ON THE ROLE OF VAGI AND SINUS NERVES IN THE REFLEXOGENIC INHIBITION OF SYMPATHETIC DISCHARGES INDUCED BY STROSPESIDE IN CATS

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It was reported that the occurrence of bradycardia by cardiac glycosides was connected with not only vagi (1, 2) but also sinus nerves (2-4). Recently, it was demonstrated that strospeptide inhibited efferent discharges in the pre- and postganglionic stellate fibers (5), and that dichloroisoproterenol prevented the production of bradycardia by strospeptide in vagotomized cats (6). These evidences show that sympathetic nerves as well as sinus nerves play an important role as an extravagal factor of bradycardia produced by strospeptide.

Abiko (2) set forth the opinion that there are at least two possible pathways of reflex in producing bradycardia by cardiac glycosides: One is the vagal nerve which exerts slowing on the heart rate by vago-vagal reflex and the other is the carotid sinus-sympathetic nervous chain which exerts a slowing effect on the heart rate by way of the sinus nerve, cervical cord and the stellate ganglia.

However, a question has arisen as to whether the inhibition of efferent sympathetic activity is induced solely by sinus nerves, independent of afferent fibers of vagi or not. The present study deals with this question.

METHODS

Cats were anesthetized with an intravenous administration of 30 mg/kg of pentobarbital sodium. After both vagi and/or sinus nerves were severed, 0.05 mg/kg of strospeptide was injected intravenously at five minute intervals until death. Vagi were severed at the height of laryngeal cartilage.

Prior to every injection of strospeptide, the heart rate was counted, and electrocardiograms (standard limb lead II) and efferent discharges in the left postganglionic stellate fibers (cardiac branch) were recorded photographically.

For the recording of efferent discharges in the postganglionic stellate fibers, the same method was applied as described in the previous papers (5, 6).

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RESULTS

Cats were divided into three groups (A, B and C) according to the site of severance of nerves. The results obtained are summarized in Table 1 and the details for each group are given as follows:

A. Cats in which both vagi were severed

Twelve cats were examined in this group. Fractional administration of strospeptide was initiated after both vagi were severed.

TABLE 1. Relation of vagi and sinus nerves to bradycardia and sympathetic inhibition due to strospeptide.

Group	Nerves cut	Cases showing effect/Total cases	
		Decrease in the heart rate (Bradycardia)	Inhibition of the sympathetic efferent discharges
A	Vagi	11/12	10/12
B	Vagi and sinus nerves	0/13	2/9
C	Sinus nerves	6/7	7/7

Twenty to thirty per cent LD of strospeptide produced a moderate degree of sinus bradycardia in 11 cases out of 12, and inhibited efferent discharges in the left ganglionic stellate fibers in 10 cases out of 12. These results are in accordance with results reported in the previous paper (5). In Fig. 1, it can be seen that 20% LD of strospeptide produced bradycardia and inhibition of efferent discharges in sympathetic cardiac nervous fibers.

B. Cats in which both vagi and both sinus nerves were severed

Thirteen cats were used in this type of experiment. After cutting both vagi and both sinus nerves, fractional doses of strospeptide were injected until death. In 9 cases out of 13, efferent discharges in the left postganglionic stellate fibers were recorded, and the effect of strospeptide on the sympathetic discharges was observed.

The heart rate was not reduced by

FIG. 1. A production of a bradycardia and an inhibition of sympathetic cardiac discharges by strospeptide in vagotomized cat.

(a) Before administration of strospeptide (heart rate 172/min).

(b) After administration of 20% LD of strospeptide (heart rate 168/min).

Upper: ECG (standard limb lead II), Lower: Efferent discharges in the left postganglionic stellate fibers.

FIG. 2. Neither bradycardia nor sympathetic inhibition was produced by strospeside after vagi and sinus nerves had been severed.

(a) Before administration of strospeside (heart rate 176/min).

(b) After administration of 20% LD of strospeside (heart rate 176/min).

Upper: ECG (standard limb lead II),
Lower: Efferent discharges in the left
postganglionic stellate fibers.

the administration of strospeside in all cases tested, but, on the contrary, it showed a tendency to increase gradually with the increase of doses. Efferent discharges in the sympathetic cardiac nerves were slightly inhibited in 2 cases out of 9. In most cases in this group of cats, strospeside hardly decreased the amplitude of sympathetic cardiac discharges as indicated in Fig. 2. It can be seen that 20% LD of strospeside neither produced bradycardia, nor inhibited efferent sympathetic cardiac nervous discharges.

From the results obtained in the experiments of group A and B, it was concluded that bradycardia produced by strospeside in vagotomized cats was due to the inhibition of efferent sympathetic discharges, and the inhibition of sympathetic activity was exerted by way of the sinus nerves. In other words, strospeside inhibited the sympathetic nervous center by possibly increasing afferent impulses in sinus nerves. The increase in afferent discharges in sinus nerves

may have resulted from the stimulating action of strospeside on baro- and/or chemoreceptors. In fact, the stimulating action of cardiac glycosides on chemoreceptors in the carotid body was reported by Schmitt *et al.* (7, 8). And, this reflexogenic inhibitory action of strospeside on the sympathetic center is considered to be the most important factor, with the exception of vago-vagal reflex, of bradycardia produced by strospeside.

Thus, the question arises as to whether the vagi are concerned with the inhibition of sympathetic nervous discharges produced by strospeside or not. In order to answer this question, the following experiment was performed.

G. Cats in which both sinus nerves were severed

Seven cats were used in this experiment. After cutting both sinus nerves, fractional administration of strospeside was commenced at five minute intervals until death.

Twenty to forty per cent LD of strospeside markedly decreased the heart rate. The bradycardia produced by strospeside was confirmed in 6 cases out of 7, and efferent discharges in the left postganglionic stellate fibers were inhibited markedly in all cases tested.

Fig. 3 shows a case in which 20% LD of strosposide produced a slowing in the heart rate and an inhibition of efferent discharges in the left postganglionic stellate fibers.

From the above results, it was concluded that the inhibition of efferent sympathetic cardiac discharges by strosposide resulted from the reflexogenic inhibition of the sympathetic center which was induced not only by sinus nerves but also by afferent fibers of vagal nerves. And, it was also confirmed that the inhibition of efferent sympathetic cardiac discharges played an important role as an extravagal factor in strosposide-induced bradycardia.

DISCUSSION

Heymans *et al.* (3, 4) demonstrated that the bradycardic effect of ouabain was abolished by cutting cardio-aortic nerves and sinus nerves. The evidence was also confirmed by other investigators (2, 9, 10). In 1958, Schmitt *et al.* (7, 8) showed that cardiac glycosides stimulated chemoreceptors in the carotid body, and that bradycardia by cardiac glycosides was not produced when 0.5 N acetic acid was administered intrasinusally into the carotid sinus. It was reported by Gernandt (11) that 0.5 N acetic acid selectively inhibited afferent chemical impulses originating in the carotid body, without producing any changes in the impulses originating in the baroreceptors. Hence, it may be said that bradycardia produced by cardiac glycosides may be due to the stimulation of chemoreceptors in the carotid body as pointed out by Schmitt *et al.* (7, 8). This is also supported by the fact that the stimulation of chemoreceptors in the carotid body produced a decrease in the heart rate (12).

Regarding the relationship between carotid sinus nerves and efferent sympathetic discharges, Bronk *et al.* (13) reported that electrical stimulation in lower frequencies of central end of carotid sinus nerves produced response discharges in the efferent sympathetic cardiac nervous fibers, but that the sympathetic discharges were inhibited when stimuli in high frequencies were applied. Marguth *et al.* (14) reported the inhibition

FIG. 3. An inhibition of efferent sympathetic cardiac discharges was induced by strosposide after severance of both sinus nerves.

(a) Before administration of strosposide (heart rate 196/min).

(b) After administration of 20% LD of strosposide (heart rate 185/min).

Upper: ECG (standard limb lead II), Lower: Efferent discharges in the left postganglionic stellate fibers.

20% LD of strosposide produced bradycardia with A-V block, and markedly inhibited efferent discharges in the sympathetic cardiac nervous fibers.

of sympathetic discharges by an intravenous administration of adrenaline, and they found that the inhibition of sympathetic activity produced by adrenaline was abolished by cutting sinus nerves, depressor nerves and cervical vagi. The sympathetic discharges were inhibited also by noradrenaline, pitressin, transfusion of blood and temporary occlusion of the abdominal aorta, but the sympathetic inhibition was not seen after severance of sinus nerves, depressor nerves and cervical vagi (15). Thus it is probable that efferent sympathetic discharges change with the changes in blood pressure and/or changes in chemical constituents of the blood, through sinus nerves, depressor nerves and vagi.

In the present experiment, it was confirmed that strospe-side inhibited efferent discharges in the postganglionic stellate fibers through sinus nerves and vagi. However it is not clear whether depressor nerves are also involved in the inhibition of sympathetic discharges by cardiac glycosides or not. In our experiment, depressor nerves were severed when severance of vagi was carried out since it was almost impossible to divide depressor nerves from vagi at the height of laryngeal cartilage.

It is still not clear at the present time, whether the inhibition of efferent sympathetic discharges produced by cardiac glycosides is due to the stimulating action of cardiac glycosides in the chemoreceptors, or due to secondary hypertension induced by the inotropic action of cardiac glycosides.

SUMMARY

The role of vagi and sinus nerves on the inhibitory action of strospe-side upon efferent discharges in sympathetic cardiac fibers, were investigated using cats anesthetized with pentobarbital sodium.

1. In vagotomized cats, 20-30% LD of strospe-side produced a bradycardia and an inhibition of efferent discharges in the left postganglionic stellate fibers.

2. In cats in which both vagi and both sinus nerves were severed, strospe-side neither produced bradycardia, nor inhibited efferent discharges in the left postganglionic stellate fibers.

3. In cats in which only both sinus nerves were severed, 20-40% LD of strospe-side produced a marked bradycardia and an inhibition of efferent discharges in the left postganglionic stellate fibers.

From the foregoing results, it is concluded that sinus nerves and vagi are both afferent routes of reflexes by which an inhibition of efferent sympathetic cardiac discharges by strospe-side is induced and that the inhibition of sympathetic discharges is considered to be an important extravagal factor of bradycardia produced by strospe-side.

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