A POSSIBLE MECHANISM OF ARRHYTHMIA INDUCED BY 1-ADAMANTANAMINE

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1-Adamantanamine hydrochloride (Ada) has been reported to be an effective agent against influenza and rubella viruses (1-3). In the course of pharmacological study of Ada in this laboratory it was observed that the compound induced cardiac arrhythmia in rabbit. This was confirmed by Kaji et al. (4).

In the present experiment, the mechanism of arrhythmia inducing action of Ada was studied using the guinea-pig isolated atria and rabbit electrocardiogram.

In vitro experiment: The isolated atria of guinea-pig of either sex weighing 300 to 400 g were used in vitro experiments.

Ada (10^-4 g/ml) caused an increase in amplitude of contraction, preceded by a tentative decrease in amplitude (Fig. 1). On the atria obtained from animal pretreated with reserpine 2 mg/kg 24 hours before, Ada (10^-4 g/ml) did not produce the positive inotropic effects, but long lasting negative inotropic effect which was not antagonized by atropine (10^-6 g/ml) (Fig. 1-A). By preinfusion of β-blocking drug, propranolol (10^-7 g/ml), the effect of Ada is also modified in the similar way as in reserpinized animal (Fig. 1-A). Moreover, cocaine (5×10^-6 g/ml) inhibited the positive inotropic effect of Ada and Ada (10^-5 g/ml) potentiated the response of atria to noradrenaline. The results suggest that Ada may have at least both the catecholamine releasing action and the direct cardiac inhibiting action. The mode of catecholamine releasing action of Ada resembles that of tyramine.

In situ experiment: Rabbits weighing 2.0-2.5 kg were used. The II lead electrocardiogram of anesthetized rabbits with pentobarbital 50 mg/kg were recorded. Ada 30 mg/kg i.v. caused arrhythmia, ventricular flutter or fibrillation, for 300 seconds. In animals pretreated with reserpin 2 mg/kg 24 hours before, 30 mg/kg of Ada did not produce arrhythmia (Fig. 1-B). In addition, a single injection of propranolol (1 mg/kg) markedly suppressed the duration and grade of arrhythmia induced by Ada.

The sympathetic system has long been implicated in the production of cardiac arrhythmias. The administration of adrenaline or isoprenaline has been shown to induce arrhythmias (6) and its effect has been sensitized by chloroform (7). In the present experiment it was shown that Ada had both catecholamine releasing action and direct cardiac inhibiting action and Ada induced arrhythmia was markedly reduced by the pretreatment with reserpine or propranolol.

These findings suggest that the catecholamine releasing action of Ada may contribute to the production of cardiac arrhythmia.

REFERENCES


Fig. 1A. Effect of 1-adamantanamine (A) on the isolated atria of guinea-pigs.
Upper: normal atrium
Middle: reserpinized atrium (2 mg/kg of reserpine was administered 24 hours before)
Lower: propranolol-pretreated atrium (10^{-7} g/ml of propranolol was given 15 minutes before).

B. Effect of 1-adamantanamine (30 mg/kg i.v.) on the ECG of normal rabbit, the reserpinized rabbit (2 mg/kg of reserpine was administered 24 hours before), and the propranolol-pretreated rabbit (1 mg/kg of propranolol was given 15 minutes before).