CHANGES IN SENSITIVITY OF THE MYOCARDIUM TO SUBSTANCES INDUCING ARRHYTHMIA AFTER RESERPINE ADMINISTRATION AND ADRENERGIC RECEPTOR BLOCK

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UDC 615.22.015.45:612.172

Experiments on the explanted myocardium of the chick embryo showed that preliminary injection of various doses of reserpine into the yolk sac considerably retards or completely prevents the appearance of strophanthin and aconitine arrhythmias. Aconitine arrhythmia was more sensitive to catecholamine deficiency than strophanthin arrhythmia. Blocking the β-adrenergic receptors with propranolol retarded the onset or prevented the appearance of aconitine but not of strophanthin arrhythmia. Blocking the α-adrenergic receptors with ergotamine had no effect on the development of the arrhythmias.

Catecholamines are considered to play the leading role in the production of myocardial infarcts and ventricular fibrillation [13, 14]. There is evidence to show that reserpine and blocking β-adrenergic receptors can prevent the development of various types of arrhythmias, including those induced by poisoning with cardiac glycosides [5, 7]. It has also been shown that the content of catecholamines in the myocardium influences both the cardiotonic and the cardiotoxic effects of strophanthin [12. 16]. However, the opposite view is held, namely that the production of arrhythmia is independent of catecholamines [10], and exhaustion of the catecholamine reserves by reserpine leads to an increase in the sensitivity of the heart to cardiac glycosides [18]. In view of these contradictions it was decided to investigate changes in the sensitivity of the embryonic myocardium to substances inducing arrhythmia after treatment of the embryos with reserpine and after selective blocking of the α- and β-adrenergic receptors.

EXPERIMENTAL METHOD

Chick embryos incubated for 5-7 days were used. Wollenberger and Halle injected reserpine into chambers containing the contracting cells. In the present investigation, by contrast, reserpine (Rausedil, Ciba) was injected in a dose of 0.01-0.5 mg/g weight of embryo into the yolk sac [3] 1-5 h before the main experiment. The effect of reserpine on the catecholamine concentration in the embryonic myocardium has been described previously [8].

To produce a selective block of the β-adrenergic receptors, propranolol (Inderal) was used, while β-adrenergic receptors were blocked by ergotamine. Spontaneous contractions of the myocardial explants of the chick embryo were recorded by means of their photoelectric effect on an apparatus designed and built by workers at the Institute of Cardiology and Cardiac Surgery [1]. Arrhythmias were produced by strophanthin K and aconitine.

Laboratory of Pharmacology, Institute of Cardiology and Cardiac Surgery, Ministry of Health of the Armenian SSR, Erevan. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 74, No. 12, pp. 54-56, December, 1972. Original article submitted May 26, 1972.

TABLE 1. Times (in min) of Development of Arrhythmia in Response to Strophanthin and Aconitine Injected before and after Exhaustion of Catecholamine Reserves by Reserpine (exposure 5 h)

Dose of reserpine (in mg/g)	Drug producing arrhythmia	Concentration (in g/ml)	Time of onset of arrhythmia (in min)	P
—	Strophanthin	$1 \cdot 10^{-5}$	4±1	0,001
—	Aconitine	$1 \cdot 10^{-13}$	7±1	0,001
0,05	Strophanthin	$1 \cdot 10^{-5}$	15±4	0,05
0,1	Strophanthin	$1 \cdot 10^{-5}$	No arrhythmia produced	0,001
0,05	Aconitine	$1 \cdot 10^{-13}$	» »	0,005
0,05	Aconitine	$1 \cdot 10^{-11}$	28±2	0,001

EXPERIMENTAL RESULTS

Injection of reserpine in a dose of 0.5-0.25 mg/g 1 and 5 h before the experiment caused death of the embryo. The heart appeared whitish in color, and petechial hemorrhages were observed all over the embryo's body. In a dose of 0.01 mg/g reserpine did not affect the reaction of the explants to the drugs producing arrhythmia. After injection of reserpine in a dose of 0.05-0.1 mg/g 1 h before the beginning of the experiment, the onset of arrhythmia in response to standard arrhythmia-inducing concentrations of strophanthin and aconitine was slightly delayed (by 3 ± 1 min). Injection of reserpine in a dose of 0.05-0.1 mg/g with an exposure of 5 h led to marked changes in the times of onset of arrhythmia in response to the subsequent injection of both strophanthin and aconitine (Table 1).

Preliminary blocking of the β-adrenergic receptors by propranolol in concentrations of between $1 \cdot 10^{-9}$ and $1 \cdot 10^{-4}$ g/ml (subtoxic) did not affect the times of the possibility of appearance of strophanthin arrhythmia, whereas the appearance of aconitine arrhythmia was delayed or prevented by injection of propranolol in concentrations of $1 \cdot 10^{-8}$ and $1 \cdot 10^{-7}$ g/ml respectively.

Blocking the α-adrenergic receptors with ergotamine in concentrations of $1 \cdot 10^{-9}$-$1 \cdot 10^{-4}$ g/ml neither prevented nor abolished the arrhythmia induced by strophanthin or by aconitine. In some cases the toxic action of these substances was evidently actually increased, for after administration of these drugs the spontaneous activity of the heart stopped at once regardless of whether arrhythmia developed or not. The aconitine model of arrhythmia thus proved to be more sensitive to the presence of catecholamine reserves than strophanthin arrhythmia.

Although propranolol and pronethalol are known to have an antiarrhythmic effect [9, 15], its dependence on the specific action of the drug in blocking β-adrenergic receptors is not yet generally recognized. The results of these experiments show that the antiarrhythmic effect of propranolol is unconnected with its local cardiac β-adrenergic blocking action. During recent years most workers have inclined to the view that the antiarrhythmic effect of β-adrenergic blocking drugs is due to their interference with the mechanism of utilization of the energy liberated during metabolism and available for different purposes [2, 6, 11, 17].

It can be concluded from the facts described above that the development of aconitine arrhythmia is intimately connected with the adrenergic regulation of the heart, for the irreversible arrhythmia induced by this substance is readily abolished by administration both of reserpine and of β-adrenergic blocking agents. The experiment confirmed the important role of the catecholamine reserves in the mechanism of development of the various arrhythmias.

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