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Prostaglandin D_2 (PGD_2) – A Potent Coronary Vasoconstrictor Agent in the Guinea Pig Isolated Heart

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Summary. The action of prostaglandin D_2 (PGD_2) on myocardial force of contraction (MFC) and coronary vascular resistance (CVR) was studied in the isovolumetrically perfused guinea pig heart at constant driving frequency (180 beats/min). PGD_2 ($2 \cdot 10^{-9}$ – $1 \cdot 10^{-6}$ M) produced a concentration-dependent increase in the CVR while the MFC remained unchanged. The ED_{50} (50% of maximum response) of the coronary vasomotor action amounted to $4.3 \cdot 10^{-8}$ M PGD_2. The results give evidence for a potent coronary vasoconstrictor activity of PGD_2.

Key words: Isolated guinea pig heart – Coronary vascular resistance – Myocardial force of contraction – Prostaglandin D_2 (PGD_2).

INTRODUCTION

Like a number of other organs and tissues the heart is capable of synthesizing prostaglandins after incubation with precursor fatty acids (Needleman, 1976). As far as the formation of primary prostaglandins is concerned, the simultaneous production of PGE_2, $PGF_{2\alpha}$ and PGD_2 was demonstrated for the guinea pig heart after incubation with arachidonic acid (Schrör et al., 1978). In contrast to PGE_2 and $PGF_{2\alpha}$, there is little information about the cardiovascular activity of PGD_2. We have investigated the action of PGD_2 on the heart and the coronary vessels in vitro.

METHODS

Guinea pigs of either sex (body weight 320–400 g) were killed by a blow on the head. The hearts were quickly removed and perfused isovolumetrically (10 ml/min) with Tyrode's solution (Ca^{2+} 1.8 mM) containing $2 \cdot 10^{-6}$ M atropine via the aorta. The hearts were electrically driven at constant rate of 180 beats/min. Left ventricular peak systolic pressure (LVP), maximum velocities of contraction (LV dp/dt_{max}) and relaxation (LV dp/dt_{min}), time to peak tension (TPT) as well as the coronary perfusion pressure (CVP) were measured simultaneously as described earlier (Krebs and Schrör, 1975). The CVP was assumed to be a direct expression of the coronary vascular resistance.

PGD_2 stock solutions were prepared as follows: 10 mg was dissolved in 1 ml absolute ethanol, 9 ml Na_2CO_3 (20 mg/100 ml) was added and the pH adjusted to 6–7.5. More diluted solutions were made by adding physiologic saline, aliquots of which were applied to the perfusing fluid. The final pH of the Tyrode's solution was 7.4. To exclude the possible involvement of endogenous prostaglandin-like substances, all experiments were carried out in the presence of $3 \cdot 10^{-6}$ M indomethacin, which was dissolved in the bicarbonate buffer of the Tyrode's solution.

Statistical analysis was performed using the *t*-test for non-paired samples. The level of significance was 0.05. *n* is the number of observations. The mean and standard error ($\bar{x} \pm$ S.E.M.) are quoted in the text.

RESULTS AND DISCUSSION

The cumulative application of PGD_2 to the perfusion fluid of 12 hearts led to a marked increase in the CVP. This increase was concentration-dependent between $2 \cdot 10^{-9}$–$1 \cdot 10^{-6}$ M PGD_2 (Fig. 1). Ventricular mechanics remained unchanged up to 10^{-7} M PGD_2. At higher concentrations, there was some tendency to decrease, which, however, was statistically not significant ($P > 0.05$) (Fig. 1). There were also no alterations in LV dp/dt_{min}, amounting to 774 ± 68 mm Hg/s under control conditions and 692 ± 71 mm Hg/s in presence of $2.8 \cdot 10^{-6}$ M PGD_2 ($P > 0.05$). The same was seen with the TPT, which was 131 ± 2 ms in the control hearts and 132 ± 3 ms in presence of maximum concentration PGD_2 ($P > 0.05$).

Twenty minutes wash-out in PGD_2-free Tyrode's solution was followed by a decrease in the CVP from 77.1 ± 3.8 to 47.0 ± 4.5 mm Hg ($P < 0.05$). This value was still significantly higher than control before application of PGD_2 to these animals, 37.4 ± 3.2 mm Hg

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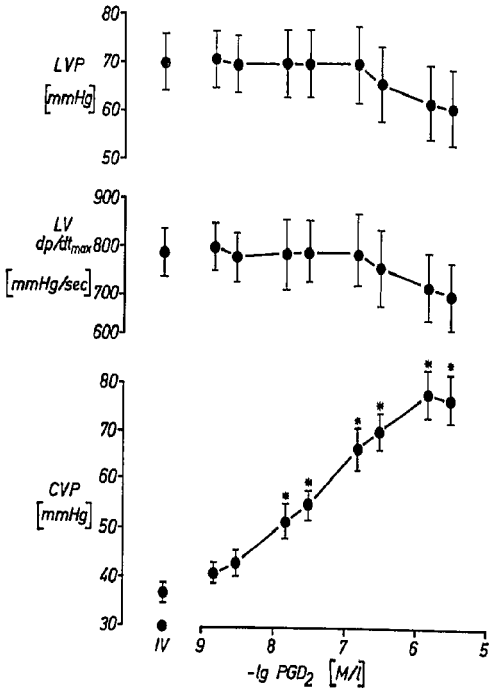

Fig. 1. Changes in left ventricular pressure (*LVP*), left ventricular maximum velocity of contraction ($LV\ dp/dt_{max}$) and coronary perfusion pressure (*CVP*) in response to $-\log$ molar concentration of prostaglandin D_2 (PGD_2) in 12 animals. Vertical lines show S.E. mean. $^*P < 0.05$ as compared with the initial value (*IV*) before PGD_2-application

($P < 0.05$, $n = 6$). The vasoconstrictor effect of PGD_2 was reversible for the same extent, when $2.8 \cdot 10^{-6}$ M PGD_2 were applied for 2 times, interrupted by one wash-out period: 74.8 ± 6.0 and 77.8 ± 5.1 mm Hg ($P > 0.05$, $n = 6$).

For each animal the coronary reaction was estimated in % of its individual maximum response. The ED_{50}, i.e. 50% of the maximum increase in the CVP was estimated graphically and was found to be 43 ± 14 nM.

The results give evidence for a reversible coronary constrictor action of PGD_2 in the guinea pig isolated heart in the absence of changes in myocardial force of contraction. Compared with other prostaglandins PGD_2 is a highly potent coronary vasoconstrictor. The ED_{50} for $PGF_{2\alpha}$ in the same isolated preparations was found to be higher than $2 \cdot 10^{-6}$ M (Schrör, unpublished), that for PGA_2 $2.2 \cdot 10^{-6}$ M (Schrör and Krebs, 1977). A high bioactivity of PGD_2 for increase in blood pressure of sheep and guinea pig have recently been described (Hamberg et al., 1975; Jones, 1976).

Increased release of $PGF_{2\alpha}$ but not of PGE_2 was seen after challenging sensitized guinea pig hearts with antigen (Liebig et al., 1975; Levi et al., 1976). At the same time there was marked reduction in coronary flow, which in one of these studies could be prevented by indomethacin pretreatment (Levi et al., 1976). Formation of PGD_2 was not measured. As essentially all primary prostaglandins may be formed from the common precursor arachidonic acid (Flower and Vane, 1974), PGD_2 or the endoperoxides themselves seem to be more likely candidates for prostaglandin-mediated vasoconstriction than $PGF_{2\alpha}$.

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