH-pretreated rats had the higher stereotypy rating (Table 1). This result suggested behavioral sensitization in the AMPH-pretreated group.

The stereotyped behaviors of the AMPH-pretreated group were more enhanced after AMPH challenge, but the locomotor activity showed no significant difference though the average activity was ten times greater than that before challenge. The failure to show a significant difference in locomotion may have come from high individual variability (Table 1).

Table 2. Effects of 14-Day Intraperitoneal Administration of NS and AMPH Followed by an Abstinence Period of 7 Days, without or with Challenge, in Local Cerebral Glucose Utilization of Conscious Rats

	Non-challenge		Challenge	
	NS(5)	AMPH(5)	NS(4)	AMPH(5)
Neocortex				
Ant. Cingulate Cortex	116±3	113±5	136±5	119±1 [a]
Auditory Cortex	154±77	171±8	205±10	171±4 [a]
Frontal Cortex	100±3	112±2 [a]	106±7	104±4
Med. Prefrontal Cortex	112±2	113±3	116±9	108±5
Motor Cortex	112±4	115±3	139±4	113±3 [a]
Olfactory Cortex	140±10	128±6	160±21	125±7
Post. Cingulate Cortex	118±7	116±5	176±9	133±6 [a]
Somatosensory Area I	138±4	140±6	200±6	171±7 [a,b]
Somatosensory Area II	129±3	157±7 [a]	182±12	164±4
Sensory-motor System				
Inf. Colliculus	127±6	150±13	188±19	172±10
Lat Geniculate Nu.	102±5	100±4	141±16	127±5 [b]
Med. Geniculate Nu.	117±4	135±4 [a]	148±8	137±6
Sup. Colliculus	98±5	99±5	111±9	105±5
Limbic and Related Areas				
Ant. Pretectal Nu.	100±5	115±6	153±11	144±8 [b]
Arcuate Nu. Hypothalamus	60±1	56±3	56±6	53±4
Basomedial Amygdala Nu.	70±3	73±3	75±6	67±4
Bed Nu. Stria Terminalis	66±4	60±3	56±5	59±4
Interpeduncular Nu.	130±3	140±4	144±8	130±9
Lat. Habenular Nu.	107±5	114±3	90±7	94±3 [b]
Lat. Septal Nu.	72±2	71±3	75±5	70±5
Mammillary Body	133±7	139±6	189±9	161±9
Med. Habenular Nu.	90±4	80±3	68±6	75±4
Med. Preoptic Nu.	74±6	54±2 [a]	56±5	57±3
Med. Septal Nu.	73±4	79±3	94±9	80±6
Nu. Accumbens	91±1	91±2	112±4	99±3 [a]
Nu. Diagonal Band of Broca				
Horizontal Limb	97±3	98±4	155±7	122±5 [a,b]
Vertical Limb	89±4	79±3	101±7	88±5
Ventral Tegmental Areas	81±4	82±4	85±7	84±7
Ventromedial Hypothalamus	68±1	64±3	67±6	63±5
Thalamus				
Anteroventral Nu.	129±8	121±5	187±8	158±6 [a,b]
Centromedial Nu.	97±5	99±3	118±12	119±6 [b]
Parafascicular Nu.	100±7	109±5	142±13	131±2 [b]
Paratenial Nu.	105±5	105±4	137±11	111±3 [a]
Reunion Nu.	96±8	98±3	115±12	107±6
Ventrobasal Nu.	108±3	109±6	163±11	139±5 [b]
Ventromedial Nu.	128±7	132±8	196±20	169±6 [b]
Extrapyramidal Systems				
Caudatoputamen	115±2	114±4	172±8	141±2 [a,b]
Globus Pallidus	71±2	72±3	92±7	88±3 [b]
Sub. Nigra Pars Compacta	88±3	89±3	106±7	109±6 [b]
Sub. Nigra Pars Reticulata	67±3	70±4	113±8	108±8 [b]
Subthalamic Nu.	92±4	104±4	174±12	154±5 [b]
Red Nu.	97±3	98±3	117±11	110±6

Values are means ± SEM of the local cerebral glucose utilization values (μmol/100 g/min); number of rats is indicated in parenthesis.
[a] $p < 0.05$ for the comparison between NS-pretreated and AMPH-pretreated animals.
[b] $p < 0.05$ for the comparison between non-challenged and challenged animals.

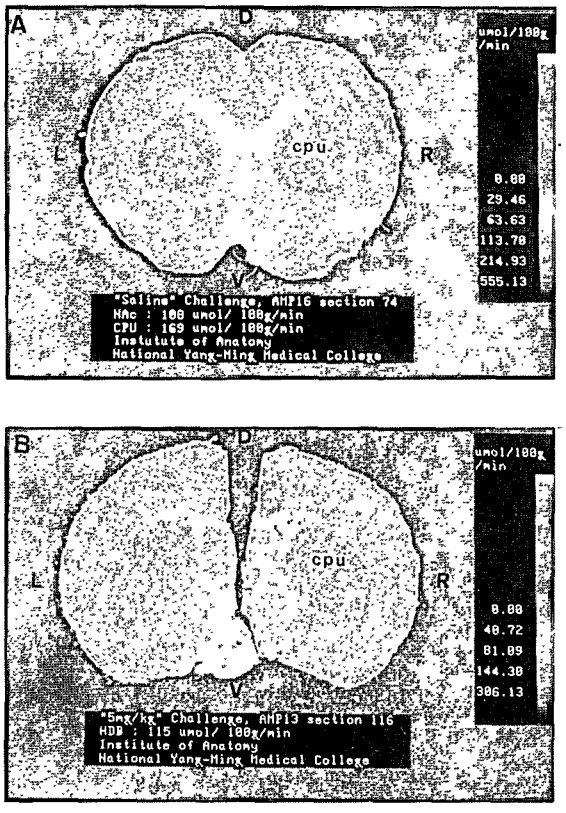

Fig. 1. Autoradiographic visualization of the effects of AMPH on LCGU in the caudatoputamen (CPU). (A) NS pretreatment with AMPH challenge. (B) AMPH pretreatment with AMPH challenge.

2. Local Cerebral Glucose Utilization

Results of the 2-deoxyglucose study demonstrated that during the steady state there were metabolic changes in a limited number of regions. One auditory (medial geniculate nucleus) and one sensory (somatosensory II) component had metabolic enhancement in rats pretreated with AMPH. The reason for the increment is unclear and may have been caused by outside stimuli during experiment. Control of environmental conditions may be necessary for further studies.

After challenge with 5.0 mg/kg AMPH, the AMPH-pretreated group produced an increase in local cerebral glucose utilization in a number of components of the extrapyramidal motor system as well as in some nuclei of the thalamus when compared with its non-challenged counterpart. Decrease in glucose utilization after AMPH administration was found in the lateral habenular nucleus. These findings are compatible with previous reports using acute AMPH administration (Wechsler *et al.*, 1979; Orzi *et al.*, 1983; Porrino *et al.*, 1984) and chronic AMPH administration (Tsai *et al.*, 1994). Few regions of the thalamus are innervated by dopaminergic nerve fibers, and the thalamus has few dopaminergic neurons. Although AMPH is thought to act primarily at the dopaminergic synapses, the alterations in metabolism of the thalamus in this study and the previous report (McCulloch and Kelly, 1981) are not indicative of the presence of dopaminergic cell bodies or terminals intrinsic in that region. The reason is that measurement of LCGU cannot distinguish between the direct and indirect actions of a drug effect; 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). Using specific antagonists or lesion study, it may be possible to differentiate between the direct and the indirect effects of AMPH. The general metabolic rate of the AMPH-pretreated group after AMPH challenge was higher than that of rats pretreated with 0.5 mg/kg AMPH and challenged with 1.0 mg/kg AMPH in our previous study (Tsai *et al.*, 1994). The difference could have been caused by the variance in the pretreatment dose or the challenge dose. The later was more likely the reason because the NS-pretreated groups with different challenge dose in these two studies also showed a difference in general metabolism.

The most striking finding was that, after challenge, the AMPH-pretreated group showed less metabolic response in the caudate nucleus than did the NS-pretreated group (Fig. 1) while the former showed behavioral sensitization with a higher stereotypy score (Table 1). The dissociation between metabolic change in the behavior-associated region and the behavioral response is in contrast with a previous report using acute AMPH treatment which described strong coupling between behaviors and the glucose utilization of the related regions (Porrino *et al.*, 1984). There were four possibilities for this finding. First, Segal and Kuczenski (1992) using *in vivo* microdialysis showed a diminished AMPH-induced DA response corresponding to behavioral sensitization produced by repeated AMPH pretreatment. Other non-DA neurochemical systems and/or mechanisms which may have contributed to the behavioral sensitization were proposed by the authors, and these could also help to explain this finding. Second, glucose utilization within any given brain region is determined by the intrinsic activity of the neurons of that area, together with the sum of the activities (excitatory and inhibitory) in afferent ways (Kelly and McCulloch, 1987). Thus, the result showing a diminished metabolic response in the behavior-related region may have come from less inhibitory input into the region (Robinson and Becker, 1986). Third, one may argue that the rats

studied for metabolic changes were partially restrained instead of free-moving; that may have affected glucose utilization. This is unlikely, since the stereotyped movement rated was repetitive head movement and sniffing, which are not influenced by restraint and also could be found during the metabolic study. Finally, another possibility is that seven-day abstinence may not have been long enough; therefore, the effect of decreased metabolism during stimulant-withdrawal may have masked the metabolic response of the behavioral sensitization. Further study with a longer withdrawal interval is necessary to clarify this.

More regions with metabolic differences were found between the challenged groups than between the non-challenged groups. Since animals sensitized by stimulant pretreatment have been used as animal models of schizophrenia (Robinson and Becker, 1986), there are some clinical implications from these results. The limited findings in deoxyglucose PET studies in the schizophrenic may be just like those found in the steady state of this study. Further challenge with stimulants may provoke metabolic changes, especially when patients are not in the acute stage. There have been reports demonstrating that acute administration of stimulants such as AMPH (Wolkin *et al.*, 1985) and apomorphine (Cleghorn *et al.*, 1991) decreased brain glucose metabolism both in normal and schizophrenic subjects, and these results seemed to be incongruent with animal studies (for a review, see Orzi *et al.*, 1993) and the present results. The differences may be due to the dose of the stimulants for challenge and the time for glucose measurement. Furthermore, heterogeneity among schizophrenics is another problem which has caused controversial results in PET studies. It has been suggested that using homogenous psychotic patients such as amphetamine psychotics for PET studies may lead to more uniform results but the time period after drug withdrawal is crucial.

In summary, this study has examined regional glucose metabolism of sensitized rats with and without AMPH challenge. During the steady state, NS- and AMPH-pretreated rats showed no difference in behavioral testing, and limited metabolic differences were found. After challenge, the NS-pretreated group had higher metabolic response, which was dissociated from the behavioral changes. In addition more regional metabolic differences were found after challenge, which suggested that stimulant challenge could be helpful in PET study of psychotics. The choice of stimulant, dose and time-course need further study.

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大白鼠經長期安非他命處理後之腦局部葡萄糖代謝率及行爲之改變

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摘　要

動物若重覆給予安非他命，會產生行爲增強的敏感化現象且持續一段時間，故常以此用做精神症的動物模型。本實驗以此動物模型，使用去氧葡萄糖方法([^{14}C]dexyglucose method)研究大白鼠腦區葡萄糖代謝率改變情形，並與行爲測試作比較。

方法是以大白鼠每日腹腔注射安非他命或等量食鹽水，在給或不給安非他命刺激下測42個腦區葡萄糖代謝率改變情形。同樣處理之另一大組大白鼠則作行爲測試。

結果顯示經安非他命刺激後，局部葡萄糖代謝率較未刺激組升高很多。雖然安非他命前處理組有較顯著的重覆行爲反應，但與此行爲相關之腦區的葡萄糖代謝率增強卻不若若食鹽水前處理組。此不一致的現象將在內文討論。另外經安非他命刺激後，兩種前處理組間的局部葡萄糖代謝率差異處較未經安非他命刺激組間的差異多，顯示在臨床研究精神症之萄萄糖代謝率時，給予刺激物可能得到更多的訊息。