Cholinergic Cerebral Vasodilator Effect of Ketamine in Rabbits

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To analyze the mechanism of the cerebral vasodilator effect of ketamine in anesthetized rabbits, we measured the internal carotid blood flow with an electromagnetic flowmeter, the arterial pressure, intracranial pressure, end-tidal CO₂, and the electroencephalogram. Ketamine injection (1 mg/kg) induced a significant cerebral vasodilatation that was blocked by scopolamine, a cholinergic antagonist. In contrast, the increase in cerebral blood flow after ketamine was additive to the cerebral vasodilator actions of inhaled CO₂ and of physostigmine infusion, two procedures that activate cholinergic mechanisms. These observations suggest that in rabbits, ketamine activates a cholinergic cerebral vasodilator system. (Stroke 1987;18:445–449)

Ketamine is a potent analgesic and dissociative agent used extensively for pediatric anesthesia, but which is not recommended for neurodiagnostic or neurosurgical procedures because of its reported tendency to increase intracranial pressure (ICP). It is generally accepted that the elevation in ICP is secondary to the cerebral vasodilatation that may accompany the alterations in brain electrical activity and possible changes in metabolism elicited by the drug. However, while the cerebral vasodilator effect of ketamine is generally supported, its cerebral metabolic effect is controversial.

If the increase in brain metabolism is inconsistent, it is difficult to understand how this may mediate such a consistent effect as the cerebrovascular dilatation. On the contrary, this apparent poor correlation between cerebral metabolism and blood flow may result from the activation by ketamine of a nonmetabolic mechanism. We studied the cerebrovascular effects of ketamine in rabbits to analyze the possible participation of a neurogenic cholinergic mediator of vasodilatation, using a muscarinic antagonist, scopolamine, and a cholinergic agonist, physostigmine. The existence of such a mechanism has been proposed by others and supported by our work on the vasodilator effect of CO₂ and halothane.

Materials and Methods

The experiments were performed on 30 New Zealand white rabbits weighing 2.7–4.1 kg anesthetized inside a box with 5% halothane in air and maintained by mask until a tracheostomy was performed. The animals were then mechanically ventilated with end-expired CO₂ kept at 4%, paralyzed with pancuronium bromide (0.2 mg/kg/hr), and maintained on 0.5–1% halothane in 35% O₂ and N₂. Respiratory rate was maintained at 40/min and peak inspiratory pressure at 15 cm H₂O, a combination that maximized the matching between end-tidal CO₂ and PacO₂ and provided excellent oxygenation, with a PaO₂ always above 100 mm Hg. The femoral artery and vein were cannulated for arterial pressure monitoring and drug injection, respectively. Internal carotid blood flow (ICBF) was measured using an electromagnetic flowmeter placed around the common carotid artery after the laryngeal, occipital, and external carotid arteries were tied off. A miniature hydraulic occluder placed distal to the probe was used for frequent zero-flow measurements. Our previous studies have shown that with this technique ICBF represents hemispheric blood flow without extracerebral contamination. The animals were turned prone, and the head was supported by a rigid holder. Parietal EEG electrodes were screwed into the skull, and a polyethylene cannula was inserted into the cisterna magna and tightly secured with cyanoacrylate cement. After this stage the anesthetic for all animals was changed from halothane to 60-65% N₂O in O₂. This mixture provided an adequate PaO₂, above 100 mm Hg, by keeping the respiratory settings as described before. In addition, arterial pressure was controlled by electrical stimulation (2-second train at 50 Hz, 1 msec duration, 1–3 V, repeated after a 3-second interval) of the lumbar spinal cord via fine platinum electrodes introduced via a laminotomy. Possible ascending central nervous system effects of the stimulation were blocked by a spinal transection at C₁-C₂. The lumbar location of the electrodes and the low intensity of the stimulation prevented excitation of the high thoracic sympathetic motoneurons and the possibility of cerebrovascular sympathetic effects. The lack of changes in pupillary diameter during spinal stimulation was used as another check of the absence of cephalic sympathetic spread. ICBFs recorded before and during spinal stimulation were very similar, provided that the mean arterial pressure (MAP) differed by <15%. Arterial pressure, end-tidal CO₂ (ETCO₂), ICBF, ICP, and EEG were continuously
monitored on an 8-channel Model 7 Grass polygraph. Rectal temperature was maintained at 39°C by radiant heat. Arterial blood gases were monitored at frequent intervals.

Each animal was tested for cerebrovascular reactivity to inhaled CO2. The study proceeded only if ICBF increased by at least 20% when ETCO2 was changed from 4% to 8%. Ketamine hydrochloride (Ketalar), 1 mg/kg, was injected i.v. This dose was selected after pilot studies had shown a consistent cerebral vasodilator effect. The agent was administered according to the following protocols: Group 1, single injection; Group 2, multiple injections at 20-minute or 1-hour intervals; Group 3, before and, 60 minutes later, after the EEG slowing induced by scopolamine hydrobromide (2 mg/kg i.v.) had occurred (approximately 3 minutes); in another series, scopolamine (2 mg/kg i.v.) was given initially followed by ketamine at 3-, 60-, and 120-minute intervals; Group 4, before and, 60 minutes later, during the infusion of physostigmine salicylate (0.01 mg/kg/min). The data for before and 2–5 minutes after injection, while the peak effect of ketamine was stable, were analyzed. In some animals of Group 1, CO2 reactivity was also tested 5 minutes after the peak effect of ketamine was recorded. Changes in ICBF, ICP, and MAP were evaluated using the t test for paired samples and were considered significant if p < 0.05. In addition, Pearson’s correlation coefficient, r, was used to compare cerebrovascular reactivities to ketamine and CO2.

Results

Group 1. Ketamine injection was followed by a rapid increase in ICBF that peaked in 2–4 minutes. This change was associated with a small but significant increase in ICP (Table 1). The percent increase in ICBF after ketamine injection observed in each animal was compared with the percent increase in ICBF secondary to CO2 inhalation measured before ketamine injection. The study of the relation between the cerebrovascular responsiveness to ketamine and to inhaled CO2 in each animal showed a significant correlation...
using Pearson’s $r$ coefficient (Figure 1). This relation is further illustrated in Figure 2, which displays the responses to CO$_2$ and ketamine in one animal and outlines the characteristics of the changes, especially the time course of the cerebral vasodilatation. Interestingly, while ICBF was increased almost to the same level by CO$_2$ and ketamine, ICP changed more with CO$_2$. The response to CO$_2$ inhalation was measured in 9 animals before and during the effect of ketamine, and Table 2 shows that in spite of the significant difference after baseline blood flow, the changes were not significantly different.

Group 2. A small group of 4 rabbits received 4 ketamine injections given at 60-minute intervals, when the blood flow had just returned to baseline. Table 3 shows that the extent of the cerebral vasodilatation was progressively decreased after each successive injection and that the baseline blood flow progressively decreased. Interestingly, ICP increased significantly after each injection and the baseline did not return to normal.

This progressive diminution of the response to ketamine with repeated injections was not observed when the interval was longer, i.e., 60 minutes. Table 4 shows the marked similarity of the changes observed after 2 mg/kg doses of ketamine injected at a 60-minute interval. The constancy of the response with this interval between injections supported the design of the next experiment.

Group 3. Ketamine (1 mg/kg) was injected before any other treatment and again, 60 minutes later, after scopolamine (2 mg/kg). Table 5 shows the difference between the effects of the injections. After scopolamine, ICBF did not change following ketamine administration. Scopolamine administration markedly changed the EEG into a continuous pattern of high-voltage slow waves. However, the control MAP, ICBF, and ICP were not significantly different before and after the drug injection.

Group 4. Ketamine was injected before and, 60 minutes later, after a steady-state vasodilatation had been elicited during the infusion of physostigmine. This is represented in Table 7, where it is shown that the magnitude of the changes in ICBF after ketamine was the same.

**Discussion**

Our results in rabbits confirm the marked cerebral vasodilator effect of ketamine previously reported in different species. 1-7,12,13 This occurred when successive ketamine injections were separated by a 1-hour interval. Injections at intervals of 20 minutes, however, led to progressively decreased responses to ketamine, as well as to a lowering of baseline CBF, perhaps as a result of mounting ICP and a consequent decrease in net perfusion pressure. Since 1 mg/kg of ketamine injected at intervals of 1 hour yielded a reproducible increase in CBF without changes in MAP of > 15%, no other doses were systematically explored. The most important finding was the abolition by scopolamine, a cholinergic muscarinic antagonist, of...
the cerebral vasodilator response to ketamine, with no effect on baseline blood flow. Other drugs, such as thiopental, which reduce the cerebral dilator effect of ketamine, may also act to some extent through interference with a cholinergic mechanism, indicated by the blocking of cortical acetylcholine release by a barbiturate.14

A further indication of the association of a cholinergic mechanism with the ketamine effect may be the positive correlation between the proportionate responses to ketamine and CO2 in each animal. This finding suggests that both changes share a common mechanism. We propose that this could be a cholinergic vasodilator system, based on our present findings with scopolamine and the study of Scremin et al describing that part of the vasodilator response to CO2 in rats9 and rabbits10 resulted from the excitation of a cholinergic pathway. The latter was shown to be activated in rabbits by electrical stimulation of the mesencephalon using stereotactically guided electrodes.15

We assume that both ketamine and CO2 may act directly at some level of this central cholinergic system. Moreover, when CO2 inhalation was tested during the effect of ketamine, we showed that both effects were simply additive, with no evidence of potentiation or diminution. A comparable summation of effects was also observed during phystostigmine infusion. This drug increases CBF without an elevation of cerebral metabolism, very likely through activation of a cholinergic mechanism. A previous study had also shown that the responses to inhaled CO2 and phystostigmine were additive.16 Altogether, the vasodilator effect of ketamine is added to that of a potential (CO2) or a known (physostigmine) cholinergic agonist, suggesting that the additive interaction may result from the activation of a common mechanism by all these agents.

It is possible that an increase in cerebral metabolic rate induced by ketamine either directly, as has been proposed,13 or secondary to activation of a cholinergic mechanism might account for the vasodilatation. However, Oren et al14 have shown that ketamine injection in rabbits does not affect cerebral cortical oxygen uptake. Likewise, a direct effect of ketamine on cerebral blood vessels proposed by Fukuda et al17 is not supported by our experiments because of the blockade of the vasodilatation by scopolamine, unless it is assumed that ketamine in rabbits is a direct agonist, acting on cholinergic receptors in vascular smooth muscle.

It is unlikely that the cerebral vasodilator effect of ketamine was the result of a passive response to changes in MAP. In many instances there were no significant alterations of this parameter (Table 1), and the significant changes reported were very small and in different directions (Tables 3, 4, and 5). Those modifications resulted from the interaction of the primary hypotensive effect of ketamine in rabbits with some overcompensation with the electrical stimulation of the spinal cord. The changes in MAP were significant because in general the control was successful in making the variance small, thus enhancing the statistical value of minor variations. Comparable increases in ICBF followed a MAP increase of 1% (Table 1) or a 15% decrease (Table 5). Similarly, ICBF increased 30% after MAP increases of 1 or 5% (Table 4). However, the marked vasodilatation (72%) reported in Table 3 may have been assisted in part by the 10% increase in MAP. More importantly, the abolition of the vasodilatation by scopolamine was associated with a minor (4%) decrease in MAP (Table 5) or no significant changes (Table 6).

In summary: The present results strongly support the presence in rabbits of a cholinergic mechanism, either a central neurogenic pathway or a vascular receptor that, activated by ketamine, induces a marked cerebral vasodilatation.

### References

Reicher et al  Cerebral Vasodilatation After Ketamine

12. Ivanokovich AD, Miletich DJ, Reimann C, Albrecht RF, Zahed B: Cardiovascular effects of centrally administered ketamine in goats. Anesth Analg 1974;53:924-933

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