INHIBITORY EFFECT OF STROSPESIDE ON THE EFFERENT DISCHARGES IN THE SYMPATHEATIC CARDIAC NERVES IN CATS

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It has generally been accepted that the vagal effect participates in bradycardia due to cardiac glycosides (1, 2). However, the vagal effect may not be the only factor which produces the cardiac slowing, because cardiac glycosides can produce bradycardia even after bilateral severance of vagus nerves or under the effect of atropine (3, 4). Gold et al. (5, 6) suggested a direct bradycardiac action of cardiac glycosides on the heart muscle. However, the results on the effect of cardiac glycosides on the heart rate are still controversial in the experiments with isolated hearts. Heymans et al. (7, 8) reported that cardiac glycosides did not produce bradycardia in dogs when vagus nerves and also carotid sinus nerves were completely severed. The present author has also obtained a similar finding in cats using a cardiac glycoside, strospeside (9).

In recent work of the present author (9), a hypothesis has been postulated on the mechanism of bradycardia produced by cardiac glycosides: There are two different kinds of nervous reflex systems, quite independent of each other, in producing bradycardia by cardiac glycosides. One is the vago-vagal reflex and the other is the carotid body-sympathetic nervous reflex chain possibly composed of the sinus nerve, cervical cord, stellate ganglion and the sympathetic fibers to the heart.

The purpose of the present experiment is the presentation of some evidences for the possibility of the sympathetic portion of the hypothetical carotid body-sympathetic nervous chain, which is assumed to be the extravagal factor, by observing the effect of strospeside on the efferent discharges in the cardiac sympathetic nerves in cats.

METHODS

Cats were anesthetized with pentobarbital sodium (30 mg/kg i.v.) and bilateral vagus nerves were cut at the neck. During the experiments, further injections of pentobarbital were given as required, in order to prevent the appearance of jerks in response to sensory stimuli.

The drugs were injected into a cannula introduced into a femoral vein. Strospeside was dissolved in saline and fractional doses (single dose = 0.05 mg/kg) were injected intra-
venously at intervals of 5 minutes until death occurred. The heart rate was counted at one minute before every injection of strospeside.

Efferent discharges in the cardiac sympathetic nerves and electrocardiograms (standard limb lead II) were recorded simultaneously immediately before the injection of strospeside.

Recording method: In most of the experiments, the electrical activity in the efferent cardiac sympathetic fibers was recorded. The left stellate ganglion was exposed by making a resection of the second and third ribs under artificial respiration. In order to minimize artifacts, the upper lobe of the left lung was removed and the thorax was filled with paraffin oil. Electrical activity was recorded by placing the central ends of pre- and postganglionic (cardiac branch) stellate fibers which had been cut distally across a pair of electrodes. The potentials picked up by the electrodes were amplified with a condensor-coupled amplifier (time constant = 0.1 sec (10)) and displayed on a cathod-ray oscilloscope. The amplified action potentials and the electrocardiograms were recorded photographically. Heart rate was counted by means of electrocardiogram which had been fed into an audio-amplifier.

In such cases where respiratory artifacts were so prominent that the efferent discharges were not constantly recorded, 1-3 mg/kg of Flaxedil (gallamine triethiodide) were injected at more than 20 minutes prior to the first injection of strospeside.

RESULTS

The results of the experiments were illustrated in Figs. 1-4. Each of the figures is divided into two parts, namely part (a) and (b), which represent data obtained from the same cat. Part (a) shows the changes in the heart rate, and part (b) shows the changes in the electrocardiogram and the patterns of the efferent discharges in the pre- and postganglionic stellate fibers by the increasing doses of strospeside. The numbers shown in part (a) and (b) indicate points at which records have been taken: The number shown in part (b) corresponds to the same number in part (a) of the same figure.

I. Efferent discharges in the left postganglionic stellate fibers (cardiac branch)

a) Normal discharges

One of the most striking characteristics of the efferent discharges in the postganglionic stellate fibers was the grouping of the impulses at a frequency equal to that of the heart beats as already reported by Adrian (11), Bronk (12) and other investigators (10). Respiratory grouping of the impulses was another remarkable feature, but some of the cats failed to show respiratory grouping.

The amplitude of the impulses was reduced temporarily immediately after 1-3 mg/kg of Flaxedil or 5-10 mg/kg of further injection of pentobarbital, but returned again to the normal level in less than 20 minutes and remained constant for one hour or more. Thus, the injection of strospeside was initiated 20 minutes after administration of Flaxedil or pentobarbital.
b) Effect of strospeside

As shown in Fig. 1, remarkable bradycardia was produced by 20-30% LD of strospeside in vagotomized cats. The efferent discharges in the postganglionic stellate fibers were markedly reduced by strospeside in such doses that produced the sinus bradycardia without any arrhythmic beats. This reduction of the efferent discharges, together with the sinus bradycardia, was observed in 8 cases out of 9 vagotomized cats.

When further injections of strospeside caused typical toxic signs such as A-V block, negative displacement of ST segment, premature beats, ventricular tachycardia and

![Graph showing heart rate and dose of strospeside](image)

**Fig. 1. Vagotomized cat.**

Bradycardia and inhibition of the efferent discharges in the postganglionic stellate fibers were produced by strospeside in doses of about 20-30% LD.

(a) : Changes in the heart rate.

(b) : Changes in the electrocardiogram (upper record) and the efferent discharges in the postganglionic stellate fibers (lower record).

Numbers appearing in (b) indicate the records taken at the points shown with the respective numbers in (a).
other abnormal waves, the reduced efferent discharges in the postganglionic stellate fibers were markedly reactivated, even though the frequency of their grouped impulses was not equal to that of the heart beats as was in normal discharges, and in the presence of ventricular fibrillation, the efferent discharges became continuous and violent without showing the grouped impulses which are synchronous to the heart beats. The efferent discharges became more violent and continuous after the stand-still of the heart.

Fig. 2. Vagotomized cat.

Even after atropine, bradycardia and inhibition of the efferent discharges in the postganglionic stellate fibers were produced by strospeside in doses of about 20-30% LD.

(a) : Changes in the heart rate.
(b) : Changes in the electrocardiogram (upper record) and the efferent discharges in the postganglionic stellate fibers (lower record).

Numbers appearing in (b) indicate the records taken at the points shown with the respective numbers in (a).
was confirmed by electrocardiogram, and the discharges persisted for more than 5 minutes after death.

c) **Effect of atropine on the action of stropeside**

An example of this experiment is shown in Fig. 2. Atropine (0.1 mg/kg) was administered intravenously prior to the injection of stropeside. In vagotomized cats, 0.1 mg/kg of atropine was administered intravenously prior to the injection of stropeside. The efferent discharges in the preganglionic stellate fibers were induced by strospeside in doses of about 20-30% LD.

(a) Changes in the heart rate.

(b) Changes in the electrocardiogram (upper record) and the efferent discharges in the preganglionic stellate fibers (lower record).

Numbers appearing in (b) indicate the records taken at the points shown with the respective numbers in (a).
mg/kg of atropine caused either a slight increase or no change in the heart rate. The efferent discharges in the postganglionic stellate fibers were not influenced by this dose of atropine.

Strospeside injection was commenced 5 minutes after administration of atropine. Similar reduction of the efferent discharges with cardiac slowing was produced by increasing doses of strospeside also in atropinized cats as seen in non-atropinized animals.

Fig. 4. Vagotomized cat.

The efferent impulses were continuously discharged in the preganglionic stellate fibers. No cardiac grouping of impulses was seen.

 Bradycardia and inhibition of the efferent discharges in the preganglionic stellate fibers were produced by strospeside in doses of about 20-30% LD.

(a) : Changes in the heart rate.

(b) : Changes in the electrocardiogram (upper record) and the efferent discharges in the preganglionic stellate fibers (lower record).

Numbers appearing in (b) indicate the records taken at the points shown with the respective numbers in (a).
From the data, it is evident that the inhibitory actions of strospeside on the heart rate and cardiac sympathetic impulses were not modified by 0.1 mg/kg of atropine.

II. Efferent discharges in the left preganglionic stellate fibers

A question arose in the possible explanation of the reduction of the efferent discharges in the postganglionic stellate fibers, because two possibilities were presented concerning the effect of strospeside upon the postganglionic impulses: An inhibition of the sympathetic center and a blocking (13) of the stellate ganglia.

To answer this question, the following experiments were conducted to study the effect of strospeside on discharges in the preganglionic stellate fibers.

a) Normal discharges

Two types of waves were noticed in the pattern of discharges of preganglionic stellate fibers: One was a type of high-amplitude discharges which showed grouped impulses at a frequency equal to that of the heart rate, and the other was a type of low-amplitude impulses discharged continuously without making any groupings. The amplitude of the efferent discharges was much smaller in the preganglionic stellate fibers than in the postganglionic stellate fibers.

b) Effect of strospeside

Three cases out of four showed similar reduction of the efferent discharges in the preganglionic stellate fibers as in postganglionic fibers when 20-30% LD of strospeside were injected, and this inhibition of preganglionic impulses occurred also synchronously with cardiac slowing by strospeside. In one case, however, the preganglionic discharge was not so markedly reduced by strospeside as seen in the three cases.

The results obtained in the experiment with the cat which presented grouped impulses of high-amplitude in preganglionic fibers were shown in Fig. 3. This shows that strospeside inhibits sympathetic preganglionic discharges in the doses capable of producing cardiac slowing. Similar results were also observed in the cat presenting low-amplitude impulses which were continuously discharged in preganglionic fibers as seen in Fig. 4.

DISCUSSION

The author (9) has already reported that strospeside produced a marked cardiac slowing in the cat unless its vagi and stellate ganglia were completely severed on both sides. Data obtained from the present experiment showed further information on the role of the sympathetic nerves played in the mechanism of bradycardia. If cardiac sympathetic nerves on one side were intact, strospeside produced bradycardia in vagotomized cats, even though the pre- and postganglionic stellate fibers of the other side had been cut. This suggests that the cardiac sympathetic nerves of either side are capable of producing bradycardia. Thus, it is evident that a sympathetic factor participates in producing bradycardia.

Two possibilities were suggested for the explanation of the sympathetic mechanism of bradycardia: 1) Strospeside may increase the efferent activity of the cholinergic
fibers which are possibly contained in the cardiac sympathetic nerves as pointed out by Burn and Rand (14). 2) Strospeside may reduce the efferent activity of the adrenergic fibers which are contained in the cardiac sympathetic nerves.

As a matter of fact, atropine did not prevent bradycardia in the vagotomized animals and the efferent discharges in the postganglionic stellate fibers were markedly reduced synchronously with cardiac slowing by strospeside. It appears, therefore, that the first possibility is ruled out, and the fact that the efferent discharges in the preganglionic stellate fibers were also reduced synchronously with bradycardia makes the second possibility acceptable. In other words, the bradycardia by strospeside is partly due to the inhibition of the efferent activity in the adrenergic fibers.

The next point which arises is to determine the site of the inhibitory effect of strospeside on the efferent discharges in the cardiac sympathetic nerves. As shown in Figs. 3 and 4, the efferent activity of the preganglionic stellate fibers was also inhibited by strospeside in doses capable of producing bradycardia without causing arrhythmia. This fact suggests that the site of the inhibitory action of strospeside on the sympathetic discharges seems to be more central than the stellate ganglia, although the direct blocking action of strospeside on the stellate ganglia was not completely neglected. Konzett et al. (13) pointed out that large doses of cardiac glycosides block the sympathetic ganglia while small doses of cardiac glycosides potentiate the effect of preganglionic stimulation on the effector organ. The doses of cardiac glycosides necessary for the ganglionic blocking are much larger than doses which produce cardiac slowing. Accordingly, it is difficult to believe that the stellate ganglia are blocked by such small doses of strospeside as used in these experiments.

As already reported (7-9), carotid sinus nerves were closely connected with the production of bradycardia by cardiac glycosides in vagotomized cats. Thus, it seems reasonable to conclude that strospeside reflectly inhibits the efferent discharges of pre- and postganglionic sympathetic fibers and the inhibition of the discharges participates in producing bradycardia. The evidence presented here also suggests that carotid sinus nerves and sympathetic nerves form a reflexogenic pathway which is considered to be one of the extravagal factors of bradycardia produced by strospeside.

SUMMARY

The effect of strospeside on the heart rate and the efferent discharges in the pre- and postganglionic stellate fibers were studied using anesthetized cats.

1. Bradycardia and inhibition of the efferent discharges in the pre- and postganglionic stellate fibers were noticed synchronously when 20-30% LD of strospeside were administered.

2. Atropine (0.1 mg/kg) did not prevent the inhibitory actions of strospeside on the heart rate and on the efferent discharges in the postganglionic stellate fibers.

3. The mechanism of bradycardia due to strospeside was discussed with special reference to the sympathetic factor.
4. It was concluded that the results strongly supported a possibility of the hypothetical carotid body-sympathetic nerve pathway, which has previously been postulated by the author (9) as one of the extravagal factors participating in the production of bradycardia by cardiac glycosides, and that the sympathetic mechanism of the bradycardia produced by strospeside was inhibitory in nature.

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