Vasoconstriction Induced by β-Adrenergic Antagonist in the Tail of Chronic Spinal Rats

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Abstract: Adult Wistar male rats were used for this experiment. Spinal cord was transected between the C_7 and Th_1 vertebrae under anesthetic condition. After the surgical operation, rats were reared in a warm room (30 ℃) as chronic spinal rats, and experiment was also performed in a climatic chamber (30 ℃, 60 % r.h.). During the experiment, conscious spinal rats were placed in a small wire-mesh cage. Propranolol hydrochloride (Prop., 8mg/kg; β-adrenergic antagonist) was injected intraperitoneally. Rectal temperature (Tre), tail skin temperature (Ttail) and ambient temperature (Ta) were detected by thermistor probes and recorded simultaneously. In some cases, in addition to such parameters mentioned above, heart rate (HR) calculated by electrocardiogram (ECG) and arterial blood pressure (BP) through the femoral catheter were also recorded. As the index of the tail blood flow, the difference (dTtail) between Ttail and Ta was calculated (dTtail=Ttail-Ta). A sustained decrease in dTtail for 50 min was observed after the Prop. injection in Group-A (S<1W; less than 1 week (W) after the spinalization, N=6), Group -B (1W<S<2W, N=10) and Group-C (2W<S, N=6). In Group-A, mean dTtail was 1.5±0.3 ℃ before the injection and 0.8±0.3 ℃ ($p<0.05$) at 30 min after the injection, mean Tre was 36.3±0.2 ℃ before the injection and 36.2±0.2 ℃ (not significant) at 30 min after the injection. In Group-B, mean dTtail was 1.3±0.4 ℃ before the injection and 0.2±0.2 ℃ ($p<0.01$) at 30 min after the injection, mean Tre was 37.2±0.3 ℃ before the injection and 37.2±0.3 ℃ at 30 min after the injection. In Group-C, mean dTtail was 1.6±0.4 ℃ before the injection and 0.5±0.4 ℃ ($p<0.05$) at 30 min after the injection, mean Tre was 38.2±0.6 ℃ before the injection and 38.8±0.7 ℃ ($p<0.05$) at 30 min after the injection. By the Prop. injection HR decreased markedly and it stayed at the low level of about 300 beats/min. Mean HR was 394±25 beats/min before the injection, and 292±13 beats/min at 10 min, 285±13 beats/min at 20 min, 285±19 beats/min at 30 min ($p<0.05$). Arterial BP did not change or slightly increased from just after the injection. Mean value of BP was 82±6 mmHg before the injection, 82±8mmHg at 30 min after the injection. After intraperitoneal injection of the physiological solution, neither BP nor Tre changed. From these results it is assumed that decrease of dTtail after the Prop. injection in chronic spinal rats is due to the vasoconstriction in the tail but not due to the reduction in temperature of circulating blood. The possible explanations for this phenomenon were discussed, as follows; 1, an enhancement of α-adrenergic vasoconstrictor effect by β-adrenergic antagonist 2, the sympathetic reflex triggered by the hemodynamic changes after administration of β-adrenergic antagonist. However from these results, it is difficult to concluded decisively and to explain the underlying mechanisms of the phenomenon. It remains to be solved whether the vasoconstrictor nerves were involved in this response or not in chronic spinal rats.

Key Wards; Chronic spinal rats, Propranolol, Tail skin temperature, Vasoconstriction, Heart rate, Blood pressure

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INTRODUCTION

During the evaluation of autonomic nervous tone by change in the heart rate induced by intraperitoneal administration of the propranolol hydrochloride (Prop., nonselective β–adrenergic antagonist) or atropine sulfate (Lin and Horvath,1972), a decrease in the tail skin temperature was observed after the prop. administration but not after the atropine sulfate one (Tsuchiya *et al.*, 1987). This drug was used for anti–hypertensive treatment. Raynaud's phenomenon (digital vasospastic phenomenon) was reported in patients treated with Prop. (Eliasson *et al.*, 1979; Marshall *et al.*, 1976). Hemodynamic changes by Prop. administration were investigated in monkey and human. By the Prop. administration, heart rate (HR) and cardiac output decreased, but blood pressure (BP) changed scarcely, and total peripheral resistance increased (Nies,1973; Ulrych *et al.*, 1968). They suggested that the sympathetic reflex was due to the reduction of cardiac output (Nies,1973; Nickerson and Collier, 1975). But the reflex arc was not explained, nor the change in the sympathetic nerve activity was demonstrated. Another possible explanation was discussed about the fact that the effects by α–adrenergic factor were enhanced by administration of β–adrenergic antagonist (Burks and Cooper, 1967). Because sympathetic nervous system of the spinal level is separated from the supraspinal components, chronic spinal rats is the advantageous experimental model to clarify the underlying mechanisms of the vasoconstrictor response by β– adrenergic antagonist.

MATERIALS AND METHODS

Adult male rats of Wistar strain were used. Three or four rats were reared in one plastic cage with wood shavings at the thermoneutral condition (22–24 ℃). After laminectomy under the pentobarbital (Nembutal® , 50mg/kg, Abbot Laboratories, USA) anesthesia, the spinal cord was transected between the C_7 and Th_1 vertebrae by aspiration (Waibl,1973; Osborn *et al.*, 1989). After intramuscular application of antibiotics, disodium sulbenillin (Lilacillin® , Takeda, Japan), spinal rats were reared individually at a warm room (30 C, 50% r.h.). Food and water were available *ad libitum*. Experiment was done in the climatic chamber, air temperature (Ta) was controlled at 30 ℃, 60 % r.h.. For experiment on conscious spinal rats, 1 day before the experiment, a polyethylene tube filled with heparinized physiological saline was implanted into the right femoral artery under light anesthesia with sodium pentobarbital, for measuring systemic BP by a pressure transducer (MP–0.5,TMI, Nihon Kohden, Japan). The arterial mean pressure was calculated after numerical evaluation of the recorded pressure as $P_{diast.} + 1/3(P_{syst.}–P_{diast.})$. Just before the experiment, needle electrodes for recording electrocardiogram (ECG) were attached at both axillary portions. HR was calculated by R–R interval of ECG. One thermistor probe was inserted more than 3 cm beyond the anus. The other thermistor probe was attached at the middle portion of the tail, and tip of the probe was covered with a layer of adhesive tape. By these thermistor probes (2mm,ϕ), rectal (Tre) and tail skin (Ttail) temperatures were detected. All parameters were recorded continuously in a UV oscillograph (Type 5L, Senei). As the

index of the tail blood flow the difference (dTtail) between Ttail and Ta was calculated.

Adrenaline β-antagonist, propranolol hydrochloride (Prop., 8mg/kg,; Inderal® , Sumitomo kagaku, Japan) was injected intraperitoneally. In this experiment, amount of injected solution was less than 3 ml. During the experiment, conscious spinal rats were placed in a small wire-mesh cage. Control values ("Before") are mean values calculated from the values at 7 time-points every 5 min for 30 min before the injection. All values are presented as means±S.E. and the statistical significance was assayed by Wilcoxon matched-pairs signed-ranks test and Mann-Whitney U-test.

RESULTS

A) Effect of propranolol on Tre and dTtail in chronic spinal rats.

1)Changes in dTtail

Propranolol hydrochloride (Prop.) 8 mg/kg was administered intraperitoneally to rats under warm ambient temperature (Ta), 27-30 ℃. Chronic spinal rats were divided into 3 groups as follows, Group-A (N=6), less than 1 week; Group-B (N=10) , more than 1 week and less than 2 weeks, Group-C (N=6), more than 2 weeks after the spinalization. After injection of Prop., in conscious chronic spinal rats, tail skin temperature (Ttail) decreased sustainedly in these three groups.

By the injection of Prop., the index of blood flow in the tail, dTtail (dTtail=Ttail-Ta) decreased significantly ($p<0.05$) in Group-A , Group-B and Group-C. In Table 1-B, mean values of dTtail before the injection (control) and at 5 min, 10 min, 20 min, 30 min, 40 min, 50 min and 60 min after the injection were shown. Mean values of dTtail, before the injection was 1.5±0.3 ℃ in Group-A, 1.3±0.4 ℃ in Group-B, and 1.6±0.4 ℃ in Group-C, respectively. There were no significant differences among these values. Values of dTtail at 10 min, 20 min, 30 min, 40 min, and 50 min after the injection in the three groups were significantly low ($p<0.05$ or $p<0.01$ as shown in the lower part of Fig. 1 and Table 1-B) compared to control values.

Changes (dTtail−control value) of dTtail at 20 min and at 40 min after the injection were −0.9±0.2 ℃, −0.7±0.2 ℃ in Group-A, −0.9±0.3 ℃, −1.1±0.4 ℃ in Group-B, and −1.4±0.3 ℃, −1.3±0.2 ℃ in Group-C, respectively. Decrease of dTtail at 40 min after the injection in Group-C was significantly greater ($p<0.05$) than that in Group-A.

2) Changes in Tre

In the upper part of Fig.1, changes of Tre in the three groups are shown. In Group-A, mean values of Tre changed slightly, whereas in Group-B and Group-C, mean values of Tre increased after the injection. Mean values of Tre before the injection were 36.3±0.2 ℃ in Group-A, 37.2±0.3 ℃ in Group-B, and 38.2±0.6 ℃ in Group-C, respectively. Values in Group-B and Group-C were significantly high ($p<0.05$ for Group-B, $p<0.01$ for Group-C) compared to value in Group-A. Mean values of Tre were shown in Table 1-A. As shown in Table 1-A, mean value of Tre at 50 min in Group-A was significantly low ($p< 0.05$) compared to control. Values of Tre

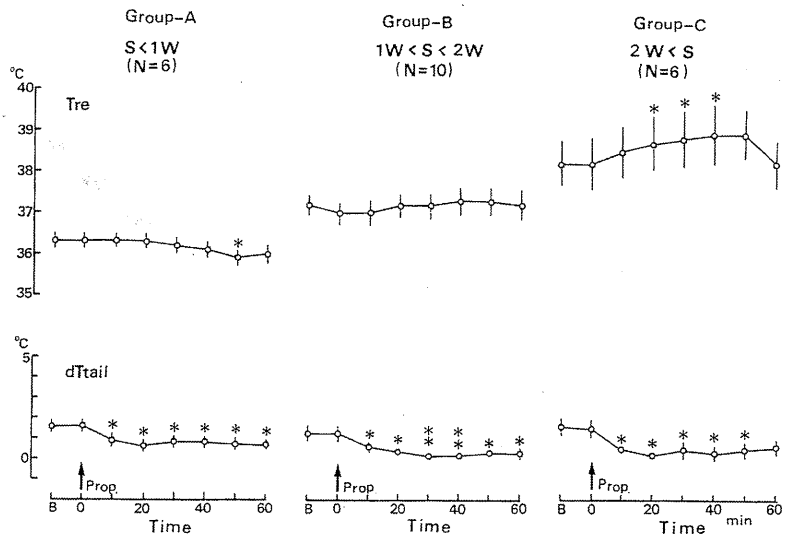

Fig. 1. Effect of propranolol hydrochloride (Prop.) on rectal temperature (Tre; upper tracings) and the difference (dTtail) between the tail skin temperature (Ttail) and ambient temperature (Ta) in conscious spinal rats (dTtail=Ttail-Ta; lower tracings).
Group-A:less than one week after the spinalization (N=6), Group-B: between 1 week and 2 weeks, (N=10), Group-C: more than 2 weeks after the spinalization (N=6). Arrows indicate the intraperitoneal injection of propranolol, 8 mg/kg. "B" under the horizontal axis mean "Before". Values of "Before" are mean values of those observed at 7 time-points every 5 min for 30 min before the injection. Values are mean ± S.E.. Vertical bars indicate S.E.(**; $p<0.01$, *; <0.05 compared to control ("Before").

Table 1. Mean values (mean ± S.E.) of rectal temperature (Tre,Table 1-A) and the difference (dTtail,Table 1-B) between tail skin temperature (Ttail) and the air temperature (Ta), (dTtail=Ttail - Ta) at 5 min, 10 min, 20 min, 30 min, 40 min, 50 min and 60 min after the injection of Prop.(8 mg/kg,i.p.) in conscious spinal rats

A	Before	5min	10 min	20 min	30 min	40 min	50 min	60 min
Group-A	36.3 ±0.2	36.2 ±0.1	36.3 ±0.2	36.3 ±0.2	36.2 ±0.2	36.1 ±0.2	35.9* ±0.2	36.0 ±0.2
Group-B	37.2 ±0.3	36.9* ±0.3	37.0 ±0.3	37.2 ±0.3	37.2 ±0.3	37.3 ±0.4	37.3 ±0.4	37.2 ±0.4
Group-C	38.2 ±0.6	38.2 ±0.6	38.5 ±0.7	38.7* ±0.7	38.8* ±0.7	38.9* ±0.8	38.9 ±0.8	38.2 ±0.6
B								
Group-A	1.5 ±0.3	1.2 ±0.3	0.9* ±0.3	0.6* ±0.3	0.8* ±0.3	0.8* ±0.3	0.7* ±0.3	0.7* ±0.3
Group-B	1.3 ±0.4	1.2 ±0.4	0.6* ±0.2	0.4* ±0.2	0.2** ±0.2	0.2** ±0.2	0.3* ±0.2	0.3 ±0.3
Group-C	1.6 ±0.4	1.0* ±0.3	0.5* ±0.2	0.2* ±0.2	0.5* ±0.4	0.3* ±0.3	0.5* ±0.4	0.6 ±0.4

Values of "Before" are means of values calculated from those observed at 7 time-points every 5 min for 30 min before the injection of Prop..
In table, asterisks indicate the statistical significance (**;$p<0.01$ and ,*;$p<0.05$ compared to the values of "Before", respectively).

at 20 min, 30 min, 40 min in Group-C were significantly high ($p < 0.05$) compared to control value.

Changes (Tre−control value) at 20 min and at 40 min were 0±0.1 ℃ and −0.2±0.1 ℃ in Group-A, 0±0.1 ℃ and 0.1±0.2 ℃ in Group-B, 0.5±0.1 ℃ and 0.7±0.2 ℃ in Group-C, respectively. Values in Group-C were significantly greater ($p < 0.05$ at 20 min, $p < 0.01$ at 40 min) than those in Group-A.

B) Effects of Prop. on HR , BP, Tre and dTtail in chronic spinal rats.

Conscious spinal rats with a catheter in the femoral artery and the ECG electrodes were placed in a small cage (N=6, 28±7 days after the spinalization). Same dose (8 mg/kg, i.p.) of Prop. was injected intraperitoneally to the rat. As shown in Fig.2, HR decreased markedly but BP increased slightly. These changes began immediately after the injection. Mean value of HR before the injection was 394±25 beats/min. By the injection HR decreased to a level of 300 beats /min and stayed at this level. HR was 318±12 beats/min at 5 min, 292±13 beats/min at 10 min, 285±13 beats/min at 20 min, 285±19 beats/min at 30 min after the injection. These values are significantly low ($p < 0.05$) compared to value of control. Before the injection, mean values of Tre and mean BP were 37.8±0.2 ℃, 82±6 mmHg, respectively. Both Tre and BP did not change significantly after the injection. Mean value of dTtail decrease sustainedly after the injection. Mean value of dTtail was 1.4±0.9 ℃ before the injection, 0±0.6 ℃ at 10min, −0.5±0.4 ℃ at 20 min, −0.6±0.4 ℃ at 30 min after the injection, respectively. These values were significantly low ($p < 0.05$) compared to the controls.

By the intraperitoneal injection of physiological saline to the conscious rats, neither Tre nor dTtail changed.

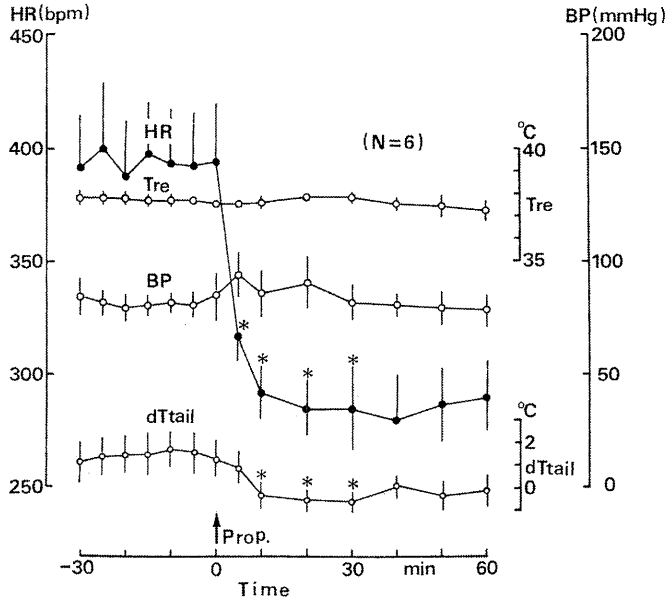

Fig. 2. Effect of Prop. on HR, BP, Tre and dTtail in conscious spinal rats. Prop.(8 mg/kg) was injected intraperitoneally at time 0 which was indicated by an arrow. "B" under the horizontal axis means "Before" . Values of "Before" are means of values observed at 7 time-points every 5 min for 30 min before the injection. Values are mean±S.E. Vertical bars indicate S.E.(**;$p < 0.01$, *< 0.05 compared to control ("Before").

Discussion

In this study, effect of Prop., nonselective adrenaline β-antagonist on the tail blood flow was studied in conscious chronic spinal rats. Intraperitoneal injection of Prop. induced a decrease of dTtail and no change or an increase in Tre for 50 min after the injection. Both decrease in dTtail and increase in Tre became more prominent with the lapse of days after the spinalization. Because Tre increased after the injection of Prop. in Group-C of chronic spinal rats, a decrease in Tre is not due to the change in the temperature of circulating blood. HR decreased markedly by Prop. injection, but BP did not change or slightly increased just after the injection. As mentioned in the introduction, in case of atropine sulfate injection during assay of autonomic nervous tone, such a decrease in dTre was not observed (Tsuchiya *et al.*, 1987). After the injection of physiological saline to conscious spinal rats, neither Tre nor dTtail changed. From above mentioned facts, it is reasonable that the decrease in dTtail is due to vasoconstriction in the tail arteries but not due to the reduction of metabolic rate by adrenaline β-antagonist.

Rat tail is the important organ for temperature regulation. During body or spinal cord heating, the reflex vasodilation in the tail increases the blood flow resulting in an increase in heat dissipation from the glabrous tail skin (Rand *et al.*, 1965; Hales et al., 1978). Arteriovenous anastomoses (AVA) are abundant in the rat tail (Gemmel and Hales, 1977; Anderson and McLachlan, 1991). These AVA are predominantly controlled by the hypothalamus and are extensively supplied with the sympathetic vasoconstrictor nerves (Folkow,1995). The rat tail arteries including AVA are innervated by the sympathetic vasoconstrictor nerves which are mediated by both α_1- and α_2-adrenergic receptors (Medgett, 1985; Sittracha *et al.*, 1987; Anderson and McLachlan, 1991; Hacker *et al.*, 1991). Although existence of the active vasodilator nerve was reported in the muskrat tail (*Ondathra zibehica*) (Johansen, 1962), O'leary *et al.*(1985) concluded that the reflex vasodilator response of the rat tail during body heating occurred solely via withdrawal of the vasoconstrictor nerve activity.

On the other hand, there were numerous reports concerning the vasodilator responses mediated by β-adrenergic receptors. It was suggested that in dog skeletal muscle, β_2-adrenergic receptors mediating vasodilator responses might be humorally controlled and were not innervated by the vasoconstrictor nerves (Youmans *et al.* 1955; Russel and Moran, 1980). Chohen and Coffman (1981) also suggested from their experimental results that β-adrenergic receptors mediating vasodilation in human digital AVA might be only humorally activated. In chronic spinal rats, a sustained vasodilation in the tail was observed without stimulus in the warm room. In these animals tail arteries are in intermediate state, neither fully constricted and nor fully dilated. But the degree of vasodilation gradually decreased with the lapse of days after spinalization (Tsuchiya, 1986).

Young (1984) pointed out that role of the circulating plasma adrenaline secreted from the adrenal medulla was important for life sustenance when sympathetic nervous activity is suppressed. Existence of a low level of plasma noradrenaline and a certain level of adrenaline were reported in chronic spinal rats (Tsuchiya *et al.* 1995). In chronic spinal rats, the humoral factors

in the circulating blood were not exactly known. It was reported that "pressor response" of the isolated mesentery arteries to α–adrenergic agonist was enhanced by application of β–adrenergic antagonist (Burks and Cooker, 1967). It was suggested that Prop. has little or no direct effect on the peripheral vasculature (Brick *et al.*, 1966). In this study, if there are α–adrenergic vasoconstrictor factors in the circulating blood, Prop. might enhance the vasoconstrictor effect.

Vasodilator responses in rat tail arteries to acute administration of isoproterenol (Isop., adrenaline β–agonist) have been reported frequently (Fregly *et al.*, 1983; Barney *et al.*, 1980; Katovich *et al.*, 1981). The vasodilator response was used as the index for the cold acclimation of the rat. Fregly (1983) suggested from the pharmacological study that the rat tail vasodilation induced by Isop. was not the result of a direct effect on the vasculature but an indirect effect occurring secondarily to an increase in metabolic rate mediated β_1–adrenergic receptors. It remains to be examined that Isop. has any effect on the tail arteries in the chronic spinal rats.

Digital vasospastic phenomenon (Raynaud's phenomenon) was reported in patients treated with Prop. (Marshall *et al.*, 1976; Eliasson *et al.*, 1979). By the investigation of hemodynamic effect of Prop. in normotensive and hypertensive patients (Ulrych *et al.*, 1968) and in anesthetized rhesus monkey (Nies, 1973), it was revealed that administration of Prop. induced a significant fall in HR, a decrease in cardiac output, a slight change in systemic BP and an increase in total peripheral resistance. It was supposed that an increase in calculated total resistance was probably due to an increase in sympathetic nerve activity as a result of the compensatory sympathetic reflex (Nies ,1973 ; Nickerson and Collier, 1975). But authors did not demonstrate the neurophysiological evidences of increase in sympathetic nerve activities, and a supposed reflex arc was not explained. In anesthetized chronic spinal cats, a significant recovery of systemic BP and a change in BP by administration of ganglion blocker were first recognized at 9–14 days after spinalization (Ardell *et al.*, 1982). Moreover, Osborn *et al.*, (1989) reported that in chronic spinal rats under conscious condition, systemic BP gradually recovered towards the control level within the 1st week and it attained control level by 9 days after the spinalization. But they suggested that sympathetic nervous activities were not involved in these recovery of BP in the rat.

In this study, the sustained vasoconstrictor responses after Prop. administration were recorded in the conscious chronic spinal rats. Two possible explanation were discussed, the enhancement of α–adrenergic constrictor effect by β–adrenergic antagonist, and the sympathetic vasoconstrictor reflex triggered by hemodynamic changes due to Prop. effect. For a decisive conclusion to explain the underlying mechanisms, it has to be examined whether the vasoconstrictor nerves are involved in these responses or not.

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