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Effects of Ouabain on Sympathetic Never Activity in Awaked Rabbits : A Preliminary Report

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Digitalis glycosides has a direct action on myocardium to increase contractile force and an indirect action through the autonomic nervous system to reduce heart rate. Because of these actions, the digitalis is still major mainstays in the treatment of congestive heart failure or arrhythmias.

As we reported before on the effects of digitalis on sympathetic nerve activity in anesthetized rabbits, its effects on the autonomic nervous system resulted in the decrease in sympathetic nerve activity. Furthermore, this phenomenon was developed by hyperactivated baroreflex. There are two opposite reports which indicate that digitalis increases or decreases sympathetic nerve activity in anesthetized animals. As reported before, in baroceptor intact rabbits, sympathetic nerve activity was suppressed by ouabain. Furthermore, in human subjects, it was proved by the measurement of catecholamine that digoxoin decreased sympathetic nerve activity. However, it is not clear yet what effects this drug exerts on autonomic nervous system in awaked rabbits. Rabbits that were implanted an electrode were subjected. Arterial blood pressure and EKG were recorded simultaneously. At least 24 hours were taken after the last anesthesia. Ouabain (30 μg/Kg of body weight) was administered intravenously.

Immediately after the administration of ouabain, renal sympathetic nerve activity (RNA) started to reduce. Heart rate (HR) was decreased as well. However, arterial blood pressure (AP) did not show any significant change.

Thus, it is concluded that digitalis exerts its suppressive effects on the sympathetic nerve activity. This mechanism must be important to produce hemodynamic changes in digitalis therapy.

Key Words

Ouabain,
Awaked Rabbits,
Renal sympathetic nerve activity,
Suppressive action.

INTRODUCTION

Digitalis glycoside is one of the major treatments of congestive heart failure or cardiac arrhythmias. Its main actions are inotropic and chronotropic effects on the heart. These offects are produced by both direct actions on the heart and indirect actions mediated by the autonomic nervous system (1–4). Despite the extensive investigation of the mechanism of adverse effects (5) such as arrhythmias, there are still many questions concerning the effects of digitalis glycoside in therapeutic dose on the autonomic nervous system.

As we reported before (2) on the effect digitalis on sympathetic nerve activity in anesthetized rabbits, its effects on the autonomic nervous system resulted in decrease in sympathetic nerve activity. Furthermore, this phenomenon was developed by hyperactivated baroreflex. In human subjects (6) it was proved by a measurement of catecholamine that digox-

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in decreased sympathetic nervecativity. However, it is not clear yet what effects this drug exerts on sympathetic nerve activity in awaked rabbits.

It is reported that, in the therapeutic actions of digitalis, the slowing in supraventricular automaticity which resulted in bradycardia are all due to a digitalis-induced increase in parasympathetic nerve activity and dęcrease in sympathetic nerve activity (7,8). As we and others (2,3) reported, this phenomenon is induced by hypersensitized baroreflex with digitalis. However there is opposite report which indicate increase in sympathetic nerve activity in anesthetized cats(9). This question must be answered by recording the activity in awaked animals.

In awaked animals, as for the sympathetic nerve activity, it is possible to quantity the level of activity by measuring serum catecholamine level. Although it is better to record nerve activity directly, there is a technical difficulty in recording electrical sympathetic nerve activity. However, in recent years, a method (10) to record sympathetic nerve activity has been developed for several days. In this report, we attempted to evaluate the effects of digitalis (ouabain) on renal sympathetic nerve activity (RNA). This must contribute to clarify the mechanism of the action of digitaliv at therapeutic dose.

MATERIALS AND METHOD

1. Surgical Procedures

Three adult rabbits of unselected as to sex and ranging from 2.5 to 3.0 kg in weight were used. They were anesthetized with nembutal (30mg/kg) administered intravenously.

The left external jugular vein was cannulated for intravenous administration of drugs. Blood pressure was recorded through a cannula inserted into the left external carotid artery. EKG was recorded as well.

Efferent sympathetic nerve activity was recorded from a bundle of the left renal nerve. The nerve was exposed under a binocular microscope and implanted in a collagen electrode. The nerve activity was recorded using a high gain amplifier. These were recorded on chart paper simultaneuosly with arterial blood pressure and heart rate.

2. Protocol for Intervention

Twenty-four hours after the anesthesia, rabbits became awaked. To observe the effect of dgitalis at the therapeutic dose, ouabain was given intravenously in a dose of 30 $\mu g/Kg$ and the effects were observed.

3. Materials

The drugs used in this experiment were as in the following.: Ouabain (Takeda Prarm. Co.), Nembutal (Dainihon Seiyaku Co), Urethane (Wako Chem. Co.).

RESULTS

(1) EFFECTS ON SYMPATHETIC NERVE ACTIVITY IN AWAKED RABBITS

Figure 1 and 2 show effects of intravenous administration of ouabain on the changes in EKG, arterial blood pressure (NP) and renal sympathetic nerve activity (RNA). Fig 1. represents the change before administration.

The result which was seen in Fig 2. was obtained 10 minutes after the administration of ouabain. Heart rate was decreased from 315 to 250 beats/minutes. RNA was decreased by 35% from the control level without changes of AP.

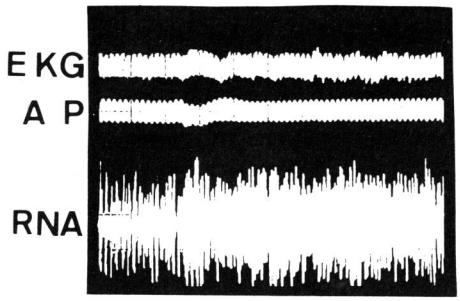


Figure 1. EKG, AP and RNA before adminstration of ouabain in awaked rabbit.
Following abbreviations are used. EKG: electrocardiogram AP: arterial pressure RNA: renal nerve activity

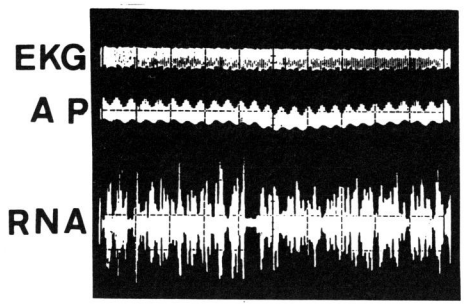


Figure 2. EKG, AP and RNA after administration of ouabain (30 μg/kg) in awaked rabbit.
The result was obtained 10 minites after the administration of ouabain from the same rabbits as presented in Fig 1. Heart rate was decreased from 315 to 250 beats/minutes. RNA was decreased without changes of AP. The decreased ratio of RNA was 35%.

DISCUSSION

As we and others have reported (1–4), sympathetic nerve activity was reduced by administration of digitalis glycoside. Digitalis has an action of slowing heart rate. The chronotropic effects are important in its pharmacological effects for the treatment of some types of arrhythmia. The cardiac chronotropism of digitalis glycoside resulted in longer ventricular filling period and reduction in arrhythmias.

At least in a part of chronotropic action, the autonomic nervous system must play an important role. Accetuated sympathetic nerve activity increases heart rate and contractility by stimulating the heart. Vagal nerve activity decreased heart rate by direct inhibition on the myocardial conduction system. There is two types of opinion about the role of sympathetic nerve activity in the effects of digitalis. One (6) is that sympathetic nerve activity is reduced to exert the chronotropic action. The other (8,9) is that sympathetic nerve activity is increased to accentuate the contractile force and not to play important role in chronotropism. Because all these works were done on anesthetized condition, very little is known the changes in sympathetic nerve activity in the awaked animal. It is mainly due to the difficulty of recording sympathetic nerve activity in awake animals.

(1) BRADYCARDIA AND SYMPATHETIC NERVE ACTIVITY

From our results which showed decrease in RNA and HR without change in AP, it was suggested that at least in a part ouabain produced an increase in vagal nerve activity without significant change in sympathetic neerve activity. This indicates the major contribution of vagal aerve activity in bradycardia.

Digitalis primarily has stimulating effects on the sinus node and enhances the automaticity (11–13). However, bradycardia is one of the important effects of the drug and must be produced by the

autonomic nervous system.

In anesthetized experiment, it has been reported that activation of the parasympathetic nervous system and inhibition of the sympathetic nervous system were responsible for the effects on the heart rate. Ten Eick Hoffman(13) reported the primary mechanism of bradycardia produced by ouabain was inhibition of the sympathetic nervous system in anesthetized cats.

It was also reported that each digitalis derivatives had different effects on heart rate. As Pace(14) reported, digoxin did not induce slowing of sinus rate after spinal cord transection even though the vagus nerves were intact, while sinus rate slowing was observed after spinaj cord transection in case of digitoxin. This was supported by other investigators's reports in the use of pharmacological techniques (6).

Consistent with the observation on experimental animals are findings in patients with transplanted heart given digoxin. From the results, no significant slowing in sinus rate was noted. (15,16). Thus, it was suggested that the bradycardia was mediated by the autonomic nervous system in awaked condition.

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