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Intrathecal Dexmedetomidine Attenuates Hypercapnic but Not Hypoxic Cerebral Vasodilation in Anesthetized Rabbits

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Background: **Systemic dexmedetomidine (DXM) attenuates the cerebral vasodilation induced by hypercapnia and decreases the cerebral blood flow response to hypoxia. We determined whether lumbar intrathecal DXM affected the cerebrovascular reactivity to hypercapnia and hypoxia.**

Methods: **Rabbits (n = 55) anesthetized with pentobarbital were prepared for measurement of pial vessel diameters using a closed cranial window preparation. The first study evaluated the response to hypercapnia after intrathecal administration of DXM (2 μg/kg; n = 7) or normal saline (n = 8). The second evaluated the response to hypercapnia after intrathecal DXM in the presence of yohimbine (20 μg/kg followed by DXM 2 μg/kg; n = 7). The third evaluated the response to mild or moderate hypoxia after intrathecal DXM (2 μg/kg; n = 7) or normal saline (n = 7). The hypercapnic responses were also examined in the presence of systemic DXM (2, 10 μg/kg; n = 6), topical DXM (10^{-8} M, 10^{-6} M; n = 6) and of intrathecal clonidine (2 μg/kg; n = 7).**

Results: **The pial arteriolar dilator response to hypercapnia was significantly attenuated after intrathecal administration of DXM. Pretreatment with yohimbine completely blocked the decreased reactivity to hypercapnia. Intrathecal clonidine, although less than DXM, also attenuate the hypercapnic response. Intrathecal DXM did not affect the vasodilation of pial arterioles induced by mild or moderate hypoxia. The systemic DXM 10 μg/kg and topical DXM 10^{-6} M, but not systemic 2 μg/kg and topical 10^{-8} M, attenuated hypercapnic vasodilation of pial arterioles.**

Conclusions: **The presence of α_2-adrenoceptor agonist administered intrathecally into the lumbar spinal region attenuates hypercapnic but not hypoxic cerebral vasodilation, probably *via* a stimulation of central α_2-adrenergic receptors of the central nervous system. (Key words: α_2-Adrenoceptor agonists; carbon dioxide; cerebral vessels; oxygen; spinal analgesia.)**

α_2-ADRENERGIC agonists such as dexmedetomidine (DXM) and clonidine exert their effects by stimulating presynaptic and postsynaptic α_2-adrenergic receptors centrally and peripherally. Published evidence suggests that α_2-adrenergic receptors in the cerebral arteries play an important role in cerebrovascular constriction.[1] Systemic and topical α_2-adrenergic agonists cause the central nervous system vasculature to constrict.[1–3]

The vascular responses to hypercapnia and hypoxia seem to be limited in the presence of α_2-adrenergic agonists. For instance, systemic DXM decreases cerebral blood flow (CBF) without influencing the cerebral metabolic use of oxygen during normocapnia and hypercapnia.[2,4,5] The decrease in CBF to DXM has been suggested to be caused by an increase in cerebral vascular resistance mediated by postsynaptic α_2-adrenergic receptors located within the cerebral vasculature.[6]

Intracerebroventricular administration of DXM decreases CBF response to hypoxia.[3,7] However, there is as yet no report available concerning the reactivity of cerebral vessels to hypercapnia and hypoxia after the intrathecal α_2-adrenergic agonists. Since intrathecal α_2-adrenergic agonists are clinical development for use in the perioperative interval, we believe that it is important to know their influence on cerebral vessels during hypercapnia and hypoxia. We hypothesized that intrathecal DXM may alter the cerebrovascular reactivity to hypercapnia and/or hypoxia. Therefore, in the present study, we investigated the effects of intrathecal DXM on

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the cerebral pial vascular reactivity to hypercapnia and hypoxia and clarified the mechanism involved using the cranial window technique in rabbits. Because we found that the intrathecal DXM altered the pial vascular response to hypercapnia, we further examined the effects of systemic DXM, topical DXM, and intrathecal clonidine on the vascular reactivity to hypercapnia.

Materials and Methods

The procedures used in this study conformed to the Guiding Principles in the Care and Use of Animals approved by the Council of the American Physiologic Society, and the experimental protocols were approved by the Institutional Committee for Animal Care at Gifu University School of Medicine. The experiments were performed on 55 anesthetized rabbits weighing 2.3–2.6 kg. Each animal was anesthetized with pentobarbital sodium (20 mg/kg intravenously) and maintained with a continuous infusion of the same agent (4 $mg \cdot kg^{-1} \cdot h^{-1}$), and each was mechanically ventilated through a tracheotomy tube with oxygen-enriched room air (arterial oxygen content, 14–15 vol%). The tidal volume and respiratory rate were adjusted to maintain arterial carbon dioxide partial pressure between 35 and 40 mmHg. Catheters were placed in the femoral vein and artery for administration of fluid and drugs and for the continuous monitoring of the mean arterial blood pressure (MAP) and heart rate (HR) and for blood sampling, respectively. Rectal temperature was maintained between 37.5 and 38.5°C by means of a heating blanket.

A closed cranial window was used to observe the cerebral pial microcirculation. Each animal was placed in the sphinx posture, the scalp was retracted, and a 5-mm-diameter hole was made in the parietal bone. The dura and arachnoid membranes were opened carefully, and a ring with a cover glass was placed over the hole and secured with dental acrylic. The space under the window was filled with artificial cerebrospinal fluid (aCSF). The composition of aCSF was Na^+ 151 mEq/l, K^+ 4 mEq/l, Ca^{2+} 3 mEq/l, Cl^- 110 mEq/l, and glucose 100 mg/dl. This fluid was maintained at 37.0°C, pH 7.48, and continuously bubbled with a gas mixture of 5% CO_2 and air. Two polyethylene catheters were inserted through the ring; one was attached to a reservoir bottle containing aCSF to maintain the desired level of intrawindow pressure (5 mmHg), and the other was used for continuous monitoring of intrawindow pressure. The volume below the window was between 0.5 and 1 ml. The lumbar paraspinal muscles were exposed by a longitudinal midline skin incision from the lower lumbar level to the upper sacral level. After the spinous process had been removed using a rongeur, a laminectomy was performed with an electric drill at the sixth lumbar vertebra. A polyethylene catheter was inserted into the intrathecal space for a distance of 1 cm rostrally.

The diameters of three pial arterioles were measured in each cranial window using a videomicrometer (Olympus Flovel videomicrometer, Model VM-20; Flovel, Tokyo, Japan) on a television monitor, which received pictures from a microscope (Model SZH-10; Olympus, Tokyo, Japan). The data from the pial views were stored on videotape for later playback and analysis. We averaged the pial arteriolar diameters from each animal to yield an average diameter per animal and handled that single value statistically. Pial arterioles ranged from 50 to 120 μm in diameter.

The study was divided into three parts. In the first, we evaluated the effects of intrathecal DXM (Abbott Laboratories, North Chicago, IL) on the cerebral vasodilator response to hypercapnia. In the second, we evaluated the effects of DXM on the cerebral vasodilator response to hypercapnia in the presence of intrathecal yohimbine (Wako, Osaka, Japan), an α_2-adrenoceptor antagonist. In the third, we evaluated the effect of DXM on the cerebral vasodilator response to hypoxia. All experiments were conducted after at least 30-min recovery from the surgical preparation.

In the first set of experiments, the changes in pial arteriolar diameter induced by hypercapnia and various physiologic variables (including MAP, HR, rectal temperature, arterial blood gas tensions, and *p*H) were evaluated (STAT Profile-5; NOVA Biomedicals, Waltham, MA) whenever we measured the diameters of pial arterioles before and 30, 60, and 90 min after the intrathecal administration of DXM (2 μg/kg in 0.1 ml/kg normal saline; n = 7) or normal saline (0.1 ml/kg; n = 8) being given as a control. Hypercapnic challenges were induced before and 30, 60, and 90 min after the intrathecal administration of the aforementioned drugs by carbon dioxide gas addition to inspiratory gases. After 5 min at a stable level (arterial carbon dioxide partial pressure, approximately 60 mmHg), pial arteriolar diameters were measured.

In the second set of experiments, intrathecal yohimbine (20 μg/kg) was given as pretreatment, and 30 min later, DXM was administered intrathecally (2 μg/kg in 0.1 ml/kg normal saline; n = 7). Measurements of phys-

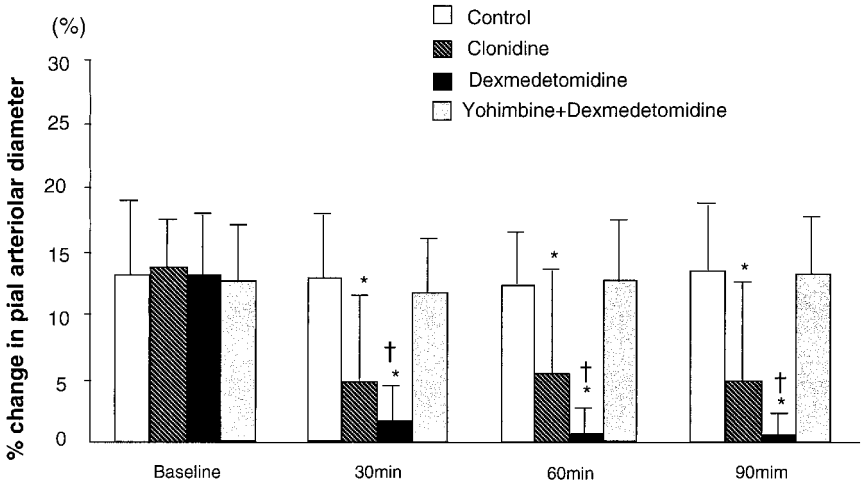

Fig. 1. Effects of intrathecal normal saline (control; n = 8), dexmedetomidine (DXM; n = 7), DXM pretreatment with yohimbine (n = 7), and clonidine (n = 7) on reactivity of cerebral pial arterioles to hypercapnia. Data are expressed as percentage change increase in diameter at baseline (before administration) and 30, 60, and 90 min after intrathecal administration. DXM attenuated the arteriolar dilation induced by hypercapnia. Pretreatment with yohimbine completely blocked the decreased reactivity to hypercapnia induced by DXM. Values are mean ± SD. *$P < 0.05$ compared with corresponding control. †$P < 0.05$ compared with corresponding clonidine.

iologic variables were made as in the first set of experiments.

In the third set of experiments, we examined the effects of intrathecal DXM (2 μg/kg in 0.1 ml/kg normal saline; n = 7) or normal saline (0.1 ml/kg; n = 7) as a control, on the cerebral vasodilation induced by mild (oxygen content, 8–10 vol%) or moderate (oxygen content, 5–7 vol%) hypoxia (OSM3, Radiometer, Copenhagen, Denmark). We performed a hypoxic challenge test before and 30 min after the intrathecal administration of DXM. Fifteen minutes after the arteriolar diameter returned to baseline value after the hypoxic challenge, we performed another hypoxic challenge test. We completed the hypoxic experiments within 60 min after the administration of DXM. We randomized the induction of mild or moderate hypoxia. These oxygen levels were produced by adding supplementary nitrogen to the inspired gas. Changes in physiologic variables were measured as in the first set of experiments.

In an additional set of experiments, we examined the effects of systemic DXM (2 μg/kg and 10 μg/kg; n = 6), topical DXM (10^{-8} M and 10^{-6} M; n = 6), and lumbar intrathecal clonidine (2 μg/kg; n = 7; Boehringer Ingelheim, Ridgefield, IL) on pial arteriolar diameter and on the change induced by hypercapnia. At 15 min after intravenous injection of 2 μg/kg DXM, we performed hypercapnic challenge. Fifteen minutes after arteriolar diameter returned to baseline value, we administered 10 μg/kg DXM intravenously. The second hypercapnic challenge was induced 15 min after intravenous injection of 10 μg/kg DXM. In topical administration studies, hypercapnia was induced 5 min after topical application of 10^{-8} M DXM. We flushed the window continuously with aCSF for 30 min to establish baseline arteriolar diameter value and then administered 10^{-6} M DXM. A second hypercapnic challenge was induced 5 min after topical administration of 10^{-6} M DXM. For the intrathecal clonidine study, rabbits were treated similarly to those given DXM as described in the first set of experiments. Measurements of physiologic variables were made similarly as in the first set of experiments.

Statistical Analysis

All physiologic variables within groups were examined by a one-way analysis of variance for repeated measurements followed by the Scheffé F test for *post hoc* comparisons. The differences between groups were examined by a two-way analysis of variance. An unpaired *t* test with Bonferroni's correction was used to assess differences found between groups. A paired *t* test was used to assess differences found between variables before and after hypercapnia or hypoxia. Significance was considered to be demonstrated at $P < 0.05$. All results are expressed as mean ± SD.

Results

Hypercapnic Responses of Cerebral Pial Arterioles to Lumbar Intrathecal Administration of DXM

In the presence of DXM, the pial arteriolar dilator response to hypercapnia was significantly less than in control (normal saline) at 30, 60, and 90 min after the intrathecal DXM ($P < 0.05$; fig. 1). Although intrathecal yohimbine alone did not change arteriolar diameters, pretreatment with yohimbine completely blocked the attenuation of the arteriolar dilator response to hypercapnia induced by DXM (fig. 1). Intrathecal DXM into

Table 1. Effect of Intrathecal Administration of Test Drugs on Pial Arteriolar Diameter (μm) during Hypercapnia

Time after Test Drug	Control (Normal Saline)	DXM	Yohimbine + DXM	CL
Baseline (before administration)				
Normocapnia	71.4 ± 12.4	72.4 ± 10.4	82.1 ± 11.9	73.2 ± 20.6
Hypercapnia	80.6 ± 13.3*	81.5 ± 11.9*	92.3 ± 12.0*	83.1 ± 18.9*
30 min				
Normocapnia	71.4 ± 13.7	73.0 ± 10.0	83.9 ± 12.4	78.0 ± 19.5
Hypercapnia	80.4 ± 14.6*	74.0 ± 10.1	93.3 ± 12.1*	81.3 ± 20.0*
60 min				
Normocapnia	71.4 ± 13.4	73.2 ± 10.4	83.9 ± 11.9	76.9 ± 19.8
Hypercapnia	80.0 ± 14.3*	73.6 ± 10.3	94.2 ± 11.7*	81.9 ± 23.3*
90 min				
Normocapnia	71.7 ± 12.9	73.0 ± 10.7	83.7 ± 12.0	75.8 ± 20.8
Hypercapnia	81.1 ± 13.7*	73.4 ± 11.1	94.4 ± 11.5*	79.8 ± 21.6*

Values are mean ± SD.

* $P < 0.05$ compared with corresponding normocapnic value.

DXM = dexmedetomidine; CL = clonidine.

the lumbar region, *per se*, did not affect the pial arteriolar diameter (table 1). MAP after the intrathecal administration of DXM was significantly lower than that of control at 30, 60, and 90 min ($P < 0.05$), but it was not changed by hypercapnia in any of the groups (except at 30 min after the administration of DXM in the yohimbine-pretreatment group; table 2). HR did not change after the intrathecal administration of DXM in any of the groups, but it decreased significantly in response to hypercapnia ($P < 0.05$; table 2). Arterial *p*H decreased significantly in response to hypercapnia without changes in arterial oxygen tension (table 2).

Table 2. Changes in Physiologic Parameters Induced by Hypercapnia

		Baseline		30 min		60 min		90 min	
		Normocapnia	Hypercapnia	Normocapnia	Hypercapnia	Normocapnia	Hypercapnia	Normocapnia	Hypercapnia
MAP (mmHg)	Control	90 ± 12	92 ± 12	91 ± 8	93 ± 10	92 ± 9	92 ± 9	91 ± 6	92 ± 7
	DXM	95 ± 7	99 ± 9	86 ± 6†	89 ± 10	88 ± 7†	90 ± 11	90 ± 7†	93 ± 12
	Yohimbine + DXM	94 ± 8	102 ± 6	89 ± 8	98 ± 7*	91 ± 9	99 ± 7	91 ± 10	100 ± 9
	CL	84 ± 18	84 ± 18	61 ± 15†	69 ± 15	68 ± 22†	72 ± 18	71 ± 20†	75 ± 17
HR (beats/min)	Control	267 ± 40	227 ± 50	276 ± 33	219 ± 51*	284 ± 25	222 ± 48*	288 ± 30	218 ± 42*
	DXM	252 ± 31	185 ± 28*	245 ± 29	187 ± 22*	255 ± 25	189 ± 13*	259 ± 27	192 ± 23*
	Yohimbine + DXM	283 ± 44	204 ± 45*	290 ± 38	202 ± 42*	291 ± 36	218 ± 27*	298 ± 41	231 ± 27*
	CL	266 ± 34	223 ± 63	243 ± 47	207 ± 51	242 ± 44	201 ± 42	254 ± 34	218 ± 34
pHa	Control	7.42 ± 0.03	7.25 ± 0.02*	7.41 ± 0.03	7.25 ± 0.03*	7.41 ± 0.03	7.24 ± 0.04*	7.41 ± 0.03	7.23 ± 0.03*
	DXM	7.42 ± 0.05	7.20 ± 0.04*	7.41 ± 0.06	7.19 ± 0.04*	7.40 ± 0.04	7.21 ± 0.02*	7.38 ± 0.04	7.21 ± 0.03*
	Yohimbine + DXM	7.40 ± 0.04	7.18 ± 0.04*	7.37 ± 0.04	7.15 ± 0.04*	7.36 ± 0.05	7.14 ± 0.03*	7.37 ± 0.05	7.16 ± 0.03*
	CL	7.40 ± 0.05	7.25 ± 0.06*	7.38 ± 0.06	7.25 ± 0.06*	7.37 ± 0.06	7.24 ± 0.05*	7.40 ± 0.03	7.23 ± 0.06*
Pa_{CO_2} (mmHg)	Control	36 ± 2	62 ± 6	36 ± 4	64 ± 3	36 ± 2	64 ± 7	37 ± 3	66 ± 3
	DXM	38 ± 2	63 ± 3	39 ± 2	65 ± 4	38 ± 2	65 ± 5	40 ± 2	66 ± 4
	Yohimbine + DXM	37 ± 2	66 ± 6	38 ± 3	67 ± 5	37 ± 3	66 ± 4	37 ± 4	66 ± 3
	CL	39 ± 3	60 ± 4	40 ± 4	62 ± 3	41 ± 5	63 ± 4	40 ± 4	65 ± 3
Pa_{O_2} (mmHg)	Control	183 ± 42	205 ± 33	193 ± 39	211 ± 32	197 ± 38	213 ± 33	194 ± 40	220 ± 24
	DXM	220 ± 28	222 ± 35	230 ± 29	215 ± 17	219 ± 20	216 ± 18	222 ± 21	218 ± 18
	Yohimbine + DXM	176 ± 28	181 ± 32	154 ± 67	184 ± 39	192 ± 24	201 ± 32	171 ± 30	198 ± 30
	CL	174 ± 18	176 ± 22	176 ± 24	185 ± 28	173 ± 25	175 ± 26	177 ± 28	173 ± 33

Values are mean ± SD.

* $P < 0.05$ compared with normocapnia.

† $P < 0.05$ compared with corresponding baseline value.

DXM = dexmedetomidine; CL = clonidine; MAP = mean arterial blood pressure.

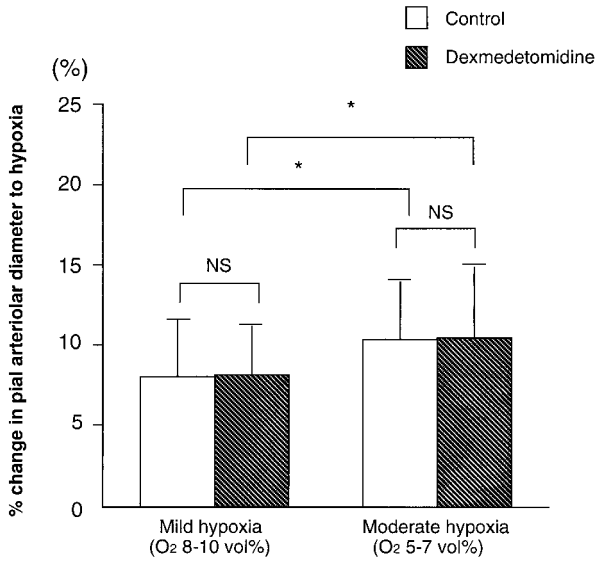

Fig. 2. Effects of intrathecal normal saline (control; n = 7) and dexmedetomidine (DXM; n = 7) on reactivity of cerebral pial arterioles to hypoxia. Data are expressed as percentage change increase in diameter. DXM did not affect the arteriolar dilation induced by either level of hypoxia. Values are mean ± SD. NS = not significant between corresponding values. *$P < 0.05$ compared with corresponding values.

Hypoxic Responses of Cerebral Pial Arterioles to Lumbar Intrathecal Administration of DXM

Intrathecal DXM did not alter the dilation of pial arterioles to mild or moderate hypoxia compared with control (fig. 2). Pial arteriolar diameter was not changed by the intrathecal DXM (table 3). MAP decreased after the intrathecal DXM and increased significantly during mild and moderate hypoxia ($P < 0.05$) but did not change in the response to mild or moderate hypoxia in the control group (table 4). HR did not change after the intrathecal administration of DXM but was decreased significantly by both mild and moderate hypoxia in both control and DXM groups ($P < 0.05$; table 4). Arterial *p*H, carbon dioxide tension, and total hemoglobin were unchanged by either level of hypoxia in either group (table 4).

Table 3. Effect of Intrathecal Administration of Test Drugs on Pial Arteriolar Diameter (μm) during Hypoxia

(Normal Saline)	Control	DXM
Baseline (normoxia)	90.5 ± 16.3	91.3 ± 16.0
Mild hypoxic study		
Normoxia	90.5 ± 16.3	90.7 ± 15.2
Hypoxia	98.6 ± 16.3*	98.4 ± 15.7*
Moderate hypoxic study		
Normoxia	90.8 ± 15.8	90.5 ± 15.6
Hypoxia	99.6 ± 16.6*	100.4 ± 14.9*

Values are mean ± SD.

* $P < 0.05$ compared with corresponding normoxic value.

DXM = dexmedetomidine.

Hypercapnic Responses of Cerebral Pial Arterioles to Systemic Administration of DXM

The cerebral pial arteriolar dilator responses to hypercapnia were not significantly altered by systemic administration of DXM 2 μg/kg but were attenuated by systemic administration of DEX 10 μg/kg ($P < 0.05$; fig. 3). The larger dose of systemic DXM (10 μg/kg) constricted pial arterioles compared with DXM 2 μg/kg (−3.0 ± 3.3% and −0.6 ± 2.5%, respectively). MAP did not change in response to hypercapnia but HR decreased significantly in the control and DXM 2 μg/kg groups (table 5). Arterial *p*H decreased significantly in response to hypercapnia in the systemic DXM study (table 5).

Hypercapnic Responses of Cerebral Pial Arterioles to Topical Administration of DXM

The cerebral pial arteriolar dilator responses to hypercapnia were not significantly altered by topical DXM 10^{-8} M but were attenuated by topical administration of DXM 10^{-6} M ($P < 0.05$; fig. 3). Topical DXM 10^{-6} M, but not 10^{-8} M, constricted pial arterioles (−11.4 ± 3.7% and −0.2 ± 1.0%, respectively). MAP did not change in response to hypercapnia but HR decreased significantly in the control and DXM 10^{-8} M and 10^{-6} M groups (table 6).

Hypercapnic Responses of Cerebral Pial Arterioles to Lumbar Intrathecal Administration of Clonidine

Pial arteriolar diameter was not affected by the intrathecal clonidine (table 1). Although the cerebral dilator response to hypercapnia was significantly attenuated in the presence of clonidine, the attenuation of arteriolar dilation at 30, 60, and 90 min after clonidine administration was significantly less than that after DXM at the same time point ($P < 0.05$; fig. 1).

Discussion

The major findings of the present study were that intrathecal administration of DXM into the lumbar spinal regions attenuated the dilation of cerebral pial arterioles

Table 4. Changes in Physiologic Parameters Induced by Hypoxia with or without Intrathecal DXM

		Baseline (Normoxia)	Mild Hypoxic Study		Moderate Hypoxic Study	
			Normoxia	Hypoxia	Normoxia	Hypoxia
MAP (mmHg)	Control	90 ± 7	90 ± 6	99 ± 12	88 ± 6	97 ± 16
	DXM	91 ± 7	82 ± 7†	94 ± 12*	82 ± 7†	98 ± 12*
HR (beats/min)	Control	245 ± 37	245 ± 37	173 ± 57*†	244 ± 38	163 ± 42*†
	DXM	250 ± 32	250 ± 33	173 ± 36*†	248 ± 31	163 ± 40*†
pHa	Control	7.37 ± 0.03	7.37 ± 0.03	7.38 ± 0.03	7.37 ± 0.05	7.37 ± 0.03
	DXM	7.35 ± 0.02	7.35 ± 0.06	7.36 ± 0.04	7.36 ± 0.03	7.36 ± 0.07
Pa_{CO_2} (mmHg)	Control	37 ± 3	38 ± 2	38 ± 4	37 ± 5	37 ± 3
	DXM	40 ± 3	41 ± 3	43 ± 4	42 ± 3	41 ± 5
Pa_{O_2} (mmHg)	Control	169 ± 17	169 ± 16	37 ± 2	170 ± 15	30 ± 3
	DXM	152 ± 13	153 ± 12	38 ± 4	152 ± 14	30 ± 4
tHb (g/dl)	Control	11.4 ± 1.0	11.4 ± 0.9	11.1 ± 0.8	11.4 ± 0.5	11.4 ± 0.6
	DXM	11.2 ± 0.9	11.2 ± 0.8	11.3 ± 0.6	11.2 ± 0.9	11.2 ± 0.7
Sa_{O_2} (%)	Control	97.6 ± 2.4	97.7 ± 2.5	58.2 ± 9.8	97.9 ± 2.6	41.5 ± 4
	DXM	98.3 ± 1.4	98.5 ± 1.5	55.0 ± 5.5	97.9 ± 1.3	38.8 ± 3
O_2 content (vol %)	Control	15.4 ± 1.4	15.4 ± 1.4	8.7 ± 0.4	15.6 ± 1.6	6.6 ± 0.7
	DXM	15.0 ± 1.0	15.0 ± 0.9	8.6 ± 0.6	15.2 ± 1.1	6.1 ± 0.7

Values are mean ± SD.

* $P < 0.05$ compared with corresponding normoxia.

† $P < 0.05$ compared with baseline.

DXM = dexmedetomidine; Sa_{O_2} = arterial O_2 saturation; tHb = total hemoglobin.

induced by hypercapnia, and that this effect of DXM was completely blocked by yohimbine, an α_2-adrenergic antagonist. Intrathecal DXM did not itself induce any vasoconstriction of cerebral vessels. In the study of topical administration of DXM into the cranial window, cerebral vasoreactivity to hypercapnia was attenuated by higher concentration (10^{-6} M) of DXM but not by its lower concentration (10^{-8} M), although a significant vasoconstriction of cerebral vessels was observed with its only higher concentration of DXM. Thus, the direct effect of DXM on the vascular smooth muscle of the central nervous system vasculature could not totally account for the attenuation of cerebral vasoreactivity to hypercapnia during intrathecal DXM. In addition, intrathecal DXM did not affect the dilation of pial arterioles induced by mild or moderate hypoxia. Therefore, it seems that α_2-adrenergic stimulation has different effects on cerebral vasodilation depending on whether it results from hypercapnia or hypoxia.

Systemic α_2-adrenergic agonists have been found to decrease the CBF[4–6] or constrict cerebral vessels.[8] The mechanisms underlying the change in cerebral vascular tone caused by systemic α_2-adrenergic agonists may involve both a direct effect on cerebral vessels and an

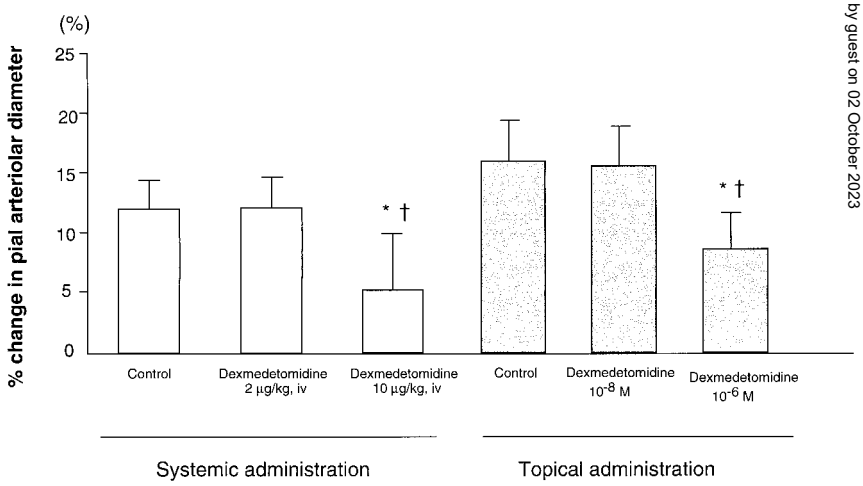

Fig. 3. Effect of systemic dexmedetomidine (DXM; 2 and 10 µg/kg intravenously; n = 6; *left*) and topical DXM (10^{-8} M, 10^{-6} M in the cranial window; n = 6; *right*) on reactivity of cerebral pial arterioles to hypercapnia. Data are expressed as percentage change increase in diameter. Values are mean ± SD. *$P < 0.05$ compared with corresponding control (normal saline). †$P < 0.05$ compared with corresponding response to DXM 2 µg/kg or 10^{-8} M.

Table 5. Changes in Physiologic Parameters Induced by Hypercapnia with Intravenous DXM

		Normocapnia	Hypercapnia
MAP (mmHg)	Control	79 ± 4	84 ± 8
	DXM2	77 ± 3	83 ± 7
	DXM10	61 ± 9	67 ± 5
HR (beats/min)	Control	244 ± 34	166 ± 27*
	DXM2	246 ± 39	184 ± 30*
	DXM10	218 ± 39	184 ± 40
pHa	Control	7.38 ± 0.05	7.21 ± 0.06*
	DXM2	7.35 ± 0.03	7.17 ± 0.04*
	DXM10	7.37 ± 0.05	7.18 ± 0.05*
Pa_{CO_2} (mmHg)	Control	39 ± 2	63 ± 4
	DXM2	39 ± 2	66 ± 3
	DXM10	38 ± 2	66 ± 3
Pa_{O_2} (mmHg)	Control	207 ± 43	218 ± 57
	DXM2	209 ± 44	214 ± 47
	DXM10	207 ± 41	214 ± 48

Values are mean ± SD.

* $P < 0.05$ compared with normocapnia.

DXM = dexmedetomidine; DXM2 = intravenous dexmedetomidine 2 μg/kg; DXM10 = intravenous dexmedetomidine 10 μg/kg.

remote central neuronal effect without direct effect on cerebral vascular smooth muscle.[7,9] Using the cranial window technique, topical application of DXM under the window causes cerebral vasoconstriction *via* local α_2-adrenoceptor stimulation.[1,10] In the present study, the spinal intrathecal α_2-adrenergic agonists did not itself change the diameter of cerebral vessels, suggesting that intrathecal DXM, with doses given at the lumbar region, does not have any stimulatory effects on α_2-adrenoceptors of the cerebral vasculatures. Systemic DXM (2 μg/kg) induced no effect on both pial vascular diameter and reactivity to hypercapnia. In the topical DXM study, any concentration of DXM did not blunt the vasoreactivity to hypercapnia without direct cerebral vasoconstriction. Thus, the attenuated response of pial arterioles to hypercapnia in the presence of intrathecal DXM (2 μg/kg) is unlikely to be induced by its systemic effect as a result of systemic absorption, and likely to be due to, at least in part, indirect or remote effect on cerebral vasculature. However, because a larger dose of systemic DXM (10 μg/kg) attenuated their reactivity to hypercapnia, without measuring the serum or CSF level of DXM, we may not exclude the possibility that the systemic effect of intrathecal α_2-adrenergic agonists on hypercapnic cerebral vasodilation might be involved in the present results.

It is well known that hypercapnia induced a dilation of pial vessels.[8,11] With regard to the effects of α_2-adrenergic agonists on hypercapnic vasodilation, it has been reported that: (1) systemic DXM did not affect hypercapnic CBF reactivity[2]; (2) the intracarotid injection of clonidine caused an enhanced cerebrovascular reactivity to hypercapnia[12]; and (3) systemic DXM and clonidine both attenuated the hypercapnia-induced dilation of pial arterioles.[4,8] However, there is little information about the effect on the reactivity of cerebral vessels that might be induced by α_2-adrenergic agonists administered into the spinal intrathecal space. α_2-Adrenergic agonists may act on a supraspinal brainstem center, possibly the locus coeruleus or rostral ventrolateral medulla.[7,13,14] Indeed, Elam *et al.*[15] reported that systemic clonidine suppressed locus coeruleus firing induced by hypercapnia, whereas Fale *et al.*[2] inferred from the findings of Cedarbaum and Aghajanian[16] that systemic DXM altered the CBF response to hypercapnia by a mechanism involving an indirect inhibition of neurons within locus coeruleus. It is possible that even a very small amount of 2 μg/kg DXM given into the lumbar region can reach the brainstem neurons *via* the CSF circulation. Thus, locus coeruleus can be implicated in some way in the attenuation of hypercapnic vasodilation induced by α_2-adrenergic stimulation by spinal intrathecally administered DXM. Furthermore, complete inhibition of the DXM-induced attenuation by yohimbine should also support the involvement of α_2-adrenoceptor action for this attenuation. The activation of the sympathetic nervous system would increase cerebrovascular resistance and decrease arterial dilation during hypercapnia.[17–19] However, it is

Table 6. Changes in Physiologic Parameters Induced by Hypercapnia with Topical DXM

		Normocapnia	Hypercapnia
MAP (mmHg)	Control	90 ± 6	89 ± 8
	$DXM10^{-8}$	93 ± 7	94 ± 3
	$DXM10^{-6}$	93 ± 7	93 ± 4
HR (beats/min)	Control	247 ± 37	160 ± 45*
	$DXM10^{-8}$	250 ± 34	180 ± 30*
	$DXM10^{-6}$	266 ± 23	192 ± 36*
pHa	Control	7.39 ± 0.03	7.25 ± 0.02*
	$DXM10^{-8}$	7.37 ± 0.03	7.24 ± 0.05*
	$DXM10^{-6}$	7.37 ± 0.04	7.25 ± 0.05*
Pa_{CO_2} (mmHg)	Control	40 ± 3	63 ± 1
	$DXM10^{-8}$	41 ± 1	64 ± 1
	$DXM10^{-6}$	41 ± 1	63 ± 1
Pa_{O_2} (mmHg)	Control	137 ± 5	147 ± 13
	$DXM10^{-8}$	136 ± 10	136 ± 9
	$DXM10^{-6}$	136 ± 10	139 ± 11

Values are mean ± SD.

* $P < 0.05$ compared with normocapnia.

DXM = dexmedetomidine; $DXM10^{-8}$ = topical dexmedetomidine 10^{-8} M; $DXM10^{-6}$ = topical dexmedetomidine 10^{-6} M.

not clear whether the result obtained may be related to the attenuated vasodilation to hypercapnia by DXM, which can reduce sympathetic outflow.

In the hypoxic study, we used the arterial oxygen content as an index of hypoxia, because the arterial oxygen content is related to the amount of hemoglobin present and is a more reliable guide to the level of hypoxia than is the arterial oxygen tension.[20,21] It is well known that hypoxia increases CBF, but the mechanism underlying hypoxic vasodilation is not clearly defined at present. In the present study, the stimulation of α_2-adrenergic receptors caused by intrathecal DXM did not attenuate the dilation of pial vessels caused by mild or moderate hypoxia. McPherson *et al.*[7] reported that intracerebroventricular DXM did not affect the percentage increase in CBF seen during hypoxia, an observation that is consistent with the present results.

The reactivity of cerebral vessels to hypercapnic condition, but not to hypoxic condition, is suppressed by the presence of an α_2-agonist around the spinal cord. The reasons for this difference remain unclear. Underwood *et al.*[22] suggested that rostral ventrolateral medulla, an area of the brainstem, was involved in mediating the cerebral vasodilator response to hypoxia but not that to hypercapnia. Such differences between the responses to hypercapnic and hypoxic condition might be in some way related to the different results observed in these two conditions of the present study. In addition, we should consider a potential effect of pentobarbital as a basal anesthetic, which seems to have the least effect on isolated cerebral vessels.[23] However, Fale *et al.*[2] reported that pentobarbital would inhibit the cerebrovascular response to DXM. Thus, we cannot exclude the participation of pentobarbital in the present results. Moreover, because we studied a single dose of intrathecal DXM for the present study, we cannot completely exclude the possibility that a lack of dose–response study may have an effect on the difference between the hypercapnia and hypoxia studies.

In conclusion, the present study shows that intrathecal DXM attenuates the dilation of cerebral pial arterioles that occurs in response to hypercapnia, but not the dilation that occurs during hypoxia, even though these drugs given into the lumbar spinal region did not produce a vasoconstrictor effect on cerebral vessels. Because pretreatment with yohimbine completely prevented the decreased vasoreactivity induced by DXM during hypercapnia, this effect of DXM is likely to be mediated *via* α_2-adrenergic stimulation. The differential effects of α_2 stimulation on the cerebral vasodilator responses induced by hypercapnia and hypoxia may result from differences in the central mechanisms involved.

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