ON THE MECHANISM OF BRADYCARDIA PRODUCED BY STROSPESIDE IN CATS

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Received for publication January 12, 1963

In spite of numerous reports on bradycardia produced by cardiac glycosides hitherto, the mechanism is not completely clarified.

Ackermann (1) reported that early digitalis bradycardia was prevented by vagal severance or by administration of atropine. This observation has generally been accepted. Heymans and Heymans (2) obtained additional evidence using cross-circulation dogs. They reported that ouabain-induced bradycardia was not due to the central action of ouabain but had its origin in the vagal reflex. Furthermore, Hering (3) and Heymans et al. (4, 5) showed that ouabain-induced bradycardia was nullified by severing both sinus nerves and both cardio-aortic nerves in dogs. Morimoto et al. (6) also demonstrated that digitalis bradycardia was prevented by destruction of the carotid sinus tissues and resection of cardio-aortic nerves in dogs. Fukuda and his associates (7, 8) maintained that the bradycardia produced by large doses of digitalis was mainly due to the cardio-cardiac reflex. This assertion is supported by the fact that the action potentials of cardiac nerves (centripetal vagal nerves) increased by cardiac glycoside administration in cats (9). However, Schmitt et al. (10, 11) found that the action potentials originating in the chemoreceptors in the carotid body were increased by cardiac glycosides and they concluded that the chemoreceptors were closely related to the occurrence of digitalis bradycardia in cats.

Thus, opinions have differed on the origin and pathways of impulses of reflexogenic bradycardia produced by cardiac glycosides.

The present study was conducted to elucidate the probable pathways of the reflex by which cardiac glycosides produce bradycardia.

METHODS

Forty-three healthy cats weighing from 1.1 to 4.5 kg were used in this study regardless of sex. The cats were anesthetized by an intravenous injection of 30 mg/kg of pentobarbital sodium. After severing the vagus nerves, carotid sinus nerves or cervical cord, or extirpating the stellate ganglia, one-tenth of the probable lethal dose of strospeside was administered intravenously every five minutes until cardiac arrest was confirmed.
with electrocardiogram. The electrocardiogram was recorded from standard limb lead II one minute before every injection of strospeside. The vagus nerves were cut at the height of laryngeal cartilage, and the cervical cord was transected at C3-4. The extirpation of stellate ganglia was performed after the second ribs on both sides were resected. Artificial respiration was conducted throughout the experiment.

RESULTS

Figs. 1 and 2 illustrate the relationship between injected amounts of strospeside (expressed in % LD) and the grade of decrease in heart rate produced by strospeside (expressed in % of the heart rate before strospeside) under various conditions. Schematic illustrations shown in the center of Figs. 1 and 2 represent the localization of severance.

a) Control group (7 cats)

Seven cats were used as control and the mean data are shown in Fig. 1 “Control”. In this group, cardiac slowing started to appear when 10% LD of strospeside was injected. In doses of more than 30% LD of strospeside, the heart rate was decreased by more than 15% as compared with the heart rate before the injection of strospeside. It is evident that strospeside produces a remarkable bradycardia constantly in normal cats.

b) The group in which both vagus nerves were severed (6 cats)

The mean values of the data obtained in this group are shown in Fig. 1 (1) and Fig. 2 (1). The heart rate decreased gradually as the dose of strospeside increased. However, the grade of bradycardia was not as marked as compared with the control group in doses less than 40% LD. As doses exceeded 50% LD, the heart rate decreased markedly.

c) The group in which carotid sinus nerves were severed (6 cats)

As seen in Fig. 1 (2), the heart rate decreased as doses increased. The grade of bradycardia was almost the same as seen in the control group.

d) The group in which both vagus nerves and both sinus nerves were severed (5 cats)

It can be seen in Fig. 1 (1)+(2), that the heart rate of cats was not decreased by strospeside after both vagus nerves and both sinus nerves were severed. In contrast to the above, a tendency of acceleration in heart rate was observed in this group.

e) The group in which both vagus nerves were severed and cervical cord was transected (5 cats)

The mean values of the data obtained in this group are shown in Fig. 2 (1)+(2). This shows that the bradycardia was definitely not produced by strospeside after both vagi and cervical cord were severed.

f) The group in which only cervical cord was transected (5 cats)

In cats in which both vagi were left intact, and only the cervical cord was transected, strospeside produced a marked bradycardia as seen in Fig. 2 (2).

g) The group in which both vagus nerves were severed and both stellate ganglia were extirpated (5 cats)

The mean values of the data are presented in Fig. 2 (1)+(3). The heart rate was
Fig. 1. Cats, pentobarbital anesthesia.

Control: Both vagus nerves, both sinus nerves, both stellate ganglia and cervical cord are intact.

(1) Both vagus nerves severed.
(2) Both sinus nerves severed.
(1)+(2) Both vagus nerves and both sinus nerves severed.

Ordinates: Changes in heart rate (%).
Abscissae: Injected amounts of strospeside (% LD).
I Standard error.

Strospeside produced slowing in heart rate in control cats, in both-vagus-nerves-severed-cats and in both-sinus-nerves-severed-cats. However, the bradycardia was prevented by cutting both vagus nerves and both sinus nerves at the same time.
not decreased by strospeside but a tendency of acceleration in the heart rate was seen in this group.

h) The group in which both stellate ganglia alone were extirpated (4 cats)

In this group, a marked bradycardia was produced by strospeside as shown in Fig. 2 (3).
FIG. 3. Schematic illustration showing probable pathways in producing strospeside-bradycardia in cats.

- : Vagus nerve,
----- : Carotid body-sympathetic nerve chain.

Vagus nerves and carotid body-sympathetic nerve chain are two different kinds of pathways in producing reflexogenic bradycardia by strospeside. These pathways are quite independent of each other, so it is possible to produce bradycardia even when only one pathways is intact.

**DISCUSSION**

The results stated above can be summarized as follows:

1) Bradycardia was produced by strospeside when either both vagus nerves or both carotid sinus nerves and sympathetic pathways were intact.

2) However, bradycardia was not produced by strospeside in cats in which both vagus nerves and both carotid sinus nerves were simultaneously severed even when the sympathetic nerves were intact.
3) Neither extirpation of stellate ganglia nor transection of the cervical cord inhibited the occurrence of strospeside bradycardia.

4) However, strospesides did not slow the heart rate of the cats in which both vagus nerves and both stellate ganglia were simultaneously severed. A combination of cervical cord transection with the severance of both vagus nerves also inhibited the occurrence of cardiac slowing.

It would seem that these observations suggest the following pathways of the reflexogenic bradycardia produced by strospeside in cats: One is in the vagus nerves which contain both afferent and efferent fibers and the other is connected with the sympathetic nervous system. Further these two are quite independent of each other in producing cardiac slowing. Impulses sent to the central nervous system by way of the sinus nerves are suggested to exert an inhibitory effect on the sympathetic center. This inhibitory effect is relayed to the heart probably through the cervical cord and the stellate ganglia (Fig. 3).

That digitalis produces bradycardia by the vago-vagal reflex has been shown by Fukuda et al. (8), Kurotsubo (7) and Kharkevich et al. (12). This was also confirmed by the experiments mentioned above. On the other hand, Heymans et al. (4, 5) and Morimoto (6) indicated in their experiments with vagotomized animals that the digitalis bradycardia was related to the carotid sinus nerves. Schmitt et al. (10, 11) reported that cardiac glycoside stimulated chemoreceptors in the carotid body. Fig. 2 indicates that sinus nerves take part in producing strospeside bradycardia in vagotomized cats, provided that the cervical cord and the stellate ganglia are intact. Thus, we are of the opinion that the impulses originated in the chemoreceptors in the carotid body, pass through the cervical cord and the stellate ganglia to the heart to exert an inhibitory effect on the heart rate. As reported by McLain et al. (13), the bradycardia produced by cardiac glycoside is not completely blocked by atropine. This suggests that the postsynaptic fibers from stellate ganglia participating in the bradycardia are not cholinergic in function but adrenergic. Méndez et al. (14, 15) pointed out recently that cardiac glycosides have adrenergic blocking action. However, this is not contradictory to the author's hypothesis.

**SUMMARY**

The present study was conducted to investigate probable pathways related to the reflexogenic bradycardia produced by strospeside in cats anesthetized with pentobarbital. From the results obtained, it was concluded that there are two possible pathways of reflex which are quite independent of each other in producing strospeside-bradycardia: One is the vagus nerve which exerts slowing in the heart rate by vago-vagal reflex and the other is the carotid body-sympathetic nerve chain which exerts a slowing effect in the heart rate by way of the sinus nerves, cervical cord and the stellate ganglia.
Acknowledgement: I wish to express my deep gratitude to Professor Tsuneyoshi Tanabe for his valuable advice, criticism and encouragement throughout this study and for his help in preparing the manuscript.

I am indebted to Shionogi & Co., Ltd. for the donation of strospeside used in this study.

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