THE MECHANISM OF BRADYCARDIA CAUSED
BY CARDIAC GLUCOSIDES

E. A. Veselova and V. P. Demikhov

From the Department of Pharmacology (Head - Active Member AMN SSSR V. V. Zakusov) and the Laboratory of Transplantation of Organs of the Department of Operative Surgery (Head - V. P. Demikhov) of the I. M. Sechenov First Moscow Order of Lenin Medical Institute

(Received July 7, 1958. Presented by Active Member AMN SSSR V. V. Zakusov)

Bradycardia is one of the characteristic signs of the action of the cardiac glucosides. The mechanism of its production, despite the abundant work on the subject, remains, however, unexplained and debatable. This is revealed by the contradictory results described in the literature. Several authors explain the bradycardia by the influence of the cardiac glucosides on the vagus nerve centers [8, 9, 18]. Others point out the sensitization of the myocardium to the influence of the vagus and to the action of acetylcholine [4, 16] or the sensitization of the intramural ganglia to acetylcholine [15]. The majority of research workers regard bradycardia as a cardiovascular reflex [5, 6, 13 and others], although these authors present no direct proof of the reflex mechanism of this action.

With the possibility of using a new method of transplantation of the heart, suggested by V. P. Demikhov, we carried out the present research for the purpose of studying the mechanism of bradycardia caused by the cardiac glucosides.

EXPERIMENTAL METHOD AND RESULTS

Experiments were conducted on 12 dogs in which the heart was transplanted by V. P. Demikhov's method. As a result of the transplantation, the animal, after operation, had two hearts: one - its own (with its innervation intact), the other - the grafted heart, "denervated" in the sense of exclusion of central influences. In dogs such as these we studied the action of strophanthin-g and of a standard extract of digitalis in therapeutic and toxic doses. The activity of the heart was recorded by means of a Hurtle's manometer from the brachial arteries of the animal, and in some experiments electrocardiographically. The experiments were performed on dogs under morphine-sodium amytal anesthesia on the day of operation, and on controls on the second day. The results of the investigation enabled the direct influence of the cardiac glucosides on the intramural ganglia of the heart, the M-cholinoceptors and the myocardium to be elucidated.

It was shown by the experiments on dogs with two hearts that the dog's own heart and the denervated heart reacted differently to injection of the cardiac glucosides. Strophanthin-g, for instance, when injected intravenously in a dose of 50 μg/kg, caused bradycardia of the dog's own heart. In the course of time the bradycardia increased, and the rate then gradually returned to the original value. Under these circumstances the rate of the denervated heart was quite unchanged.

* A detailed survey of the literature was given in the article by V. V. Zakusov in the journal "Farmakologiya i Toksikologiya", No. 1 (1957).

** Receptors of the parasympathetic system.
Fig. 1. The effect of a standard extract of digitalis in a dose of 0.5 cat unit/kg on the rhythm of cardiac contractions. Significance of the curves (from above down): record of the contractions of the dog's own heart; of the denervated heart; injection marker; time marker (2 seconds).

A similar picture was observed in response to injection of a standard extract of digitalis in a dose of 0.3-0.5 cat units/kg (Fig. 1).

It may be seen from the kymogram (see Fig. 1) that, under the influence of this preparation, a marked bradycardia of the dog's own heart developed sharply, in individual experiments falling to 40% of the original rate, whereas the rhythm of the denervated heart remained unchanged. It must be mentioned that the rate of the denervated heart subsequently became slightly quickened and extrasystoles appeared, evidently on account of the muscular action. The amplitude of both the dog's own heart and the denervated heart rose considerably during the action of the cardiac glucosides.

In toxic and lethal doses, strophanthin-g caused in the dog's own heart the typical picture of the action of the cardiac glucosides (Fig. 2).

For instance, after injection of strophanthin in a dose of 0.15 mg/kg, in the first period of action of the drug a considerable bradycardia of the dog's own heart developed, to be replaced later by an increase in the rate and then by cardiac arrest. The rhythm of the denervated heart was, as a rule, unchanged in response to the injection of lethal doses of the glucoside during the first hour, and a well-marked slowing of the rhythm then appeared. In some experiments the bradycardia was temporary in character and rapidly changed into tachycardia and arrhythmia.

In order to ascertain the character of the bradycardia developing in response to lethal doses of cardiac glucosides, the dog was given an intravenous injection of atropine sulfate in a dose of 0.5 mg/kg, and of hexamethonium in a dose of 5 mg/kg. In these cases atropine caused a quickening of the rate of the dog's own heart and had no effect on that of the denervated heart. Hexamethonium, like atropine, did not abolish the bradycardia of the denervated heart. The standard extract of digitalis in a dose of 1 cat unit/kg caused similar changes in the rhythm.

Histological examinations of the heart of dogs dying from lethal doses of strophanthin-g, carried out by M. F. Bystrova, showed that after injection of this drug, well-marked vascular changes were observed in the