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Dexmedetomidine-induced cerebral hypoperfusion exacerbates ischemic brain injury in rats

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Abstract
Purpose. Dexmedetomidine has been used for purposes of anesthesia and sedation, and experimental studies have demonstrated its neuroprotective effects. However, it has also been shown that the constriction of cerebral vessels in response to high doses of dexmedetomidine decreases cerebral blood flow. We tested the hypothesis that dexmedetomidine-induced cerebral hypoperfusion exacerbates ischemic cerebral injury.
Methods. The effects of dexmedetomidine on cerebral blood flow and mean arterial blood pressure were studied first. Six rats received intravenous infusions of dexmedetomidine in doses ranging from 0.01 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At the end of this phase of treatment, the alpha-2 adrenergic antagonist yohimbine was administered (3 $mg \cdot kg^{-1}$ ip). Cerebral blood flow and mean arterial blood pressure were recorded continuously. A second series of experiments was then performed using a rat model of transient middle cerebral artery occlusion. Forty-two rats received 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine with or without pretreatment with either of the alpha-2 adrenergic antagonists yohimbine or rauwolscine. Five days after middle cerebral artery occlusion and reperfusion, the rat brains were removed and the infarct volumes were measured.
Results. In the first protocol, increasing the dose of dexmedetomidine significantly decreased cerebral blood flow. Mean arterial blood pressure decreased to 79.9% relative to baseline with a dose of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine, and increased to 119.9% relative to baseline with a dose of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine. In the second protocol, the infarct volume in the control group was 9.5% of the total brain volume; the infarct volume increased to 11.3% in rats treated with 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine and the volume increased to 24.5% in rats treated with 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine. Pretreatment with an alpha-2 adrenergic antagonist, either yohimbine or rauwolscine, reduced the size of these high-dose dexmedetomidine-induced infarct volumes.
Conclusion. Hypertension following the administration of high-dose dexmedetomidine is associated with cerebral hypoperfusion and the exacerbation of ischemic brain injury, possibly through alpha-2-induced cerebral vasoconstriction.

Key words Dexmedetomidine · Cerebral blood flow · Alpha-2 adrenoceptor · Yohimbine · Middle cerebral artery occlusion

Introduction

Dexmedetomidine, a specific but subtype-nonselective alpha-2 adrenoceptor agonist, has become widely used in the operating room and intensive care unit for anesthetic and sedative purposes. The majority of previous reports regarding the use of dexmedetomidine for sedation in pediatric patients limited the dose to 0.5–1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ [1–4]. However, dose escalation may be needed when long-term infusions result in tolerance or when routine doses fail to achieve sedation [1,2].

Dexmedetomidine activates all three subtypes of alpha-2 adrenoceptors, i.e., alpha-2A, alpha-2B, and alpha-2C [5]. Among these receptors, the activation of alpha-2A receptors by dexmedetomidine exerts a neuroprotective effect [6–9]. In contrast, the activation of alpha-2B receptors by high concentrations of dexmedetomidine has been reported both to constrict cerebral vessels, thus decreasing cerebral blood flow (CBF) [10–12], and to constrict systemic vessels, resulting in increased systemic blood pressure [13]. However, the relationship between the vasoconstriction induced by high doses of dexmedetomidine and ischemic brain damage remains unclear. Therefore, in this study we examined the hypothesis that dexmedetomidine-induced cerebral vasoconstriction exacerbates ischemic brain injury following middle cerebral artery occlusion (MCAO) in a rat model. We also assessed the changes in cerebral blood flow, cerebral vascular resistance, and

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systemic blood pressure with various doses of dexmedetomidine.

Materials and methods

General preparations

Forty-eight male Sprague-Dawley rats (weighing 350–400 g) were used; the approval of the Institutional Animal Care and Use Committee (IACUC) was given for the study. After intraperitoneal (ip) injection of pentobarbital sodium (50 $mg \cdot kg^{-1}$), a tracheal tube was inserted and the rats were mechanically ventilated with air. End-tidal CO_2 was continuously measured and kept within the normal range (35–40 mmHg) throughout the experiment. Brain temperature was measured with a 22-gauge stainless steel needle thermometer placed in the left temporal muscle, and normothermia was maintained by using an overhead heating lamp and a heating pad throughout the experiment. Dexmedetomidine is known to affect thermogenesis through several distinct mechanisms [14]. We therefore warmed the rats' heads as well as their bodies continuously in order to maintain normothermia. Catheters were inserted into the femoral artery for monitoring blood pressure and into the femoral vein for administering drugs. Pancuronium was administered in a continuous infusion (0.01 $mg \cdot kg^{-1} \cdot min^{-1}$) for paralysis. Pentobarbital sodium was administered as appropriate in order to maintain an adequate level of anesthesia. Blood glucose values ranged from 123 to 174 $mg \cdot dl^{-1}$ (with no significant differences between groups).

Cerebral blood flow (CBF) on the side ipsilateral to the occlusion in the parietal cortex was monitored using a laser-Doppler probe (Omegawave; Tokyo, Japan) placed 6 mm lateral and 2 mm posterior to the bregma.

Dexmedetomidine and CBF

After general preparations, six rats received intravenous infusions of dexmedetomidine. The doses of dexmedetomidine were gradually increased from 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Each concentration of dexmedetomidine was kept at a constant infusion rate over 45 min. Following dexmedetomidine administration, the rats received 3 $mg \cdot kg^{-1}$·(ip injection) of the alpha-2 adrenergic antagonist, yohimbine or the alpha-2 adrenergic antagonist rauwolscine. The dose of yohimbine was based on previous observations [15–17]. Based on the structural similarity of yohimbine and rauwolscine, the same dose of rauwolscine was applied. During dexmedetomidine administration, CBF and mean arterial blood pressure (MABP) were monitored continuously in order to calculate cerebral vascular resistance.

Dexmedetomidine and the volume of cerebral infarction

After the general preparations, the 42 rats were assigned to one of six treatment groups. Group 1 ($n = 7$) received intravenous infusion of saline vehicle as a control (control). Group 2 ($n = 7$) received intravenous infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine (Dex10). Group 3 ($n = 7$) received intravenous infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine (Dex1). Group 4 ($n = 7$) received intravenous infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine and 3 $mg \cdot kg^{-1}$ yohimbine (ip injection 45 min before occlusion; Dex10 + Y). Group 5 ($n = 7$) received intravenous infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine and 3 $mg \cdot kg^{-1}$ of the alpha-2 adrenergic antagonist rauwolscine (ip injection 45 min before occlusion; Dex10 + R). Group 6 ($n = 7$) received intravenous infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine and 3 $mg \cdot kg^{-1}$ yohimbine (Dex1 + Y). We administered yohimbine or rauwolscine 30 min before dexmedetomidine, and MCAO was initiated 15 min after dexmedetomidine administration.

We induced transient focal cerebral ischemia by MCAO, using an intraluminal technique as previously described [18]. Vascular occlusion was maintained for 1 h. The occluding filament was then withdrawn and the brain was reperfused. CBF and MABP were monitored continuously from the beginning of the infusion until 20 min after reperfusion. Dexmedetomidine was discontinued at 20 min after reperfusion. Several hours after each experiment, the tracheal catheter was removed and the rats were fed for 5 days. We continued to feed the rats for 5 days because of the clinical importance of cerebral edema, a delayed neurological effect that occurs secondary to altered apoptosis several days after focal ischemia [19].

Five days after reperfusion, the brains were collected, immediately sectioned (seven 2-mm-thick coronal sections per brain), and stained with 2, 3, 5-triphenyltetrazolium chloride (TTC). This method is commonly used and is highly reproducible for determining infarct volume in the brain [20–23]. Hemotoxylin-and-eosin (H & E) staining was also performed to confirm the infarction. We analyzed the infarct area of all slices and evaluated the infarct volume as a percentage of the total brain volume (Scion image; Frederick, MD, USA).

Statistical analysis

All data are expressed as means ± SEM. Treatment groups were compared by repeated or nonrepeated

analysis of variance (ANOVA) and post-hoc with the Student-Newman-Keuls test for multiple comparisons. Differences were considered statistically significant with $P < 0.05$.

Results

In the first protocol, at a dose of 0.01 μg·kg^{-1}·min^{-1} dexmedetomidine, MABP decreased to 79.9% in comparison with baseline values. With increasing doses of dexmedetomidine, the MABP increased, increasing to 119.9% relative to baseline at 10 μg·kg^{-1}·min^{-1} dexmedetomidine. At doses of 0.01 μg·kg^{-1}·min^{-1}, 0.1 μg·kg^{-1}·min^{-1}, and 1 μg·kg^{-1}·min^{-1} of dexmedetomidine, CBF was significantly decreased (to 66%, 76%, and 74% of baseline, respectively). At a dose of 10 μg·kg^{-1}·min^{-1} dexmedetomidine, CBF decreased rapidly and cerebral vascular resistance increased dramatically, to 268% of baseline (Fig. 1). With the administration of yohimbine, cerebral vascular resistance was restored to 121% of baseline. Based on these findings, we chose two doses of dexmedetomidine, 1 μg·kg^{-1}·min^{-1} and 10 μg·kg^{-1}·min^{-1}, for the second series of experiments.

Figure 2 shows the changes in CBF during MCAO and reperfusion. In the Dex1 group, CBF decreased to 52% of baseline (range, 48%–55%) during occlusion. After reperfusion, CBF increased to 125% of baseline. In the Dex10 group, CBF decreased to 49% of baseline (range, 44%–53%), but after reperfusion the trend was not the same as in the other groups; CBF remained at approximately 50% of baseline, significantly lower than that in the other groups. In the Dex1 + Y group, CBF decreased to 55% of baseline (range, 52%–57%) during occlusion and increased to 101% of baseline after reperfusion. In rats with an infusion of 10 μg·kg^{-1}·min^{-1} dexmedetomidine plus yohimbine (Dex10 + Y), CBF decreased to 50% of baseline (range, 46%–60%) during occlusion and increased to 103% of baseline after reperfusion. In rats with an infusion of 10 μg·kg^{-1}·min^{-1} dexmedetomidine plus rauwolscine (Dex10 + R), CBF decreased to 50% of baseline (range, 45%–54%) during occlusion and increased to 135% of baseline after reperfusion.

With regard to the MABP data for each of the groups that received dexmedetomidine, the rats in the Dex10 group exhibited a significant increase in MABP as compared to the control group. On the other hand, the group that received yohimbine displayed a significant decrease in MABP in the first several minutes (Fig. 3).

Figure 4A,B shows photographs representative of TTC-stained coronal slices. In comparison to the vehicle controls (Fig. 4A), the infarct volume was larger in the Dex10 group (Fig. 4B). Cerebral infarction was confirmed in all rats that received 10 μg·kg^{-1}·min^{-1} or

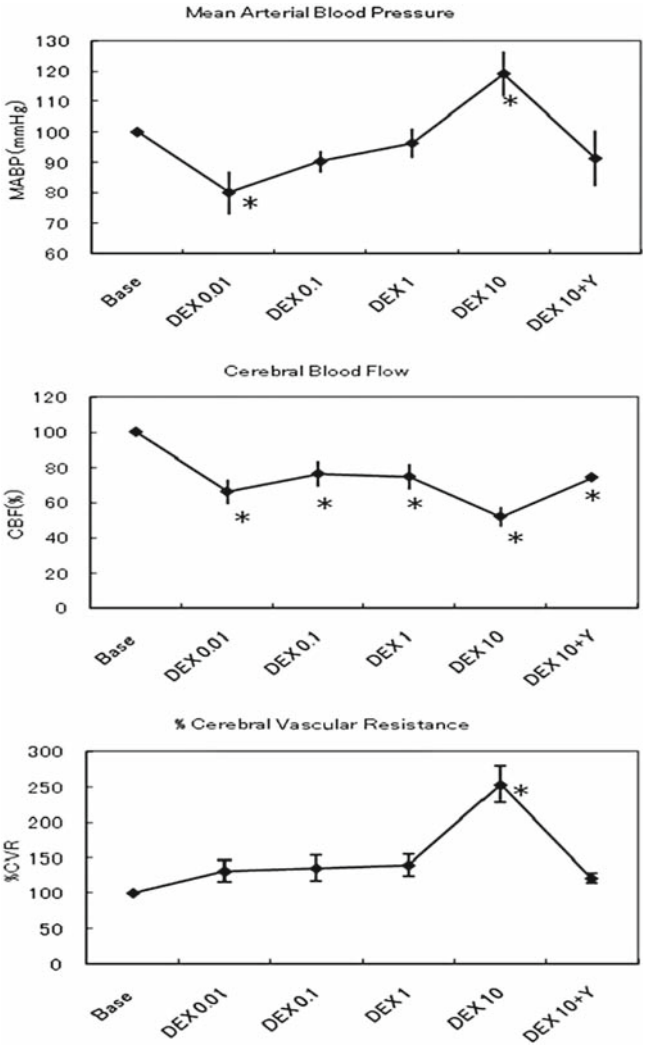

Fig. 1. Cerebral vascular resistance in rats that received dexmedetomidine in doses ranging from 0.01 μg·kg^{-1}·min^{-1} to 10 μg·kg^{-1}·min^{-1} (*DEX 0.01, DEX 0.1, DEX 1, DEX 10*). With the administration of 10 μg·kg^{-1}·min^{-1} dexmedetomidine, cerebral vascular resistance increased to 268% of baseline. Data are presented as means ± SEM. *$P < 0.05$ vs baseline value. MABP, mean arterial blood pressure; CBF, cerebral blood flow; %CVR, cerebral vascular resistance. *DEX 10 + Y*, dexmedetomidine 10 μg·kg^{-1}·min^{-1} plus yohimbine 3 mg·kg^{-1}

1 μg·kg^{-1}·min^{-1} of dexmedetomidine following TTC staining, but clear infarctions following TTC were not seen in six of the seven rats in the Dex1 + Y group. In the Dex10 + Y group, clear infarctions were not seen in two of the seven rats. Additionally, in the Dex10 + R group, infarctions were not seen in four of the seven rats. In these rats that did not have clear infarctions, we defined the infarct areas under a microscope with H & E staining. One rat in the Dex10 group died from a subarachnoid hemorrhage.

Figure 5 shows a comparison of the infarct volumes in the different groups. The infarct volume in the vehicle

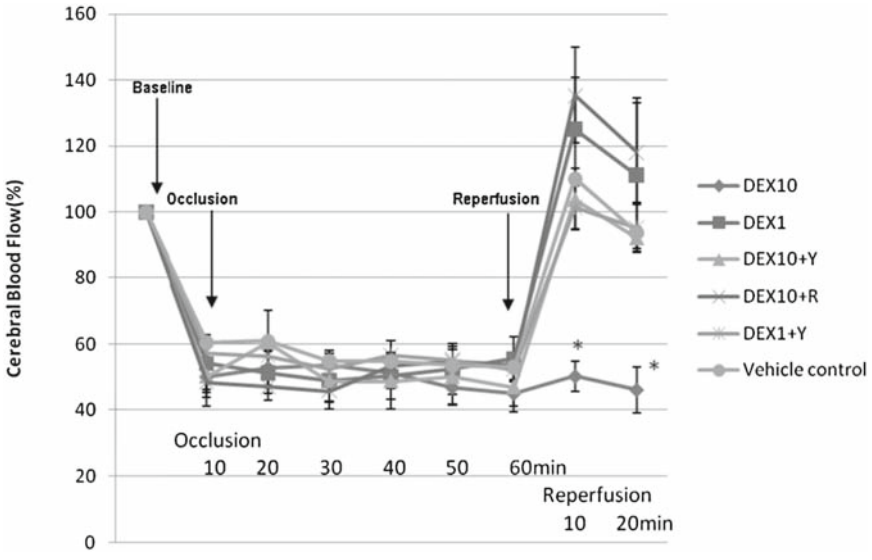

Fig. 2. Cerebral blood flow following middle cerebral artery occlusion (MCAO). During focal cerebral ischemia, CBF decreased to a similar degree (reaching approximately 50% of baseline) in each group. After reperfusion, CBF showed hyperemia in all groups except for the DEX10 group. In the DEX10 group, CBF did not recover. Data are presented as means ± SEM. $*P < 0.05$ vs Vehicle-treated group. *DEX 10 + R*, Dexmedetomidine 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ plus rauwolscine 3 $mg \cdot kg^{-1}$; *DEX 1 + Y*, dexmedetomidine 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ plus yohimbine 3 $mg \cdot kg^{-1}$

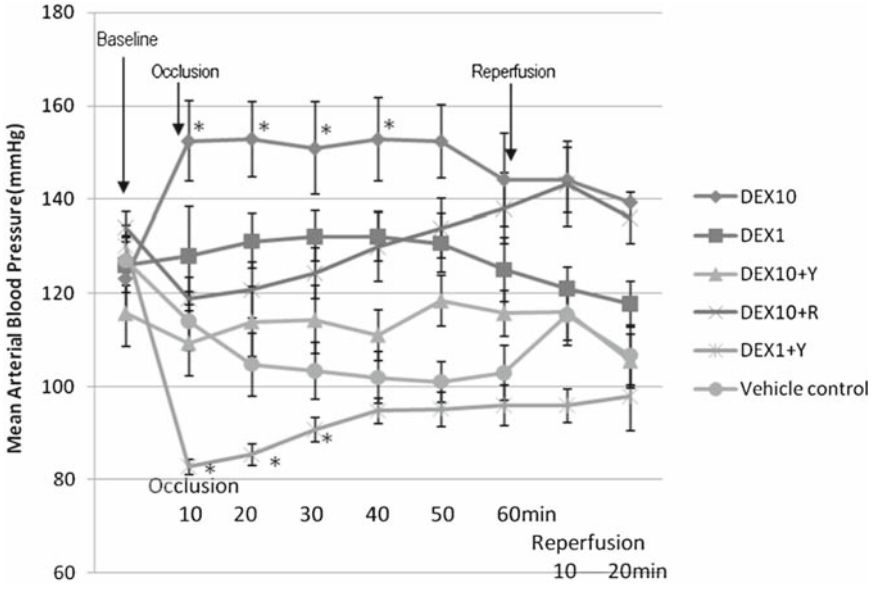

Fig. 3. Mean arterial blood pressure (MABP) following middle cerebral artery occlusion. During focal cerebral ischemia, MABP increased in the DEX10 group for the first 50 min after occlusion. In the DEX1 + Y group, MABP decreased for the first 30 min after occlusion. Data are presented as means ± SEM. $*P < 0.05$ vs Vehicle-treated group

control group was 9.5% of the total brain volume; this infarct volume increased to 11.3% in the Dex1 group and 24.5% in the Dex10 group ($P < 0.05$ vs vehicle control). In DEX1 + Y rats, the infarct volume was 0.5% ($P < 0.05$ vs Dex1). In Dex10 + Y rats, the infarct volume was 8.0% ($P < 0.05$ vs Dex10). The infarct volume in both groups that underwent pretreatment with an alpha-2 receptor antagonist was significantly smaller than that in the rats treated with dexmedetomidine alone. In Dex10 + R rats, the infarct volume was 1.9%, significantly smaller than the infarct volume in the Dex10 rats ($P < 0.05$).

There was no significant difference between groups with regard to the background data, or brain and body temperature. In addition, there was no difference between the groups of rats with regard to the dose of pentobarbital used as basal anesthesia (5 $mg \cdot kg^{-1} \cdot h^{-1}$).

Discussion

Dexmedetomidine continues to gain popularity as a sedative agent; it is also used in patients with traumatic brain injury because of its beneficial effects on intracranial pressure (ICP) and CBF [24–27]. Dexmedetomidine has the potential to decrease blood pressure (BP) in a dose-dependent manner due to its alpha-2 agonist activity on the sympathetic ganglia and the resulting sympatholytic effects [10,28]. Recently, however, there have been reported incidents of hypertension following

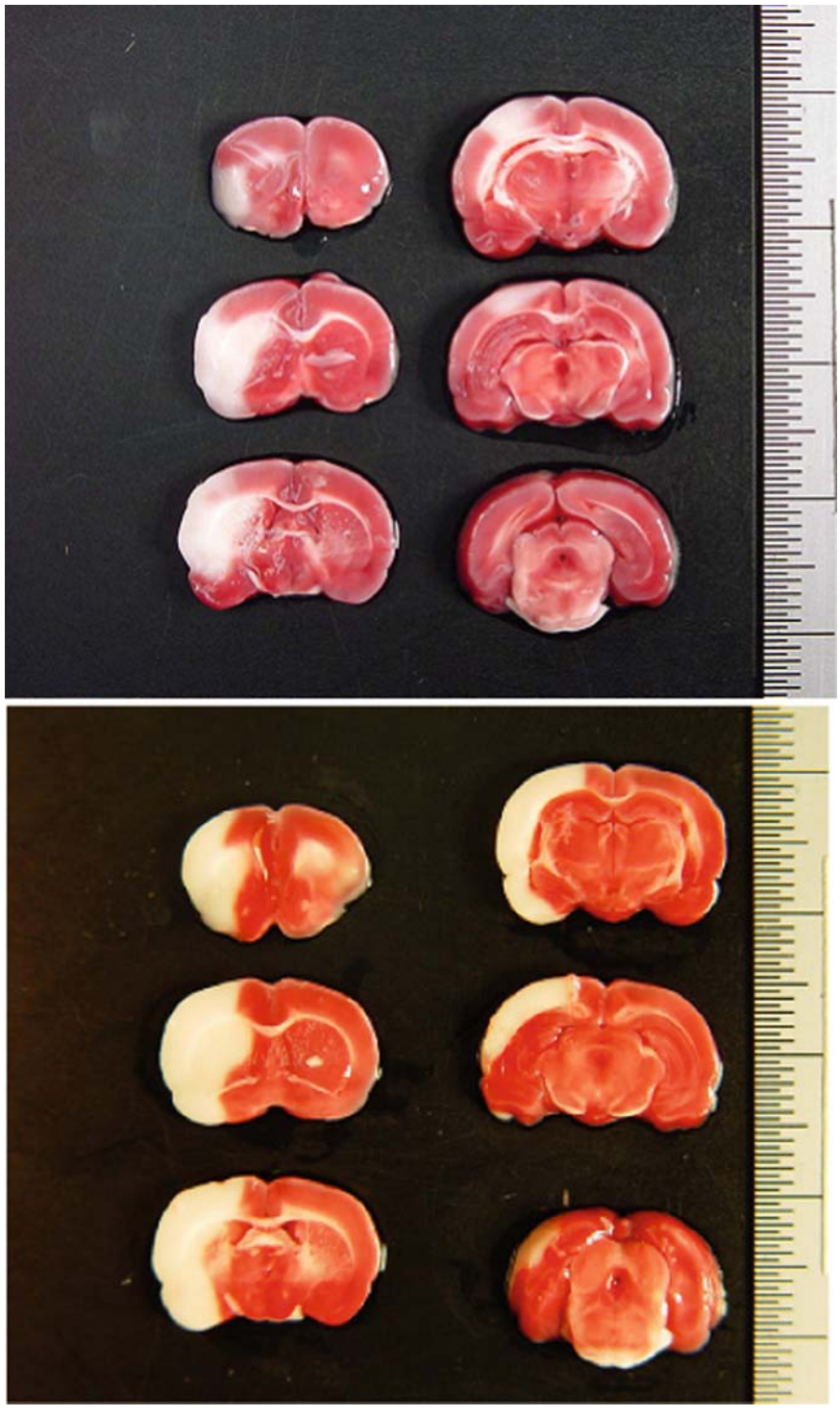

Fig. 4A,B. Photographs of infarct areas on 2, 3, 5-triphenyltetrazolium chloride (TTC)-stained brain slices. The effect of dexmedetomidine on infarct volume was measured 5 days after reperfusion following MCAO. Representative photomicrographs of TTC-stained coronal slices are shown for the vehicle control group (A) and the DEX10 group (B). Infarct size was significantly increased in the DEX10 group

treatment with high doses of dexmedetomidine during sedation [29,30]. Mason et al. [30] used a loading dose of 2 $\mu g \cdot kg^{-1}$ over 10 min followed by an infusion of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$; 30 of 250 patients (12%) had a BP above the normal range during loading, and 17 of the 250 patients (6.8%) had a BP above the normal range during the infusion. These authors did caution against the use of this agent in patients who may not tolerate these fluctuations [30]. In this line of thought, our study is important because it examines the effects of relatively high doses of dexmedetomidine on increasing BP and decreasing CBF.

In the present study, the systemic BP decreased to 79.9% of baseline with a dose of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine. With increasing doses of dexmedetomidine, the MABP increased, increasing to 119.9% relative

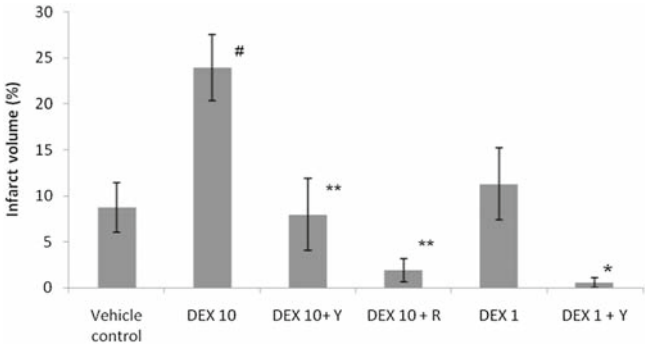

Fig. 5. Infarct volumes. The infarct volume in the vehicle control group was 9.5% of the total brain volume; the infarct volume was 11.3% in the DEX1 group, and 24.5% in the DEX10 group. In the DEX1 + Y group, the infarct volume had decreased to 0.5% and in the DEX10 + Y group, infarct volume had decreased to 8.0% compared to the group without yohimbine. In the DEX10 + R group, the infarct volume was 1.9% ($P < 0.05$ vs DEX10). Data are presented as means ± SEM. *$P < 0.05$ compared to the DEX1 group; **$P < 0.05$ compared to the DEX10 group; #$P < 0.05$ compared to the control group

to baseline at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine. This increase in BP with a high dose of dexmedetomidine is the opposite of the sympatholytic effect observed at lower doses. The hypertensive effects of high doses of dexmedetomidine have been reported previously in wild-type mice as well as in alpha-2A and -2C adrenoceptor knockout mice. In these same reports, this high-dose dexmedetomidine-induced hypertension was blunted in alpha-2B adrenoceptor knockout mice [13,31]; based on these studies, we suggest that the dexmedetomidine-induced hypertension seen in our study was mediated by alpha-2B adrenoceptors. The dose-related affinity of dexmedetomidine (high dose, alpha-2B; low dose, alpha-2A) for the alpha-2 adrenoceptor subtypes remains uncertain. However, Erkonen et al. [29] and Mason et al. [30] recently reported that dexmedetomidine tended to increase BP, particularly in children,. Furthermore, Kurnik et al. [32] reported substantial individual variability in the response to dexmedetomidine. These variations may be due to differences in the expression and/or sensitivity of the alpha-2B receptor subtype.

In our study, CBF decreased significantly at doses of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dexmedetomidine, possibly due to the sympatholytic effect of alpha-2A adrenoceptor stimulation caused by the concomitant decrease in MABP. At the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dose of dexmedetomidine, CBF rapidly decreased with increasing MABP, and cerebral vascular resistance thus significantly increased. One explanation for this finding is that stimulation of alpha-2B adrenoceptors by high doses of dexmedetomidine overcomes the effect of dexmedetomidine on alpha-2A adrenoceptors and interferes with CBF autoregulation, resulting in the constriction of cerebral vessels.

In previous studies, low doses of dexmedetomidine (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) have exhibited neuroprotective effects, preventing focal cerebral ischemia [8]. These neuroprotective effects have also been shown to be completely abolished in alpha-2A knockout mice, indicating that the effects are mediated by the alpha-2A adrenoceptor subtype [9,13]. Stimulation of alpha-2A adrenoceptors has been shown to decrease plasma catecholamine levels and cause vasodilation, the combination of which may lead to neuroprotection [33].

In the present study, high doses of dexmedetomidine increased infarct volumes, and this effect was decreased by pretreatment with yohimbine or rauwolscine. Because it has been previously reported that yohimbine itself does not affect neurological outcomes after forebrain ischemia and reperfusion [34], these findings suggest that the observed anti-neuroprotective effects of the higher doses of dexmedetomidine are mediated by alpha-2 adrenoceptors, possibly via alpha-2B adrenoceptor-induced cerebral vasoconstriction.

Halonen et al. [35] and Kuhmonen et al. [36] also reported the dose-related neuroprotective characteristics of dexmedetomidine in experimental models. Based on our work, in combination with these studies, it is possible that alpha-2A and alpha-2B adrenoceptors exhibit opposite functions with regard to their neuroprotective properties.

Our study did have some limitations. First, there may have been an interaction between pentobarbital (the basal anesthesia) and dexmedetomidine. Second, the high doses of dexmedetomidine studied here exceed those doses recommended for clinical use. Third, receptor expression varies significantly between species. Recently, Drummond et al. [37] showed that the CBF/cerebral metabolic ratio (CMR) was maintained constant in normal humans during infusion of dexmedetomidine. Thus, the effects observed in our study may not exist in humans or may be less pronounced. Due to a lack of data regarding the vascular effects of dexmedetomidine in patients with neurovascular disease, further study will be needed. Lastly, the effects of dexmedetomidine, yohimbine, and rauwolscine on each alpha-2 adrenoceptor subtype, which may have had a substantial impact on our results, are still unclear. Further studies using knockout mice for each alpha-2 adrenoceptor subtype are needed.

In conclusion, hypertension following the administration of high-dose dexmedetomidine is associated with cerebral hypoperfusion and the exacerbation of ischemic brain injury, possibly through alpha-2-induced cerebral vasoconstriction.

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