Effect of dimethindene, an antihistaminic drug, on the transmembrane potentials of mammalian myocardium

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Summary. Dimethindene (DMI) decreased the maximum rate of rise of action potential (AP) without changing the resting potential in cat ventricular myocardium. DMI abolished the histamine-induced slow APs in left atria but not in right ventricular papillary muscles of guinea-pig, suggesting that DMI blocked the histamine H1-receptors.

DMI (Forhistil®, Fenistil®) is a well-known antihistaminic drug used in the treatment of different allergies. This activity of DMI has been attributed to antagonize the effects of histamine at the H1-receptors. It was demonstrated that the drug exerted many other actions, such as induction of histamine release, decrease of arterial blood pressure and peripheral resistance in anesthetized dogs. Recently, it has been shown that DMI has an antiarrhythmic activity.

The aim of the present work was to study the effect of DMI on the normal and slow APs of the mammalian myocardium.

Methods. Experiments were carried out on isolated right ventricular papillary muscle of cat and guinea-pig, and on left atrial muscle of guinea-pig. The animals were anesthetized with ether, and the muscles were dissected from the heart as quickly as possible and mounted in an organ chamber. The preparations were driven electrically at 2.0 or 0.5 Hz. The transmembrane potentials were recorded by means of conventional glass microelectrode technique.

The slow response APs were elicited with histamine (10-5 M) or caffeine (2 mM) in partially depolarized (up to −40 mV) left atrial and right ventricular myocardium of guinea-pigs. The membrane was depolarized by means of elevated K+ (26 mM)-Krebs solution (an isosmolar substitution of K+ for Na+). DMI (Fenistil®, Zyma-Biogal) was freshly dissolved and added to the organ chamber containing Krebs solution (composition in mM): NaCl 118, KCl 4.7, CaCl2 2.5, NaH2PO4 1.0, MgCl2 1.2, NaHCO3 24.9, glucose 11.5, which was gassed with 95% O2 and 5% CO2 and kept at 37°C.

Results. In the 1st series of experiments, the effect of DMI was examined on normal APs in right ventricular papillary muscle of cat. Figure 1 shows the dose-dependent effect of DMI. The control APs obtained in 5 preparations had the following parameters: overshoot 21.4 ± 0.7 mV, the maximum rate of rise of AP (Vmax) 128.3 ± 0.5 V/sec, duration at 50% repolarization 170.5 ± 0.9 msec. The resting potential was −79.3 ± 1.2 mV (means ± SEM of 5 experiments).

Application of DMI (5 × 10−6 M) decreased the Vmax to a level was depressed but increased by acute cold exposure. It has been shown that catecholamines inhibit insulin release mediated by an α-receptor- and stimulate it by a β-receptor-mechanism. Furthermore, insulin release is known to be enhanced by glucagon. The diminution of basal insulin level by ACS in warm controls may be caused by the elimination of stimulatory action of catecholamines through a β-receptor and by the decrease of plasma glucagon. The increased glucagon release induced by acute cold exposure, together with the lack of α-receptor-mediated inhibitory action of catecholamines due to ACS in cold-exposed ACS rats, may augment insulin release.

Inhibitory action of catecholamines due to ACS in cold-exposed ACS rats, may augment insulin release. The diminution of basal insulin level by ACS in warm controls may be caused by the elimination of stimulatory action of catecholamines through a β-receptor and by the decrease of plasma glucagon. The increased glucagon release induced by acute cold exposure, together with the lack of α-receptor-mediated inhibitory action of catecholamines due to ACS in cold-exposed ACS rats, may augment insulin release. However, the extent of increment was significantly smaller in the ACS group, however, was significantly larger in the SV one (p < 0.001). The change in plasma glycerol level is considered to be a better index of magnitude of overall lipolysis, since plasma FFA released together with glycerol is metabolized more rapidly than glycerol. Therefore, the plasma glycerol level is believed to reflect a degree of magnitude of lipolysis, that is, an activation of lipolysis is accompanied by a corresponding increase in the plasma glycerol level. From the present results, it is suggested that mobilization as well as utilization of lipids is significantly suppressed in the cold-exposed ACS rats.

In the 1st series of experiments, the effect of DMI was examined on normal APs in right ventricular papillary muscle of cat. Figure 1 shows the dose-dependent effect of DMI. The control APs obtained in 5 preparations had the following parameters: overshoot +21.4 ± 0.7 mV, the maximum rate of rise of AP (Vmax) 128.3 ± 0.5 V/sec, duration at 50% repolarization 170.5 ± 0.9 msec. The resting potential was −79.3 ± 1.2 mV (means ± SEM of 5 experiments). The diminution of basal insulin level by cold exposure may be also closely associated, at least in part, with the cold-induced responses, especially nonshivering thermogenesis, through its lipolytic action.
value of 58.1 ± 0.6 V/sec, without changing the resting potential, at 2 Hz stimulation frequency. The DMI effect became more pronounced at higher concentrations. At a lower stimulation frequency (0.5 Hz), 5 x 10^-5 M DMI decreased the V_{max} from 129.7 ± 1.2 V/sec to 87.4 ± 1.9 V/sec.

In the 2nd series of experiments, DMI was tested for its effects on the slow APs induced by histamine or caffeine in K^-depolarized atrial and ventricular myocardium of guinea-pig. In these preparations the fast Na^+ channels were voltage-inactivated, whereas the slow Ca^{2+} channels remained fully available. In left atrial myocardium, DMI (5 x 10^-3 M) completely abolished the slow APs induced by 10^-5 M histamine (fig.2,A), whereas the caffeine (2 mM)-induced ones were only slightly reduced by the same concentration of the drug (fig.2,C). On the other hand, in right ventricular myocardium, DMI (5 x 10^-3 M) hardly decreased the amplitude and V_{max} of slow APs induced by either 10^-5 M histamine (fig.2,B) or 2 mM caffeine (fig.2,D).

Discussion. Two main conclusions seem to arise from these experiments: 1. DMI exerts a quinidine-like membrane-stabilizing effect by decreasing the V_{max} of AP in cat ventricular myocardium. It has been demonstrated that DMI has a quinidine-like antiarrhythmic effect in different arrhythmia models. The results presented here suggest that this favorable antiarrhythmic effect of DMI can be explained by the Na^+ channel blocking effect of the drug. Several drugs (e.g. quinidine, lidocaine, and procainamide) are known to have an antiarrhythmic activity related to their ability to reduce the V_{max} of AP in cardiac muscle (class 1 action). Since DMI more strongly decreases the V_{max} of AP at higher stimulation frequency than at lower ones, we suppose, on the basis of Hondeghem-Katzung model, that DMI exerts a use-dependent block on the fast Na^+ channels.

2. DMI is capable of selectively blocking the histamine H_1-receptors. Results obtained in experiments with K^-depolarized heart preparations of guinea-pig indicate that DMI, even at high concentration (5 x 10^-3 M), has only a very weak decreasing effect on the slow APs mediated mainly by slow Ca^{2+} channels. The caffeine-induced slow APs were decreased by DMI in neither atrial nor ventricular myocardium. Caffeine stimulates the slow Ca^{2+} channels directly. The histamine-induced slow APs were diminished by DMI in left atrium but not in right ventricle. It has been shown that guinea-pig left atrium contains H_1-receptors, whereas the right ventricle contains H_2-receptors. Therefore, it can be concluded that DMI, like meperidine, has a specific H_1-receptor blocking activity, if we take into account that the slow AP-evoking effect of histamine is mediated by H_1-receptors in guinea-pig left atria and by H_2-receptors in right ventricular myocardium.

We suppose that membrane-stabilizing property of DMI might not be related to any H_2-receptor blocking activity, and that DMI might release endogenous histamine, which can modify the direct effect of the drug.

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