CARDIAC STIMULATING EFFECTS OF MACROCYCLIC POLYAMINES

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Polyamines are naturally occurring chemical substances which have been implicated in numerous growth processes (1, 2). It has been reported that polyamines have physico-chemical properties such as conformation, amine basicites, metal affinities and lipophilicities (3, 4) which enable to be taken up by an active transport mechanism in Escherichia coli (5). More recently biogenic actions of polyamines were reported at the molecular level (6). However there is no available report on the cardiovascular effects of polyamines in mammals. In the present study, we made an attempt to investigate the cardiac effects of three kinds of polyamines, i.e., tetra-amine, cyclam, and dioxocyclam, using the isolated and blood-perfused canine atrial preparation which was developed by Chiba et al. (7, 8).

Nine adult mongrel dogs were anesthetized with 30 mg/kg of sodium pentobarbital i.v. After treatment with 200 units/kg of heparin, the right atrial muscle was quickly removed and immersed in cold Tyrode solution at 4-10°C. The sinus node artery of the atrium was cannulated with a small polyethylene tubing and the atrial muscle was fixed to the stainless steel bar at 2 ventricular sides. The muscle was then suspended in the blood bath at a constant temperature of 37°C, and the preparation was perfused with warm arterial blood which was introduced from the support dog. The details of the preparation are described in previous papers (7, 8). Compounds used in this study were 1,4,8,11-tetraazacyclotetradecane (cyclam), 1,4,8,11-tetraazacyclotetradecane-12,14-dione (dioxocyclam), 3,7-diazanonane-1,9-diamine (tetra-amine), norepinephrine hydrochloride (Sankyo), propranolol hydrochloride (Sumitomo Chemicals), acetylcholine chloride (Daichi) and atropine sulfate (Takeda). Each compound was injected into the cannulated sinus node artery over a 4 sec period.

When tetra-amine, cyclam or dioxocyclam was injected into the cannulated sinus node artery, positive chronotropic and inotropic effects were induced in a dose-related manner. The threshold dose of tetra-amine for inducing positive effects was approximately 100 ng. However, a dose of 100 ng of cyclam induced only a positive inotropic effect but no significant chronotropic change. The threshold dose of cyclam for a positive chronotropic effect was approximately 1 mg. Dioxocyclam caused positive chronotropic and inotropic effects at extremely large doses. The order of the potency for inducing positive effects was tetra-amine>cyclam>dioxocyclam. The summarized data are shown in Fig. 1. Extremely large amounts of these compounds occasionally produced initial brief and slight negative chronotropic and inotropic effects. When 0.1 μg of norepinephrine was injected into the sinus node artery, positive chronotropic and inotropic effects were induced. These positive effects were significantly inhibited by 3 μg of propranolol.
Fig. 1. Chronotropic and inotropic effects induced by tetra-amine, cyclam and dioxocyclam in isolated dog atria. Values are the mean of 5 observations and the vertical bars refer to the standard errors.

On the other hand, positive chronotropic and inotropic effects induced by 1 mg of tetra-amine, 3 mg of cyclam and 3 mg of dioxocyclam were never influenced by pretreatment with propranolol. The summarized data are shown in Fig. 2. The bradycardia induced by a large dose of cyclam was not modified with an adequate dose of 100 μg of atropine which completely blocked the bradycardia induced by 1–3 μg of acetylcholine in two experiments.

In the present experiments, we demonstrated that polyamines have cardiac stimulating properties. Especially, tetra-amine caused significant positive chronotropic and inotropic effects, although the doses are relatively too large. Since their cardiac stimulating effects were not modified by pretreatment with an adrenergic beta-receptor blocking agent propranolol, which significantly inhibited positive chronotropic and inotropic responses to norepinephrine (NE), tetra-amine (TE), cyclam (CY) and dioxocyclam (DI) in 5 isolated dog atria. The control sinus rate was 114±5 beats/min (mean±S.E.M) in 5 atrial preparations. Vertical bars show the S.E.M.

Fig. 2. Effects of 3 μg of propranolol on the positive chronotropic and inotropic responses to 0.1 μg of norepinephrine (NE), tetra-amine (TE), cyclam (CY) and dioxocyclam (DI) in 5 isolated dog atria. The control sinus rate was 114±5 beats/min (mean±S.E.M) in 5 atrial preparations. Vertical bars show the S.E.M.

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