CORONARY VASODILATORY AND CARDIOTONIC EFFECTS OF PARATHYROID HORMONE IN THE DOG

Keitaro Hashimoto
Department of Pharmacology
Yamanashi Medical College
Tamaho-cho, Japan

INTRODUCTION

Since Crass and Pang (1) reported coronary vasodilator and positive inotropic effects of parathyroid hormone (PTH), it has become clear that PTH definitely increased the coronary blood flow in dogs and decreased the blood pressure of rats (2-4). We also reported soon after Crass and Pang cardiovascular effects of PTH in the dog (2). However, questions relating to those effects of PTH, such as on the species difference, selectivity on vascular muscle or cardiac muscle, cellular mechanisms of action, physiological role or its possible clinical implications are still open for discussion. This paper deals with the analysis of our previous paper (2) with a review of recently published papers.

PTH is a polypeptide containing 84 amino acids, the first 34 of which are necessary for its main biological action of raising serum Ca levels. Bovine, porcine, and human PTH differ slightly in the first 34 amino acid residues of the sequence. Crass and Pang demonstrated effects of the synthetic bovine polypeptide with 34 amino acids, PTH-(1-34), on the canine coronary artery of the in situ heart preparation, but the precise modes of action on the coronary vasculature have not been documented (1). We wanted to examine (a) whether the coronary vasodilatory effect of synthetic bovine PTH-(1-34) reported by Crass and Pang (1) is an indirect one resulting from the increase in O2 consumption due to its positive inotropic and chronotropic effects, (b) whether natural PTH has similar vasodilatory action, (c) whether changes in the serum Ca level accompany the coronary dilator action, and (d) whether smaller fragments of PTH also have coronary vasodilator action. We examined five polypeptides: natural bovine PTH-(1-84) and synthetic bovine PTH-(24-28) containing 5 amino acids, and synthetic PTH-(25-27) containing 3 amino acids for their coronary and cardiac action using the canine heart-lung preparation.

METHODS

We used canine heart-lung preparation supported by a donor, and this allowed us to examine specifically the effects of PTH on coronary vasculature and cardiac functions. Mongrel dogs of either sex, weighing 7-12 kg were anesthetized with pentobarbital sodium (35 mg/kg, i.p.). Heart-lung preparations were prepared as described previously. Coronary...
sinus outflow was drawn out by a Morawitz cannula and sent to the donor via the femoral vein. The donor dogs, weighing 20-30 kg, were anesthetized with intravenous chloralose (45 mg/kg) and urethane (450 mg/kg) after premedication with morphine (1.5 mg/kg, s.c.). A cannulating-type probe (2 mm i.d.) of an electromagnetic flowmeter (Nihon Kohden MF-26) was placed between the Morawitz cannula and the donor to record the coronary blood flow. By using the donor the coronary vascular tone could be maintained in the heart-lung preparation long enough to compare several drugs in one preparation. The level of the venous reservoir of the heart-lung preparation was kept constant by overflowing, and the excess blood was returned to the larger reservoir by gravity. Systemic output was measured using an electromagnetic flowmeter probe (Nihon Kohden MF-26, 1 cm i.d.) placed at the tubing from the aorta. Myocardial contractility was assessed from recordings of the right atrial pressure and the first differential (dP/dt) of the left intraventricular pressure, which was recorded by inserting a polyethylene cannula at the apex. The heart rate was recorded with a cardiotachometer (Nihon Kohden RT-5) triggered by R waves of the electrocardiogram. The oxygen consumption of the myocardium was calculated by multiplying the coronary-arteriovenous O₂ difference of the blood (vol. %) by the corresponding coronary flow (ml/min/100g heart). The arteriovenous O₂ content difference was continuously and automatically recorded using an Avox Systems, which gave O₂ saturation (%) x hemoglobin content (g/dl) x 0.0136 (O₂ capacity of the hemoglobin, ml/g).

Plasma Ca and inorganic P (P₄) was assayed using the method of Trinder (5), and P₄ was assayed by the method of Delsal and Manhourí (6), but there were no significant changes during the experiment.

RESULTS

Effects of PTH-(1-34) on the heart and coronary circulation

PTH-(1-34) introduced into the left atrium (hereafter referred to as intra-arterial injection) increased the coronary flow, decreased the arteriovenous O₂ difference and slightly increased the heart rate (Fig. 1). These prominent coronary vasodilatory effects were produced by a dose of 100 U (10 µg) PTH-(1-34), but these actions could also be observed after the low dose of 10 U (1 µg). The positive inotropic effect of PTH-(1-34) was observed as the decrease in the right atrial pressure and by the increase in the dP/dt of the intraventricular pressure, however it was not as prominent as the coronary vasodilatory effect. This was confirmed by a later paper of Crass et al. (4), that at least in the dog PTH has a prominent coronary vasodilator effect, but has only a weak positive inotropic effect.

Figure 2 shows summarized data of the effects of 100 U PTH-(1-34) from six experiments. PTH-(1-34) almost doubled the coronary blood flow, decreased the right atrial pressure, and only slightly increased the heart rate. This increase in the coronary flow was approximately two thirds of the maximal increase in the coronary flow inducible by adenosine. O₂ consumption increased 30 sec after injection but soon returned to the control value.

The responses to intravenous and intra-arterial injection of PTH-(1-34) were compared in two experiments, and there were no quantitative or qualitative differences. This suggests that there was no inactivation of PTH-(1-34) by the lung. It is interesting that effects of many physiologically important mediators of vascular smooth muscle tone are known to be enhanced or decreased by the passage through the pulmonary circulation.

Figure 3 shows the relationship between the percentage increase in the O₂ consumption and the percentage increase in the coronary blood flow observed 5 min after intra-arterial injection of PTH-(1-34), 30-300 U.