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Intrathecal phentolamine increases blood flow and skin temperature in the hind limbs of dogs

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Abstract: Spinal anesthesia with local anesthetics increases blood flow and skin temperature in the lower extremities. Although the effect of α_2 adrenoceptor agonists on the spinal cord has been confirmed, there has been no such report of the effects of α-adrenoceptor antagonists. We studied the effects of intrathecal administration of phentolamine on the blood flow in the femoral artery and skin temperature in the hind limbs of seven dogs. One ml of 3% lidocaine (L group) or 1 ml of 0.1% phentolamine (P group) was injected into the intrathecal space. Blood flow significantly increased at 3 min in both groups, and no significant difference was observed between the groups at any phase. Pad skin temperature in the hind limbs increased significantly at 5 min in the L group and at 3 min in the P group ($P < 0.05$). The only significant difference was observed at 30 min. High pad skin temperature continued for 60 min in the L group and for 90 min in the P group. With phentolamine i.v. (1 mg), there were no changes in blood flow in the femoral artery or pad skin temperature; there was only a decrease in blood pressure. In conclusion, the intrathecal α-adrenoceptor antagonist, phentolamine, increases blood flow in the femoral artery and pad skin temperature in hind limbs in dogs similar to lidocaine.

Key words: α-Adrenoceptor antagonist, Alpha-adrenoceptor, Blood flow, Intrathecal administration, Skin temperature

Introduction

In spinal or epidural anesthesia, blood flow and skin temperature increase in the lower limbs due to the blockade of sympathetic nerves [1,2]. Various medullospinal descending systems have been suggested to modulate sympathetic preganglionic neuron activity [3].

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In some studies, it has been found that the intrathecal administration of α_2-adrenoceptor agonists produces antinociception in laboratory animals and analgesia in humans [4,5]. However, there has been no report of the effects of α-antagonist on the spinal cord. In this study, the effects of intrathecal administration of phentolamine (an α-adrenoceptor antagonist) or lidocaine on the arterial blood flow in the femoral artery and pad skin temperature in the hind limbs of dogs were studied to determine whether or not intrathecal α-adrenoceptor antagonists can block sympathetic nerve activity.

Materials and methods

Dogs were obtained from a central animal care center and guidelines for the humane treatment of laboratory animals as outlined by the University of Tsukuba were followed. Seven mongrel dogs weighing 9.0 ± 0.4 kg (mean ± SD) were used. Anesthesia was induced with thiopental 20 mg/kg injected through the right cephalic vein. The animal was placed on an operating table and was ventilated artificially (Harvard Respirator, Chicago, Ill.) after tracheal intubation. Anesthesia was maintained with 30% oxygen, 69% N_2O, and 1% halothane. Lactated Ringer's solution was given 5 ml/kg/h. End-tidal CO_2 was maintained at 30–35 mmHg (4700 OxiCap, Ohmeda, Colo.).

In the prone position, a laminotomy was performed at the 4th lumbar vertebra and the epidural space was opened roundly about 5 mm in diameter. The dura was punctured using a 19G epidural Tuohy needle (Minipack, Portex), and a clear nylon catheter (OD: 0.63 mm) was inserted 3 cm cephalad into the subarachnoid space. A small piece of bone wax and a few drops of adhesive (Aron Alpha, Toagosei Chemical Industry, Tokyo, Japan) were applied to the punctured

dura to prevent leakage of cerebrospinal fluid. The muscles and subcutaneous tissues were sutured and the incision was closed.

The dogs were then turned to the supine position, and a catheter was placed surgically into the right axillar artery for monitoring arterial pressure. The right femoral artery was exposed and a flow probe (ID: 3 mm, Electromagnetic Blood Flowmeter, Nihon Koden, Tokyo, Japan) was placed on it. Skin temperature probes, 7 mm in diameter (Core temp, Terumo, Tokyo, Japan) were attached to both pads of the hind limbs which had been shaved at the beginning of the study. The concentration of halothane decreased to 0.3% during the next 30 min. Then, the following studies were performed under 0.3% halothane. In three dogs, 1 ml of 3% lidocaine was injected into the intrathecal space through the catheter (L group). Systolic arterial blood pressure (BP), heart rate (HR), blood flow in the femoral artery, and skin temperature at the pads of hind limbs (P-skin temperature) were continuously recorded by an oscillometric recorder (8k-12, Sanei, Tokyo, Japan) and Coretemp. Two hours were allowed for the recovery of blood flow and P-skin temperature to baseline levels, and 1 ml of 0.1% phentolamine diluted in saline was injected into the intrathecal space in the same dogs (P group). In the other three dogs, the above procedures were performed in the opposite order, phentolamine at first, then lidocaine was injected. Skin temperature of the right hind limb was adopted as data for P-skin temperature. In one dog, 1 mg of phentolamine was injected intravenously to evaluate the systemic effect.

Analysis of data was performed using Student's *t*-test and analysis of variance. A P value less than 0.05 was considered to be significant.

Results

Intrathecal injection of lidocaine or phentolamine resulted in an increase of blood flow in the femoral artery (Figs. 1, 2). Blood flow significantly increased at 3 min in both groups, and no significant difference was observed between the groups at any phase (Table 1, Fig. 3).

Intrathecal injection of either drug resulted in an increase of P-skin temperature (Figs. 4, 5). P-skin temperature increased significantly at 5 min in the L group and at 3 min in the P group. No significant difference was observed between the groups except at 30 min (Table 2, Fig. 6). High p-skin temperatures continued for about 60 min in the L group and 90 min in the P group.

BP in the L group did not decrease significantly at any phase after the injection. BP in the P group decreased significantly at 3 and 5 min and recovered at 10 min after injection. However, no significant difference was observed between the two groups (Table 3). In the L group, the change in HR was not significant. In the P group, HR increased significantly at 60, 90, and 150 min after the injection. HR in the P group was greater than that of the L group at 60, 90, and 150 min.

With intravenously injected phentolamine (1 mg), there were no changes in blood flow in the femoral

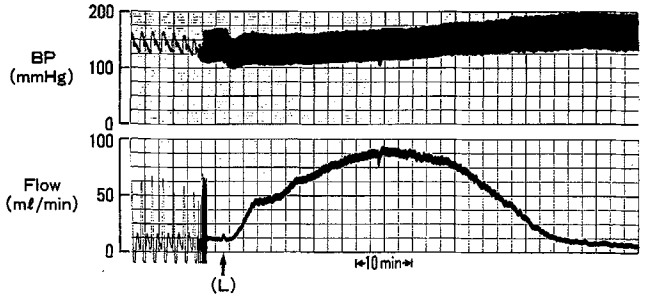

Fig. 1. Typical example of blood pressure (*BP*) and blood flow response to 30 mg of intrathecal lidocaine (*L*)

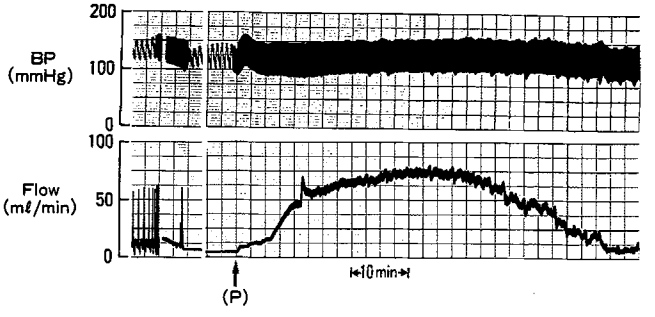

Fig. 2. Typical example of BP and blood flow to 1 mg of intrathecal phentolamine (*P*)

Table 1. Effects on blood flow of femoral artery (mean ± SD)

	Time (min)									
	0	3	5	10	15	30	60	90	120	150
Lido.	27.8 ± 20.0	62.2 ± 30.6*	72.8 ± 33.0*	79.0 ± 40.4*	82.4 ± 36.1*	89.2 ± 43.6*	63.4 ± 52.3	41.4 ± 27.7	33.6 ± 24.5	26.4 ± 18.1
Phento.	15.4 ± 6.3	39.6 ± 23.9*	44.2 ± 28.9*	61.2 ± 23.2*	62.0 ± 26.5*	66.0 ± 29.0*	40.6 ± 30.5	25.8 ± 27.3	17.0 ± 8.1	15.6 ± 10.0

Lido. lidocaine; Phento. phentolamine
* $P < 0.05$ *vs* 0 min.

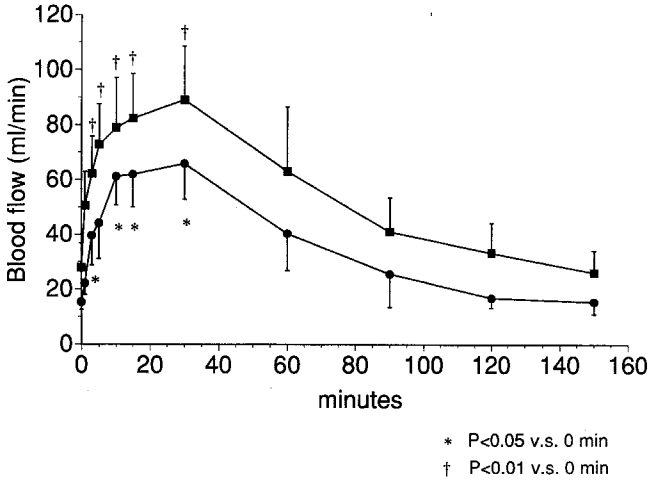

Fig. 3. Blood flow curves following intrathecal injection of lidocaine (*squares*) and phentolamine (*circles*)

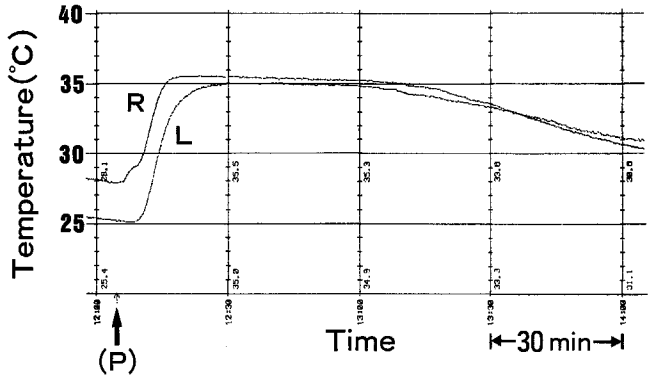

Fig. 5. Typical example of P-skin temperature. (*P*), intrathecal injection of phentolamine; *R*, pad of right hind limb; *L*, pad of left hind limb

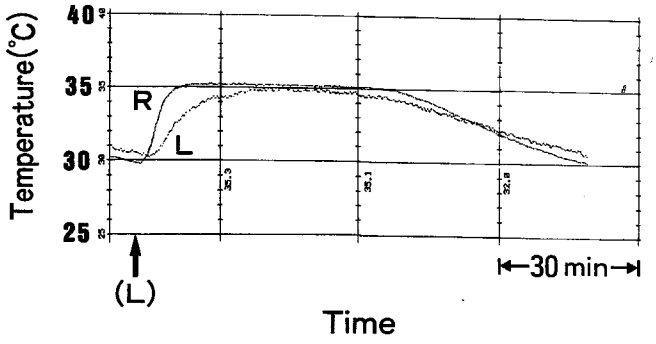

Fig. 4. Typical example of the temperature of the pads of the hind limbs in the P group (P-skin temperature). (*L*), intrathecal injection of lidocaine; *R*, pad of right hind limb; *L*, pad of left hind limb

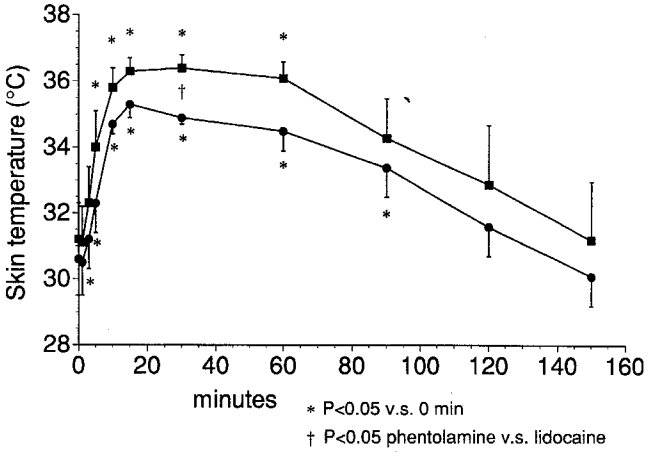

Fig. 6. Pad skin temperature curves following intrathecal injection of lidocaine (*squares*) and phentolamine (*circles*)

Table 2. Effects on pad skin temperature in hind limbs (mean ± SD)

	Time (min)									
	0	3	5	10	15	30	60	90	120	150
Lido.	31.2 ± 2.6	32.3 ± 2.4	34.0 ± 2.5*	35.8 ± 1.3*	36.3 ± 0.9*	36.4 ± 0.9*	36.1 ± 1.1*	34.3 ± 2.8	32.9 ± 4.0	31.2 ± 4.0
Phento.	30.6 ± 2.4	31.2 ± 2.0*	32.4 ± 1.9*	34.7 ± 0.8*	35.2 ± 0.9*	35.3 ± 1.1*#	34.5 ± 1.4*	33.4 ± 2.0*	31.6 ± 2.0	30.1 ± 2.0

Lido., lidocaine; Phento., phentolamine.
* $P < 0.05$ *vs* 0 min; # $P < 0.05$ *vs* lidocaine.

artery and P-skin temperature. The only change observed in the P group was a decrease in blood pressure (Fig. 7).

Discussion

The present study showed that, in dogs with intrathecally administered phentolamine or lidocaine blood flow in the femoral artery and P-skin temperature increased in a similar manner. The effects on blood flow and P-skin temperature brought about by intrathecal lidocaine and phentolamine revealed no significant differences between the two drugs. Intravenous bolus injection of 1 mg of phentolamine had no effect on blood flow in the femoral artery or on P-skin temperature except in cases of hypotension. These data show that phentolamine exerts an α-adrenergic blockade in the intrathecal space.

It is well established that sympathetic nerve blockade can increase blood flow and skin temperature in the upper and lower limbs [6,7]. In spinal anesthesia, local

Table 3. Effects on systolic blood pressure (BP) and heart rate (HR) (mean ± SD)

	Time (min)									
	0	3	5	10	15	30	60	90	120	150
BP										
Lido.	155.8 ± 18.0	137.6 ± 12.0	140.6 ± 13.3	143.0 ± 18.5	139.6 ± 16.3	153.4 ± 20.1	167.2 ± 28.6	165.6 ± 22.6	166.6 ± 24.1	171.2 ± 20.5
Phento.	142.6 ± 21.0	127.6 ± 29.6*	123.8 ± 33.2*	125.6 ± 34.0	127.4 ± 32.7	138.4 ± 26.2	139.4 ± 25.7	148.2 ± 17.6	160.8 ± 15.9	160.2 ± 23.6
HR										
Lido.	193.4 ± 15.7	205.2 ± 7.3	204.6 ± 11.2	198.0 ± 16.7	183.2 ± 34.2	178.6 ± 29.1	171.2 ± 19.7	173.6 ± 28.0	176.2 ± 23.0	172.4 ± 22.2
Phento.	200.0 ± 22.1	204.8 ± 22.7	191.6 ± 24.2	186.8 ± 27.0	188.2 ± 26.4	204.4 ± 20.5	218.6 ± 21.6**	213.4 ± 24.0**	213.2 ± 27.8	216.0 ± 24.6*

Lido., lidocaine; Phento., phentolamine.
* $P < 0.05$ *vs* 0 min; # $P < 0.05$ *vs* lidocaine.

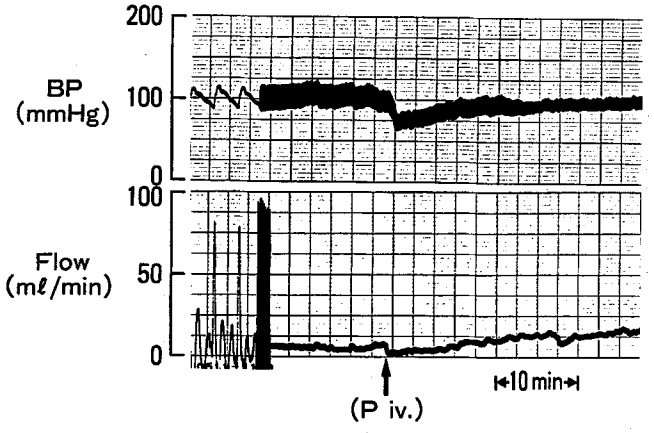

Fig. 7. Typical example of bolus intravenous injection of phentolamine. (*P iv*), 1 mg of phentolamine i.v.

anesthetics produce preganglionic sympathetic denervation [8]. Increased blood flow can be explained by a diminished sympathetic tone, and elevated P-skin temperature in a sign of increased blood flow in arteriovenous anastomosis at the tips of the extremities [9]. In the present study, the blood flow in the femoral artery and P-skin temperature were assumed to be indicators of the activity of the sympathetic nerves innervating the hind limbs.

Some α-adrenoceptor agonists injected intrathecally have been reported to exert an antinociceptive effect [10–13]. α-Adrenoceptor antagonists have been used only to reverse these effects on the spinal cord. For example, the analgesic effects of norepinephrine and clonidine have been reversed by phentolamine [14–16]. However, the primary action of phentolamine on the spinal cord has not been described.

A variety of medullo-spinal descending systems have been implicated in the modulation of sympathetic preganglionic neuron activity. There is a high density of binding to α_2-adrenoceptor in the intermediolateral cell column of the spinal cord [3]. It appears that the primary antinociceptive action site of clonidine is in the dorsal horn of the spinal cord [12,13], and the effect of clonidine is attenuated by intrathecally administered phentolamine. In the present study, the effects on the sympathetic nervous system of the spinal cord by phentolamine may suggest that this inhibition is partly due to the inactivation of α_2-adrenoceptors on sympathetic preganglionic neurons.

It has been reported that lateral horn cells have electrical membrane characteristics similar to postganglionic neurons [17]. Glutamate is known to depolarize many lateral horn cells. Thus, the lateral horn cells which may control the preganglionic sympathetic neurons might have been affected by phentolamine.

In the present study, BP decreased in the early phase in the P group. Though Eisenach and Tong [18] described a complex action of intrathecal clonidine on hemodynamic parameters, we suspect that the decrease in BP in our study may be due to vasodilation caused by intrathecal phentolamine. HR was significantly high in the P group in the late phase after injection. In addition to the α-blocking action, it is known that phentolamine releases endogenous norepinephrine and produces a sympathetic stimulation. Thus, increased HR may be related to the sympathetic stimulation caused by systemically absorbed phentolamine.

In conclusion, phentolamine, an intrathecal α-adrenoceptor antagonist, increased blood flow in the femoral artery and pad skin temperatures in the hind limbs in dogs. The duration of the effects of one mg phentolamine and 30 mg lidocaine were almost the same. More detailed studies, such as intrathecal α_1- and α_2-adrenoceptor antagonists, should be carried out concerning the pharmacological effect of α-adrenoceptor antagonists on the spinal cord.

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