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Pulmonary and Systemic Vascular Responses to Vasoactive Agents after Chemical Sympathectomy(40810)

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The sympathetic nervous system (SNS), in conjunction with the adrenal medulla, has been shown to play an important role in the maintenance of systemic arterial blood pressure (1–3). In the pulmonary circulation, on the other hand, sympathetic influences appear to be unimportant in the primary control of pressure and vascular resistance (4). However, the lung is abundantly supplied by the autonomic nervous system (5–7), and this raises a question as to the role of the SNS in the lung. One possibility is that the sympathetics modulate the response of the vascular bed to humoral agents. The opposite interaction, modulation of adrenergic transmission by humoral agents, has been previously demonstrated using a number of tissue preparations (8–14). It is possible that pulmonary sympathetics exist to provide the proper microvascular environment for the action of other chemical controllers. Removal of a vasoconstrictor or vasodilator influence may lead to hyperactivity of other controlling mechanisms, in order to maintain homeostasis. Thus, the reactivity of vascular beds to humoral agents may be increased after removal of sympathetic neural influences.

The purpose of this investigation was to determine if the SNS modulates the physiological actions of humoral agents. Cardiac and vascular reactivity to several substances was determined before and after chemical sympathectomy with 6-hydroxydopamine (6-OHDA). Particular emphasis was placed on comparisons of differences in the pulmonary and systemic vascular beds. The results of this study indicate that cardiovascular responses to some humoral agents are modified following chemical sympathectomy.

Materials and methods. Control studies. Eight mongrel dogs, weighing 12.0 to 20.3 kg, were anesthetized with intravenous sodium pentobarbital (30 mg/kg, Abbott Labs, North Chicago, Ill.), intubated with a cuffed endotracheal tube, and allowed to breathe room air spontaneously. Polyethylene catheters were placed in the main pulmonary artery via the jugular vein and in the abdominal aorta via the femoral artery. A Swan–Ganz flow-directed catheter was passed into a peripheral pulmonary artery for determination of pulmonary arterial wedge pressure. A fourth catheter was placed in the superior vena cava for infusion purposes. Pulmonary arterial, pulmonary wedge, and systemic arterial pressures were transduced with strain gauges (Statham P23Db) calibrated with a mercury manometer and zeroed at the level of the right atrium. Cardiac output was determined by injecting known amounts of indocyanine green dye (Cardio-Green) into the superior vena cava and sampling of arterial blood with a cuvette densitometer (Waters TD-1A) and an infusion-withdrawal pump (Harvard). The electrical outputs of the pressure transducers, the densitometer, the electrocardiograph, and a pneumotachograph were recorded with an Electronics for Medicine recorder (Model VR-6). Cardiac output was computed using the method of Williams *et al.* (15). Pulmonary vascular resistance was calculated by dividing the pulmonary pressure gradient by cardiac output. Systemic vascular resistance was obtained by dividing mean systemic arterial pressure by cardiac output. Body temperature was monitored continuously with a thermistor probe placed in the esophagus (Yellow Springs Telethermometer).

Each of the following substances was randomly infused intravenously for 4 min

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after completion of surgical preparation: prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 2 μg/kg/min, The Upjohn Co., Kalamazoo, Mich.), 5-hydroxytryptamine, creatinine sulfate complex (5-HT, 10 μg/kg/min, Sigma Chemical Co., St. Louis, Mo.), histamine phosphate (10 μg/kg/min, Eli Lilly & Co., Indianapolis, Ind.), and phenylephrine hydrochloride (4 μg/kg/min, Winthrop Labs, New York). Heart rate, respiratory rate, and blood pressures were recorded throughout the experiments. Cardiac output and vascular resistances were determined at least twice before each infusion and once during the last minute of the infusion.

The catheters were removed and the incisions were closed at the end of each control study. The dogs were returned to their cages and treated with antibiotics as required. All animals recovered completely within 2 or 3 days.

Chemical sympathectomy. The animals were prepared for the chemical sympathectomy regimen 1 to 2 weeks following the control studies. 6-OHDA hydrobromide (80 mg/kg, Regis Chemical Co., Morton Grove, Ill.), was dissolved in saline containing ascorbic acid (1 mg/ml) and was injected intravenously in fractionated increasing doses over an 8-hr period (2). Salivation and vomiting occurred during the course of the injections. Diarrhea, miosis, and relaxed nictitating membranes (classical signs of sympathectomy) were noted in all dogs within 12 hr after the last injection.

Post 6-OHDA studies. The cardiovascular reactivity of each animal to the previously described agents was reevaluated 2 days after the administration of 6-OHDA. The dosages and order of the infusions were identical to those of the control study. The results obtained before and after pretreatment with 6-OHDA were compared using appropriate analysis of variance techniques.

Results. Significant reductions in systemic arterial blood pressure (SAP) and systemic vascular resistance (SVR) were found in the dogs 2 days after 6-OHDA (Tables I and II). However, pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR), and cardiac output (CO) were unchanged by 6-OHDA pretreatment. In addition, chemical sympathectomy did not alter arterial pH (7.35 ± 0.01 vs 7.35 ± 0.02), PO_2 (81 ± 4 vs 83 ± 3 mm Hg), PCO_2 (35 ± 3 vs 32 ± 2 mm Hg), hematocrit (35 ± 2 vs 34 ± 1%), ventilation (3.0 ± 3 vs 3.3 ± 0.4 liters/min), or respiratory rate (16 ± 2 vs 22 ± 4 breaths/min).

Prior to 6-OHDA pretreatment, $PGF_{2\alpha}$ and phenylephrine infusions produced pulmonary and systemic vasoconstriction accompanied by reflex reductions in CO and HR (Table I). Several of these responses were significantly ($P < 0.05$) modified 2 days after chemical sympathectomy. Thus, attenuated elevations in PVR and SVR as well as an increase in CO were observed with $PGF_{2\alpha}$. The PAP, SAP, and HR responses to $PGF_{2\alpha}$ were not altered by 6-OHDA. On the other hand, potentiated increases in PAP, SAP, and SVR were found with phenylephrine, although the maximum SAP and SVR attained with phenylephrine was not different before and after 6-OHDA. The PVR response to phenylephrine was unaltered by 6-OHDA.

Histamine and 5-HT infusions caused significant ($P < 0.05$) increases in PAP, PVR, and CO associated with significant decreases in SVR during the control studies (Table II.) A significant fall in SAP with histamine and an insignificant rise in HR with 5-HT were also induced in normal dogs. None of these responses were altered by chemical sympathectomy.

Respiratory rate of normal dogs was significantly ($P < 0.05$) increased by 76 and by 93%, respectively, during infusion of $PGF_{2\alpha}$ and histamine. Two days after chemical sympathectomy, these responses were reduced to 41% for $PGF_{2\alpha}$ and to 48% for histamine. 5-HT and phenylephrine had no effect on respiratory rate either before or after 6-OHDA pretreatment.

Discussion. Direct evidence of chemical sympathectomy was not obtained in the present study. Infusions of tyramine, which causes the release of any norepinephrine present in nerve terminals, and histological examination of lung and systemic tissues were not employed. However, chemical sympathectomy can be assumed based on

TABLE I. HEMODYNAMIC RESPONSES TO $PFG_{2\alpha}$ AND PHENYLEPHRINE BEFORE AND AFTER 6-OHDA

		$PGF_{2\alpha}$		Phenylephrine	
		Control	Change	Control	Change
PAP[a]					
(mm Hg)	Pre	14 ± 1	+14 ± 2	16 ± 1	+10 ± 1
	Post	13 ± 1	+10 ± 2	16 ± 2	+14 ± 1*
PVR					
(mm Hg/liter/min)	Pre	6.0 ± .9	+6.9 ± .9	7.2 ± .9	+4.8 ± .9
	Post	6.0 ± 1.0	+4.8 ± 1.1*	7.1 ± .9	+6.8 ± 1.7
SAP					
(mm Hg)	Pre	131 ± 4	+8 ± 3	134 ± 4	+40 ± 4
	Post	93 ± 4*	+5 ± 3	91 ± 3*	+83 ± 6*
SVR					
(mm Hg/liter/min)	Pre	67.9 ± 8.1	+8.6 ± 1.6	71.0 ± 7.2	+55.2 ± 7.6
	Post	47.3 ± 4.5*	+0.5 ± 2.5*	44.0 ± 3.1*	+82.2 ± 6.7*
CO					
(liter/min)	Pre	2.1 ± .2	−0.2 ± .1	2.0 ± .1	−0.6 ± .1
	Post	2.0 ± .1	+0.1 ± .05*	2.2 ± .1	−0.7 ± .1
HR					
(b/min)	Pre	150 ± 11	−6 ± 8	146 ± 11	−28 ± 7
	Post	132 ± 8	+6 ± 2	140 ± 8	−20 ± 6

[a] Abbreviations: PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; SAP, systemic arterial pressure; SVR, systemic vascular resistance; CO, cardiac output; HR, heart rate; Pre, before 6-OHDA; Post, after 6-OHDA.

* Different from comparable Pre value at $P < 0.05$ level.

the use of an established dose of 6-OHDA, the significant fall in systemic blood pressure, and the classical signs of sympathectomy (described under Materials and methods section).

The present results suggest the development of a postsynaptic supersensitivity to α receptor agonists in the canine pulmonary and systemic vascular beds within 2 days following 6-OHDA pretreatment. This conclusion is supported by the potentiated pressor and vasoconstrictor responses to phenylephrine, since this substance is preferentially a postsynaptic α agonist (16–18). However, since the maximal systemic pressure and resistance attained with phenylephrine was similar before and after 6-OHDA, the dose of phenylephrine may have been supramaximal. Despite a reduced baseline pressure and resistance, a supramaximal stimulation could still elicit similar maximal responses. Lower doses of phenylephrine were not employed, so this mechanism for increased reactivity is viable.

Several studies have demonstrated the development of both pre- and postsynaptic supersensitivity after chemical sympathectomy. Barron *et al.* (19) observed potentiated pulmonary and systemic arterial pressor responses to phenylephrine and norepinephrine in conscious dogs 7 days after chemical sympathectomy with 6-OHDA. Yong and Chen (20) have also observed increased responses to phenylephrine, norepinephrine, and methoxamine (another preferentially postsynaptic α agonist) in the perfused central ear artery of rabbits 7 days after 6-OHDA pretreatment. Furthermore, Shibata *et al.* (21) have demonstrated postjunctional supersensitivity in isolated aortic tissue just 2 days after pretreatment with 6-OHDA. In conscious dogs, Gauthier *et al.* (22) observed a potentiated systemic pressor response to phenylephrine 3 days following 6-OHDA, but these changes were not found to be significant. The appearance of postsynaptic supersensitivity so soon after sympathec-

TABLE II. HEMODYNAMIC RESPONSES TO HISTAMINE AND 5-HT BEFORE AND AFTER 6-OHDA

		Histamine		5-Hydroxtryptamine	
		Control	Change	Control	Change
PAP[a]					
(mm Hg)	Pre	14 ± 1	+4 ± 1	14 ± 1	+8 ± 1
	Post	15 ± 2	+5 ± 2	15 ± 2	+8 ± 1
PVR					
(mm Hg/liter/min)	Pre	6.4 ± .8	+2.1 ± .7	6.4 ± .8	+2.4 ± .3
	Post	6.5 ± .9	+1.4 ± .4	6.8 ± 1.0	+3.5 ± .7
SAP					
(mm Hg)	Pre	134 ± 4	−31 ± 4	135 ± 3	−2 ± 3
	Post	96 ± 4*	−24 ± 2	96 ± 4*	−6 ± 3
SVR					
(mm Hg/liter/min)	Pre	67.2 ± 5.6	−20.7 ± 2.8	67.5 ± 4.2	−10.5 ± 2.2
	Post	47.4 ± 4.4*	−17.6 ± 2.4	48.1 ± 4.2*	−5.5 ± 3.7
CO					
(liter/min)	Pre	2.0 ± .1	+.3 ± .1	2.0 ± .1	+.3 ± .1
	Post	2.1 ± .2	+.4 ± .1	2.1 ± .2	+.1 ± .1
HR					
(b/min)	Pre	138 ± 11	+8 ± 10	141 ± 9	+16 ± 5
	Post	139 ± 8	+20 ± 7	137 ± 7	+7 ± 2

[a] Abbreviations: PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; SAP, systemic arterial pressure; SVR, systemic vascular resistance; CO, cardiac output; HR, heart rate; Pre, before 6-OHDA; Post, after 6-OHDA.

* Different from comparable Pre value at $P < 0.05$ level.

tomy has been questioned (22) because following surgical denervation this type of supersensitivity develops gradually over a period of 12 to 16 days (23). Since postsynaptic supersensitivity is apparently evident within 2 days after 6-OHDA treatment, this variance in viewpoint may simply reflect a temporal difference in the responses to chemical and surgical sympathectomy.

The heart rate and cardiac output responses to phenylephrine were of considerable interest. Phenylephrine induced significant reductions in cardiac output and heart rate that were not altered 2 days after 6-OHDA. The bradycardia, in response to the systemic hypertension, was probably of vagal origin, and therefore should have been, and in fact was, unaffected by chemical sympathectomy (24). If the fall in cardiac output was due to α receptor stimulation, then one would have expected a further depression of this hemodynamic variable after chemical sympathectomy. However, the cardiac output response was similar after 6-OHDA, indicating that its reduction was not mediated directly by α receptor stimulation, but perhaps by indirect actions on venous return.

Interactions between the SNS and the histaminergic and serotonergic systems were not demonstrated using 6-OHDA. Pulmonary and systemic vascular and cardiac responses to histamine and 5-HT were unchanged by chemical sympathectomy. Isolated hearts from guinea pigs treated with 6-OHDA have also been found to be equally responsive to histamine compared to untreated controls (25). Heart rate and contractility responses were neither diminished nor enhanced in the 6-OHDA treated animals. The absence of an effect of 6-OHDA on histamine vasoreactivity was somewhat unexpected since this humoral agent has been shown to modulate norepinephrine release during nerve stimulation. McGrath and Shepherd (10) provided evidence that histamine, acting

through H_2-receptors, could reduce the amount of norepinephrine released. However, the present data indicate that the SNS does not modulate the pulmonary and systemic vascular actions of histamine. Thus, vascular and cardiac histamine and 5-HT receptors do not require the presence of sympathetic nerves for their actions.

Evidence of prostaglandin interaction with the SNS was obtained in the present study. The pulmonary and systemic vasoconstrictor responses to $PGF_{2\alpha}$ were reduced, whereas the heart rate and cardiac output responses were reversed. In the absence of an intact SNS, prostaglandin-induced vasoconstriction was attenuated. This implies that there may be some facilitation between the SNS and prostaglandin "receptors." $PGF_{2\alpha}$ has been suggested to facilitate reflex vasoconstriction in the rabbit and rat kidney (26), and in canine skeletal muscle and perfused hindpaws (8). Similarly, in the rabbit pulmonary artery, $PGF_{2\alpha}$ was shown to increase the vasoconstrictor response to nerve stimulation by enhancing the postsynaptic effect of norepinephrine (13). Therefore, a significant interaction between the SNS and $PGF_{2\alpha}$ is evident. Not only does $PGF_{2\alpha}$ act as a modulator of adrenergic transmission, but, in addition, the pulmonary and systemic vascular responses to $PGF_{2\alpha}$ appear to be influenced by the SNS.

Summary. The primary aim of this study was to determine if the sympathetic nervous system modulates the cardiovascular actions of vasoactive agents. Anesthetized dogs, instrumented to determine pulmonary and systemic vascular resistances, were administered several vasoactive agents prior to and 2 days following chemical sympathectomy with 6-hydroxydopamine (6-OHDA). Classical signs of sympathectomy were used to demonstrate the effectiveness of the chemical sympathectomy regimen. Pulmonary and systemic hemodynamic responses to infusions of histamine and 5-hydroxytryptamine were unaltered by chemical sympathectomy. However, pulmonary and systemic vasoconstriction induced by prostaglandin $F_{2\alpha}$ was attenuated and the pulmonary and systemic pressor responses to phenylephrine were potentiated 2 days after 6-OHDA. These results suggest the development of postsynaptic supersensitivity to α receptor stimulation in both the pulmonary and systemic vascular beds. In addition, an interaction between prostaglandin $F_{2\alpha}$ and the sympathetic nervous system is also suggested.

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