ANTIARRHYTHMIC PROPERTIES OF SOME INDOLALKYLAMINES

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Serotonin, if injected intravenously in a dose of 5 mg/kg, has an antiarrhythmic action in rats with aconitine arrhythmia, in cats with arrhythmia produced by electrical stimulation of the atrium and ventricle, and in dogs with arrhythmia produced by ligation of the left coronary artery.

The antiarrhythmic effects of serotonin in cats are accompanied by an increase in potassium-ion concentration and a decrease in sodium-ion concentration in the heart tissue. Besides serotonin, 5-methoxytryptamine (2.7 mg/kg, intravenously) also has a distinct antiarrhythmic action. After intravenous injection of tryptamine (2.42 mg/kg), α-methyltryptamine (2.5 mg/kg), and dimethyltryptamine (5.15 mg/kg), no definite antiarrhythmic effect was observed.

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The antiarrhythmic properties of the indolalkylamines has not been adequately studied. We investigated the effect of some preparations of this group in various forms of experimental arrhythmia. Tests were carried out with serotonin, 5-methoxytryptamine (mexamine), tryptamine, α-methyltryptamine (indopan), and dimethyltryptamine*.

EXPERIMENTAL METHOD

The experimental models used were arrhythmia produced in rats by aconitine (40 μg/kg, intravenously), arrhythmia produced in cats by electrical stimulation of the heart (unipolar stimulation of the auricle of the right atrium or the left ventricle, frequency 10/sec, pulse duration 1-2 msec, voltage from 1.5-3 to 4-5 V, duration of stimulation 10-15 sec), and arrhythmia produced in dogs by ligation of the left coronary artery [4].

In the experiments on cats and dogs, changes in rhythm were analyzed from kymographic recordings of the arterial pressure, and in experiments on rats from the ECG.

The effect of serotonin on the concentration of sodium and potassium ions in the myocardium of the cats was also studied. The heart was removed 1 or 10 min after injection of serotonin and all blood carefully washed from it. A piece of heart muscle weighing 500 mg was taken and dropped into concentrated nitric acid (15 ml/100 mg). The residue was diluted to 75 ml with distilled water. The ion concentrations were determined by flame photometry [3].

Serotonin and indolalkylamines were injected intravenously in equimolar doses corresponding to 5 mg/kg serotonin creatinine-sulfate.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that serotonin possesses marked antiarrhythmic properties. In experiments on rats, for instance, 10-20 min after injection of the preparation the arrhythmias produced by aconitine disappeared completely.

In experiments on cats, the antiarrhythmic action of serotonin was more marked in the atrial type of arrhythmia. The drug abolished the disturbances of atrial rhythm whatever the voltage of the current used for stimulation. Ventricular arrhythmia was blocked only if the voltage of the stimulating current was

* The principal results of this investigation were described at the Khabarovsk Conference on Pharmacology of Natural Medicaments, 1967.

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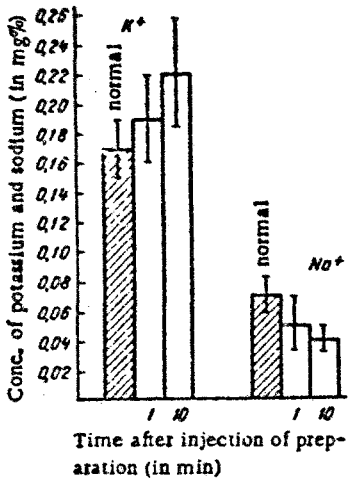

Fig. 1. Effect of serotonin on potassium and sodium concentrations in heart muscle.

1.5-3 V, and if the voltage were increased to 4.5 V, no effect was observed. The action of serotonin in this series of experiments began to appear 10-40 min after its injection.

In 5 of 6 cases administration of serotonin at the maximum of the arrhythmia produced by disturbance of the coronary circulation (0.5-7.5 h after ligation of the coronary artery) completely blocked the arrhythmia. Similar results were previously obtained by Arora [6]. It is interesting to note that in this series of experiments serotonin exhibited its action immediately after administration, while in experiments on rats and cats its action was noted only after a definite latent period. We do not know the reason for this.

An important role in the genesis of cardiac arrhythmias is played by the ratio between the concentrations of potassium and sodium ions in the heart muscle. It has been claimed that the outflow of potassium ions from the cell is increased in ectopic foci of excitation because of increased permeability of the muscle fiber [2, 7]. Antiarrhythmic drugs cause the opposite changes. By inhibiting the entry of sodium into the cell they produce a secondary blocking of the potassium outflow and the changes thus taking place in transmembrane potential cause an increase in the refractory period and in conductivity within the heart muscle [1, 5].

Faced with these facts, we decided to study the effect of serotonin on the potassium and sodium concentrations in the heart muscle.

Tests showed that 10 min after injection of serotonin the concentration of potassium ions was increased and the concentration of sodium ions decreased in the heart tissue (Fig. 1). Hence, the possibility is not ruled out that one cause of the antiarrhythmic action of serotonin may be the change it produces in electrolyte metabolism in the heart.

Besides serotonin, 5-methoxytryptamine also had a blocking action on aconitine arrhythmia (arrhythmia completely blocked in all 5 experiments). The action of the preparation developed 10-20 min after its administration. The other preparations tested in this series of experiments had no antiarrhythmic properties.

Besides serotonin, 5-methoxytryptamine also had a protective action against the arrhythmia produced by atrial stimulation (arrhythmia blocked in all 10 experiments). The remaining preparations either gave a weak antiarrhythmic effect or was completely ineffective. None of the tested substances showed definite antiarrhythmic properties in arrhythmia produced by stimulation of the ventricle.

On the basis of the results obtained it is difficult to draw a final conclusion regarding the structural properties of the indolalkylamines responsible for their antiarrhythmic action. We can merely speculate that marked antiarrhythmic properties of indolalkylamines with a straight carbon chain are maintained only if their molecule is substituted in position 5.

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