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Title : KETAMINE ALTERS REGIONAL GLUCOSE UTILIZATION IN RAT BRAIN

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Introduction. Ketamine, an analog of phencyclidine (PCP), has been described as a dissociative anesthetic (1). Little is known of its mechanism of action, but cortical and limbic seizure activity as well as thalamocortical depression have been reported (1,2). Numerous neurotransmitters, including catecholamines and enkephalins, have been implicated in its analgesic and hallucinatory actions. Although structure-specific changes in cerebral glucose utilization (CMRG) have recently been reported, the study was qualitative and examined few brain structures (3). We report here the first quantitative measurement of regional cerebral glucose utilization following ketamine administration.

Methods. Regional CMRG was measured by the [^{14}C]deoxyglucose method ([^{14}C]DG) (4) in 8 control rats, 5 treated with 10 mg/kg, and 4 treated with 30 mg/kg of ketamine. The drug was given intravenously 2-5 min prior to the injection of [^{14}C]DG. Arterial blood gas tensions, pH, blood pressure, and rectal temperature were monitored and, except for a brief decrease in blood pressure in the high dose group, these variables remained in the normal range. The autoradiographs produced by the [^{14}C]DG method were analyzed with a microdensitometer, and CMRG was calculated as previously described (4). Statistical comparisons were carried out with the Dunnett's test for multiple comparisons.

Results. Data obtained in selected structures are presented in Table I. Some structures showed statistically significant changes; others indicated a trend which, because of the small sample size, failed to achieve statistical significance. The regions with altered CMRG after ketamine can be grouped into systems. First, CMRG in some sensory regions, especially auditory (cortex, medial geniculate and inferior colliculus) and somatosensory areas, is decreased. The visual cortex, however, suggests increased CMRG, while sub-cortical visual structures (lateral geniculate and superior colliculus) are unchanged. Second, some limbic structures, namely cingulate gyrus and hippocampus, are stimulated. Third, the basal ganglia, especially caudate nucleus and globus pallidus, also are activated. Last, an unexpected finding was the increased CMRG in the corpus callosum, whereas in descending white matter CMRG was decreased.

Discussion. The study of Nelson et al. (3) reported, on the basis of qualitative examination of the autoradiographs, increases in CMRG in hippocampus and decreases in the medial geniculate and inferior colliculus. Meibach et al. (5) reported similar findings in rats given PCP and also noted increases in the cingulate gyrus, thalamus and substantia nigra. The results of the present studies establish that ketamine has effects in limbic and auditory structures. Unlike previous reports, however, we note changes in cortical CMRG suggesting auditory and somatosensory deprivation. In contrast, the visual cortex is stimulated. In addition, the basal ganglia are activated, a finding consistent with behavioral observations and reports indicating that ketamine increases dopamine turnover in rat brain (6). The finding of changes in white matter is surprising and makes the interpretation of the data of Nelson et al. (3) difficult, inasmuch as they used the corpus callosum as a reference, against which the optical densities of other structures were compared. Furthermore, the white matter changes in CMRG suggest increased traffic between cortices, while interaction between cortical and subcortical structures is decreased. A PCP receptor, which also binds ketamine, has been isolated from rat brain and is found in high concentration in cortex, corpus striatum, and hippocampus (7), areas which exhibited significant changes in CMRG. Ketamine may act through binding on this PCP receptor to produce changes in dopamine or other neurotransmitter levels. The anesthetic action of ketamine may result from decreased auditory and somatosensory input while the stimulation of the visual cortex could explain the visual hallucinations which patients sometimes report after this drug.

References.

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Table I. Regional Glucose Utilization (μmoles/100g/min)

	Control (8)	Ketamine (5) (10 mg/kg)	Ketamine (4) (30 mg/kg)
Visual cortex	94 ± 3	109 ± 8	118 ± 10 *
Auditory cortex	128 ± 4	103 ± 9 *	93 ± 9 **
Sensory-motor cortex	97 ± 2	80 ± 7 *	69 ± 4 **
Medial geniculate body	100 ± 3	80 ± 6 *	85 ± 10
Lateral geniculate body	78 ± 2	79 ± 5	81 ± 5
Inferior colliculus	166 ± 5	109 ± 10 **	97 ± 9 **
Superior colliculus	76 ± 3	74 ± 7	68 ± 7
Thalamus: lateral nucleus	91 ± 2	110 ± 5 *	115 ± 10
Hippocampus	73 ± 2	114 ± 7 **	127 ± 13 *
Cingulate gyrus	73 ± 7	122 ± 7 **	128 ± 14 **
Amygdala	56 ± 3	45 ± 6	52 ± 5
Caudate-putamen	94 ± 2	109 ± 6	117 ± 9 *
Globus-pallidus	55 ± 3	72 ± 4 *	85 ± 7 **
Substantia nigra	63 ± 2	79 ± 5	83 ± 9
Corpus callosum	35 ± 1	43 ± 2 *	50 ± 6
Internal capsule	34 ± 2	28 ± 2 *	30 ± 2
Cerebellar white matter	36 ± 1	30 ± 2 *	30 ± 2 *

* $p < 0.05$ ** $p < 0.01$

Data are means ± standard errors obtained in number of animals in parentheses.