Laboratory Investigations

High-dose S(+)-ketamine improves neurological outcome following incomplete cerebral ischemia in rats

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Purpose: To determine the effects of the non-competitive NMDA-receptor antagonist S(+)-ketamine on neurological outcome in a rat model of incomplete cerebral ischemia.

Methods: Thirty rats were anesthetized, intubated and mechanically ventilated with isoflurane, O₂ 30% and nitrous oxide 70%. Following surgery animals were randomly assigned to one of the following treatment groups: Rats in group 1 (n=10, control) received fentanyl (bolus: 10 µg·kg⁻¹ iv; infusion 25 µg·kg⁻¹·h⁻¹) and N₂O 70% / O₂. Rats in group 2 (n=10) received O₂ 30% in air and low-dose S(+)-ketamine (infusion: 0.25 mg·kg⁻¹·min⁻¹). Rats in group 3 (n=10) received O₂ 30% in air and high-dose S(+)-ketamine (infusion: 1.0 mg·kg⁻¹·min⁻¹). Following 30 min equilibration period ischemia was induced by combined unilateral common carotid artery ligation and hemorrhagic hypotension to 35 mmHg for 30 min. Plasma catecholamines were assayed before and at the end of ischemia. Neurological deficit was evaluated for three postischemic days.

Results: Neurological outcome was improved with high-dose S(+)-ketamine when compared to fentanyl / N₂O - anesthetized controls (9 vs 1 stroke related deaths, $P < 0.05$). Increases in plasma catecholamine concentrations were higher in fentanyl / N₂O - anesthetized (adrenaline baseline 105.5 ± 92.1 pg·ml⁻¹, during ischemia 948 ± 602.8 pg·ml⁻¹, $P < 0.05$; noradrenaline baseline 407 ± 120.2 pg·ml⁻¹, ischemia 1267 ± 422.2 pg·ml⁻¹, $P < 0.05$) than in high-dose S(+)-ketamine-treated animals (adrenaline baseline 71 ± 79.5 pg·ml⁻¹, ischemia 237 ± 131.9; noradrenaline baseline 317.9 ± 310.5 pg·ml⁻¹, ischemia 310.5 ± 85.7 pg·ml⁻¹).

Conclusion: Neurological outcome is improved following incomplete cerebral ischemia with S(+)-ketamine. Decreases in neuronal injury may be related to suppression of sympathetic discharge.

Objectif : Déterminer les effets de l'antagoniste non compétitif du récepteur NMDA, la S(+)-kétamine, sur l'évolution neurologique d'un modèle rat d'ischémie cérébrale incomplète.

Méthode : L'isoflurane et un mélange d'O₂ (30 %) et de protoxyde d'azote (70 %) ont servi à l'anesthésie, à l'intubation et à la ventilation mécanique de 30 rats. Après l'opération, on a réparti les rats au hasard en trois groupes. On a administré du fentanyl (bolus : 10 µg·kg⁻¹ iv; perfusion de 25 µg·kg⁻¹·h⁻¹) avec N₂O 70 % / O₂ au groupe 1 (n=10, témoin); de l'O₂ à 30 % dans de l'air et de faibles doses de S(+)-kétamine (perfusion : 0,25 mg·kg⁻¹·min⁻¹) au groupe 2 (n=10) et de l'O₂ à 30 % dans de l'air et de fortes doses de S(+)-kétamine (perfusion : 1,0 mg·kg⁻¹·min⁻¹) au groupe 3 (n=10). Après une équilibration de 30 min, l'ischémie a été provoquée par la combinaison d'une ligature unilatérale de l'artère carotide primitive et d'une hypotension hémorragique à 35 mmHg pendant 30 min. Les catécholamines plasmatiques ont été évaluées avant et après l'ischémie. Le déficit neurologique a été étudié pendant trois jours après l'ischémie.

Résultats : L'évolution neurologique a été meilleure avec de fortes doses de S(+)-kétamine qu'avec l'alfentanyl / N₂O (9 vs 1 décès reliés à un accident ischémique cérébral, $P < 0,05$). L'augmentation des concentrations plasmatiques de catécholamines a été plus marquée avec l'alfentanyl / N₂O (l'adrénaline de base à 105,5 ± 92,1 pg·ml⁻¹; pendant l'ischémie, 948 ± 602,8 pg·ml⁻¹, $P < 0,05$; la noradrénaline de base à 407 ± 120,2 pg·ml⁻¹; pendant l'ischémie, 1267 ± 422,2 pg·ml⁻¹, $P < 0,05$) qu'avec de fortes doses de S(+)-kétamine (l'adrénaline de base à 71 ± 79,5 pg·ml⁻¹; pendant l'ischémie, 237 ± 131,9; la noradrénaline de base à 317,9 ± 310,5 pg·ml⁻¹; pendant l'ischémie, 310,5 ± 85,7 pg·ml⁻¹).

Conclusion : L'utilisation de S(+)-kétamine permet une évolution neurologique supérieure après une ischémie cérébrale incomplète. Cette situation peut être reliée à la suppression de décharge sympathique.

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S (+)-KETAMINE (2-Orthochloro-2-methylamino-cyclohexan HCl) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist^{1,2} and represents the laevo-rotatory enantiomere of racemic ketamine. An identical depth of anesthesia is achieved by injection of half of the dose of racemic ketamine. There is also more rapid recovery of psychomotor function and performance.³⁻⁵

Studies in laboratory animals have shown that racemic ketamine exhibits some neuroprotective potential when infused prior to incomplete cerebral ischemia or following traumatic brain injury.⁶⁻⁹ For example, studies in this animal model of incomplete hemispheric ischemia have shown that neurological outcome was improved at three days from insult with racemic ketamine.⁶ Similarly, studies in rats using a non-penetrating impact have shown that racemic ketamine improved neurological outcome and decreased the extension of the lesion even when given two hours post trauma.^{7,8} More recently, studies in rat hippocampal neuronal cultures have shown that racemic ketamine and S(+)-ketamine attenuated the injury after glutamate exposure or axonal transection. In this study the bioenergetic state of the neurons and morphological recovery of axons was better preserved with S(+)-ketamine.⁹ However, it is unclear whether the neuroprotective and neuroregenerative effects of S(+)-ketamine in hippocampal cell cultures are reproducible in animal models of cerebral ischemia. The purpose of the present study was to investigate the effects of S(+)-ketamine on the neurological deficit and infarct size after incomplete cerebral ischemia in a rat model.

Material and methods

Following approval from the Institutional Animal Care Committee (Government of Bavaria, No. 211-2531-16/95), 30 non fasted Sprague-Dawley rats (male, 370-560 g) were anesthetized in a bell jar filled with isoflurane, their tracheas intubated and the lungs mechanically ventilated (volume-controlled, small animal ventilator, Harvard Apparatus; Inc., Natick, Massachusetts, USA) with isoflurane 2% (ForeneTM, Abbott, USA) and N₂O 70% / O₂. Heart rate (HR) was measured using standard 3-lead-ECG. Catheters were inserted into the right femoral artery and femoral vein for mean arterial blood pressure (MAP) measurement, blood sampling and drug administration. One catheter was inserted into the right jugular vein for blood withdrawal and reperfusion. The right common carotid artery was isolated and a loose ligature was placed around the vessel for later clamping. Vecuronium (NorcuronTM, Organon Teknika) was given as a continuous infusion (0.1 mg·kg⁻¹·min⁻¹) to

maintain neuromuscular blockade. Pericranial temperature was measured using Yellow Springs thermistor probes and was maintained constant at 37°C by servo-control using an overhead heating lamp. Mechanical ventilation was adjusted to maintain PaCO₂ between 35 and 42 mmHg. Arterial pH was maintained at physiological levels by bicarbonate infusion. At the completion of surgery, the incisions were infiltrated with bupivacaine 0.25%. Isoflurane was removed from the inspiratory gas mixture and the animals were allowed for an equilibration period of 30 min according to one of the following treatment groups: rats in group 1 (n=10, control) received fentanyl (bolus: 10 µg·kg⁻¹ *iv*; infusion 25 µg·kg⁻¹·hr⁻¹) and N₂O 70%/ O₂ 30%. Rats in group 2 (n=10) received O₂ 30% in air and S(+)-ketamine (infusion: 0.25 mg·kg⁻¹·min⁻¹). Rats in group 3 (n=10) received O₂ 30% in air and S(+)-ketamine (infusion: 1.0 mg·kg⁻¹·min⁻¹, Harvard Infusion/Withdrawal PumpTM, Harvard Apparatus; Inc., Natick, Massachusetts, USA).

Cerebral ischemia was induced by a combination of right common carotid artery occlusion and hemorrhagic hypotension to 35 mmHg MAP for 30 min. A range of 1 mmHg was allowed for the MAP target pressure. After 30 min ischemia, the carotid artery was unclamped and the withdrawn blood reinfused for ten minutes. Arterial blood gas and plasma glucose analyses were performed at baseline, during ischemia and 15 min following reperfusion. Plasma catecholamines (adrenaline, noradrenaline and dopamine) were determined by HPLC before and at the end of ischemia (sensitivity of all assays 5 ng·ml⁻¹; coefficient of variation 5% for adrenaline and noradrenaline and 10% for dopamine assays). Anesthesia was discontinued 30 min after reperfusion. During recovery, the catheters were removed and the incisions closed. The animals were then extubated and transferred to their home cages.

Neurological outcome scores were evaluated by an investigator blinded to the treatment conditions every 24 hr for three days, starting 24 hr after ischemia. For the neurologic examination, a score of "0" represented no detectable neurological deficit and a score of "17" represented stroke related death.¹⁰ Stroke related death was determined after a minimum of three hours following extubation only if the rat showed progressive signs of stroke impairment.

In rats surviving the three postischemic days, infarct size was examined using TTC (2,3,5-triphenyl-tetrazolium-chloride)-staining.

Data are reported as mean ± standard deviation. Since there were some groups not normally distributed, non-parametric statistical tests were used. Differences between groups were analysed using the

H-test of Kruskal-Wallis followed by Harter's test for posthoc comparisons. Wilcoxon Signed Rank Test was used for intra-group comparisons. Significance was assumed at a level of $P < 0.05$.

Results

Tables I and II show HR, MAP, arterial blood gases, arterial pH and plasma catecholamine and glucose concentrations before, during and after incomplete cerebral ischemia. During baseline, HR was lower with high-dose than with low-dose S(+)-ketamine or control background anesthesia. During and after ischemia HR was lower with any dose of S(+)-ketamine when compared to fentanyl/N₂O. MAP was lower with

high-dose S(+)-ketamine (group 3) before and after ischemia than with low-dose S(+)-ketamine (group 2) and with N₂O-fentanyl (group 1). According to the protocol, MAP was decreased to 35 mmHg in all groups during ischemia. Arterial blood gases and pH remained within the physiological range over time. Plasma glucose concentrations were increased during ischemia in all groups but were lower with high and low-dose S(+)-ketamine than in controls.

Adrenaline and noradrenaline, but not dopamine concentrations were higher with fentanyl/N₂O anesthesia (group 1) than in low- (group 2) and high-dose (group 3) S(+)-ketamine. At the end of ischemia adrenaline and noradrenaline concentrations were

TABLE I Heart rate, mean arterial blood pressure, arterial blood gases and arterial pH at baseline, during ischemia and during recovery

	<i>Treatment</i>	<i>HR</i> (bpm)	<i>MAP</i> (mmHg)	<i>PaO₂</i> (mmHg)	<i>PaCO₂</i> (mmHg)	<i>pH</i>
Group 1 (n=10) N ₂ O 70%/fentanyl	baseline	214.7 ± 20.6	120.7 ± 13.9	118.4 ± 17.2	38.2 ± 2.9	7.4 ± 0.03
	15 min ischemia	237.5 ± 12.8	(35)	138.2 ± 7.3	38.4 ± 3.6	7.36 ± 0.05
	30 min ischemia	232.8 ± 16.3	(35)	131.8 ± 16.7	39.4 ± 4.2	7.37 ± 0.04
	recovery	239.1 ± 21.8	116.4 ± 9.3	120.3 ± 20	39.1 ± 4	7.4 ± 0.05
Group 2 (n=10) 0.25 mg·kg ⁻¹ ·min ⁻¹ S(+)-ketamine	baseline	218.9 ± 22.8	134.4 ± 14.5	126.8 ± 21.5	39.2 ± 2.5	7.41 ± 0.02
	15 min ischemia	195.2 ± 16.6*	(35)	136.5 ± 19.8	38.6 ± 2.3	7.36 ± 0.05
	30 min ischemia	197.5 ± 14.8*	(35)	145.5 ± 24.8	35.4 ± 4.2*	7.46 ± 0.07*
	recovery	204.9 ± 24.5*	112.2 ± 18.9	142.8 ± 21.4	34.3 ± 2.9	7.45 ± 0.05
Group 3 (n=10) 1.0 mg·kg ⁻¹ ·min ⁻¹ S(+)-ketamine	baseline	186.2 ± 19.2*†	93.4 ± 16.0*†	114.7 ± 16.6	38 ± 1.8	7.42 ± 0.06
	15 min ischemia	186.9 ± 25.4*	(35)	124.7 ± 17.4	38.9 ± 2.3	7.37 ± 0.04
	30 min ischemia	179.8 ± 25.1*	(35)	123.4 ± 16.5†	37.7 ± 3.4	7.43 ± 0.05
	recovery	191.6 ± 30.1*	91.3 ± 20.1*†	121.5 ± 21.4	36 ± 2.2	7.45 ± 0.05

Data reported as mean ± SD;

* $P < 0.05$ vs group 1 at each respective treatment

† $P < 0.05$ differences vs group 2 at each respective treatment

‡ $P < 0.05$ differences vs baseline within group

TABLE II Plasma catecholamines and plasma glucose

	<i>Treatment</i>	<i>Adrenaline</i> (pg/ml)	<i>Noradrenaline</i> (pg/ml)	<i>Dopamine</i> (pg/ml)	<i>Glucose</i> (mg/dl)
Group 1 (n=10) N ₂ O 70%/fentanyl	baseline	105.5 ± 92.1	407 ± 120.2	40.9 ± 21.7	125 ± 33.8
	15 min ischemia				297 ± 36.1‡
	30 min ischemia	948 ± 602.8‡	1267 ± 422.2‡	76.5 ± 95.1‡	268.1 ± 55.1‡
	recovery				183.1 ± 35.4‡
Group 2 (n=10) 0.25 mg·kg ⁻¹ ·min ⁻¹ S(+)-ketamine	baseline	126.5 ± 95.2	493.4 ± 99.6	102.4 ± 136.8	96.5 ± 38
	15 min ischemia				228 ± 38*‡
	30 min ischemia	642.7 ± 167.5‡	920.2 ± 317.9*‡	130 ± 241.9	129.5 ± 55.2*‡
	recovery				65.8 ± 40.1*
Group 3 (n=10) 1.0 mg·kg ⁻¹ ·min ⁻¹ S(+)-ketamine	baseline	71 ± 79.5†	317.9 ± 218.8†	37 ± 41.6	94.1 ± 29.3
	15 min ischemia				187 ± 72.2*‡
	30 min ischemia	237.5 ± 131.9*‡‡	310.5 ± 85.7*	41.8 ± 33.1*	114.3 ± 78.3*‡
	recovery				61 ± 38.5*

Data reported as mean ± SD;

* $P < 0.05$ vs group 1 at each respective treatment

† $P < 0.05$ differences vs group 2 at each respective treatment

‡ $P < 0.05$ differences vs baseline within group

FIGURE 1 Neurological outcome (3rd postischemic day, score 1-17)

lower in group 3 than in groups 1 and 2. In groups 1 and 2 noradrenaline increased 310% and 186% during ischemia, respectively. In contrast, noradrenaline plasma concentrations did not increase during ischemia with high-dose S(+)-ketamine (-2,3%). The intra-ischemic increase of adrenaline *vs* baseline was significantly higher in group 1 than in group 3. Dopamine plasma concentrations did not change regardless of the anesthetic treatment.

Figure 1 shows the neurological outcome in individual animals on the third postischemic day. In group 1 (fentanyl/N₂O) seven animals died for stroke-related reasons and three rats survived with severe neurological deficits. Similarly, in group 2 (low-dose S(+)-ketamine) six animals died and four rats survived with moderate or no functional deficits. An improvement in neurological outcome was observed in group 3 (high-dose S(+)-ketamine). In this group one animal died of stroke, whereas nine rats had no neurological deficit.

Statistical evaluation of the brain slices stained with TTC was not possible due to the low survival rate in group 1. The examination of the three survivors in group 1 showed extensive cortical necroses of the ipsilateral hemispheres (Figure 2a). Histopathological analyses in surviving animals of group 2 also showed necrosis in cortical and subcortical tissues although these changes appeared to be less extensive compared to group 1 (Figure 2b). Animals receiving high-dose S(+)-ketamine (group 3) did not show cortical or subcortical infarcts (Figure 2c).

Discussion

Ketamine has never been considered an attractive agent in neurosurgical patients because it produces regionally specific stimulation of cerebral metabolism

FIGURE 2 Infarct size (TTC) following incomplete cerebral ischemia

- a) fentanyl/N₂O-anesthesia (control)
- b) S(+)-ketamine, low-dose
- c) S(+)-ketamine, high-dose

and increases CBF.¹¹ Historical studies have shown that racemic ketamine increases ICP, but this adverse effect was likely related to hypercapnic cerebrovascular dilation in spontaneously breathing subjects.^{12,13} In contrast, recent data in head injured patients with

controlled physiological variables indicate that ICP is decreased with racemic ketamine.¹⁴ Despite reports of potentially harmful effects during bolus administrations of phencyclidine derivatives the role of ketamine in neurosurgical anesthesia needs to be reevaluated as several experiments indicate substantial neuronal protection with these compounds.⁶⁻⁹

The present study demonstrates a dose-dependent improvement in neurological outcome, following incomplete cerebral ischemia, with S(+)-ketamine. These results are consistent with previous observations where neurological deficit and histopathological damage were reduced with racemic ketamine in this model and following models of experimental brain injury.⁶⁻⁸ These data are also consistent with experiments using hippocampal neurons showing reduced cell loss after glutamate exposure following pretreatment with racemic ketamine. However, neuroregenerative effects following axonal transection were demonstrated with S(+)-ketamine only since R(-)-ketamine did not exert neuronal protection following glutamate exposure or axonal transection.⁹ These data suggest that S(+)-ketamine is the compound which mediates the neuroprotection seen with racemic ketamine.

It is possible that ketamine decreases neurological injury by mechanisms related to blockade of ionotropic glutamate receptors. The contribution of glutamate and its analogues to neuronal death occurring in animal models of neurological diseases is well established.¹⁵⁻¹⁸ The neuronal cytotoxicity is mediated by excessive Ca^{2+} - and Na^{+} -influx through ionotropic glutamate receptors (NMDA-, AMPA- and Kainate-receptor), which trigger intracellular catabolic processes such as the activation of proteases, lipid peroxidases and phospholipases. This will lead to destruction of biological membranes and consecutive cellular necrosis. Although glutamate- or NMDA-receptor kinetics were not measured during the present study, the dose dependent protection seen with S(+)-ketamine suggests a receptor-related effect.

Previous studies have shown that decreases in peripheral and/or central sympathetic tone improve neurological outcome and reduce infarct size in this model of incomplete hemispheric ischemia. In rats subjected to unilateral carotid occlusion plus systemic hypotension, infusion of the ganglionic blocking agent hexamethonium or the α -2-adrenergic agonist dexmedetomidine was associated with reductions in neurological deficit.^{19,20} Neuroprotection was also seen with halothane, isoflurane, or sevoflurane anesthesia, an effect that was likely related to decreases in central or peripheral sympathetic tone.^{10,21} This is consistent with the present result where S(+)-keta-

mine improved neurological outcome along with decreases in circulating catecholamines. It is possible that these observations reflect the relation between sympathetic activity and neuronal excitation. Experiments in barbiturate anesthetized rats (EEG-isoelectricity) have shown that infusion of catecholamines reversed the suppression of basal metabolism induced by mild hypothermia.²² These data are consistent with increased neuronal excitability and enhancement of glutamatergic activity by catecholamines.²³ Although central (brain) catecholamine concentrations were not measured during the present study, low plasma catecholamine concentrations in the high-dose S(+)-ketamine group may be an important factor in the decrease of neuronal injury in this group. Since necrosis and functional recovery within three days were used as end-points during the present experiments, the data do not allow for any conclusions as to the neuroprotective effects of S(+)-ketamine beyond this interval.

Both, hyper- and hypoglycemia worsen neurological outcome following cerebral ischemia.²⁴⁻²⁶ Hyperglycemia appears to exert its injurious effect by elevating brain stores of glucose with consecutive anaerobic metabolism and accumulation of tissue lactic acid.²⁷ During the present study, intraischemic plasma glucose concentrations were lower with low-dose and high-dose S(+)-ketamine than in fentanyl/ N_2O -anesthetized controls. However, plasma glucose concentrations were similar with low-dose and high-dose S(+)-ketamine while neurological deficit was improved with high-dose S(+)-ketamine only. Although we are unable to exclude completely modulations of neurological outcome by differences in the dynamics of plasma glucose, the present data suggest that reductions in intraischemic plasma glucose concentrations are not the major mechanism by which S(+)-ketamine is neuroprotective in this model.

We used N_2O /fentanyl as the background anesthetic treatment in control animals because this drug combination provides similar baseline cerebral blood flow (CBF) values than in awake animals.²⁸

It is possible that postischemic hypothermia induced by S(+)-ketamine is one of the major mechanisms by which this drug reduces neurological and histopathological damage. During the present study an attempt was made to extend the control of body temperature into the immediate postoperative period. Rectal (rather than pericranial) temperature was measured for two hours after the animals were returned to their home cages for recovery and observation. Although this procedure may not be entirely sufficient to compensate for thermoregulatory effects of keta-

mine it is unlikely that pharmacological hypothermia was a major mechanism by which S(+)-ketamine improves neurological outcome.

It has been questioned whether the use of N₂O/fentanyl (group 1) provides adequate anesthesia and sedation in control animals. Previous studies using this model have shown that N₂O/fentanyl reduces EEG-activity to an amplitude and frequency consistent with an anesthetic state.²⁹ Additionally, studies in rats have shown identical plasma catecholamine concentrations when using N₂O/fentanyl or 1 MAC isoflurane as a background anesthetic.³⁰ This suggests that the present experiments were performed in adequately anesthetized non-stressed animals.

In summary, our results indicate that S(+)-ketamine reduces neurological deficit and histopathological damage following incomplete cerebral ischemia. Similar to racemic ketamine this effect is unlikely related to plasma glucose levels but is associated with lower plasma catecholamine concentrations in S(+)-ketamine-treated animals. The reduced peripheral catecholamine turnover along with reduced Ca⁺⁺- and Na⁺ influx into postsynaptic cells may be an explanation for improved outcome with S(+)-ketamine. Further experiments repeating the present study design with exogenous administration of glucose or catecholamines may clarify the impact of the above mentioned confounding factors.

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