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Cardiovascular Action of Adenosine and Other Nucleosides.* (26467)

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Several studies have been reported on the cardiovascular actions of adenosine and other purine and pyrimidine nucleosides(1-5), some of which exert a positive inotropic effect in isolated preparations(6-10). Similarly a negative chronotropic effect and a general vasodilator action have been found under a variety of experimental conditions(1,5,11). Due to the key biochemical role that some of these compounds may play in smooth and cardiac muscle energetics, it was desirable to test in the same preparation, *in vivo*, the inotropic, chronotropic and hypotensive activities of some of these compounds, to obtain quantitative data on specificity and potency.

Materials and methods. Mongrel dogs of either sex weighing from 7.8 to 14.2 kg were anesthetized with intraperitoneal injections of sodium pentobarbital. Blood pressures were measured through an Hg manometer. Myocardial contractility was measured with a Walton strain gauge arch(12) sutured on the left ventricular myocardium. Records of myocardial tension and ECG were obtained on a 2-channel Sanborn recorder. All injections were made intravenously into the jugular vein over a 10 minute period. Solutions were freshly prepared from the powdered compounds in 50 ml of normal saline. The list of compounds tested included: Adenosine, guanosine, inosine, cytidine, thymidine, uridine, adenine sulfate and guanine sulfate. All compounds were purchased from Nutritional Biochemicals, New York. Except as otherwise indicated, all animals were given 1 mg/kg of atropine at beginning of each experiment.

Results. The following compounds produced no detectable cardiovascular actions in the doses indicated: Adenine (2-10 mg/kg), guanine (2-10 mg/kg), guanosine (2-25 mg/kg), inosine (2-100 mg/kg), cytidine (2-5 mg/kg), thymidine (2-50 mg/kg), and uridine (2-50 mg/kg). These were tested in 2 to 4 animals each. In larger doses (25 mg/kg) cytidine produced moderate hypotension and negative chronotropic and inotropic effects, but such doses were considered too large to deserve further study.

Of all the compounds tested only adenosine exhibited cardiovascular actions of a sufficient magnitude and consistency to warrant further study.

Quantitative results on the inotropic, chronotropic and hypotensive effects of adenosine were obtained at several dose levels (0.1 to 2 mg/kg) from a total of 113 injections in 10 dogs (Fig. 1). Doses larger than 2 mg/kg, up to 25 mg/kg, produced no greater effects. In all instances recovery to control levels was attained within a few seconds (Fig. 2). Since in all of the above mentioned experiments the animals were fully atropinized, the observed actions of adenosine can not be classified as cholinergic in spite of the apparent similarity to the cardiovascular actions of acetylcholine. In these animals atropine was used to eliminate the reflex vagal effects on heart rate associated with hypotension.

Since there have been reports that atropine and vagotomy may abolish some of the cardiovascular actions of adenosine, experiments were designed to test this point using

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non-atropinized animals. In repeated tests neither vagotomy nor atropine were found to interfere with the cardiovascular actions of adenosine.

Discussion. Studies with isolated heart and heart-lung preparations suggested that some of the nucleosides may have a positive while others have a negative inotropic effect (6-10). The *in vivo* studies reported here are not in general agreement with this concept since, with the exception of adenosine, most of the nucleosides tested had no significant cardiac actions. The effects of adenosine in isolated preparations are similar to those reported herein, however the positive inotropic actions found among certain nucleosides (guanosine, uridine, thymidine, inosine) (8,9) must be associated with some conditions which obtain only in isolated preparations. It is also possible that this activity is manifested only in failing preparations under special conditions. In this connection it is noteworthy that digitalis produces a positive inotropic effect when contractility is measured with a cardiac strain gauge arch *in vivo* (13).

Recently Thorp and Cobbin(5) have reported that 2-chloro-adenosine is more active than adenosine at least regarding its vasodilator potency. Furthermore this compound is said to have a longer duration of action. These authors report that atropine blocks the negative chronotropic effects of 2-chloro-adenosine which is at variance with our findings with adenosine. However our results are in agreement with studies on the effect of

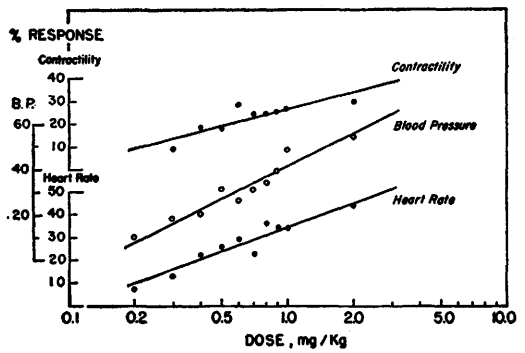

FIG. 1. % decrease in blood pressure, cardiac contractility and heart rate with submaximal doses of adenosine.

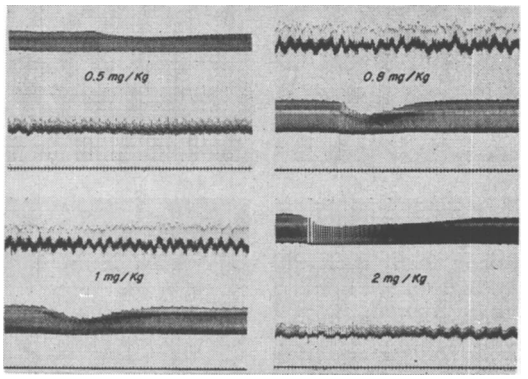

FIG. 2. Records of adenosine effects on contractility and heart rate (time markers 0.1 sec.).

adenosine, acetylcholine and atropine on atrial resting and action potentials by Johnson & McKinnon(10).

Summary. The cardiovascular effects of adenosine and other nucleosides were studied in dogs. Adenosine produced hypotension and negative chronotropic and inotropic effects of short duration. Quantitative dose-effect relationships were obtained in each case. Other nucleosides tested exhibited no significant cardiovascular actions *in vivo*.

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