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Electrophysiological effects of azelastine in isolated guinea pig atrial and ventricular fibers

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Introduction

Azelastine (AZE) is a new antihistaminic drug with long acting antiasthmatic and antiallergic properties [1]. AZE, besides blocking H_1 receptors, exerts many other effects, e.g. it decreases the release of histamine and leukotrienes from mast cells and leucocytes, and inhibits smooth muscle contraction [1–4]. These activities of AZE have been explained as resulting from alterations of $[Ca^{2+}]_i$ mobilisation [4, 5]. AZE depresses myocardial contractility and Ca^{2+}-dependent electrical activity, modulating either Ca^{2+} influx or Ca^{2+} release from the sarcoplasmic reticulum [6]. Some of the H_1 antagonists have antiarrhythmic activity and alter cardiac action potentials and ionic currents [7]. The aim of the present study was to characterize the electrophysiological effect of AZE on propagated (fast) and slow action potentials of guinea-pig atrial and ventricular muscles.

Materials and methods

The isolated left auricles and right ventricular papillary muscles of guinea-pigs were placed in a 37 ml tissue chamber, perfused with oxygenated (95% O_2–5% CO_2) Tyrode solution (34 °C, pH 7.4) and stimulated by rectangular pulses (0.3–1 Hz, 0.5 ms). Transmembrane potentials were recorded by intracellular capillary microelectrodes and stored using an IBM computer. The drugs used were azelastine HCl (Asta Pharma AG), isoprenaline (Boehringer Ingelheim), and 4-aminopyridine (Sigma).

Results and discussion

The effects of different concentrations (10^{-7} to 10^{-5} M) of AZE, examined for at least 30 min, on action potentials (APs) in electrically paced guinea-pig left auricles and right ventricular papillary muscles are summarized in Fig. 1. AZE at these concentrations did not significantly modify the resting potential (RP) nor the amplitude of AP (APA) in either atrial or in ventricular fibers. AZE resulted in a concentration-dependent significant depression of the maximum rate of rise of the depolarization phase ($\dot{V}_{max}$) in both preparations. Up to 95×10^{-5} M concentration of AZE caused a stronger decrease of $\dot{V}_{max}$ (by 35% and 40% in ventricle and atrium, respectively) but at this concentration RP and APA were also significantly depressed. The effect of AZE on the early repolarization phase (plateau) of AP was not the same in the two types of muscles. While the duration of AP (APD_{20} and APD_{50}) was dose-dependently shortened in the ventricle, the atrial APD was increased. In ventricular papillary muscle pretreated with the K^+ channel blocker, 4-amino-pyridine (4-AP), the shortening effect of AZE on APD was not seen. 4-AP (10^{-3} M) significantly prolonged the APD_{20} (from 52.3 ± 2.4 ms to 65.7 ± 2.7 ms). In the presence of 4-AP, AZE (10^{-5} M) shortened the APD_{20} to 56.4 ± 2.2 ms which was practically the same as the control value. To study the action of AZE on the Ca^{2+}-dependent slow AP, we examined its effect on isoprenaline (5×10^{-7} M) induced slow AP in atrial muscle in which the fast Na^+ channels were inactivated by partial depolarization in 25 mM K^+ Tyrode solution. Fig. 2 illustrates a typical experiment, in which AZE reduced $\dot{V}_{max}$ and the amplitude of the slow AP. Complete block of the slow AP occurred at a drug concentration of 10^{-4} M.

The results obtained in the present study show that AZE reduced the $\dot{V}_{max}$ of fast and slow APs without changing the RP in both atrial and ventricular fibers. These results are in good agreement with other data obtained in ventricular papillary muscle [6]. Considering that these parameters can be regarded as indirect indicators of the activity of Na^+ and Ca^{2+} channels, these results show that AZE inhibits both ion channels. The ability of AZE to block the fast Na^+ channel is similar to that of the most important class I antiarrhythmic agents (e.g. quinidine, lidocaine) [8]. Its marked suppressing effect on Ca^{2+}-dependent parameters, however, suggests that AZE, in addition to its inhibitory action on the Ca^{2+} current in smooth muscle, also inhibits the myocardial Ca^{2+} channels [4]. AZE had a different effect on the plateau phase of AP in atrial and ventricular muscle. In atrial fibers, AZE prolonged the early repolarization phase of AP while, in ventricular muscle, it caused a shortening of the plateau phase. While the atrial effect of AZE mimics the action of quinidine,

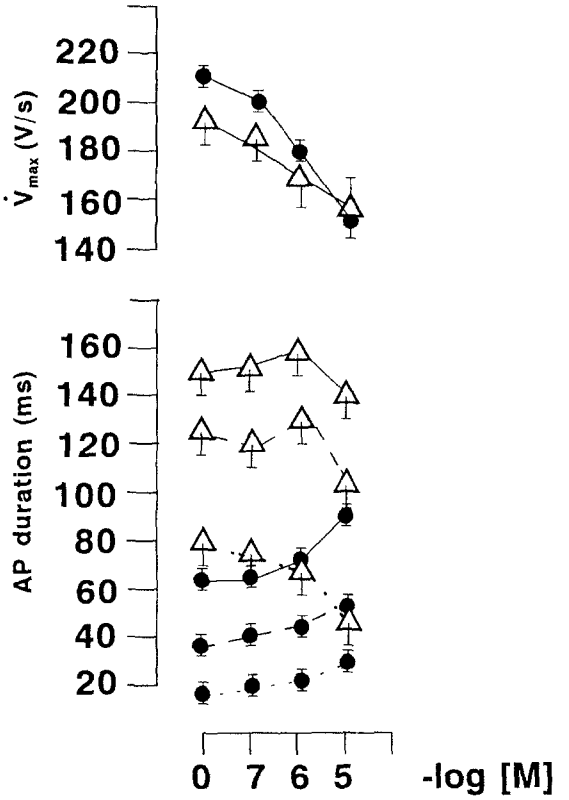

Fig. 1. Effect of azelastine on action potential (AP) characteristics of guinea-pig atrial (●) and ventricular papillary muscles (△). $\dot{V}_{max}$ = maximum rate of rise of the AP depolarization phase. APD_{20}(...), APD_{50}(- - -) and APD_{90}(—) = AP duration measured at 20%, 50% and 90% level of repolarization. Each point represents the mean values from 5 experiments; vertical bars show S.E.M. and $^*p < 0.05$.

the ventricular effect is similar to that of lidocaine [8]. The duration of cardiac AP is determined by a fine balance of inward and outward (mainly K^+ carried) currents. The inhibitory action of AZE on inward currents (Na^+ and Ca^{2+}) may explain the prolongation of the atrial plateau phase but cannot be responsible for the shortening of ventricular APD. The K^+ channel blocker, 4-AP, prevented this AZE-induced shortening of APD. This suggests that AZE may stimulate the K^+ channel in ventricular muscle. Certain H_1 receptor antagonists, such as dimethindene, have antiarrhythmic activity and

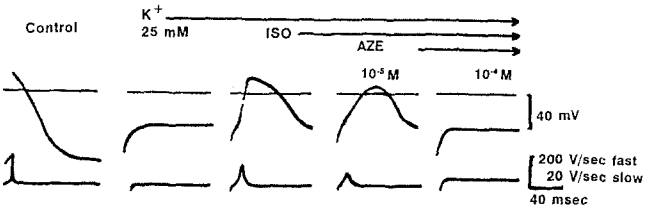

Fig. 2. Effects of azelastine on isoprenaline (ISO. 5×10^{-5} M)-induced slow AP in electrically paced (0.3 Hz) left auricle depolarized by 25 mM K^+ Tyrode solution.

depress the fast Na^+ current but hardly act on the Ca^{2+} channel [7]. In the myocardium AZE appears to inhibit both the fast Na^+ and the slow Ca^{2+} channels, but its effect on K^+ currents cannot be excluded.

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