Effect of Ketamine on Cerebral Cortical Blood Flow and Metabolism in Rabbits

Ruth E. Oren, Nada A. Rasool, and Eduardo H. Rubinstein

The effects of intravenous ketamine (1 mg/kg) on cerebral cortical blood flow and O2 uptake were evaluated in 13 anesthetized, ventilated rabbits. Blood flow was measured either directly (Group 1) or by the H2 clearance method (Group 2). In those animals of Groups 1 and 2 with normal control arterial pH (pHb), ketamine produced a significant increase in cerebral cortical blood flow of 18 and 34%, respectively, but had no effect on cerebral cortical O2 uptake. However, in rabbits with low control pHb, ketamine caused an increase in blood flow (30%) accompanied by a significant increase in O2 uptake (22%). Ketamine produced nonsignificant changes in mean arterial blood pressure and arterial blood gases, except for a significant reduction in pressure in animals with low pHb. It is concluded that ketamine is a cerebral vasodilator without cerebral metabolic effect when mean arterial blood pressure and arterial PCO2, Po2, and pH are held constant at physiologic levels. The vasodilator effect of ketamine is probably due to direct dilating action or activation of a cholinergic cerebral vasodilator system. (Stroke 1987;18:441-444)

AFTER the introduction of ketamine as an anesthetic agent in 1966, many studies were conducted on experimental animals and humans to characterize the effect of this agent on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO2). While most investigators have reported increases in CBF of up to 80% after ketamine,1-7 Kreuscher and Grote8 found a 50% decrease and Schwedler et al9 reported that ketamine had no effect on CBF. Even more variable results have been published regarding ketamine’s effect on CMRO2. Dawson et al10 and Baldy-Moulinier et al11 described a 16 and 10% increase in CMRO2, respectively, while Take-shita et al12 and Kreuscher and Grote6 reported a small decrease. In contrast, Schwedler et al4 described a marked reduction in CMRO2.

The wide difference in results reported in those publications, previously discussed by Schwedler et al,4 prompted the present study. We were interested in evaluating the possible cerebral metabolic effect of ketamine in a rabbit preparation to elucidate the role of a cholinergic cerebral vasodilator mechanism activated by ketamine recently proposed by Reicher et al13 to explain their findings.

Materials and Methods

Thirteen male New Zealand rabbits weighing 2.7–3.5 kg were anesthetized with 6% halothane added to O2 and room air until all surgical procedures were finished. Halothane was then discontinued, and the animals were maintained under 50% N2O-50% O2 for at least 1 hour before the beginning of CBF and O2 consumption measurements. Pancuronium bromide (Pavulon, Organon) at 0.2 mg/kg/hr was given to ensure muscle paralysis. Mechanical ventilation with a T-system was adjusted to maintain end-tidal CO2 (ETCO2) at 3.5–4% monitored with a Beckman LB-2 analyzer. The femoral artery and vein were cannulated for blood pressure measurement, blood sampling, and drug administration.

Two screw electrodes were placed in the left parietal region for continuous recording of the electroencephalogram (EEG). Rectal temperature was continuously monitored and maintained at 38.5–39.0°C by radiant heating or ice-water cooling of the animal. Arterial pressure, ETCO2, EEG, and hydrogen (H2) clearance were recorded on a Grass Model 7 polygraph. Arterial blood samples (0.5–0.8 ml) were collected every hour for analysis of pH, PCO2 and Po2 (I.L., System 1303, pH/blood gas analyzer) and hemoglobin (Hb) and HbO2 (I.L., Co Oximeter 282).

Measurements of CBF

Group 1. CBF was measured volumetrically in 8 rabbits, using a technique slightly modified from Pearce et al16 and Scremin et al.17 The animal’s head was supported with a stereotactic holder, and the sagittal sinus and the confluens were exposed via a 3 x 6 mm opening drilled through the skull. A 16-gauge 1/4 inch Teflon catheter (Angiocath, Deseret) was introduced through the confluens into the sagittal sinus and advanced approximately 5 mm into it, guided with a micromanipulator mounted on the stereotactic frame. This catheter size and the extent of its advancement were selected because they assured a tight fit between the sagittal sinus and the catheter, as supported by previous anatomical studies. Heparin (500 U/kg) was administered i.v. immediately before cannulation and...
was supplemented by 500 U every 20 minutes. The venous effluent dripped into a small reservoir, which drained into the right atrium via a large silicon rubber catheter previously placed through the right external jugular vein. Volumetric flow measurements were obtained by collecting timed samples of sagittal sinus blood in a plastic tuberculin (1 ml) syringe.

Cerebrovascular reactivity was assessed by measuring CBF before and during CO₂ inhalation for 2 minutes at an ET₇C₀₂ of 8%. The experiments were continued only when CBF increased by > 50%.

CBF and O₂ consumption measurements were taken before and 2-4 minutes after the i.v. injection of ketamine (Ketalar, Parke-Davis, 1 mg/kg), and only after the EEG displayed a characteristic high-voltage, low-frequency pattern,¹²,¹³ which corresponded to the highest steady flow observed in our pilot studies and previous reports.²,⁵

GROUP 2. CBF was measured in 5 animals with a H₂ clearance technique that allowed flow recording and sampling without heparinizing the rabbit. The sagittal sinus was exposed as described for Group 1, and an insulated platinum electrode (75 µm diameter, 0.5 mm bare tip) held in a micromanipulator was advanced into the sinus via a 26-gauge needle hole. A 20-gauge 1½ inch Teflon cannula (Angiocath, Deseret) was inserted through the confluens and advanced with a micromanipulator until its tip was just dorsal to the implanted electrode. This size of cannula was chosen as it allowed free flow of blood around the cannula. The cannula was flushed with a heparin-saline solution (2 U/ml) at a rate of 0.1 ml/10 min.

CBF was calculated in ml/100 g/min using the H₂ clearance technique described by Aukland et al.¹⁴ and Aukland as previously used in rabbits.¹⁰,¹¹ Five percent H₂ was added to the inspired gas mixture until the H₂ polarographic current between the platinum electrode in the sinus and a distant subcutaneous Ag-AgCl electrode reached a sustained plateau for 3 minutes. H₂ inflow was stopped, and the H₂ concentration (H₂ current) was continuously recorded during the whole desaturation period until the H₂ current returned to baseline. The calculation was based on the expression

\[ K = 100 \times \ln 2 \times T_w, \]

where K is the blood flow and T_w is the half-time of the washout slope in minutes.¹⁴,¹⁶

The half-time was taken at between 60 and 30% of the plateau H₂ current. Previous observations indicated that during this interval, the arterial H₂ concentration was negligible and the slope was monoexponential. Arterial and sagittal sinus blood samples were collected half-way during the H₂ washout period. The effect of ketamine was studied after a control clearance was measured. Ketamine (1 mg/kg) was injected after the H₂ current reached and maintained a steady level for 3 minutes. Two to four minutes after the injection of ketamine, H₂ inflow was stopped and arterial and venous samples were again taken. This approach, based on our observations with volumetric flow measurement and the findings of Reicher et al.,⁹ allowed estimation of the highest blood flow, which peaks at 2-4 minutes and remains at this level for another 7-8 minutes. Such stability of flow is necessary for quantitative validity of both H₂ clearance and O₂ consumption measurements.

Measurement of Cerebral Oxygen Uptake

In Group 1, cerebral O₂ consumption was calculated as the product of volumetric blood flow (ml/min) and the difference in O₂ content between arterial (a) and sagittal sinus (ss) blood. In Group 2, CMRO₂ was calculated as the product of H₂ clearance flow (ml/100 g/min) and the a-ss O₂ content difference. Arterial and sagittal sinus O₂ contents were calculated by¹⁷

\[ C_{O_2} = Hb \text{ content} \times O_2 \text{ capacity} \times \% HbO_2 + PaO_2 \] (or PsSO₂) × 0.003

Hb content, % HbO₂, and PaO₂ were measured as described above, and O₂ capacity of Hb was estimated at 1.3 ml O₂/g Hb.

Statistical Analysis

The data were analyzed by the paired Student’s t test for small samples. A value of p < 0.05 was considered to reflect significant differences throughout this study.

Results

The i.v. injection of ketamine had no significant effect on mean arterial blood pressure (MABP) provided that the arterial pH of the animal was normal (Groups 1a and 2; Table 1, columns 1 and 3). This stability was observed with both methods of flow recording. Interestingly, heparinization required for volumetric flow measurement was associated with a high incidence of acidosis, relative hypoxemia, and hypercarbia. In those animals, ketamine injection was associated with marked and sustained hypotension. There were only 4 animals with those baseline characteristics because their MABP, which dropped initially (Table 1, column 2), recovered within 2-4 minutes after injection. Two of these rabbits were acidic from the start, and the other 2, which initially had normal control pH, developed acidosis during the experiment. Ketamine administration had no effect on arterial blood gases of either normal or acidic rabbits as shown in Table 1.

Ketamine increased CBF in all the animals tested while the effect on CMRO₂ depended on the preinjection arterial pH. In animals with normal pH, ketamine increased CBF with no change in O₂ uptake regardless of the method used (volumetric or H₂ clearance, Tables 2 and 3). In contrast, the animals with low pH showed a nonsignificant increase in CBF associated with a significant increase in cerebral O₂ consumption in response to ketamine (Table 2). Interestingly, the acidotic animals showed baseline CBF significantly lower than the normal animals, as well as a nonsignificantly lower oxygen consumption.

Discussion

CBF and CMRO₂ were studied in rabbits using 2 different techniques after we observed that in many animals, heparinization was associated with acidosis,
hypercarbia, and hypoxemia as well as with hypotension after ketamine injection. The direct (volumetric) method, which required heparinization, was used in Group 1 and was previously found to be a valid measure of CBF in rabbits. The H$_2$ clearance method, used in Group 2, did not require heparinization. The validity of this technique, which has been established by Pearce et al and Scremin et al, requires that tissue, arterial, and venous concentrations of H$_2$ be in equilibrium before the beginning of desaturation and that no flow change occur during desaturation. These conditions were fulfilled in our experiments.

In the present study, i.v. ketamine caused a marked increase in CBF in both Groups 1a and 2. There were no concomitant MABP or PacO$_2$ elevations (shown in Table 1) that could have explained this CBF increase.

Our findings agree with those of Rockoff et al and Baldy-Moulinier et al, who found in monkeys a 12.2% and in man a 49% increase in CBF in response to ketamine. Dawson's group reported that ketamine caused an 80% increase in CBF in dogs; however, the control MABP values were high, and the slight rise in MABP observed after ketamine could have exceeded the autoregulation limit and contributed to CBF increase. Takeshita et al found an increase in CBF in patients receiving ketamine but, as criticized elsewhere, the status of cerebral autoregulation was not determined. Thus, the elevations of MABP and PacO$_2$ seen after ketamine could have added to CBF values. Ivankovich et al and Schwedler et al reported that in nonparalyzed goats, ketamine produced an increase in CBF accompanied by significant elevations in MAPB and PacO$_2$. Schwedler and colleagues found in a second study that in paralyzed, ventilated goats, when PacO$_2$ was steady, ketamine did not cause any change in CBF, and they have concluded that the increase in CBF in nonparalyzed animals was probably a secondary result of MABP and PacO$_2$ elevations. Kreuscher and Grote were the only investigators to report a marked decrease in CBF after ketamine, in a study that was previously criticized.

In the present study, the increase in CBF was associated with no concomitant increase in O$_2$ uptake in animals with normal control pH measured and calculated by 2 methods. This lack of significant change in O$_2$ uptake after ketamine confirms previous observations but contradicts the conclusion of Dawson et al that ketamine increases O$_2$ uptake and is a cerebral stimulant. In addition, our results do not support Schwedler et al, who suggested that ketamine is a mild depressant of cerebral metabolism. Our observations on cortical blood flow and metabolism do not exclude a possible different effect of ketamine in other areas of the brain. In fact, Crosby et al reported regional decreases and increases in local cerebral glucose utilization after ketamine injection in rats. However, the objective of our study was to analyze the nature of the correlation between the cerebral vasodilator effect of ketamine and its action on metabolism. In contrast to the rabbits with normal control pH (Groups 1a and 2), the acidic rabbits (Group 1b) showed a transient hypotension followed by an average increase of 30% in CBF (statistically nonsignificant because of large variation and few animals) associated with a significant increase in O$_2$ uptake. This observation may explain the diverse results reported by

### Table 1. Effect of Ketamine on Mean Arterial Blood Pressure and Physiologic Parameters in Rabbits

<table>
<thead>
<tr>
<th>Arterial blood parameters</th>
<th>Normal control pH (Group 1a, n = 6)</th>
<th>Low control pH (Group 1b, n = 4)</th>
<th>Normal control pH (Group 2, n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>Control</td>
<td>Ketamine</td>
<td>Control</td>
</tr>
<tr>
<td>P$_O_2$ (mm Hg)</td>
<td>155 ± 19</td>
<td>146 ± 26</td>
<td>106 ± 34</td>
</tr>
<tr>
<td>P$_CO_2$ (mm Hg)</td>
<td>37 ± 1.0</td>
<td>37 ± 1.6</td>
<td>45 ± 4.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.4 ± 0.0</td>
<td>7.4 ± 0.0</td>
<td>7.3 ± 0.0</td>
</tr>
<tr>
<td>HbO$_2$ (%)</td>
<td>94 ± 0.6</td>
<td>92 ± 2.6</td>
<td>89 ± 2.4</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*1 minute before and 1 minute after i.v. ketamine 1 mg/kg.
†Significantly different from control values; p < 0.01.
‡Blood samples were taken 1 minute before and 2-4 minutes after i.v. ketamine.

### Table 2. Cerebral Cortical Blood Flow (Volumetric) and Oxygen Uptake Before and 2-4 Minutes After Ketamine Injection (1 mg/kg)

<table>
<thead>
<tr>
<th>Cortical blood flow (ml/min)</th>
<th>Normal control pH (Group 1a, n = 6)</th>
<th>Low control pH (Group 1b, n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Ketamine</td>
<td>Difference (%)</td>
</tr>
<tr>
<td>Cortical blood flow (ml/min)</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Cortical O$_2$ uptake (ml/min)</td>
<td>0.05 ± 0.01</td>
<td>0.05 ± 0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*Significantly different from control values, p < 0.05.
Table 3. Cerebral Cortical Blood Flow (H₂ Clearance) and Oxygen Uptake Before and 2–4 Minutes After Ketamine Injection (1 mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ketamine</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical blood flow (ml/100 g/min)</td>
<td>53 ± 8.3</td>
<td>70 ± 11</td>
<td>17 ± 5.0* (34 ± 11)*</td>
</tr>
<tr>
<td>Cortical O₂ uptake (ml/100 g/min)</td>
<td>4.3 ± 0.5</td>
<td>4.2 ± 0.4</td>
<td>-0.1 ± 0.6 (0.1 ± 0.8)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM, Group 2, n = 5. *Significantly different from control values, p < 0.02.

others if their animals or patients were in slight metabolic imbalance. These findings indicate that low pH may modify the effect of ketamine on cerebral metabolism and stress the importance of maintaining arterial blood gases and pH at a physiologic level during analysis of the effects of ketamine and other agents.

Many of the above-mentioned investigators have suggested explanations for ketamine’s effect on CBF. Our study does not support the hypothesis of Dawson et al., that the increase in CBF is necessarily secondary to increased cerebral metabolism since ketamine had no metabolic effect in animals with normal control blood gas values. Another hypothesis, which was suggested by Takeshita et al. and recently supported by Fukuda et al., is that ketamine decreases cerebral vascular resistance by a direct dilating action on cerebral arteries that may be due in part to interference with transmembrane influx of Ca²⁺. Reicher and colleagues have suggested that ketamine activates the cholinergic cerebral vasodilator system, previously postulated by Scremin et al. Reicher’s hypothesis was supported by the observation that scopolamine, a cholinergic antagonist, blocked the increase in CBF after ketamine.

In conclusion: Ketamine seems to activate a cholinergic mechanism to induce cerebral cortical vasodilatation. In addition, it may under some circumstances (e.g., low pH, other brain areas, higher dose) increase metabolic activity, which in turn may enhance the extent of vasodilatation.

References


KEY WORDS • ketamine • cerebral cortical blood flow • cerebral cortical metabolism • rabbit
Effect of ketamine on cerebral cortical blood flow and metabolism in rabbits.
R E Oren, N A Rasool and E H Rubinstein

Stroke. 1987;18:441-444
doi: 10.1161/01.STR.18.2.441

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/18/2/441

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click Request
Permissions in the middle column of the Web page under Services. Further information about this process is
available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/