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# *Ketamine-induced Changes in Regional Glucose Utilization in the Rat Brain*

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**Ketamine appears to induce both excitatory and depressant actions in the brain; however, it is not clear which regions are affected. The 2-deoxyglucose functional mapping method of Sokoloff *et al.* was used to determine regional variations in metabolic activity of rat brain caused by injection of ketamine, 25–75 mg, intramuscularly. To compare the effects of ketamine with those of hippocampal-induced seizures, the 2-deoxyglucose method was used, following injection of penicillin G, 400–800 units, into the hippocampus. The findings from five control, seven ketamine-treated, and three penicillin G-treated rats are given. Ketamine caused a significant increase of metabolic activity in the hippocampal sulci and a decrease of activity in the medial geniculate and the inferior colliculus. Similar changes were found with hippocampal seizures caused by penicillin. The inhibition of the regions associated with sensory systems (medial geniculate and inferior colliculus) may account in part for the anesthetic action of ketamine, while the intense activity of the hippocampus may be related to the excitatory manifestations. The results indicate that ketamine produces seizures in the hippocampus, which in turn inhibit auditory and visually associated nuclei. Thus, the anesthesia may follow from the sensory depression and the cataleptic phenomena may be related to the hippocampal excitation. (Key words: Anesthetics, intravenous: ketamine. Brain: convulsions; glucose; metabolism.)**

KETAMINE, a cataleptoid anesthetic,[1] appears to induce both excitatory and depressant actions in the brain. However, reports differ as to which brain regions are activated or depressed by ketamine. Corssen and Domino[2] proposed the concept of dissociative anesthesia with ketamine, because, in cats, this drug appeared to depress activity in the neocortex and thalamus and activate the hippocampus. Others[3,4] found that ketamine produced excitatory activity in the thalamus, as well as bursts of seizure activity in the hippocampus and amygdala. Wong and Jenkins reported that systemic injections of ketamine into cats stimulated all parts of the brain studied.[5] They proposed that unconsciousness during ketamine anesthesia was secondary to cortical seizures detected by electroencephalography (EEG).[5]

The 2-deoxyglucose (2-DG) functional mapping method of Sokoloff *et al.*[6] is ideally suited for delineating which areas of the brain are activated and which are suppressed.[7,8] Therefore, this method was used to study the regional changes during ketamine anesthesia in rats. The method is based on the use of 2-deoxy-D-[$^{14}$C]glucose as a tracer for the exchange of glucose between plasma and brain and its phosphorylation by hexokinase. The [$^{14}$C]2-DG is used because the product 2-deoxyglucose-6-phosphate (2-DG-P) is trapped in the tissue during the experimental state. The accumulation of the 2-DG-P during the experimental state in the various regions of the brain is a measure of the glucose utilization over that period of time.[6] The amount of 2-DG-P that has accumulated is in turn determined by the $^{14}$C exposure of the roentgenographic film. Thus, the method which has been fully documented by Sokoloff *et al.*,[6] provides an index of the functional activity of brain regions *in vivo*.

To compare the action of ketamine with the effects of hippocampal seizures, penicillin was injected into the hippocampus, and the brain regional metabolic changes were determined. The results showed an increased metabolic activity in the hippocampus and a decreased activity in the medial geniculate and inferior colliculus, similar to the findings in ketamine-treated rats.

## Methods and Materials

Twelve male Wistar rats were used; five were controls and seven were treated with ketamine. The experimental rats received injections of ketamine, 25–75 mg, intramuscularly and after selected intervals, a bolus of 2-deoxy-D-[$^{14}$C]glucose (DG)¶, 50 $\mu$Ci, was injected intravenously. Four rats received injections of 2-DG while they were anesthetized or beginning to recover from the anesthetic. Three of the ketamine-treated rats received injections of 2-DG three to five hours after ketamine injection; the

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¶ New England Nuclear, Boston, Massachusetts.

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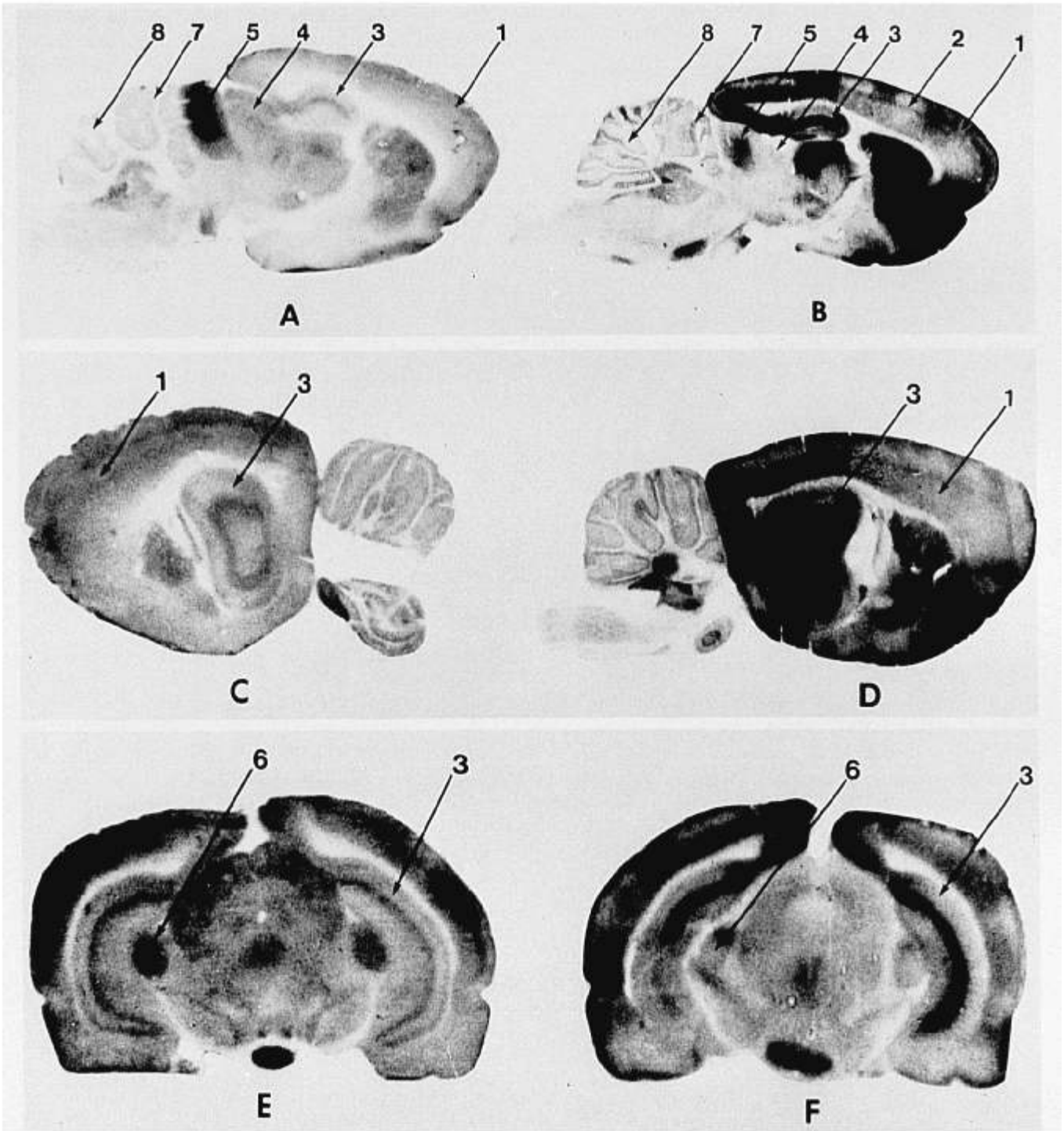


FIG. 1. Ketamine activation of brain. *A* through *D* are from sagittal sections; *E* and *F* are from coronal sections of rat brain. The autoradiographs from a control rat are on the left (*A*, *C*, and *E*) and those from a ketamine-treated rat on the right (*B*, *D*, and *F*). The ketamine-treated rat received an injection of 2-deoxy[$^{14}$C]glucose prior to recovery from anesthesia. Differences in shades of gray depicted on autoradiographs correspond to the differential rates of metabolism in brain regions.[6,7] The numbered structures are: 1 = cortex; 2 = layer 4 of cortex; 3 = hippocampus; 4 = superior colliculus; 5 = inferior colliculus; 6 = medial geniculate; 7 = granular layer of the cerebellum; 8 = molecular layer of the cerebellum.

TABLE 1. Optical-density Ratios (Gray Matter/White Matter) of Brain Regions in Rats Receiving Injections of Ketamine and Penicillin

| | Control (n = 5) | Ketamine (Anesthetized) (n = 4) | Ketamine (Recovered) (n = 3) | Penicillin (n = 3) |
|---|---|---|---|---|
| Hippocampus | 1.76 ± .12 | 2.75 ± .12* | 2.13 ± .18 | 3.26 ± .33* |
| Cortex | 2.24 ± .33 | 2.13 ± .03 | 2.54 ± .31 | 2.16 ± .52 |
| Medial geniculate | 2.43 ± .18 | 1.68 ± .07* | 2.59 ± .48 | 1.12 ± .04* |
| Inferior colliculus | 3.47 ± .32 | 2.08 ± .27* | 3.35 ± .49 | 1.78 ± .14* |
| Superior colliculus | 1.94 ± .14 | 1.68 ± .13 | 2.25 ± .13 | 2.21 ± .65 |

Rats received injections of ketamine (im) or penicillin (intracerebral—hippocampus). The ketamine-treated rats were injected with 2-deoxyglucose while anesthetized or 3 to 5 hours after ketamine (recovered). Each value is the mean optical-density ratio (gray matter/white matter) for a region of gray matter, followed by the SE. The white-matter reference was the corpus callosum.
* $P < 0.05$.

animals appeared fully recovered from the anesthesia. The stock 2-DG was an ethanol-$H_2O$ (9:1) solution. Before use, the ethanol was removed by evaporation, and the 2-DG was reconstituted in 0.5 ml of 0.9 per cent saline solution. Forty-five minutes after the 2-DG injection, the rats were decapitated and their brains removed and frozen in freon-12 ($CCl_2F_2$) cooled to −70 C. Control rats were anesthetized with halothane and allowed to recover for a minimum of two hours before injecting 2-DG. The frozen brains were sectioned at 20 $\mu$m and dried on coverslips at 60 C.

The dried sections and [$^{14}$C]methacrylate standards were exposed to two different roentgenographic films: a rapid film (four-day exposure) with relatively high background density for obtaining preliminary results and a slow-developing film (two-week exposure) with low background density for higher resolution and photography.

The differences in brain glucose between control and experimental rats was estimated by comparing optical-density ratios of different areas of gray matter. Using autoradiographs, the optical densities of brain regions were measured with a densitometer** with a 0.7-mm light aperture. A white matter (corpus callosum) density reference was determined for each brain section used and a gray matter/white matter ratio determined for hippocampus, cerebral cortex, medial geniculate, inferior colliculus, and superior colliculus. The cortex optical densities were taken from the superior lateral portions of cortex at the level of the medial geniculate.

** Model TBX® Tobias Associates, Inc., Ivyland, Pennsylvania.

Seizures originating from the hippocampus were produced in four rats by injecting penicillin G, 4–8 $\mu$l, (100,000 units/ml) into the left hippocampus. Needle tracks could be identified as passing through cortex into the hippocampus on the autoradiographs. Ten minutes after the penicillin injection, 2-DG was injected intravenously, and 45 min later, the animal was decapitated and the brain removed and frozen. A Student $t$ test was used to determine the significant differences between experimental and control groups of animals. A $P$ value of $<0.05$ was regarded as significant.

## Results

The changes in brain glucose use were most prominent in rats that had been anesthetized with ketamine. Glucose use in the hippocampus increased (fig. 1), as indicated by a significant increase in optical-density ratio in this region (table 1). Conversely, both medial geniculate and inferior colliculus had decreased optical-density ratios in the ketamine-anesthetized rats (fig. 1, table 1). On recovery from ketamine anesthesia, the glucose use in hippocampus, medial geniculate, and inferior colliculus returned to control levels (table 1). The optical-density ratios of cortex and superior colliculus in ketamine-treated rats were not different from control values (table 1).

Since it was possible that ketamine causes activation of the hippocampus, which in turn inhibits sensory nuclei, penicillin was injected into the hippocampus to determine the effect of hippocampal seizures on other areas of brain, particularly the auditory and visual pathways. Penicillin injection into the left hippocampus caused generalized seizures in all four rats, increased glucose use bilaterally in the hippocampus, and decreased glucose use in the inferior colliculus and the medial geniculate (fig. 2, table 1).

## Discussion

This study supports the hypothesis that drugs that induce seizure-like activation in certain brain regions may lead to a state of anesthesia. Winters *et al.* described an activation of EEG patterns in cats after ketamine injection which, during catalepsy, showed a continuous 1–5-Hz hypersynchrony with spikes.[4] In addition, seizure discharge was recorded from dorsal hippocampus after ketamine, 25–40 mg/kg, was given, as well as during chronic treatment of cats with ketamine; however, there was no spread of this discharge and no behavioral evidence of a seizure.[4]

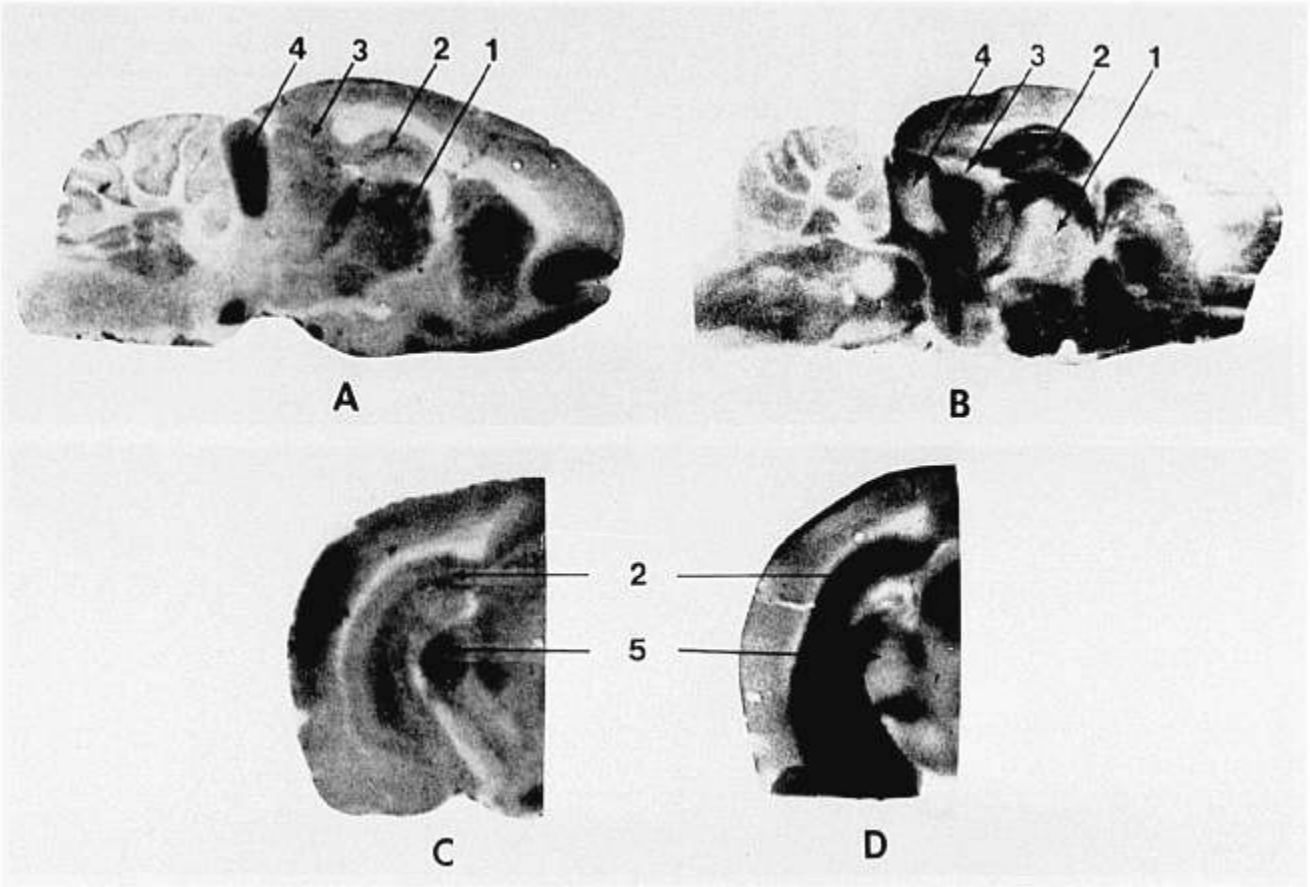


FIG. 2. Penicillin-induced activation of hippocampus. *A* and *B* are from sagittal sections; *C* and *D* are from coronal sections of rat brain. Autoradiographs from a control rat are on the left (*A* and *C*) and those from a penicillin-treated rat on the right (*B* and *D*). The numbered structures are: 1 = thalamus; 2 = hippocampus; 3 = superior colliculus; 4 = inferior colliculus; 5 = medial geniculate.

Shapiro and his associates[9] reported regional metabolic changes in the monkey brain induced by phencyclidine, the parent compound of ketamine. Their results were compatible with those reported here for ketamine in the rat brain. In particular, they found a 48 per cent increase in glucose utilization in the hippocampus, and a 45 per cent decrease in the inferior colliculus. This is almost identical to our results with ketamine in rats. They did not give values for the medial geniculate, which we found were depressed with ketamine.

In the studies reported here, high glucose utilization, indicative of increased functional activity, was present along the hippocampal sulcus, bilaterally. Furthermore, regions associated with sensory systems, such as the medial geniculate and inferior colliculus, appeared to have decreased activity, as reflected in decreased glucose utilization. We interpret these findings, taken in the context of the work of others, to mean that ketamine, and possibly the other cataleptic anesthetic agents, produce seizure activity in the hippocampus. This activity, in turn, inhibits input to auditory and visually associated nuclei. Thus, anesthesia would result from a sensory deprivation, and the dissociation of the animal from its environment would result from the hippocampal seizures.

The changes in regional glucose utilization were correlated with the anesthetic state of the animal. That is, hippocampus activation was greatest when the rat was anesthetized and during the first stages of recovery. Activation was decreased or absent four to five hours later, when the animals appeared to have recovered from the anesthesia. It is probable that the hippocampal activation induced by ketamine is directly associated with inhibition of the auditory and sensory nuclei since hippocampal-seizure activity induced with penicillin produced similar results. Ketamine may activate the hippocampus by a generalized inhibition of neurotransmitter transport postulated for this drug.[10]

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## Errata

Two errors have appeared in articles recently published in the journal:

In the last line of the left column of the letter, "Naloxone Does Not Antagonize Diazepam-induced Sedation" (ANESTHESIOLOGY 51:187, 1979), $P = 0.02$ should be changed to read $P > 0.1$.

In the article, "Right Bundle-branch Block and Complete Heart Block Caused by the Swan-Ganz Catheter" (ANESTHESIOLOGY 51:359–362, 1979), the error is in the legend accompanying figure 3, which states: "FIG. 3. Transient complete heart block during passage of a Swan-Ganz catheter through the right ventricle in a patient with pre-existing right bundle-branch block."

This should be corrected to read in part: "in a patient with pre-existing left bundle-branch block."