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**TITLE:** DEXMEDETOMIDINE IMPROVES OUTCOME FROM INCOMPLETE CEREBRAL ISCHEMIA IN THE RAT  
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The purpose of this study was to determine whether dexmedetomidine, an  $\alpha_2$ -adrenoreceptor agonist, decreases sympathetic activity and improves outcome from incomplete ischemia in the rat.

**Methods:** After institutional animal care committee approval, 45 male Sprague Dawley rats (350-450 g) were intubated and anesthetized with isoflurane. Femoral artery and vein catheters were inserted. At the end of surgery the isoflurane was replaced with an iv infusion of 25  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$  fentanyl and 70%  $\text{N}_2\text{O}$  ventilation in oxygen. There were four treatment groups. Group 1 (n=15) served as controls. Group 2 (n=10) received an intraperitoneal (ip) injection of 10  $\mu\text{g}/\text{kg}$  dexmedetomidine (DEXMED) 15 minutes before the start of ischemia. Group 3 (n=10) received an ip injection of 100  $\mu\text{g}/\text{kg}$  dexmedetomidine. Group 4 (n=10) received 100  $\mu\text{g}/\text{kg}$  dexmedetomidine and 1 mg/kg atipamezole (ATIPAM), an  $\alpha_2$ -adrenoreceptor antagonist. Ischemia was produced by right carotid ligation combined with hemorrhagic hypotension to 35 mmHg for 30 minutes. Arterial  $\text{PCO}_2$  and pH were maintained at control levels and skull temperature at 37°C during ischemia. Plasma glucose and catecholamines were measured during ischemia. After ischemia, the rats were recovered and neurologic outcome measured daily for 3 days using an 18 point scale (0 = normal, 18 = stroke related death).

**Result:** Total catecholamines (epi+norepi) during ischemia were: group 1 = 2.33±.24 ng/ml, group 2 = 0.57±.17 ng/ml (P<0.05), group 3 = 0.21±.07 ng/ml (P<0.05), group 4 = 2.50 ng/ml. Neurologic outcome was improved by dexmedetomidine and this effect was reversed by atipamezole (fig 1). Neurologic outcome was correlated with plasma catecholamines (r=0.67, P<0.05) but not plasma glucose (r=0.02).

**Discussion:** These results show that dexmedetomidine decreases catecholamines and improves outcome from ischemia by stimulation of  $\alpha_2$ -adrenoreceptors.

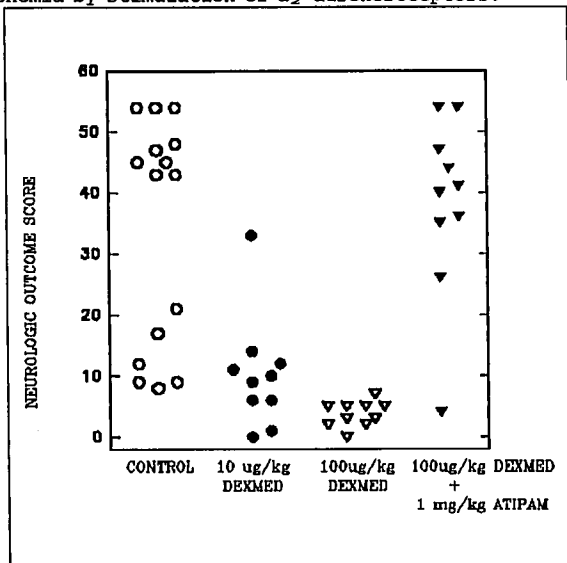


Figure 1. Total score for 3 days. DEXMED (10 and 100  $\mu\text{g}/\text{kg}$ ) improved outcome vs control (P<0.05)

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**TITLE:** EFFECTS OF MK-801 ON CEREBRAL REGIONAL OXYGEN CONSUMPTION IN FOCAL CEREBRAL ISCHEMIA  
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The purpose of this investigation was to test whether MK-801, an N-methyl-D-aspartate (NMDA) receptor antagonist, would improve the balance of O<sub>2</sub> supply and consumption in the focal ischemic area of the brain induced by occlusion of the middle cerebral artery (MCA).

Adult male long Evans rats were anesthetized with pentobarbital (50 mg/kg ip) and the MCA was ligated. Fifteen min after MCA occlusion, 5 mg/kg of MK-801 was administered iv over 2 min to the MK-801 group (N=12) and normal saline was given to the control group (N=12). One hour after MCA occlusion in each group, the regional cerebral blood flow (rCBF) was determined in 6 rats using <sup>14</sup>C-iodoantipyrine, while the regional arterial and venous O<sub>2</sub> saturation were determined using a microspectrophotometric technique in the other 6 rats. O<sub>2</sub> extraction and consumption were calculated from rCBF, A-V O<sub>2</sub> saturation difference and Hb.

Blood pressure, heart rate, PaCO<sub>2</sub>, hemoglobin concentration and temperature were not different between the two groups at the time of determination of CBF and O<sub>2</sub> saturation. rCBF was not affected by MK-801 in all the brain regions studied including the ischemic cortex (Table 1). O<sub>2</sub> extraction was significantly higher in the ischemic cortex than in the contralateral cortex for the control group. However for the MK-801 group, there was no significant difference between these cortices. O<sub>2</sub> extraction in the ischemic cortex of the MK-801 group was significantly lower than that of the control group. The regional O<sub>2</sub> extraction was not significantly different among the various non-ischemic brain regions of both the control and the MK-801 group. The distribution of venous O<sub>2</sub> saturations in the ischemic cortex of the MK-801 group was significantly shifted toward higher O<sub>2</sub> concentrations when compared with that of the same region in the control group. Calculated ischemic regional O<sub>2</sub> consumption was similar to the non-ischemic values in the control group, while the ischemic value was reduced to 61% of the value of the contralateral cortex in the MK-801 group (Figure 1).

Our study demonstrated that MK-801 improved the O<sub>2</sub> supply to consumption ratio by decreasing the O<sub>2</sub> consumption without a significant change in the O<sub>2</sub> supply of the ischemic region. Inhibition of the increase of O<sub>2</sub> extraction in the ischemic cortex of the MK-801 group may be related to the ability of MK-801 to block the NMDA receptors.

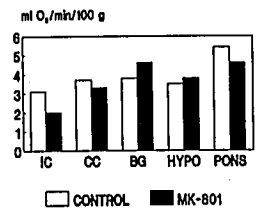


Figure 1. O<sub>2</sub> Consumption

Table 1. Cerebral blood flow, O<sub>2</sub> extraction and O<sub>2</sub> supply to consumption ratio one hour after MCA occlusion (Mean ± SD).

Brain Region	Group	Blood Flow (ml/min/100g)	O <sub>2</sub> Extraction (ml O <sub>2</sub> /100 ml blood)	O <sub>2</sub> Supply to Consumption Ratio
Ischemic Cortex (IC)	Control	36±16 <sup>+</sup>	8.8±2.1 <sup>+</sup>	2.1±0.3 <sup>+</sup>
	MK-801	33±10 <sup>+</sup>	6.1±1.0 <sup>*</sup>	2.9±0.7 <sup>*</sup>
Contralateral Cortex (CC)	Control	67±14	5.6±0.3	3.3±0.3
	MK-801	58±11	5.7±1.1	3.2±0.4
Basal Ganglia (BG)	Control	67±15	5.6±0.5	3.2±0.2
	MK-801	70±23	6.5±1.0	2.8±0.6
Hypothalamus (HYPO)	Control	67±14	5.3±0.5	3.4±0.6
	MK-801	66±14	5.8±1.2	3.2±0.6
Pons (PONS)	Control	84±16 <sup>+</sup>	6.5±1.5	2.9±0.7
	MK-801	72±15	6.4±1.3	2.7±0.4

<sup>+</sup> Significantly different from the contralateral cortex (p < 0.05).

<sup>\*</sup> Significantly different from the control (p < 0.05).