EFFECT OF ADENOSINE ON THE FREQUENCY-FORCE RELATIONSHIP IN THE ISOLATED DOG ATRIUM

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It has been suggested that cardiac effects of adenosine are mediated by a depression of the cell membrane to Ca\(^{2+}\) permeability (1). Fleckenstein (2) showed that verapamil preferentially inhibited the transmembrane influx of calcium into cardiac cells. In 1975, Bayer et al. (3) reported that, in the isolated cat papillary muscle, verapamil suppressed tension development to a much greater extent at higher frequencies. Even in the isolated dog atrial and ventricular muscles, we also demonstrated that verapamil (4, 5) and nifedipine (6) produced marked selective suppression of tension development at higher frequencies.

In the present study, we attempted to determine the effects of adenosine on the frequency-force relationship in the isolated and blood-perfused dog atrial muscle preparation developed by Chiba et al. (7). Nine adult mongrel dogs weighing 10–18 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). The right atrium was quickly removed, immersed in Tyrode solution at 4–10°C and then perfused with arterial blood led from the carotid artery of the support dog. The atrium was suspended in a bath filled with blood at a constant temperature of 37°C. The atrial muscle was electrically driven with rectangular pulses by use of an electronic stimulator (Nihon Kohden MSE-3). The stimulus strength was 0.5 msec duration and 0.5–5 volts, about twice the threshold voltage. The isometric tension development was measured with a force displacement transducer (Grass FT03B). The muscle was usually subjected to a 2 g tension. Perfusion pressure was kept constant at 100 mm Hg. The details of the preparation were as described previously (7). Adenosine (Boehringer & Sohn) was continuously infused at a rate of 50, 100 and 250 \(\mu\)g/min with an infusion pump (Harvard Apparatus 901). Verapamil (Isoptin hydrochloride, Knoll A.G.) was administered with a micro-injector over a period of 4 seconds. The frequency-force relationship of isolated dog atrial muscle was examined in a frequency range of 2–3.5 Hz. Stepwise rise of paced frequency produced an enhancement of the developed tension.

In spontaneously beating atria the sinus rate was 104±5 beats/min (mean±SEM, \(n=6\)). When stimulation frequency was increased to high levels by an electric stimulator, it showed a positive staircase of developed tension in the range from 2 to 3.5 Hz. At 4 Hz, a slight alternation of developed tension appeared.

Adenosine administered into the cannulated sinus node artery caused a dose-relatedly negative chronotropic and inotropic effect as previously reported (8, 9). Verapamil also produced a dose-relatedly negative effect, as previously reported (10). Effects of a continuous infusion of adenosine or a single injection of verapamil on the frequency-force relationship were examined in the paced atrial preparation. As shown in Fig. 1, an infusion of 50, 100 and 250 \(\mu\)g/min...
of adenosine produced a uniform depression of the developed tension, at all examined frequencies. On the other hand, verapamil caused a greater suppression of developed tension, at higher frequencies. Summarized data are shown in Fig. 2.

It was demonstrated that manganese and pentobarbital in isolated dog atrial and ventricular muscles (4), ethanol in the dog atrial muscle (11) and Ni²⁺ and La³⁺ in the isolated cat papillary muscle (1) produced an almost uniform suppression of developed tension, at all frequencies examined. On the other hand, Ca-antagonistic drugs such as verapamil and nifedipine produced marked selective suppression of tension development at higher frequencies in the isolated cat papillary muscle and dog atrial and ventricular muscles (1, 4–6).

Adenosine depresses the contractile force in guinea pig atrial muscle, decreases the plateau phase and the duration of the action potential (1, 12, 13). It is considered that the ability of adenosine to abolish the plateau of atrial action potentials and to reduce the force of atrial contractions could be due to an impairment of Ca²⁺ influx.

In the present experiments, adenosine produced a uniform depression of contraction amplitude, whereas verapamil suppressed to a greater extent the tension development at the higher frequencies.

From these results, the mode of action of adenosine on the myocardium may be similar to that of manganese but differs from that of verapamil.

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