EFFERENT ACTIVITY IN RENAL AND INTESTINAL NERVES DURING CIRCULATORY REFLEXES*

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Summary The effects of baroreceptor reflex on the sympathetic nerve activity to the intestine (INA) and kidney (RNA) were compared in anesthetized cats. Grouped discharges synchronous with the cardiac cycle was not the major pattern in INA and approximately 73% of the total INA was composed of a continuous or fluctuating pattern. With increase in mean aortic pressure from 116 to 216 mmHg after administration of norepinephrine, INA showed various response patterns: initial inhibition followed by an increase (Type A), increase without inhibition (Type B), slight inhibition (Type C) and no change (Type D), whereas RNA decreased to the noise level. Type A and B were the most common response patterns. In the open loop condition, initial inhibition in Type A disappeared, while the increase of INA in Types A and B remained unchanged. When RNA was completely inhibited by baroreceptor inputs during occlusion of the descending thoracic aorta, INA was not inhibited but rather slightly increased. It is concluded that INA showed quantitatively and qualitatively different responses to baroreceptor inputs as compared to RNA.

The resistance vessels in the various peripheral vascular beds do not respond uniformly to the baroreceptor activity in the aortic arch and carotid sinus (HADJIMINAS and ÖBERG, 1968; HEYMANS and NEIL, 1958). These differences in response may be due in part at least to non-uniform distribution of the sympathetic nerve activity (SNA) to different organs (GREEN and HEFFRON, 1966; IRIKI *et al.*, 1971; NINOMIYA *et al.*, 1971, 1973; NISIMARU, 1971; WEIDINGER and FEDINA, 1960). This in turn may be due to richer or sparser innervation of resistance vessels in some regions or to more or less baroreceptor-associated traffic in the sym-

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pathetic supply reaching the particular vessels.

The SNA to the spleen, kidney, heart, stomach, and skin show different responses to baroreceptor reflexes. Thus most of the SNA to the spleen, kidney, and heart shows complete inhibition during the baroreceptor depressor reflex (NINOMIYA *et al.*, 1971), but about 80% of the SNA to the stomach is independent of baroreceptor function (NISIMARU, 1971). Most of the SNA to the skin is also baroreceptor independent (NINOMIYA *et al.*, 1973).

Although there has been ample evidence for baroreceptor reflexes affecting intestinal blood flow (GRAYSON and MENDEL, 1965), the intestinal vascular bed seems to be only moderately involved in baroreceptor reflex as compared with the muscle resistance vessels (CELANDER and FOLKOW, 1951; FOLKOW, 1967; ÖBERG, 1964). These results suggest that the baroreceptor reflexes may have small effects on the SNA to intestinal resistance vessels as compared with other vascular beds. However, little relevant information is available concerning intestinal nerve activity. The present report describes the recording of postganglionic sympathetic nerve activity to the intestine as compared with renal nerve activity in conjunction with various baroreceptor inputs.

METHODS

Eleven cats (2–3 kg) were used in this study. After the animal was anaesthetized with sodium pentobarbital (Nembutal 35 mg/kg, ip) the trachea was intubated. On those occasions when the thorax was opened for aortic occlusion, the lungs were ventilated by intermittent positive pressure from a Harvard respiratory pump (Model 606).

Additional doses of sodium pentobarbital (5 mg/kg, iv) were injected intravenously through a catheter inserted in the left femoral vein whenever responses to pain were detected.

The intestinal nerve was separated from the sheath surrounding a branch of the mesenteric vessels near the intestinal wall, *i.e.* ileum or jejunum. The method of identifying the renal nerve was the same as previously described (NINOMIYA *et al.*, 1971). The efferent nerve discharges were recorded central to the cut end of the nerve bundle. The recording of the nerve impulses and the integration of the original neurogram have been described previously (NINOMIYA *et al.*, 1971). The original neurogram was continuously monitored by a cathode ray oscilloscope (Tektronix 502 A). The time averaging of the aortic pressure and intestinal and renal nerve activities was performed simultaneously by a hybrid computer (Hidas 200, Hitachi Ltd.). The output of the computer was displayed on an XY recorder.

RESULTS

1. Comparison of the intestinal nerve activity and the renal nerve activity

Generally, grouped discharges synchronous with but of delayed phase with respect to the cardiac pressure cycle and its respiratory modulation were readily observed in the spontaneous activity of the renal sympathetic nerve. However, continuous and fluctuating discharges appeared dominant in the intestinal nerve (Fig. 1).

Fig. 1. An example of the original neurogram. RNA, Renal nerve activity; INA, intestinal nerve activity; AP, aortic pressure.

Fig. 2. Comparison of the grouping (A) and tonic (B) nerve activities to the kidney and intestine obtained by averaging technique.

In order to detect any grouping of discharges synchronous with the cardiac cycle the integrated nerve activity was averaged over 20 to 50 cardiac cycles in 10 cats. An example of the averaged sympathetic nerve activity is shown in Fig. 2. A grouping (A in Fig. 2) and a tonic component (B in Fig. 2) were found in both

the averaged RNA and INA. The absolute magnitude of the grouped nerve activity was larger in RNA than in INA, whereas that of the tonic nerve activity was larger in INA than in RNA. The absolute magnitude of SNA (μV) varied between different animals. Therefore, the relative magnitude of grouping in SNA ($A/(A+B) \times 100$) for a given cardiac cycle was computed in each preparation for statistical analysis. The relative magnitude of grouping obtained from 47 trials was 27% in INA and 85% in RNA (Table 1A). These data in-

Table 1A. Grouping of sympathetic nerve activity to the kidney (RNA) and intestine (INA).

Cat No.	Trial No.	Grouping (%)	
		RNA	INA
1	4	97.9	26.0
2	2	89.5	38.0
3	7	91.0	14.0
4	7	81.8	41.5
5	1	81.0	20.0
6	7	66.6	28.1
7	10	94.9	19.2
8	2	86.9	32.1
9	5	89.5	36.3
10	2	77.0	17.4
10	47	85.6* $\pm$ 2.7**	27.2 $\pm$ 2.8

* Mean

** SE

Table 1B. Delay times of baroreceptor reflex on sympathetic nerve activity to the kidney (RNA) and intestine (INA).

Cat No.	Trial No.	Interval of cardiac cycle	Delay time, msec		Difference in delay time, msec
			RNA	INA	
1	4	385	185	372	187
2	1	350	190	330	140
3	3	496	163	363	200
4	7	434	170	324	154
5	4	527	197	332	135
6	2	485	185	345	160
7	2	510	210	360	150
8	4	325	175	262	87
9	2	270	195	328	133
10	2	375	190	355	165
11	3	270	180	307	127
11	34	402.4* $\pm$ 27.0**	185.4 $\pm$ 3.8	334.3 $\pm$ 10.3	148.9 $\pm$ 10.1

* Mean

** SE

indicate that RNA consists predominantly of the grouped component while INA consists of mainly the tonic component.

Assuming that the peak INA coincides with the onset of sympathetic inhibition as in the case of RNA, the time interval between the maximum positive dp/dt of aortic pressure and peak SNA in the same cardiac cycle was measured in 11 cats. The interval was 334 ± 10 msec in INA and 185 ± 4 msec in RNA. INA lagged 149 msec behind RNA (Table 1B).

2. Baroreceptor reflex effect on SNA to the intestine and kidney

a) *Effect of administration of norepinephrine on SNA with 4 major afferent pathways intact.* After the intravenous administration of $10 \mu\text{g/kg}$ of norepinephrine, complete inhibition of RNA was observed in all 35 trials of 10 cats. On the other hand, the time course of INA in response to norepinephrine administration varied from animal to animal and from experiment to experiment. Responses were classified into four patterns (Table 2). When mean aortic pressure (MAP) increased by $86 \pm 17\%$ of the control value (116 ± 8 mmHg), INA measured in 18 trials was inhibited initially to 67% of the control level which was followed by 7% increase above the control value (Fig. 3A and Type A in Table 2). In 11 other trials, INA showed only an increase of 116% above the control value when MAP increased $61 \pm 6\%$ above the control pressure of 131 ± 5 mmHg (Fig. 3B and Type B in Table 2). INA showed a slight inhibition in 2 trials (Type C in Table 2) and no detectable change in 4 trials (Type D in Table 2).

Table 2. Frequency distribution of patterns to administration of norepinephrine.

Cat No.	Trial No.	Response patterns (type) of mean intestinal nerve activity			
		A	B	C	D
1	5	4	1	0	0
2	3	2	1	0	0
3	5	0	3	1	1
4	9	7	0	1	0
5	4	0	2	0	2
6	3	2	1	0	0
7	2	1	1	0	0
8	3	1	1	0	0
9	2	1	0	0	0
10	2	0	1	0	1
10	35	18	11	2	4

Type A, decrease and then increase; Type B, increase; Type C, decrease; Type D, no change.

An example of the averaged pattern synchronous with cardiac cycle obtained before and after administration of norepinephrine is shown in Fig. 4. After the administration of norepinephrine, grouped components in both INA and RNA

Fig. 3. Norepinephrine ($10 \mu\text{g/kg}$ iv) was administered at arrows. Two types of responses (Types A and B) in INA are shown in A and B, respectively. Renal nerve activity completely abolished as aortic pressure rose.

Fig. 4. Comparison of the averaged nerve activities to the kidney and intestine at the control (A) and after the administration of norepinephrine (B).

and the tonic component in RNA disappeared, but the tonic component in INA increased against the increase in baroreceptor inputs (Fig. 4).

b) *Effect of administration of norepinephrine on SNA with opened afferent loops.* Before the open loop experiment, administration of norepinephrine caused complete inhibition in RNA and slight inhibition which was followed by a signi-

ficant increase in INA. After bilateral vagotomy, both common carotid arteries were occluded to provide an open loop condition.

Under this circumstance, SNA to kidney was not inhibited by the baroreceptor input due to the administration of norepinephrine. On the other hand, the increase in INA following the administration of norepinephrine was still observed. Similar phenomenon was recorded in 3 other experiments. These results indicate that the increase in INA caused by the administration of norepinephrine is independent of the baroreceptor input.

In the controls, with the four major afferent pathways intact, the averaged SNA to the kidney and intestine show typically a grouped pattern synchronous with cardiac cycle (Fig. 5, thin lines). When norepinephrine was administered under open loop conditions, the grouped pattern in INA as well as in RNA disappeared, although both pulse and mean aortic pressures increased (Fig. 5, thick lines). Tonic SNA to the intestine increased above the initial control level.

Fig. 5. Effect of opening 4 major baroreceptor inputs on aortic pressure (AP) and intestinal nerve activity (INA). Averaged aortic pressure and nerve activities are obtained at control (thin line) and after the blocking of carotid sinus nerves by local application of 4% xylocaine under bilateral vagotomy (thick line). The grouping activity of INA disappeared, but the tonic activity increased.

c) *Effects of occlusion of the descending aorta on SNA.* In 3 cats, sympathetic nerve activity to the kidney and intestine were measured simultaneously before and during occlusion of the descending thoracic aorta. Data are summarized in Table 3. When MAP increased above the control value, in 2 or 3 cats INA showed very little change (Fig. 6A), but in one cat INA showed an increase after slight initial inhibition (Fig. 6B). On the other hand, RNA was inhibited almost completely during occlusion. During occlusion of the descending thoracic aorta the grouped discharges synchronous with the cardiac cycle were abolished both in INA and RNA.

Table 3. Effect of occlusion of descending thoracic aorta on mean aortic pressure (MAP), renal nerve activity (RNA), and intestinal nerve activity (INA).

Cat No.	Trial No.	MAP		Occlusion (% change)	
		Control value (mm Hg)	Increase (%)	RNA	INA
1	6	158* $\pm$ 4.4**	36.7 $\pm$ 3	-93.9 $\pm$ 2	+1.6 $\pm$ 0.7
2	3	103 $\pm$ 3.0	46.7 $\pm$ 5	-91.0 $\pm$ 7	+5.9 $\pm$ 1.6
3	12	130 $\pm$ 8.4	41.7 $\pm$ 3	-97.7 $\pm$ 2	+51.4 $\pm$ 14.3

* Mean

** SE

Fig. 6. Effect of occlusion of the descending aorta (bar) on the aortic pressure, renal nerve activity and ileal nerve activity. Mean renal nerve activity (MRNA) and mean intestinal nerve activity (MINA) are also shown. Two types of responses (A and B) were observed.

DISCUSSION

Nonuniform distribution of SNA to different parts of the body has been studied by several investigators (IRIKI *et al.*, 1971; NINOMIYA *et al.*, 1971, 1973; NISIMARU, 1971). Within visceral sympathetic nerves, SNA to the stomach and the gut were different from RNA. Both gastric nerve and intestinal nerve carry baroreceptor independent activity, which has been shown to be only a minor part of the activity of the cardiac, renal and splenic nerves. This is to be expected since a large number of post-ganglionic sympathetic fibers terminate on the non-

vascular structures of the intestine, *viz.* the intestinal smooth muscle and the enteric plexus. There is, however, an identifiable component of INA which is associated with rate-proportional baroreceptor activity.

Whereas about 20% of SNA to the stomach was dependent on baroreceptor activity, in the present experiments 27% (range: 14 to 41%) of the total INA depended on baroreceptor activity. This suggests that the baroreceptor-dependent component of SNA throughout the gastrointestinal tract is approximately of the same magnitude. This activity may reasonably be inferred to reach the vascular structures. However, the distribution of this activity to the various vascular components of the tract remains unknown. Furthermore, the final potency of this activity in conferring resistive or capacitive change to the vasculature is also unknown. Experiments in which direct electrical stimulation was applied to the nerve did not illuminate this, since the stimulation bears little relation in intensity and temporal or spacial distribution to the natural neural traffic. A further complication exists that some of SNA which is independent of baroreceptor activity may nevertheless be reaching the vascular structures. The present experiments could not distinguish such traffic.

The grouped nerve activity in INA and the temporal inhibition of INA during norepinephrine injection are considered to be of baroreceptor origin. Therefore, the time interval between the maximum positive dp/dt of the aortic pressure and the peak of SNA in the same cardiac cycle was measured as an index of delay time of baroreceptor to the different SNA. In SNA to the heart, kidney, spleen, stomach and intestine it was 164, 199, 292, 291, and 322 msec, respectively (NISIMARU, 1971). Skin nerve activity lagged behind RNA by 125 msec (ÖBERG, 1964). It can therefore be stated that SNA to the skin and intestine show longer delay times than SNA to the kidney, heart and stomach. This difference in delay time is considered to be largely due to the postganglionic conduction time. Since our recording electrode was placed close to the intestinal wall, the length of conduction probably must be longest within the above-mentioned sympathetic nerves. Because of the variety of delay times in different SNA, the baroreceptor effects are not synchronized at various sites.

Skin nerve activity has been shown to increase gradually against the baroreceptor inputs during occlusion of the descending thoracic aorta (NINOMIYA *et al.*, 1973). A similar phenomenon was observed in SNA to the intestine. The increase of INA during norepinephrine administration is in a direction opposite to the expected effect of the four major baroreceptor reflex. It has been shown that the injection of epinephrine or norepinephrine causes the portal blood pressure to increase (SEMBA, 1954; SWAN and REYNOLDS, 1971). Although the origin of the increase in INA during norepinephrine administration is not yet clear, recent findings (ANDREWS *et al.*, 1972) of the presence of mesentery "venous volume" or "stretch" receptors in the portal vein suggest that norepinephrine caused the portal blood pressure to increase and this in turn caused an increase

in the efferent nerve discharge to the intestine. Thus it is possible that the increase in SNA to the intestine contrary to the baroreceptor reflex after norepinephrine administration could be explained by the stimulation of these stretch receptors in the portal vein. Another possibility for the increase in INA after norepinephrine injection is the direct action of this drug on the sympathetic ganglia. This possibility has no experimental support, as yet.

In a subsequent report (manuscript in preparation), we will show that mechanically increased tension of the intestinal wall causes an increase in intestinal nerve activity. However, norepinephrine causes relaxation of the intestinal wall and not increased tension in the wall. The increase of INA after norepinephrine therefore seems not due to the activation of the stretch receptors in the intestinal wall.

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