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Effects of Repeated High-Dose Methamphetamine on Local Cerebral Glucose Utilization in Rats

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Repeated administration of high doses of methamphetamine (MAP) to rats can induce long-lasting neurotoxicity which may be related to permanent psychotic symptoms and negative symptoms in some MAP psychotic patients. In this study, we used the 2-[^{14}C]deoxyglucose (2DG) method to analyze the effects of repeated MAP administration (12.5 mg/kg, i.p., 4 times every 2 hr within a day) 14 days and 60 days after drug administration. The results showed a widespread (26 of the 43 regions examined) decreases in the regional cerebral glucose utilization. The regions with decrease metabolism included all the extrapyramidal systems, the hippocampus formation and dorsal raphe nucleus. Rats tested 60 days after drug administration has similar finding to those with a 14-day abstinent period. The results of the functional change in this study provide support for the neurotoxic effects of repeated high dose MAP administration in rats. Furthermore, the neurotoxic effects are selective and long-lasting. We suggested the MAP neurotoxic model can be used to study the permanent psychosis and negative symptoms of MAP-induced psychosis in humans. ***[Neuropsychopharmacology 21:427–434, 1999]*** *© 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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The neurotoxic effects of amphetamine analogs on central nervous systems are well documented. In rats, repeated administrations of high doses of methamphetamine (MAP) have shown to cause neurotoxic effects on the central dopaminergic and serotonergic systems of the brain. The neurotoxic effects included degeneration of nerve terminals (Lorez 1981; Ricaurte et al. 1982), alterations in tyrosine hydroxylase immunoreactivity (Kogan et al. 1976), decreases in dopamine and serotonin levels (Koda and Gibb 1971; Wagner et al. 1980; Bakhit et al. 1981), and decreases in monoamine uptake sites (Kovachich et al. 1989). Such neurotoxic effects often lasted for a long time (Sonsalla et al. 1992; Kleven and Seiden 1992; Seiden and Sabol 1996). Bakhit et al. (1981) investigated the regional response of the serotonergic system to the effects of multiple doses of MAP and found that the decrease in concentrations of serotonin and its metabolite persisted for 110 days in all brain areas that were investigated.

In view of the widespread abuse of MAP, the possible irreversible or prolonged effects of MAP's neurotoxicity are of particular concern. In some MAP psychotics, the hallucinatory and delusional state persist for more than one month or sometimes over several years with-

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out the reuse of the drug concerned (Sato et al. 1983). Some negative symptoms of schizophrenia were also found in chronic MAP psychotics. Tatetsu (1963) mentioned lack of interest or initiative, blunting affect, and withdrawal in such patients. Tomiyama (1990) compared the negative symptoms in 11 chronic MAP psychotics with an equal number of chronic schizophrenic by the Scale for the Assessment of Negative symptoms (SANS). According to SANS, the scores of avolition-apathy, anhedonia-asociality and attentional impairment were moderately high in both groups. These findings stressed the importance of understanding the mechanism underlying MAP neurotoxicity, which may be used as a model to study the negative symptoms in schizophrenia.

Hotchkiss et al. (1979) indicated that the MAP's neurotoxic effect is limited to the dopaminergic and serotonergic systems and that other neurotransmitter systems remain intact. In addition, even in the dopaminergic or serotonergic systems, there are regional difference in vulnerability to MAP's neurotoxic effects. Seiden et al. (1988) demonstrated that high doses of MAP administered to rats produces long-lasting depletion of DA in frontal pole, amygdala, and nucleus accumbens, whereas olfactory tubercle and septum remain rather resistant to MAP-induced DA depletion.

Using the 2-[^{14}C]deoxyglucose (2DG) method, Pontieri et al. (1991) studied the effects of repeated high doses of MAP (50 mg/kg, s.c., twice a day for 4 days, a regimen known to produce long-lasting depletion of both dopamine and serotonin) administration and found significant ($p<0.05$) decreased local cerebral glucose utilization (LCGU) in four (nucleus accumbens, dorsolateral and ventral caudate , median raphe) of the five regions of the sensitive group animals examined 14 days after drug administration as cpmpared to those of the saline contral group. Furthermore, Pontieri et al. (1991) found that decreases in LCGU in the striatum of these animals were more closely correlated to dopamine rather than serotonin levels. The 2DG method does not permit distinction between transmitter systems, however, it permits simultaneous visualization of metabolic changes throughout the entire nervous system, making possible the identification of complex neuronal circuit which mediate the response to a pharmacological manipulation (Sokoloff et al. 1977). Because of the close affiliation between the energy metabolism and the functional activity, this method may provide an alternative way to explore the underlying mechanisms of MAP induced neurotoxicity. In this study, we employed the 2DG method to investigate the LCGU in 43 brain regions, 14 or 60 days after repeated four high doses of MAP administration to rats in order to locate the nuclei or neural circuit and provide the time course effects on the regional metabolic response to MAP neurotoxicity.

MATERIALS AND METHODS

Subjects

Adult male Sprague-Dawley rats weighing 200–220 g (two months old) were obtained from the Animal Center of the National Yang-Ming University and maintained in animal quarters with a standard 12:12-hour light-dark cycle and controlled humidity, temperature (22 ± 2°C), and pathogen-free conditions. Rats were placed in individual cages(one per cage) with free access to food and water. Four groups of rats (5–6 in each group) were used in this experiment.

Drug and Injection

S(+)-Methamphetamine purchased from Research Biochemicals, Inc. (Natick, MA) was dissolved in normal saline. Rats were randomly assigned to one of four regimens, each comprising four consecutive intraperitoneal injections, given at 2 hr intervals within a day, of either normal saline or 12.5 mg/kg MAP. This repeated four high doses of MAP administration to rats will cause more widespread neurotoxicity than will a single injection of MAP with similar dosage. The [^{14}C]-2DG experimental procedure was performed 14 or 60 days after discontinuation of the injections. Thus, the four drug regimens were: saline/14-day; MAP/14-day; saline/60-day; or MAP/60-day.

Local Cerebral Glucose Utilization

The 2DG study was conducted according to previously published procedures (Sokoloff et al. 1977). Briefly, catheters were placed in one femoral artery and vein under 1% halothane anesthesia. Rats were lightly restrained on wooden blocks. The animals were allowed at least 3 hr to recover from the effect of anesthesia, then a dose of 100 μCi/kg of 2-[^{14}C]deoxyglucose (New England Nuclear; specific activity = 58.0 Ci/mmol) was injected through the venous catheter.

Sixteen timed arterial blood samples were collected over the experimental period for the plasma [^{14}C]deoxyglucose counting and glucose analysis: 0.0, 0.25, 0.5, 0.75, 1, 2, 3, 5, 7, 10, 15, 20, 25, 30, 40, and 45 min. Forty-five minutes after the administration of the [^{14}C]deoxyglucose tracer, animals were sacrificed by an intravenous overdose of sodium pentobarbital.

Brains were rapidly removed, and frozen in isopentane (−50°C). Brains were then coated with embedding medium and stored in a freezer at −70°C and were sliced later on a coronal plane at −15 to −20 °C in a cryostat set for 20 μm sections. Every third section was placed on a glass slide cover, dried on a standard slide-warming tray at 65°C and then placed against Kodak SB-5 X-ray films along with a set of [^{14}C]methylmethacrylate standards (Amersham, [^{14}C] Micro-Scales

RPA 504L) previously calibrated for their equivalent ^{14}C concentration in 20 μm brain sections.

Slides containing tissue sections from the four experimental groups were randomized and placed in cassettes with calibrated Amersham standards [^{14}C]microscales. The Kodak SB-5 film was placed upon the brain sections in each prepared cassette and the cassette was closed. The resulting autoradiographs were analyzed using quantitative densitometry with a computerized-image processing system (MCID, BRS2). Tissue tracer concentrations were determined by densitometry of the autoradiograms with reference to the actual polymer activity value provided by the calibrated standards of Amersham, [^{14}C] micro-scales RPA 504L. Rates of local cerebral glucose utilization were then calculated from the local tissue [^{14}C]-concentrations, the time course of the plasma [^{14}C]deoxyglucose and glucose concentrations and the published constants derived using the operational equation of Sokoloff et al. (1977).

Statistical Analysis

Rates of local cerebral glucose utilization were measured in 43 brain areas. Data were analyzed by a 2×2 (Saline/MAP $\times$ 14 day/60 day) analysis of variance for each structure.

RESULTS

The effects of multiple injections (4 times, every 2 hr within a day) of 12.5 mg/kg MAP on LCGU 14 or 60 days after administration of drug is shown in Table 1. Administration of this dose of MAP resulted in signs of neurotoxicity (convulsions, hyperthermia, penile erection, hypermotility, stereotypy, and death) and a widespread reduction on LCGU. The main effect of drug treatment on LCGU was seen in 26 of 43 brain regions examined. Decreased LCGU was found in the entire extrapyramidal system. A decrease on LCGU in the prefrontal cortex (19% decrease in the 60 day MAP group as compared to that of the 60 day control) barely failed to reach statistical significance (ANOVA; $p = .054$). However, a significant decrease (21% decrease in the 60 day group, Duncan test; $p < .05$) was found in the anterior cingulate cortex (Figure 1). No significant decrease on LCGU was found in the nucleus accumbens. Significant decreases in LCGUs were also seen in the dorsal raphe and the hippocampus formation (26% and 25% decrease, respectively, in the 60 day group, Duncan test; $p < .05$).

The main effect of the abstinent period was found to be significant in two regions. In the substantia nigra pars reticulata, rats studied after 60 days had significant lower LCGU than rats studied after 14 days. However, in the anterior cingulate cortex, the results were divergent. We also found that in the other neocortex, rats studied after 60 days had generally higher LCGU when compared with the 14-day groups with the same drug treatment. There was no interaction of the two main effects, so we will not make further analysis of the simple effects between groups.

DISCUSSION

In this study, quantitative [^{14}C]-2-deoxyglucose autoradiography was used to demonstrate that administration of four consecutive intraperitoneal injections of MAP of 12.5 mg/kg, given at 2 hr intervals within a day, in rats leads to a wide spread reduction (26 of the 43 regions examined) on LCGU when measured either 14 or 60 days after the administration. In a previous study, we used the 2DG method to study regional metabolic change in rats seven days after repeated amphetamine treatment (1.0, 5.0, or 10.0 mg/kg, once per day for 14 consecutive days) (Tsai et al. 1995). The result showed that in the 1.0 and 5.0 mg/kg groups, only 2 in 23 regions examined had mild increase LCGU when compared with the saline group. The difference between the previous study and the present study may be due to dose of drug.

LCGU is thought to reflect predominantly activity in the nerve terminals as opposed to the cell bodies and LCGU could be seen as an index of the synaptic activity (Mata et al. 1980). Thus, the 2DG method is useful to study MAP neurotoxicity which causes destruction of nerve terminals and decreases monoamine reuptake. The magnitude of the decreased LCGU in this study varied widely among different brain regions. This finding is compatible with the previous report that regional variability in the neurotoxic effects of MAP (Ricaurte et al. 1980; Ryan et al. 1990). In addition, we have new findings with the 2DG method which has special features reflecting change in synaptic activity, showing either direct or indirect drug effect and examining many regions simultaneously in the whole brain.

Repeated administration of high doses of MAP results in depletion of striatal dopamine in rats which lasted for at least eight weeks after the injection period, and were accompanied by loss of striatal dopamine uptake sites (Wagner et al. 1980). In this study, we demonstrated that the metabolic change in the striatum lasted at least 60 days after termination of drug treatment. In addition, the LCGU changes in the extrapyramidal system were widespread, including the globus pallidus, the substantia nigra pars compacta, the substantia nigra pars reticulata and the subthalamic nucleus. There are several possible explanations for these findings. First, these regions may have direct neurotoxic effects from repeated

Table 1. Effects of Repeated Administration (MAP: 12.5mg/kg, i.p., Four Injections, Given at 2 h Intervals within a day) of Methamphetamine (MAP) and Abstinent Period (DAY) on Local Cerebral Glucose Utilization (Mean ± S.E.M. μmol/100 g/min) in Rats

Structure	NS (14D) (n = 5)	MAP (14D) (n = 5)	NS(60D) (n = 5)	MAP (60D) (n = 6)	MAP	DAY
Extrapyramidal system						
Striatum	107 ± 7	89 ± 13	98 ± 4	82 ± 4	0.037[a]	0.288
Globus pallidus	59 ± 7	44 ± 3	53 ± 4	45 ± 1	0.010[b]	0.645
Substantia nigra pars compacta	79 ± 5	65 ± 5	80 ± 5	65 ± 2	0.004[b]	0.887
Substantia nigra pars reticulata	69 ± 5	58 ± 5	57 ± 5	44 ± 1	0.004[b]	0.004[b]
Subthalamic nucleus	94 ± 8	87 ± 8	99 ± 8	75 ± 3	0.033[a]	0.551
Limbic and related areas						
Anterior pretectal nucleus	99 ± 9	86 ± 6	95 ± 7	80 ± 2	0.029[a]	0.429
Arcuate nucleus	44 ± 4	47 ± 4	52 ± 5	44 ± 3	0.595	0.612
Basomedial amygdala	55 ± 6	55 ± 4	54 ± 7	46 ± 2	0.402	0.322
Central amygdala	77 ± 8	69 ± 6	84 ± 7	68 ± 2	0.065	0.651
Hippocampus formation (CA1)	83 ± 6	74 ± 6	92 ± 9	69 ± 2	0.019[a]	0.763
Interpeduncular nucleus	114 ± 13	96 ± 7	107 ± 10	93 ± 5	0.099	0.571
Lateral habenular nucleus	120 ± 12	100 ± 7	113 ± 8	91 ± 3	0.014[a]	0.314
Lateral septal nucleus	71 ± 6	52 ± 3	70 ± 3	54 ± 3	0.001[b]	0.938
Medial mamillary nucleus	134 ± 22	92 ± 6	108 ± 7	85 ± 1	0.016[a]	0.198
Medial preoptic nucleus	52 ± 5	48 ± 4	54 ± 4	49 ± 2	0.238	0.688
Medial septal nucleus	69 ± 6	51 ± 3	70 ± 4	54 ± 3	0.001[b]	0.685
Nucleus accumbens						
core	86 ± 6	86 ± 15	78 ± 3	76 ± 3	0.835	0.263
shell	87 ± 6	89 ± 15	79 ± 2	76 ± 4	0.955	0.203
Nucleus diagonal band of Broca						
horizontal limb	80 ± 7	60 ± 5	74 ± 4	60 ± 3	0.003[b]	0.644
vertical limb	82 ± 7	62 ± 4	79 ± 4	63 ± 3	0.001[b]	0.820
Paraventricular nucleus, hypothalamus	66 ± 7	57 ± 4	68 ± 6	55 ± 2	0.039[a]	0.999
Posterior cingulate cortex	115 ± 8	98 ± 9	108 ± 8	91 ± 3	0.025[a]	0.341
Ventral tegmental areas	75 ± 4	63 ± 4	71 ± 5	57 ± 2	0.003[b]	0.209
Ventromedial nucleus, hypothalamus	50 ± 4	54 ± 4	57 ± 6	48 ± 2	0.419	0.986
Neocortex						
Anterior cingulate cortex	109 ± 13	83 ± 11	132 ± 10	104 ± 3	0.009[b]	0.029[a]
Anterior orbital cortex	141 ± 13	137 ± 23	151 ± 9	123 ± 6	0.224	0.855
Auditory cortex	167 ± 11	135 ± 16	165 ± 16	139 ± 3	0.032[a]	0.912
Frontal cortex	98 ± 9	91 ± 15	114 ± 6	100 ± 7	0.309	0.209
Medial prefrontal cortex	107 ± 9	97 ± 14	129 ± 4	104 ± 4	0.054	0.122
Motor cortex	118 ± 11	93 ± 13	121 ± 7	102 ± 5	0.027[a]	0.508
Somatosensory cortex I	125 ± 7	88 ± 13	131 ± 7	102 ± 3	0.000[b]	0.180
Somatosensory cortex II	155 ± 11	147 ± 7	163 ± 7	139 ± 5	0.043[a]	0.992
Other regions						
Centromedial nucleus, thalamus	99 ± 8	87 ± 8	97 ± 8	84 ± 3	0.081	0.727
Dorsal raphe	97 ± 9	79 ± 6	99 ± 8	73 ± 2	0.003[b]	0.735
Medial geniculate nucleus	114 ± 7	100 ± 11	108 ± 6	89 ± 2	0.026[a]	0.210
Mediodorsal nucleus, thalamus	111 ± 9	95 ± 7	107 ± 11	89 ± 4	0.055	0.558
Parafasicular nucleus	102 ± 9	97 ± 9	91 ± 7	79 ± 4	0.254	0.060
Paratenial nucleus	93 ± 7	77 ± 8	99 ± 8	84 ± 4	0.033[a]	0.342
Reunion nucleus, thalamus	94 ± 8	80 ± 7	98 ± 9	87 ± 3	0.092	0.419
Superior colliculus	87 ± 6	81 ± 8	99 ± 10	74 ± 1	0.027[a]	0.758
Ventrobasal nucleus, thalamus	82 ± 10	82 ± 3	103 ± 6	83 ± 3	0.096	0.096
Ventromedial nucleus, thalamus	109 ± 11	91 ± 8	110 ± 6	93 ± 2	0.025[a]	0.854

14D: tested 14 days after repeated injections.
60D: tested 60 days after repeated injection.
There is no interaction between the two main effects.
[a] $p < .05$.
[b] $p < .01$.

MAP treatment. The substantia nigra pars reticulata receives dopaminergic innervation from the striatum and exhibits high densities of D1 receptors which appear to be expressed on the terminals of striatal projection neurons (Harrison et al. 1990). In a previous MAP neurotoxic study, monoamine depletion were pronounced in both the neostriatum and the substantia nigra which may explain the decrease LCGU in these two regions in our

study (Ricaurte et al. 1980). Second, the LCGU change may be an indirect effect of MAP neurotoxicity. The striatal DA D2 receptor-associated output is mediated primarily through the globus pallidus and the major afferent to the subthalamic nucleus is a GABAergic projection from the globus pallidus (Carpenter et al. 1981; Ogren and Fuxe 1988). Both the globus pallidus and the subthalamic nucleus contain relative few DA D2 receptors (Boyson et al. 1986). Ryan et al. (1990) used silver staining to reveal degeneration in the striatum but not in the globus pallidus after continuous administration of amphetamine. Using the quantitative [14C]-2DG method, Lyons and Porrino (1997) found that the unilateral 6-hydroxydopamine lesions of the rostral accumbens in Sprague-Dawley rats blunted the response to cocaine effects in both sides of the shell of the nucleus accumbens, globus pallidus and the medial ventral pallidum. Since an entire pathway or circuit may be metabolically activated even though the direct action of a stimulus may occur at the origin or at some point along the pathway, a decrease on glucose utilization in response to repeated MAP treatment most likely reflects decreased activity in the striatal-pallidal-subthalamic pathways.

A decrease in LCGU in the prefrontal cortex just failed to reach statistical significance ($p = .054$) in this study. This finding is of importance because the negative symptoms in schizophrenia has been postulated to due to hypofunction of the prefrontal cortex (Weinberger et al. 1988). In addition, Cadet et al. (1987) proposed the concept of 'schizophrenia burnout' that where positive symptoms dominate initially but later yield to negative symptoms. This may be due to the formation of free radicals during an initial hyperdopaminergic state, leading to degeneration of dopaminergic neurons with resultant negative symptoms. Our finding and the clinical expression of negative symptoms in some MAP psychotics suggest the MAP neurotoxicity in rats may be used as an animal model in the study of the negative symptoms.

The rate of glucose utilization in the hippocampus was decreased in MAP-treated groups. Although the hippocampus contains few dopaminergic receptors, its major afferent projections arise from a region, the lateral septal nucleus, which contain dopaminergic nerve terminal. The lateral septal nucleus was also found to decrease LCGU in this study. Thus, the decrease LCGU may be an indirect effect of MAP neurotoxicity. However, the hippocampus also is innervated by the dorsal raphe efferents. Brunswick et al. (1992) had demonstrated that high-dose MAP can decrease serotonin uptake site in this region. Sharkey et al. (1991) examined the effects of repeated methylenedioxymethamphetamine (MDMA 20 mg/kg, s.c., twice daily for 4 days, 14 days later) upon hippocampal function by using the [14C]-2DG and [3H] paroxetine 5-HT binding site autoradiographic methods and found that profound losses of [3H] paroxetine labelled uptake sites accompanied by significant increases in LCGU in the hippocampal fields CA2, CA3 and dentate gyrus. Recently, a growing body of data points to structural alterations of the hippocampus in schizophrenia (Conrad and Scheibel 1987; Scheibel and Conrad 1993). The metabolic change in the hippocampus after repeated MAP administration suggested that this area is a potential region for the development of MAP psychosis.

In this study, the dorsal raphe was found to decrease LCGU significantly with MAP treatment. It is of interest that serotonergic raphe bodies appear to be resistant to the neurotoxic effects of a number of neurotoxic amphetamine-like compounds (Brunswick et al. 1992) The discrepancy may be due to the study method because the 2DG method detects the change in the synaptic activity rather than the neuron body.

Previous reports have suggested that the hypothalamus is relative refractoriness to MAP toxicological stress (Ricaurte et al. 1980) The finding that repeated MAP produced a metabolic change in some hypothalamic regions is significant in two respects. First, the metabolic change in these regions with decreased LCGU may be an indirect effect of the neurotoxic response to MAP administration. Second, 2DG method may be a more sensitive method in detecting the neurotoxic effect in these regions.

Both, the striatum and the nucleus accumbens are known to be innervated by dopamine-containing nerve terminals. However, in this study, we did not find metabolic change in the nucleus accumbens after MAP treatment. The failure to observe any significant changes on metabolic rate in the present work does not necessarily preclude involvement of this structure. First, it may reflect the limited resolution of the 2DG method itself or the heterogeneity of the nucleus accumbens. The size of the dopamine or serotonin depletion induced by Map may be insufficiently large to produce regional LCGU decrease. Second, various central dopamine neurons do not respond in a uniform fashion to pharmacological manipulations. It is possible that the nucleus accumbens are more resistant than the striatum to the neurotoxic effects of MAP. Previous studies show similar findings (Umezu and Moore 1979; Ryan et al. 1990; Cass 1997). Third, the absence of metabolic change may be due to compensatory changes in the injured neuronal fiber or in the pathway. Finally, the regional susceptibility may depend on the species of animals studied or the individual vulnerability to the drug. The early study by Pontieri et al. (1991) involved significantly larger doses of MAP (50 mg/kg, twice a day for 4 days) and demonstrated that only rats have initial sensitive response to MAP administration showed decreased LCGU in the nucleus accumbens after chronic exposure to this high dose MAP. Even with this high dose, there was a subgroup of rats that were non-sensi-

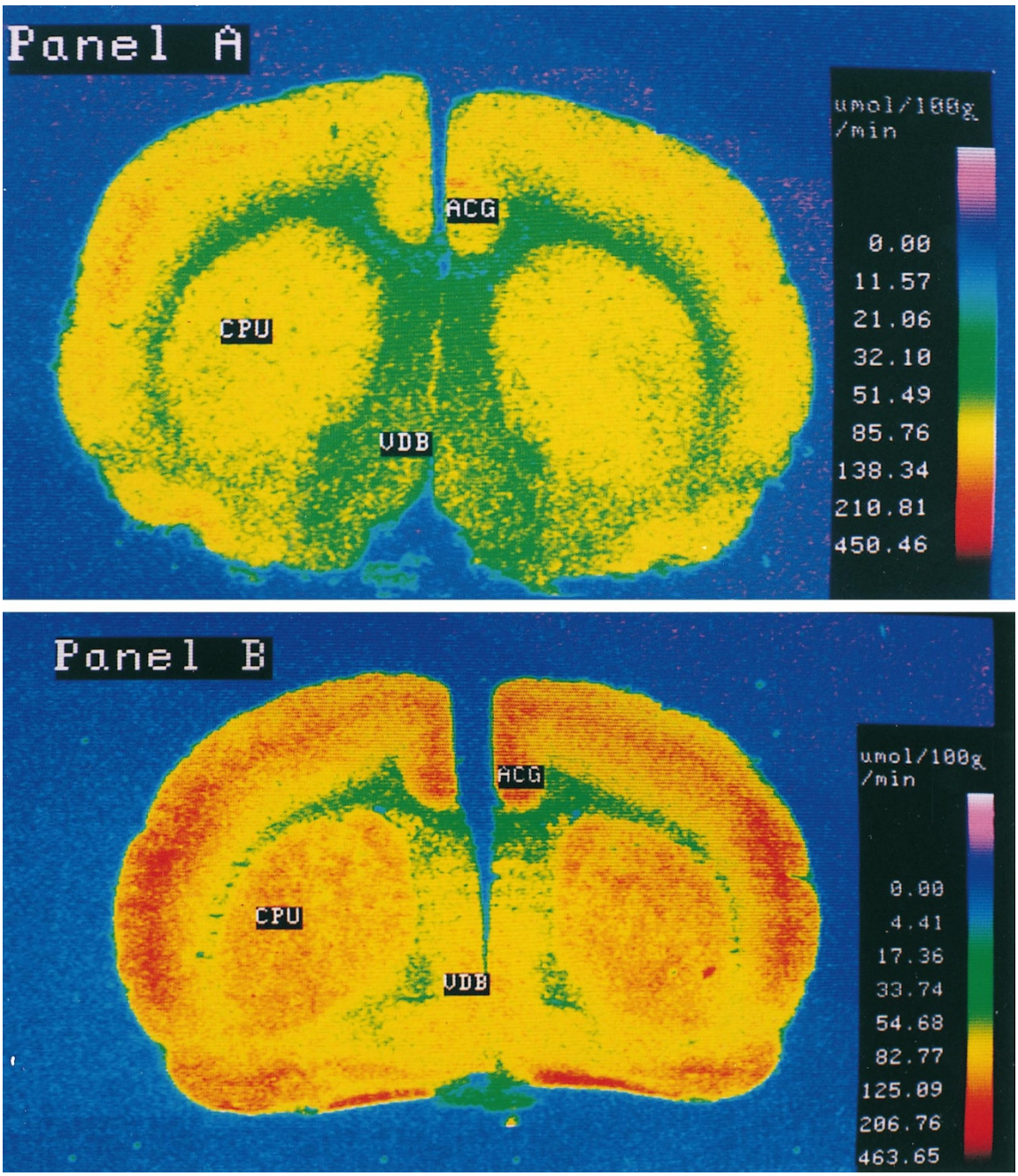

Figure 1. Effects of repeated administration (12.5 mg/kg, i.p., four injections, given at 2 hr intervals within a day) of methamphetamine (MAP), followed by a 60-day abstinent period (MAP group) on the local cerebral glucose utilization (LCGU, mean ± s.e.m ; μmol/100 g/min) of the striatum and anterior cingulate gyrus in rats, as compared to that of the saline control group (saline, i.p., four injections, given at 2 hr intervals within a day). Panel A: MAP group rat , ACG = 104 ± 3; CPU = 82 ± 4; VDB = 63 ± 3. Panel B: Saline control group rat, ACG = 132 ± 10; CPU = 98 ± 4; VDB = 79 ± 4. Significant reduction (Duncan test, $p < .05$) in the LCGU of the 60-day MAP group, as compared to that of the 60-day control group was found in the ACG and VDB with a reduction of 21% and 20%, respectively. This finding is closely related to the neurotoxicity caused by this regimen of the administration of repeated high doses of MAP. ACG, anterior cingulate gyrus; CPU, caudatoputamen, striatum; VDB, ventral limb, diagonal band of Broca.

tive and that did not exhibit any significant behavior changes or changes in glucose metabolism. In another study, neuron degeneration was seen more frequently in the Long-Evans than in the Sprague-Dawley rats (Ryan et al. 1990). This phenomenon can explain why only part of the MAP abuser developed psychosis and, among the MAP psychotics, some have permanent psychosis or negative symptoms.

In summary, the results of the current study provide evidence for the reduction of LCGU after repeated MAP administration. The metabolic change is highly regional and lasted for at least 60 days after MAP administration. We suggested the MAP neurotoxic model can be used to study the permanent psychosis and negative symptoms of MAP-induced psychosis in humans.

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