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Dexmedetomidine Improves Neurologic Outcome from Incomplete Ischemia in the Rat

Reversal by the α_2-Adrenergic Antagonist Atipamezole

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Dexmedetomidine is an α_2-adrenergic agonist that decreases central sympathetic activity and reduces the anesthetic requirement for halothane. We evaluated the effect of dexmedetomidine on neurologic and histopathologic outcome from incomplete cerebral ischemia in the rat. Anesthesia was maintained with a 25-$\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl infusion combined with 70% nitrous oxide. Incomplete ischemia was produced by unilateral carotid artery ligation combined with hemorrhagic hypotension to 35 mmHg for 30 min. Arterial blood gas tensions, *p*H, and head temperature were maintained at normal levels during the experiment. Four ischemic groups were tested: group 1 (n = 15) received an intraperitoneal (ip) saline injection (control); group 2 (n = 10) received an ip injection of 10 μg/kg dexmedetomidine 30 min before ischemia; group 3 (n = 10) received 100 μg/kg dexmedetomidine; and group 4 (n = 10) received 100 μg/kg dexmedetomidine plus 1 mg/kg atipamezole (an α_2-adrenergic antagonist). Neurologic outcome was evaluated for 3 days using a graded deficit score. Histopathology was evaluated in coronal section in caudate and hippocampal tissue segments. Dexmedetomidine (10 and 100 μg/kg) significantly decreased plasma catecholamines and improved neurologic and histopathologic outcome in a dose-dependent manner compared to control rats ($P < 0.05$). Atipamezole abolished the decrease in catecholamines and the improvement in outcome seen with dexmedetomidine, confirming that these effects were mediated by α_2-adrenergic receptors. It is concluded that α_2-adrenoreceptor stimulation decreases sympathetic activity and decreases ischemic injury in a model of incomplete cerebral ischemia. (Key words: Brain: ischemia. Sympathetic nervous system: receptors; α_2-adrenergic agonist; dexmedetomidine; α_2-antagonist; atipamezole.)

IT HAS BEEN SHOWN PREVIOUSLY that ganglionic blockade improves neurologic outcome associated with incomplete cerebral ischemia in the rat.[1] The improvement was partially reversed by infusion of catecholamines in ganglionic blocked rats. This suggests that sympathetic stimulation during incomplete ischemia worsens outcome. It is likely that this effect is mediated centrally. Stimulation of brain α_2-adrenergic receptors decrease sympathetic activity, possibly by an action in the locus coeruleus.[2,3] Clonidine, an α_2-adrenergic agonist, recently has been shown to improve outcome from incomplete brain ischemia.[4] Dexmedetomidine is a more potent and more specific α_2-adrenergic agonist than clonidine.[5] Dexmedetomidine administration has been shown to decrease the anesthetic requirement for halothane by up to 90%.[6,7] However, this drug does not decrease cerebral oxygen consumption.[8]

If cerebral metabolic depression is the primary mechanism by which anesthetics protect the brain during ischemia, we would expect dexmedetomidine to be ineffective in decreasing ischemic neuronal damage. However, previous results with ganglionic blockade and clonidine treatment suggest that sympathetic activity is important.[1,2] The purpose of this study was to determine if dexmedetomidine improves neurologic and histopathologic outcome from incomplete ischemia in the rat and whether this effect is mediated by α_2-adrenergic stimulation.

Materials and Methods

These experiments were performed after approval was obtained from the Institutional Animal Care Committee. Forty-five nonfasted male Sprague-Dawley rats (350–450 g) were anesthetized in a bell jar saturated with isoflurane; their tracheas were intubated; and their lungs were mechanically ventilated with 1.4% isoflurane and 70% nitrous oxide in oxygen. Catheters were inserted into the right femoral artery and left femoral vein for continuous blood pressure measurements, blood sampling, and drug administration. A catheter was inserted into the right jugular vein for blood withdrawal during ischemia. The right common carotid artery was isolated and a loose ligature placed around the vessel for later clamping. Vecuronium was given as a continuous infusion (0.1 $mg \cdot kg^{-1} \cdot min^{-1}$) to maintain paralysis. After surgery, isoflurane was removed from the inspiratory gas mixture. Fentanyl was given as a 10 $\mu g/kg$ intravenous (iv) bolus followed by a continuous infusion of 25 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Anesthesia was

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maintained with 70% nitrous oxide in oxygen and fentanyl for 45 min.

Treatment Groups

After the equilibration period, each rat was assigned to one of the following treatment groups. Group 1 (n = 15) received fentanyl/nitrous oxide anesthesia and an intraperitoneal (ip) saline vehicle injection as a control. Group 2 (n = 10) received fentanyl/nitrous oxide anesthesia and 10 μg/kg ip dexmedetomidine 30 min before ischemia. Group 3 (n = 10) received fentanyl/nitrous oxide anesthesia and 100 μg/kg ip dexmedetomidine 30 min before ischemia. Group 4 (n = 10) received fentanyl/nitrous oxide anesthesia, 100 μg/kg dexmedetomidine, and 1 mg/kg atipamezole (an α_2-adrenergic antagonist) ip 30 min before ischemia.

Ischemia

Cerebral ischemia was produced by the combination of right common carotid occlusion and hemorrhagic hypotension with mean arterial blood pressure at 35 mmHg for 30 min. A range of 2 mmHg was allowed for the target pressure. After 30 min of ischemia, the carotid artery was unclamped and the withdrawn blood slowly reinfused for 10 min. Skull temperature was measured by percutaneous insertion of a Yellow Springs 22-G stainless steel hypodermic thermistor probe. Skull temperature was maintained at 37° C by servomechanism using a overhead heating lamp. Arterial carbon dioxide tension was maintained between 35 and 40 mmHg by adjusting ventilation. Arterial *p*H was maintained at normal levels by bicarbonate infusion. Mean arterial blood pressure (mmHg), arterial oxygen tension (mmHg), arterial carbon dioxide tension (mmHg), *p*H, and plasma glucose (Yellow Springs Glucose Analyzer) were measured at control, during ischemia, and 20 min after reinfusion of the blood during recovery. Arterial blood samples were taken for radioenzymatic assay of plasma catecholamines (CAT-A-Kit, Amersham) at the end of the ischemic period in each rat. During the recovery period the catheters were removed, the fentanyl infusion stopped, and the incisions closed. The animals were extubated after the establishment of sufficient spontaneous respiration and were transferred to their cages.

Neurologic Outcome

Neurologic outcome scores were evaluated every 24 h for a period of 3 days, starting 24 h after ischemia (table 1). A score of 0 represented no detectable neurologic deficit, and a score of 18 represented death related to stroke, which was determined a minimum of 3 h after extubation only if the rat showed progressive signs of stroke impairment. The evaluator was blinded to the treatment condition.

Table 1. Neurologic Scoring

Consciousness	Walking
0 = normal	0 = normal
1 = restless	1 = paw adduction
2 = lethargic	2 = hypomobility
3 = stuporous	3 = circling to stroke side
4 = seizures	4 = unable to stand
Rope platform	Rotating screen
0 = climbs to platform	0 = grasps to 80° > 5 s
1 = pulls up rear legs	1 = grasps to 80° < 5 s
2 = hangs on 5 s	2 = grasps to 90°, not 180°
3 = hangs on <5 s	3 = falls from vertical screen
4 = no grasp reflex	Pain reflex
Limb tone	0 = normal
0 = normal	1 = hypoactive
1 = weak	

Total score = 18.

Brain Histopathology

Those rats surviving the 3-day neurologic examination period were anesthetized with isoflurane and their chests opened; they then were killed by transcardial perfusion of 20 ml isotonic saline followed by 20 ml 10% buffered formalin. After removal, the brain was stored in formalin for subsequent histologic examination. The forebrain was dissected into coronal blocks and imbedded in paraffin, and 7-μm sections were cut and mounted on slides. The slides were stained using hematoxylin and eosin and examined in a blinded manner by a neuropathologist using light microscopy. Neuronal histopathology was evaluated in the coronal section at the level of the caudate nucleus and also at the level of the hippocampus formation. The ischemic hemisphere in the caudate section was graded: 0 = no observable neuronal death; 1 = scattered neuronal death; 2 = small focal infarcts in caudate and cortical areas; 3 = large infarcts involving 50% of the caudate; 4 = infarcts involving at least 50% of the total ischemic hemisphere; and 5 = total hemispheric infarction. Brain tissue damage of the hippocampal section was graded: 0 = no damage; 1 = 0–25%; 2 = 26–50%; 3 = 51–75%; and 4 = 76–100% hippocampal injury. This scale included all hippocampal regions—CA1, CA2, CA3, and CA4. Scores for caudate and hippocampal sections were added so that each animal could receive a score from 0 to 9.

Statistics

Data are reported as means ± standard errors of the means. Nonparametric data, including the neurologic deficit score and histopathology, were analyzed using a Kruskal-Wallis analysis. Physiologic data were analyzed using

TABLE 2. Arterial Blood Pressure, Blood Gas Tensions, *p*H, and Plasma Glucose Concentration

Group	Blood Pressure (mmHg)	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	*p*H	Plasma Glucose (mg/dl)
Control (n = 15)					
Baseline	132 ± 3	37.0 ± .4	142 ± 3	7.42 ± .01	169 ± 5
Ischemia (n = 15)	35 ± 1*	37.1 ± .9	158 ± 2	7.36 ± .01	
Ischemia (n = 30)	35 ± 1*	39.1 ± .6	155 ± 3	7.38 ± .01	315 ± 26*
Recovery	116 ± 3	39.7 ± .9	136 ± 4	7.35 ± .01	173 ± 18
Dexmedetomidine 10 μg/kg (n = 10)					
Baseline	92 ± 5†	37.8 ± .5	141 ± 4	7.40 ± .01	221 ± 16†
Ischemia (n = 15)	35 ± 1*	37.9 ± .7	154 ± 3	7.37 ± .01	
Ischemia (n = 30)	35 ± 1*	37.3 ± .6	154 ± 2	7.37 ± .01	339 ± 18*
Recovery	113 ± 5	39.2 ± .5	136 ± 2	7.39 ± .01	238 ± 20
Dexmedetomidine 100 μg/kg (n = 10)					
Baseline	125 ± 5	36.3 ± .7	135 ± 7	7.41 ± .01	251 ± 13†
Ischemia (n = 15)	35 ± 1*	37.3 ± .5	142 ± 5	7.38 ± .01	
Ischemia (n = 30)	35 ± 1*	37.5 ± .7	142 ± 4	7.40 ± .01	357 ± 25*
Recovery	115 ± 3	36.8 ± .6	133 ± 3	7.42 ± .01	261 ± 21
Dexmedetomidine 100 μg/kg + atipamezole 1 mg/kg (n = 10)					
Baseline	126 ± 3	36.3 ± .8	141 ± 3	7.40 ± .01	192 ± 12
Ischemia (n = 15)	35 ± 1*	36.1 ± .6	150 ± 4	7.40 ± .01	
Ischemia (n = 30)	35 ± 1*	38.0 ± .6	146 ± 4	7.38 ± .01	345 ± 18*
Recovery	93 ± 6†	37.0 ± .8	126 ± 4	7.37 ± .01	203 ± 18

* $P < 0.05$ compared to baseline within each group.

† $P < 0.05$ compared to control group at each respective level.

a two-way analysis of variance and Tukey tests for *post hoc* comparisons among groups and treatments. Spearman rank-order correlations were used to correlate outcome with plasma glucose and catecholamines. Significance was assumed at a level of $P < 0.05$.

Results

Arterial blood pressure, blood gas tensions, *p*H, and plasma glucose concentrations are shown in table 2. Blood gas tensions and *p*H did not vary significantly during ischemia. Dexmedetomidine (10 μg/kg, group 2) produced a significant decrease in baseline mean arterial blood pressure compared to the control group. Dexmedetomidine (10 and 100 μg/kg) increased plasma glucose in a dose-dependent manner. During ischemia, plasma glucose increased in all treatment groups. Plasma catecholamines measured during ischemia were lower in dexmedetomidine-treated rats compared to those in control rats (table 3). This effect was abolished by atipamezole. The amount of blood withdrawn during ischemia was lower in 100 μg/kg dexmedetomidine-treated rats compared to controls (table 3).

Dexmedetomidine produced a dose-related improvement of neurologic outcome after ischemia (fig 1). The improvement in outcome seen with 100 μg/kg dexmedetomidine (group 3) was abolished by combined treatment with 100 μg/kg dexmedetomidine and 1 mg/kg atipamezole (group 4). The correlation of plasma glucose and total plasma catecholamines (norepinephrine and epinephrine) with neurologic outcome was r = 0.02 and r = 0.67 ($P < 0.05$), respectively.

TABLE 3. Plasma Catecholamine Concentrations and Blood Withdrawn During Ischemia

	Plasma Norepinephrine (ng/ml)	Plasma Epinephrine (ng/ml)	Blood Withdrawn (ml)
Control (n = 15)	1.05 ± 0.10	1.28 ± 0.20	12.1 ± 0.6
Dexmedetomidine 10 μg/kg (n = 10)	0.21 ± 0.05*	0.37 ± 0.13*	11.1 ± 0.7
Dexmedetomidine 100 μg/kg (n = 10)	0.12 ± 0.04*	0.09 ± 0.04*	9.3 ± 0.4*
Dexmedetomidine 100 μg/kg + Atipamezole 1 mg/kg (n = 10)	1.32 ± 0.15	1.18 ± 0.09	10.6 ± 0.9

* $P < 0.05$ compared to control.

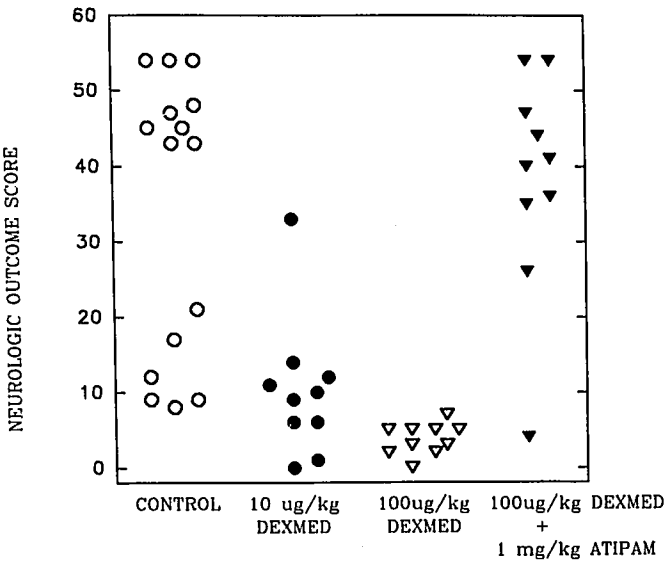

FIG. 1. Neurologic outcome with dexmedetomidine and atipamezole treatment. Individual total scores for each rat for the 3-day scoring period are shown. A high score indicates a poor outcome. Neurologic outcome with 10 and 100 μg/kg dexmedetomidine was improved compared to the control group ($P < 0.05$).

Brain histopathology was examined in the seven rats in group 1, ten rats in group 2, ten rats in group 3, and two rats in group 4 that survived to the end of the neurologic examination period. The median histopathologic score in group 1 was 9, indicating severe neuronal damage in both caudate and hippocampal sections. Median scores with 10 μg/kg and 100 μg/kg dexmedetomidine were 2 and 3, respectively. These scores were significantly better than those of the control group ($P < 0.05$). Both rats in group 4 had histology scores of 9, indicating severe injury.

Discussion

These results show that the α_2-adrenergic agonist dexmedetomidine improves outcome from incomplete ischemia by an action that is not related to differences in blood pressure, blood gas tensions, *p*H, head temperature, or plasma glucose but that is correlated with plasma catecholamines during ischemia. The improvement in outcome by dexmedetomidine was abolished by the α_2-adrenergic antagonist atipamezole. This finding supports the proposal that dexmedetomidine decreases sympathetic activity by stimulation of α_2-adrenergic receptors.[2,3,5] The improvement in ischemic outcome may be mediated by a decrease in sympathetic activity[9–11] rather than by a change in brain metabolism during ischemia since dexmedetomidine does not change cerebral oxygen consumption.[8] Rats treated with 100 μg/kg dexmedetomidine also had less blood withdrawn during ischemia, presumably because of lower plasma catecholamines. This probably was not a factor altering outcome since each treatment group had the same blood pressure during ischemia.

In this model of cerebral ischemia, inhibition of sympathetic activity with the ganglionic blocker hexamethonium significantly improved outcome from ischemia.[1] This effect was reversed by infusion of epinephrine and norepinephrine in ganglionic-blocked ischemic rats. This indicates that catecholamines worsen outcome from ischemia, possibly by stimulating central receptors.[12,13] Globus *et al.*[14] suggested that central norepinephrine release during brain ischemia increases neuronal metabolism and exaggerates the imbalance between ischemic tissue blood flow and metabolic demand. In findings consistent with this, Meyer *et al.*[15] saw positive correlations among central norepinephrine release, cerebral oxygen consumption, and infarct size during ischemia. However, other studies have shown that blockade of central and peripheral sympathetic activity worsens neuronal injury in a model of near-complete cerebral ischemia in the rat.[16,17] Gustafson *et al.*[18] reported that after ischemia in rats, infusion of idazoxan, an α_2-adrenoreceptor antagonist, decreased hippocampal neuronal death compared to a control treatment. This suggests that elevated sympathetic activity after near-complete ischemia may decrease hippocampal neuronal death. In contrast, our results show that increased sympathetic activity during incomplete ischemia is associated with a worse outcome.

It should be considered whether cerebrovascular or cerebral metabolic effects of dexmedetomidine decrease ischemic injury. Cerebral arterioles contain α_2-adrenergic receptors that mediate cerebral vasoconstriction.[19] Previous studies have shown that dexmedetomidine decreases cerebral blood flow 30–45% in dogs anesthetized with halothane or isoflurane.[8,20] This decrease in cerebral blood flow occurs without a change in cerebral oxygen consumption. This suggests that dexmedetomidine does not change neuronal metabolic demand during ischemia. This, however, may be controversial, since Crosby *et al.*[21] have shown that subarachnoid administration of the α_2-adrenergic agonist clonidine decreases spinal cord blood flow and glucose consumption in the rat. Another possibility is that cerebral vasoconstriction induced by dexmedetomidine may improve perfusion of ischemic tissue by increasing vascular resistance in nonischemic tissue.

In the current study, both 10 μg/kg and 100 μg/kg dexmedetomidine increased plasma glucose before ischemia. This effect is mediated by α_2-adrenergic inhibition of insulin release.[22] In this model of ischemia, increased plasma glucose before and during ischemia worsens outcome.[23] The ability of dexmedetomidine to improve ischemic outcome despite increased plasma glucose indicates that other mechanisms are more important in improving ischemic outcome.

The site of action of dexmedetomidine in these studies is unclear. There is a high density of α_2-adrenoreceptors in the brain[5] and possibly more than one type of receptor.[24] The membrane components of these receptors involve signal transducing G-proteins that may be functionally linked to potassium channel conductance.[2] These α_2-adrenergic mechanisms may modulate anesthetic depth[6] as well as ischemic injury. However, access to central receptors may be limited by the blood–brain barrier. Another possibility is that α_2-receptors in the area postrema mediate changes in central sympathetic activity.[3] The area postrema has a reduced blood–brain barrier and may be responsible for feedback control of adrenergic activity. This suggests that α_2-adrenoreceptors in the area postrema may improve outcome from incomplete ischemia by decreasing central and peripheral sympathetic activity.

In conclusion, dexmedetomidine improved neurologic and histopathologic outcome after incomplete ischemia in rats anesthetized with fentanyl and nitrous oxide. This effect was reversed by atipamezole, indicating that the effect is mediated by α_2-adrenergic receptors. Improvement with dexmedetomidine is not mediated by changes in plasma glucose or other physiologic variables during ischemia. Other reports have shown that dexmedetomidine does not decrease cerebral oxygen consumption.[8] This suggests that sympathetic activity and not cerebral metabolic demand improves ischemic outcome with dexmedetomidine. It is not clear whether central or plasma catecholamine activity is most important in mediating this effect.

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