Effects of Ketamine, MK-801, and Amphetamine on Regional Brain 2-Deoxyglucose Uptake in Freely Moving Mice

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Although the pathophysiology of schizophrenia remains unclear, behavioral effects in humans induced by N-methyl-D-aspartate (NMDA) antagonists, such as ketamine, provide direction for formulating new pharmacologic models of the illness. The purpose of the present study was to clarify the roles of NMDA receptor antagonism, as well as dopamine-releasing properties of ketamine, in regional brain metabolic activity and behavioral responses in mice. The effects of acute administration of ketamine (30 mg/kg, i.p.) were compared with those of the more selective non-competitive NMDA antagonist MK-801 (0.3 and 0.5 mg/kg, i.p.), and amphetamine (4 mg/kg, i.p.) on regional brain [¹⁴C]-2-deoxyglucose (2-DG) uptake, by using a high resolution autoradiographic technique in the freely moving mice. Both ketamine and MK-801 induced substantial and similar neuroanatomically selective alterations in regional 2-DG uptake. Remarkable increases in 2-DG uptake in response to the NMDA antagonists were seen in limbic

cortical regions, hippocampal formation, nucleus accumbens, select thalamic nuclei, and basolateral amygdala. The behavior of mice given amphetamine was similar to that of mice given MK-801. However, the brain activity patterns induced by amphetamine were distinctly different from those observed after ketamine and MK-801 treatment. These results suggest that generalized behavioral activation and increased dopamine release are insufficient to account for the ketamine-induced alterations in regional brain metabolism, and that the effects of ketamine on 2-DG uptake are likely related to a reduction in NMDA receptor function. The data also suggest that ketamine-induced changes in 2-DG uptake may provide a useful paradigm for translational research to better understand the pathophysiology of schizophrenia.

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Although the etiology and pathophysiology of schizophrenia have not yet been elucidated, consistent clinical observations associated with a pharmacological challenge with N-methyl-D-aspartate (NMDA) antagonists provide direction for formulating new pharmacological models of the illness. Since the late 1950s, phenylcyclidine (PCP), a potent non-competitive NMDA antagonist, has been known to induce psychotic symptoms in healthy humans that resemble some features of schizophrenia (Luby et al. 1959; Davies and Beech 1960; Bakker and Amini 1961; Allen and Young 1978; Javitt and

Zukin 1991). Recently, it has been shown that subanesthetic doses of ketamine, a non-competitive NMDA receptor antagonist, can induce positive, negative, and cognitive schizophrenia-like symptoms in normal humans (Krystal et al. 1994; Malhotra et al. 1996, 1997; Breier et al. 1997, 1998; Adler et al. 1998; Krystal et al. 1998; Newcomer et al. 1999). In chronic stabilized schizophrenic patients, subanesthetic doses of ketamine can exacerbate cognitive impairment and induce positive psychotic symptoms that mimic the active episodes of their illness (Lahti et al. 1995a, 1995b; Malhotra et al. 1997). These clinical findings have led to the hypothesis that hypofunction of NMDA receptors in the central nervous system (CNS) is involved in the pathophysiology of schizophrenia (Deutsch et al. 1989; Olney 1989; Javitt and Zukin 1991; Ulas and Cotman 1993; Olney and Farber 1995; Coyle 1996; Jentsch and Roth 1999).

The well-documented psychotomimetic effects of NMDA antagonists in humans suggest that effects of the drugs in experimental animals could represent useful pharmacological models of schizophrenia. In our recent studies, striking effects of subanesthetic doses of ketamine were observed on regional patterns of ^{14}C -2-deoxyglucose (2-DG) uptake in the rat brain (Duncan et al. 1998a, 1998b, 1999). Administration of subanesthetic doses of ketamine to rats increased 2-DG uptake in neuroanatomically specific brain regions (Duncan et al. 1998a, 1999). Ketamine-induced metabolic activation was blocked by the atypical antipsychotic drug clozapine, but not by the typical antipsychotic haloperidol (Duncan et al. 1998b). Therefore, defining neurochemical mechanisms responsible for the brain metabolic effects induced by ketamine in laboratory animals could suggest potential pathophysiological mechanisms in schizophrenia and pharmacotherapeutic actions of atypical antipsychotic drugs.

Studies of the effects of NMDA antagonists such as ketamine on brain 2-DG uptake have been limited to rats (Hawkins et al. 1979; Nelson et al. 1980; Crosby et al. 1982; Oguchi et al. 1982; Hammer and Herkenham 1983; Davis et al. 1988; Kurumaji et al. 1989; Duncan et al. 1998a, 1998b, 1999). The availability of transgenic mice deficient in specific dopamine, serotonin, or NMDA receptor subunits may present an opportunity to define neurochemical mechanisms of ketamine-induced metabolic responses and effects of antipsychotic drugs in the 2-DG-ketamine challenge model. For example, the paradigm of NMDA antagonist-induced alterations in brain 2-DG uptake in transgenic mice could be a useful tool to explore the potential involvement of individual neurotransmitter receptor subtypes in the mechanisms of action of antipsychotic drugs, as well as ketamine itself. The goal of the present study was to characterize the neurobiological responses to NMDA antagonist administration in mice.

While ketamine has well-documented NMDA receptor antagonistic properties, the drug has a number of other pharmacological actions in the CNS. Ketamine acts on opiate receptors (Smith et al. 1980), sigma receptors (Øye et al.

1991), monoaminergic systems (Ylitalo et al. 1976; Smith et al. 1981; Irifune et al. 1991, 1997; Lindefors et al. 1997), and cholinergic systems (Cohen et al. 1974; Scheller et al. 1996). The potency of ketamine at opiate, sigma, monoaminergic, and cholinergic receptors is considerably lower in comparison to NMDA antagonistic properties of the drug (Smith et al. 1980; Øye et al. 1991). However, exactly which molecular mechanisms mediate the effect of ketamine on behavior and regional brain metabolic activity remains unclear. Thus, one purpose of the present study was to clarify the role of NMDA receptor antagonism in ketamine-induced alterations in brain metabolic patterns in mice, by comparing the effects of ketamine with the more selective NMDA antagonist MK-801.

NMDA antagonists, including ketamine and MK-801, increase dopamine metabolism and release in several brain regions in rodents (Doherty et al. 1980; Rao et al. 1989; Wędzony et al. 1993; Hondo et al. 1994; Verma and Moghaddam 1996; Irifune et al. 1997; Lindefors et al. 1997; Adams and Moghaddam 1998; Irifune et al. 1998). Activation of dopaminergic systems may participate in certain behavioral effects induced by NMDA antagonists, since behavioral responses to NMDA receptor antagonists are, at least in part, suppressed by dopamine receptor antagonists in rats and mice (Corbett et al. 1995; Irifune et al. 1995; Lapin and Rogawski 1995; Verma and Moghaddam 1996). To determine the involvement of dopamine-releasing properties of ketamine and MK-801 on regional 2-DG uptake, effects of these drugs were compared to those of amphetamine, which is well known to robustly induce dopamine release (Snyder et al. 1972; Zetterstrom et al. 1983; Carboni et al. 1989; Kuczenski and Segal 1989). Comparison of the effects of amphetamine with those of ketamine and MK-801 also allows assessment of the role of generalized behavioral arousal and increased locomotor activity after 2-DG uptake induced by the NMDA antagonists.

MATERIALS AND METHODS

Animals

Twenty-six male ICR mice (Harlan Laboratories) weighing 37–49 g were used. The mice were housed under a 12 h light-dark cycle with lights on at 0700 h and had continuous access to food and water. All animal use procedures were in strict accordance with the National Institute of Health (NIH) Guide for the Care and Use of Laboratory Animals and were approved by the University of North Carolina Institutional Animal Care Committee.

High Resolution Autoradiographic Analysis of ^{14}C -2-DG Uptake

The high-resolution autoradiographic procedures for analysis of ^{14}C -2-deoxyglucose (2-DG) uptake were performed according to the method described previ-

ously (Duncan and Stumpf 1990, 1991; Duncan 1992) with the following slight modifications. Mice were transported from the animal quarters to the laboratory and singly housed for 3 h before initiation of the 2-DG experiment. Mice exhibited minimal locomotor activity after this habituation period. Ketamine (30 mg/kg), MK-801 (0.3 or 0.5 mg/kg), amphetamine (4 mg/kg), or 0.9% saline was injected i.p. (4–7 mice/treatment condition). The doses of drugs tested in the 2-DG paradigm were chosen based on preliminary behavioral studies. For ketamine, 30 mg/kg was found to be an optimal dose for locomotor activation. At lower doses of ketamine (15–20 mg/kg), less robust and less consistent locomotor activity was induced, while at higher doses (40–50 mg/kg), sedation and flat body posture with minimal locomotion was observed. For MK-801, the greatest locomotor activation was observed for 0.3–0.5 mg/kg. At 1.0 mg/kg, marked ataxia and stereotypic behavior were observed. For amphetamine, the most consistent and greatest locomotor stimulation was observed at 4 mg/kg. At higher doses (6 mg/kg and greater), the mice exhibited primarily stereotypic sniffing and rearing. Thus, the doses of drugs were chosen to induce a similar degree and quality of behavioral activation.

The 2-DG (American Radiolabeled Chemicals, 300 mCi/mmol, 1.5 μ Ci/g body weight) was injected i.p. 30 min after injection of MK-801, amphetamine, or saline. Maximal behavioral activation was observed after this time for MK-801 and amphetamine. Ketamine has a considerably shorter half-life than that of MK-801 (Reich and Silvey 1989; Vezzani et al. 1989), and a more rapid onset of behavioral activation. In preliminary studies, we found that behavioral activation was observed within 1 min after i.p. injection of ketamine and lasted for approximately 20 min. Therefore, ketamine was administered i.p. 1 min before injection of 2-DG because of the rapid onset and brief duration of behavioral activation induced by the NMDA antagonist. The robust behavioral responses induced by ketamine, MK-801, and amphetamine persisted for the duration of the 2-DG uptake period. The mice were killed by decapitation 15 min after the i.p. injection of 2-DG, in order for the period of 2-DG uptake to correspond to maximum behavioral effects of ketamine. The brains were removed and frozen on an aluminum block cooled with liquid nitrogen and stored at -80°C until sectioned. Kodak SR1 Industrex film was cut into rectangular pieces approximately $3/4$ the length of microscope slides and glued to one end of the slides with Silicone adhesive. The frozen brains were cut into 10 μm coronal or horizontal sections at -25 – -28°C in a cryostat and the sections were thaw-mounted directly onto the side-mounted film under safe-light conditions, and stored in light-tight desiccator boxes at room temperature for exposure periods of 2–4 weeks. Autoradiograms were digitized with a high-resolution scanner (Linotype-Hell, Saphir, Ultra,

Happauge NY) and quantified using NIH Image Software. The optical densities in autoradiograms were in the linear range of the film as assessed in relation to ^{14}C -standards (Amersham Microscale). Data are expressed as ratios of optical density in gray matter regions relative to that in the corpus callosum as previously described (Duncan et al. 1993).

Statistical Analysis

Regions of interest were chosen for quantitative analysis based on previous studies of effects of NMDA antagonists in rats (Duncan et al. 1998a, 1998b, 1999), and qualitative analysis of the 2-DG autoradiograms in mice. Given the relatively small number of mice examined for each condition, only large effect size would be expected to be detected in this study. PC-based SYSTAT software (version 6.0; SPSS, Chicago, IL) was used for statistical analysis. Comparison of treatment groups for 2-DG uptake data was performed by repeated measures analysis of variance. When significant F values were found ($p < .05$), pair-wise comparisons of 2-DG uptake for individual brain regions between treatment groups were made by Dunnett's tests.

RESULTS

Behavior

Administration of a subanesthetic dose of ketamine induced a characteristic behavioral response consisting primarily of side-to-side head rocking or continuous staggered locomotion. MK-801 (0.3 mg/kg) induced a state of continuous locomotor activity with quick gait but no staggering was noted. The mice treated with 0.5 mg/kg MK-801 exhibited continuous staggered locomotion, but the side-to-side head rocking seen after ketamine administration was not observed. The behavior of mice given amphetamine was qualitatively indistinguishable from that of mice given 0.3 mg/kg MK-801.

Regional 2-DG Uptake

Overview. Pronounced and neuroanatomically selective alterations in patterns of 2-DG uptake were observed after administration of ketamine, MK-801, and amphetamine. The regional patterns of 2-DG uptake observed after administration of ketamine and MK-801 were similar. The alterations in regional 2-DG uptake in response to amphetamine were strikingly different from those induced by ketamine and MK-801. Photomicrographs of representative autoradiograms are shown in Figures 1–4, and the quantitative data of relative 2-DG uptake in regions examined are presented in Table 1.

Cortical Regions. In saline-treated control mice, a con-

Figure 1. Autoradiograms of $[^{14}\text{C}]\text{-2-DG}$ uptake prepared from coronal brain sections. Mice were injected i.p. with saline, ketamine (30 mg/kg), MK-801 (0.5 mg/kg), or amphetamine (4 mg/kg). Abbreviations: MFC, medial prefrontal cortex; Acb, nucleus accumbens; Cing, cingulate cortex; CPu, caudate putamen; III/IV, somatosensory cortex, layers 3 and 4; AV, anterior ventral thalamic nucleus; Rspl, retrosplenial cortex; LD, lateral dorsal thalamic nucleus; SLM, stratum lacunosum moleculare of the hippocampus; F, fornix; APT, anterior pretectal nucleus; SN, substantia nigra.

Figure 2. Autoradiograms of [^{14}C]-2-DG uptake prepared from horizontal brain sections. Mice were injected i.p. with saline, ketamine (30 mg/kg), MK-801 (0.5 mg/kg), or amphetamine (4 mg/kg). Abbreviations: Rspl, retrosplenial cortex; IC, inferior colliculus; MFC, medial prefrontal cortex; Sub, subiculum; LD, lateral dorsal thalamic nucleus; Hip, hippocampus; CPu, caudate putamen; Ent, entorhinal cortex; SLM, stratum lacunosum moleculare of the hippocampus; AV, anterior ventral thalamic nucleus; SN, substantia nigra; Acb, nucleus accumbens.

Figure 3. Autoradiograms of [^{14}C]-2-DG uptake prepared from coronal brain sections at the level of the dorsal hippocampus. Mice were injected i.p. with saline, ketamine (30 mg/kg), MK-801 (0.5 mg/kg), or amphetamine (4 mg/kg). Abbreviations: Rspl, retrosplenial cortex; III/IV, somatosensory cortex, layers 3 and 4; SLM, stratum lacunosum moleculare of the hippocampus; Lhab, lateral habenular nucleus.

sistent laminar pattern of 2-DG uptake was observed in isocortical regions and relatively high 2-DG uptake was seen in layers 3 and 4. This notably higher uptake in layers 3 and 4 was prominent in the somatosensory cortex (Figures 1 and 3). After ketamine and MK-801 administration, decreases in 2-DG uptake were observed in layers 3 and 4 of the somatosensory cortex and slight increases in uptake were noted in layer 6 of this region (Figures 1 and 3). Amphetamine treatment increased 2-DG uptake in certain regions of the somatosensory cortex in what appeared to be vertical columns (Figure 1). Such columnar activation was not observed in any mouse treated with saline, ketamine, or MK-801. Other isocortical regions showed high relative uptake in layers 3 and 4 after amphetamine administration, similar to those in saline treated mice (Figures 1 and 2).

In allocortical regions, ketamine and MK-801 showed very similar patterns of activation. In particular, the high dose of MK-801 (0.5 mg/kg) induced quantitatively similar effects as ketamine (30 mg/kg) (Table 1). Increases in 2-DG uptake were seen in the medial prefrontal (the area defined as prelimbic cortex by Franklin and Paxinos (1997)), ventrolateral orbital, cingulate, retrosplenial, and entorhinal cortices after administration

of ketamine and MK-801 (0.5 mg/kg) (Figures 1–4). In the retrosplenial cortex, the most intense activation was observed in layer 1 for both ketamine and MK-801 (0.5 mg/kg) treated mice (Figure 3). A distinct laminar pattern of activation was seen in the entorhinal cortex after administration of ketamine and MK-801 (Figure 2).

Amphetamine treatment did not increase 2-DG uptake in the medial prefrontal or entorhinal cortical regions (Figures 1, 2, and 4). However, an activation of 2-DG uptake was seen in the ventrolateral orbital, cingulate, and retrosplenial cortices, but the effect was slightly less than that seen with ketamine or MK-801 (0.5 mg/kg) (Figures 1 and 3).

Hippocampal Formation. Pronounced increases in 2-DG uptake were observed after both ketamine and MK-801 administration in the hippocampal formation (Figure 3). The greatest increases in response to the NMDA antagonists were found in the stratum lacunosum moleculare, and these effects were more pronounced in more caudal parts of this region (Figures 1 and 2). The molecular layer of the dentate gyrus, the ventral subiculum, and CA-3 stratum radiatum also showed increased 2-DG uptake, but the increases were

Figure 4. Autoradiograms of [¹⁴C]-2-DG uptake prepared from horizontal brain sections at the level of the inferior colliculus. Mice were injected i.p. with saline, ketamine (30 mg/kg), MK-801 (0.5 mg/kg), or amphetamine (4 mg/kg). Abbreviations: IC, inferior colliculus; Sub, subiculum; SLM, stratum lacunosum moleculare of the hippocampus; LD, lateral dorsal thalamic nucleus; MFC, medial prefrontal cortex.

less than those of the stratum lacunosum moleculare (Figures 3 and 4). There were no apparent effects of ketamine or MK-801 on 2-DG uptake in the CA-1 stratum radiatum or pyramidal cells layer (Figure 3). In contrast to the prominent effects of ketamine and MK-801 on hippocampal 2-DG uptake, no apparent augmentation in relative uptake was seen after amphetamine treatment in any hippocampal subregion (Figure 3).

Amygdala. The basolateral nucleus of the amygdala

showed increased 2-DG uptake in response to ketamine and MK-801 and the greatest increases in metabolic activity were seen in more rostral regions of this nucleus (Figure 1). Uptake of 2-DG was not changed in other regions of the amygdala, by either ketamine or MK-801. In contrast to ketamine and MK-801, no changes in relative 2-DG uptake were apparent in any part of the amygdala following amphetamine administration (Figure 1).

Thalamus and Subthalamic Regions. The anterior ven-

Table 1. Relative 2-DG Uptake in Response to Ketamine, MK-801, and Amphetamine

Brain regions	Saline (n = 5)	Ketamine (30 mg/kg) (n = 6)	MK-801 (0.3 mg/kg) (n = 4)	MK-801 (0.5 mg/kg) (n = 4)	Amphetamine (4 mg/kg) (n = 7)
Medial prefrontal cortex	1.53 ± 0.08	1.88 ± 0.08*	1.71 ± 0.16	1.95 ± 0.07*	1.63 ± 0.06
Ventrolateral orbital cortex	1.64 ± 0.12	1.90 ± 0.10	1.67 ± 0.07	1.96 ± 0.07*	2.01 ± 0.14*
Nucleus accumbens	1.50 ± 0.09	1.93 ± 0.15*	1.73 ± 0.05	1.91 ± 0.11*	1.56 ± 0.08
Caudate putamen	1.86 ± 0.03	2.42 ± 0.09*	2.04 ± 0.06	2.30 ± 0.24*	1.96 ± 0.09
Cingulate cortex	1.74 ± 0.15	2.15 ± 0.12*	1.74 ± 0.08	2.27 ± 0.20*	2.06 ± 0.13
Retrosplenial cortex	1.70 ± 0.13	2.05 ± 0.06*	1.84 ± 0.10	2.18 ± 0.18*	1.99 ± 0.08
Medial septal nucleus	1.68 ± 0.17	1.70 ± 0.06	1.63 ± 0.18	1.86 ± 0.04	2.26 ± 0.14*
Globus pallidus	1.63 ± 0.09	1.71 ± 0.05	1.73 ± 0.11	1.67 ± 0.09	1.61 ± 0.09
Anterior ventral thalamic nucleus	2.16 ± 0.07	2.73 ± 0.14*	2.44 ± 0.04*	2.69 ± 0.07*	2.50 ± 0.12*
Lateral dorsal thalamic nucleus	2.07 ± 0.06	2.26 ± 0.01	2.20 ± 0.17	2.44 ± 0.11*	2.69 ± 0.14*
Medial dorsal thalamic nucleus	1.87 ± 0.05	2.06 ± 0.06	1.94 ± 0.20	2.50 ± 0.08*	2.42 ± 0.06*
Ventral medial thalamic nucleus	1.97 ± 0.03	2.09 ± 0.09	2.11 ± 0.20	2.33 ± 0.09*	2.46 ± 0.11*
Subthalamic nucleus	1.63 ± 0.21	1.93 ± 0.17	1.90 ± 0.10	1.82 ± 0.08	2.51 ± 0.09*
Medial geniculate nucleus	1.81 ± 0.27	1.54 ± 0.15	1.41 ± 0.12	1.73 ± 0.07	2.09 ± 0.13
Basolateral nucleus of the amygdala	1.48 ± 0.08	1.75 ± 0.02*	1.81 ± 0.60*	1.87 ± 0.12*	1.48 ± 0.07
Hippocampus, CA-1 stratum radiatum	1.31 ± 0.03	1.25 ± 0.05	1.34 ± 0.07	1.33 ± 0.13	1.35 ± 0.07
Hippocampus, CA-3 stratum radiatum	1.37 ± 0.07	1.43 ± 0.08	1.61 ± 0.11	1.64 ± 0.07*	1.47 ± 0.14
Stratum lacunosum moleculare (rostral)	1.63 ± 0.11	2.18 ± 0.07*	2.02 ± 0.12*	2.52 ± 0.08*	1.77 ± 0.07
Stratum lacunosum moleculare (caudal)	1.46 ± 0.12	2.43 ± 0.28*	2.05 ± 0.04*	2.20 ± 0.18*	1.58 ± 0.09
Anterior pretectal nucleus	1.73 ± 0.20	1.78 ± 0.18	1.65 ± 0.32	1.76 ± 0.07	2.55 ± 0.11*
Substantia nigra (reticular)	1.45 ± 0.15	1.43 ± 0.09	1.36 ± 0.07	1.50 ± 0.10	1.50 ± 0.04
Substantia nigra (compact)	1.50 ± 0.17	1.52 ± 0.20	1.38 ± 0.13	1.36 ± 0.12	1.63 ± 0.06
Inferior colliculus	1.52 ± 0.08	1.39 ± 0.05	1.31 ± 0.13	1.43 ± 0.08	1.60 ± 0.24

Data are means ± S.E.M. and expressed as ratios of optical density in gray matter regions relative to that in the corpus callosum. Significantly different compared to the saline group, * $p < .05$.

tral thalamic nucleus was remarkably activated by both ketamine and MK-801 (Figures 1 and 2). Pronounced increases in 2-DG uptake also appeared in the lateral and medial dorsal thalamic nuclei after treatment with ketamine and MK-801 (0.5 mg/kg) (Figures 1, 2, and 4).

Some of the most dramatic effects of amphetamine were found in the thalamus (Figures 1, 2, and 4). Amphetamine stimulated 2-DG uptake in the anterior, lateral and medial dorsal thalamic nuclei, and these effects were more prominent than those of observed after ketamine and MK-801 (0.3 mg/kg). In addition, amphetamine induced an increase in 2-DG uptake in the ventral medial thalamic nucleus. Amphetamine treatment also increased 2-DG uptake markedly in the subthalamic nucleus, while neither ketamine nor MK-801 affected this nucleus (Figure 1). In the lateral habenular nucleus, ketamine and MK-801 tended to decrease 2-DG uptake and a prominent decrease was induced by amphetamine treatment (Figure 3). No apparent changes in 2-DG uptake were observed in the medial geniculate

nucleus after administration of ketamine, MK-801, or amphetamine (Table 1).

Basal Ganglia. Both ketamine and MK-801 induced substantial increases in 2-DG uptake in the core region of the nucleus accumbens (Figure 1), and these increases were limited to the rostral part of the nucleus (Figure 2). In contrast to the NMDA antagonists, no effect of amphetamine was apparent in any level of the nucleus accumbens (Figures 1 and 2).

In the caudate-putamen, increased 2-DG uptake was observed in select "patch-like" regions after treatment with ketamine, MK-801, and amphetamine (Figure 4). The most prominent effects of ketamine and MK-801 were seen in the medial regions of the caudate-putamen (Figures 2 and 4). There were no apparent effects of ketamine, MK-801, or amphetamine on 2-DG uptake in the globus pallidus or substantia nigra (Figure 1).

Other Regions. Amphetamine induced a robust increase in 2-DG uptake in the anterior pretectal nucleus,

but no changes were observed in this region in response to ketamine or MK-801 (Figure 1). Increased 2-DG uptake was also observed in the medial septal nucleus after amphetamine treatment, but no effects of the NMDA antagonists were seen in this nucleus (Figure 1). There were no apparent effects of ketamine, MK-801, or amphetamine on 2-DG uptake in the ventral tegmental area or inferior colliculus (Figure 4). The administration of ketamine, MK-801, and amphetamine increased in 2-DG uptake in the fornix.

DISCUSSION

Although NMDA antagonistic actions of ketamine are well documented, ketamine also has a number of other pharmacological actions that complicate interpretation of effects of the drug in terms of NMDA receptor blockade (Reich and Silvy 1989). To determine the involvement of antagonistic properties at NMDA receptors in the metabolic activation observed for ketamine, the effects of ketamine were compared with those of the more selective open channel NMDA receptor antagonist, MK-801. The regional activation of brain 2-DG uptake in mice given MK-801 was remarkably similar to that induced by ketamine. This result suggests that blockade of NMDA receptors may be the primary mechanism by which ketamine exerts its prominent effect on regional 2-DG uptake.

In this study, we selected 30 mg/kg of ketamine as a subanesthetic dose in mice. The characteristic behavioral response to ketamine at this dose was similar to that previously observed at a subanesthetic dose of 25 to 35 mg/kg in rats (Duncan et al. 1998a, 1998b, 1999). Thus, the dose of ketamine used in mice appears to be equivalent to a subanesthetic dose in rats.

The present study is the first to document acute ketamine and MK-801-induced changes in 2-DG uptake in the freely moving mice. Similar to our previous findings in rats (Duncan et al. 1998a, 1998b, 1999), ketamine and MK-801 induced increased 2-DG uptake in the hippocampal formation, limbic cortical regions, anterior thalamic nucleus, and basolateral nucleus of the amygdala. Furthermore, both ketamine and MK-801 altered laminar patterns of uptake in isocortical regions, especially in the somatosensory cortex. These findings indicate that basic brain activity patterns are dramatically reorganized by the NMDA antagonists, and that similar effects are induced in both mice and rats.

Relative 2-DG uptake patterns in mice after treatment with ketamine, MK-801, and amphetamine were similar to those previously observed in rats after the same treatments, although differences between the species were seen in certain regions. In mice, the entorhinal cortex showed an intense activation of 2-DG uptake in several layers in response to ketamine and MK-801

(Figure 2), whereas the effects of the NMDA antagonists in rats were limited to layer 1 of this region (Duncan et al. 1999). In addition, despite the dramatic effect of amphetamine on 2-DG uptake in the medial septal nucleus in mice (Figure 1), no significant effect of amphetamine on uptake has been reported in this region in rats (Wechsler et al. 1979; Orzi et al. 1983; Porrino et al. 1984; Duncan et al. 1999). Furthermore, in rats, the inferior colliculus normally shows the greatest 2-DG uptake of any brain regions under control condition (Sokoloff et al. 1977; Nelson et al. 1980; Crosby et al. 1982; Kurumaji et al. 1989; Duncan et al. 1999). However, in mice, this auditory relay structure did not exhibit high 2-DG uptake in the control condition of the present investigation. This finding suggests that the basal metabolic activity of the auditory system in mice is not as high as that in rats. It has been shown that NMDA antagonists, including ketamine, MK-801, and PCP, dramatically decrease 2-DG uptake in the inferior colliculus in rats (Meibach et al. 1979; Nelson et al. 1980; Crosby et al. 1982; Tamminga et al. 1987; Davis et al. 1988; Kurumaji et al. 1989; Duncan et al. 1999) as well as in monkeys (Shapiro et al. 1975). In the present study, ketamine and MK-801 tended to decrease 2-DG uptake in the inferior colliculus, but these effects were not statistically significant compared with the saline-treated mice (Table 1). These data could be explained on the basis of relative low baseline metabolic activity of controls in the inferior colliculus in mice.

Although there were many differences in relative 2-DG uptake patterns between NMDA antagonists and amphetamine, consistent increases in 2-DG uptake were observed in certain thalamic nuclei for all drugs. The striking effects of ketamine, MK-801, and amphetamine on 2-DG uptake in the thalamic nuclei observed in the present work, including anterior ventral, lateral dorsal, and medial dorsal thalamic nuclei, are consistent with the findings of previous studies in rats (Orzi et al. 1983; Porrino et al. 1984; Kurumaji et al. 1989; Duncan et al. 1998a, 1998b, 1999).

Although certain thalamic regions were activated by amphetamine and the NMDA antagonists, distinctly different effects were induced by these drugs in many other regions. Amphetamine did not induce the marked increases in 2-DG uptake in the hippocampus, nucleus accumbens, basolateral nucleus of the amygdala, or limbic cortical regions as seen for ketamine and MK-801. In addition, the decreased 2-DG uptake observed after the NMDA antagonists in layers 3 and 4 of the isocortex was not seen after amphetamine treatment. Furthermore, amphetamine induced a robust activation in the medial septal nucleus, whereas the NMDA antagonists did not affect this region. These results indicate that the striking changes in 2-DG uptake induced by ketamine and MK-801 in many regions do not result merely from enhanced behavioral arousal or locomotor activity.

A number of studies have indicated that systematic administration of non-competitive NMDA antagonists, including ketamine and MK-801, increases the firing rate of dopamine neurons and induces a striking increase in the release of dopamine in terminal regions in rodents (Doherty et al. 1980; Rao et al. 1989; Wędzony et al. 1993; Hondo et al. 1994; Verma and Moghaddam 1996; Lindefors et al. 1997; Moghaddam et al. 1997; Adams and Moghaddam 1998). The stimulatory effects of NMDA antagonists on dopamine release are neuroanatomically selective, with effects observed in the medial prefrontal cortex and nucleus accumbens, but not the caudate putamen (Bubser et al. 1995; Moghaddam et al. 1997; Adams and Moghaddam 1998). In addition, the locomotor activating effects of MK-801 or PCP can be reduced by lesioning dopamine innervation to the nucleus accumbens (French 1986; Steinpreis and Salamone 1993; Ouagazzal et al. 1994). These findings suggest that increased dopamine release may account for the behavioral effects of ketamine and MK-801. However, more recent findings of Adams and Moghaddam (1998) demonstrate a temporal and functional dissociation between the effects of PCP on locomotor activation and dopamine release, suggesting that non-dopaminergic mechanisms are necessary for induction of behavioral effects of NMDA antagonists. In regard to the present investigation, relative 2-DG uptake in the hippocampus, nucleus accumbens, basolateral nucleus of the amygdala, and limbic cortical regions were strikingly different in mice treated with amphetamine in comparison to ketamine and MK-801. These findings indicate that increased release of dopamine is not sufficient for the prominent neuroanatomically selective metabolic activation elicited by ketamine and MK-801.

The neuroanatomically selective increase in 2-DG uptake after the NMDA antagonists treatment demonstrates a net excitatory action of the drugs in select brain regions. The mechanism for the excitatory action of ketamine and MK-801 could relate to the action of the drugs to antagonize the inhibitory neural processes, such as blocking NMDA receptors on γ -aminobutyric acid (GABA)-containing neurons (Grunze et al. 1996), therefore attenuating inhibitory tone. In fact, benzodiazepines, which potentiate GABA-mediated inhibition, can prevent the "emergence phenomena" of patients recovering from ketamine anesthesia (Coppel et al. 1973; Dundee and Lilburn 1978; Cartwright and Pingel 1984; Toft and Romer 1987). In addition, benzodiazepines inhibit NMDA antagonist-induced Fos expression (Nakao et al. 1996) and neurotoxicity (Olney et al. 1991) in the rat brain. However, subhypnotic doses of the benzodiazepine, lorazepam, were not effective in preventing ketamine-induced psychosis in healthy humans (Krystal et al. 1998), although the study has a limitation to interpretation given the lack of testing different doses of lorazepam. Furthermore, pretreatment with

the benzodiazepine, diazepam, failed to alter ketamine-induced brain regional glucose utilization in rats (Oguchi et al. 1982). Thus, examining the effects of different doses or other kinds of benzodiazepines on NMDA antagonist-induced changes in 2-DG uptake in rodents could be an intriguing line of future research.

It is possible that behavioral and brain metabolic activation induced by ketamine and MK-801 may be attributable to the ability of the drugs to increase the release of endogenous excitatory amino acids, such as glutamate. This is supported by the recent findings that systematic administration of ketamine and PCP increases the release of glutamate in the medial prefrontal cortex and nucleus accumbens (Moghaddam et al. 1997; Adams and Moghaddam 1998). Excessive release of glutamate may activate glutamatergic neurotransmission at non-NMDA receptors, including α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors, and induce excitatory responses. Indeed, several previous studies have indicated that AMPA/kainate receptor antagonists can reduce NMDA antagonist-induced hyperlocomotion (Hauber and Andersen 1993; Willins et al. 1993; Bubser et al. 1995), the heat shock gene, *hsp70* (Sharp et al. 1995), and impairment of working memory in rats (Moghaddam et al. 1997). Furthermore, a group II metabotropic glutamate receptor agonist LY354740, which attenuates glutamate release by a presynaptic mechanism, inhibits PCP-increased glutamate efflux in the prefrontal cortex, and also blocks behavioral activation elicited by PCP in rats (Moghaddam and Adams 1998). These data suggest that NMDA antagonist-induced behavioral effects are associated with increased glutamatergic activity. Therefore, there is substantial support for the hypothesis that NMDA antagonist-induced behavioral and brain metabolic activation involves increased glutamate release. To test this hypothesis further, it will be of interest to examine the effect of AMPA/kainate receptor antagonists or group II metabotropic glutamate receptor agonists on NMDA antagonists-induced alterations in 2-DG uptake.

Autoradiographic imaging with 2-DG in laboratory animals is analogous to positron emission tomography (PET) studies of brain metabolism and blood flow in humans. Subanesthetic doses of ketamine produce bilateral increases in metabolic activity in the prefrontal cortex and anterior cingulate cortex in humans (Lahti et al. 1995a; Breier et al. 1997; Vollenweider et al. 1997a, 1997b). Although it is difficult to make direct comparisons of anatomical regions between rodents and humans, the prefrontal and anterior cingulate cortex were activated by NMDA antagonists in the present work and in our previous studies in rats (Duncan et al. 1998a, 1998b, 1999). These findings suggest similar regionally selective brain metabolic activation in rodents and humans.

Although a pharmacological model of schizophrenia using ketamine remains to be validated, it is currently

one of the most viable models of schizophrenia that is applicable to both humans and laboratory animals, and thus can provide a unique tool for translational research. It is tempting to speculate that neuroanatomically selective brain metabolic activation by ketamine in rodents may be relevant to actions of the drug to induce schizophrenia-like symptoms in humans. However, exactly which brain regions are responsible for the individual clinical phenomenology induced by ketamine has not been established. Therefore, further translational studies are required to determine which brain regions are involved in the genesis of NMDA receptor-mediated psychotic symptoms and therapeutic actions of antipsychotic drugs.

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