EFFECTS OF IMIPRAMINE ON FREQUENCY-FORCE RELATIONSHIP IN ISOLATED RIGHT ATRIAL MUSCLE OF THE DOG

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A tricyclic antidepressant, imipramine produces negative chronotropic and inotropic effects on the dog heart (1-3). Dhalla et al. (4) reported that imipramine decreased calcium binding of the sarcolemmal fraction in subcellular membranes of the rat heart. Thus, it was suggested that the direct depressant properties of this compound were related to changes in the mobilization of intracellular calcium. Verapamil is a compound with calcium antagonistic properties and produces selective suppression of developed tension at higher frequencies, while agents such as manganese chloride or pentobarbital produce a rather uniform inhibition of contraction, at all frequencies, in isolated dog atria (5, 6). We now report the effects of imipramine and verapamil on the frequency-force relationship in isolated right atrial muscle of the dog.

Nine mongrel dogs of both sexes, weighing 8-15 kg, were anesthetized with 30 mg/kg of sodium pentobarbital i.v. After heparin treatment, the right atrium was quickly removed and plunged into a cold Tyrode’s solution at 4 to 10°C. The isolated atrium was then perfused with arterial blood conducted from the carotid artery of a heparinized support dog with the aid of a peristaltic pump. The atrium was suspended in the bath filled with blood at a constant temperature of 37°C, and a tension of 2 g was usually applied. The perfusion pressure was maintained at 100 mmHg. The flow rate was 4.5–5.0 ml/min. Details of the preparations have been described elsewhere (7). The atrial muscle was electrically driven with rectangular pulses by an electronic stimulator (Nihon Koden MSE-3). The stimulus was 1 msec in duration, 1 to 2 V in strength, about twice the threshold voltage, and 2 to 3.5 Hz in frequency. The drugs were injected into the sinus node artery of the isolated atrial preparation. Imipramine (imipramine hydrochloride, Fujisawa) was infused at a rate of 5–25 μg/min, by an infusion pump (Harvard apparatus model 901), and 3 μg of L-verapamil (Knoll AG) was injected over a 4 sec period.

The frequency-force relationship of the isolated right atrial muscle was examined in a frequency range of 2 to 3.5 Hz. The positive staircase phenomenon was usually produced in all non-treated atrial preparations. As shown in Fig. 1, an infusion of 25 μg/min of imipramine produced a moderate, rather uniform, depression of developed tension, at all examined frequencies. On the other hand, the positive staircase phenomenon was frequently inverted by treatment with 3 μg of verapamil. Summarized data are shown in Fig. 2. These experiments show that imipramine produces a fairly uniform suppression of the tension development at all examined frequencies, whereas verapamil produces a greater depression of the developed tension at higher frequency rates.

Dhalla et al. (4) reported that imipramine
inhibited sarcolemmal Ca\textsuperscript{2+} binding activity, and such a decrease in Ca\textsuperscript{2+} binding caused by this agent may be the result of a reduction in sarcolemmal Ca\textsuperscript{2+} stores available for release upon depolarization of the myocardium. It had been reported that verapamil not only reduced the slow Ca inward current but also inhibited the recovery from inactivation (8). It is well known that manganese decreases Ca\textsuperscript{2+} influx. Thus, as indicated by Bayer et al. (8), the complex dynamics of the cardiac actions of these agents cannot be explained by a simple inhibition of Ca\textsuperscript{2+} uptake across the membrane.

Recently, Chiba et al. (5, 6) showed that verapamil suppressed tension development to a much greater extent at higher frequencies, whereas either manganese chloride or pentobarbital produced a rather uniform depression of contraction, at all frequencies examined in isolated dog atria. The present
study demonstrated that the effect of imipramine on the frequency-force relationship was similar to the effects of manganese chloride and pentobarbital, thereby indicating that the site of action on cardiac contractile mechanisms differs between imipramine and verapamil.

REFERENCES