Effects of the Metabolites of Prostaglandin E_1 of the Systemic and Peripheral Circulations in Dogs[1] (35472)

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Änggard and Samuelsson (1) have shown that PGE_1 is rapidly metabolized into 15-keto-PGE_1 by the oxidation of the secondary alcohol group at 15-C and into dihydro-PGE_1 and 15-keto-dihydro-PGE_1 by reduction at the Δ^{13} double bond in swine and guinea pig lungs. Ferreira and Vane (2) and McGiff *et al.* (3) have demonstrated that the iv injected PGE_1 is effectively inactivated by the lungs in rats and dogs. Those investigators ascribed, therefore, the inactivation of PGE_1 to the oxidation of PGE_1 by prostaglandin dehydrogenase (4, 5). Änggard (6) showed that the iv administration of dihydro-PGE_1 caused a greater hypotensive action in rats but less in rabbits. On the other hand, 15-keto-PGE_1 caused very little hypotensive action in rabbits. No systemic study has been made on the cardiovascular effects of those metabolites in PGE_1 in dogs. Furthermore, the direct effect of these metabolites on the vascular smooth muscles remained uncertain. The present study was undertaken to compare the effects of 15-keto-PGE_1, dihydro-PGE_1, and 15-keto-dihydro-PGE_1 with those of PGE_1 on systemic and regional circulations in dogs.

Methods. Dogs, weighing between 19 and 25 kg, were anesthetized with sodium pentobarbital (30 mg/kg). The technique used to study the cardiovascular effects of PGE_1 and its metabolites was described previously (7, 8). In all experiments, the left hemithorax was opened under artificial respiration. The pericardium was incised and the heart was suspended in a pericardial cradle. Sodium heparin (2.5 mg/kg) was given intravenously every 0.5 hr.

In 24 dogs, systemic and pulmonary arterial pressures were measured continuously with Statham pressure transducers (P23AA) connected to catheters placed in the left subclavian artery through the left mammary artery and in the pulmonary artery through a small branch of the left pulmonary artery. Heart rate and myocardial contractile force were measured continuously with an Electronics for Medicine (EFM) tachometer (model TDC-1) and with a Walton-Brodie strain gauge arch (9) sutured directly to the right ventricular muscle.

In 24 dogs, in which the direct effect of PGE_1 and its metabolites on the vascular bed of dog hind limbs was studied, a femoral artery was perfused with arterial blood at a constant and known rate by means of a Sigmamotor pump (TM2), as described previously (10). Systemic arterial pressure and femoral arterial pressure were measured continuously with Statham pressure transducers (P23AA). In this setup, the direct effect of PGE_1 and its metabolites on the vascular resistance was evaluated readily by the changes in the femoral arterial perfusion pressure.

Crystalline powder of PGE_1 was obtained from Dr. J. E. Pike, Upjohn Co., Kalamazoo, Mich. 11α-Hydroxy-9,15-diketo-13-prostaenoic acid (15-keto-PGE_1) was synthesized by MnO_2 oxidation of PGE_1 in this laboratory according to the method described by Attenburrow *et al.* (11). 11α-,15*S*-dihydroxy-9-keto-prostanoic acid (dihydro-PGE_1) and 11α-, 15*S*-dihydroxy-9-15-diketo-prostanoic acid (15-keto-dihydro-PGE_1) were synthesized in this laboratory from PGE_1 and 15-keto-PGE_1, respectively, by the method described by Bergström *et al.* (12). All three metabolites were purified by thin-layer chro-

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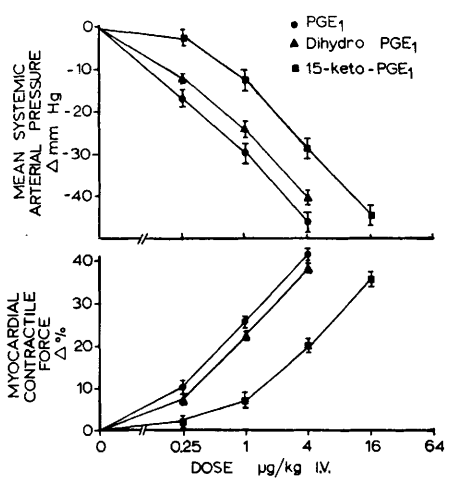

FIG. 1. Effect of the iv administration of graded doses (0.25–16 μg/kg) of PGE$_1$, dihydro-PGE$_1$, and 15-keto-PGE$_1$ on mean systemic arterial pressure in 22 dogs: (●, ▲, ■) average effects ± SEM.

matography, using a slight modification (13) of the method described previously by Green and Samuelsson (14). PGE$_1$ and its metabolites were dissolved with 20 μl of 95% ethanol and further diluted to 1–100 μg/ml solutions with 0.9% NaCl solution before its intra-arterial or intravenous injection. Each solution was made so that the amounts of the solution injected intra-arterially to dogs never exceeded 0.1 ml. The data in this paper were evaluated statistically employing the *t* test (15).

Results. The cardiovascular effects of the iv administration of geometrically increasing doses (0.25 to 16 μg/kg) of PGE$_1$, dihydro-PGE$_1$, and 15-keto-PGE$_1$ were studied in 22 dogs. The results are summarized in Fig. 1 and a tracing of the representative experiment with 15-keto-PGE$_1$ is illustrated in Fig. 2. As reported previously from this laboratory (8, 16, 17), the iv administration of 0.25 to 4 μg/kg of PGE$_1$ decreased mean systemic arterial pressure and increased heart rate, mean pulmonary arterial pressure, and myocardial contractile force essentially in proportion to the dose. On the other hand, the effects of the iv administration of 1 to 16 μg/kg of 15-keto-PGE$_1$ and dihydro-PGE$_1$ on heart rate, mean systemic pulmonary arterial pressures, and myocardial contractile force were qualitatively similar to those of PGE$_1$ (Fig. 2). However, the magnitude of the systemic hypotensive effects of the iv administration of 15-keto-PGE$_1$ and dihydro-PGE$_1$ were approximately ⅔ and ⅕ of that of PGE$_1$.

The ia injection of graded doses (0.625–160 ng/kg) of PGE$_1$, 15-keto-PGE$_1$, dihydro-PGE$_1$, and 15-keto-dihydro-PGE$_1$ were studied in 24 dogs in which the femoral arterial blood flow was kept constant throughout a period of the experiment. The results of the average maximal effects of each prostaglandin are summarized in Fig. 3. The ia injection of 2.5 ng/kg of PGE$_1$ and of 10 ng/kg of dihydro-PGE$_1$ decreased the perfusion pressure in the femoral artery without producing any significant change in heart rate, systemic arterial pressure, and myocardial contractile force, indicating the direct vasodilator action of these agents. The

FIG. 2. Effects of the iv administration of 15-keto-PGE$_1$ (16 μg/kg) on heart rate (HR), mean systemic arterial pressure (MSAP), mean pulmonary arterial pressure (MPAP) and myocardial contractile force (MCF) in a dog.

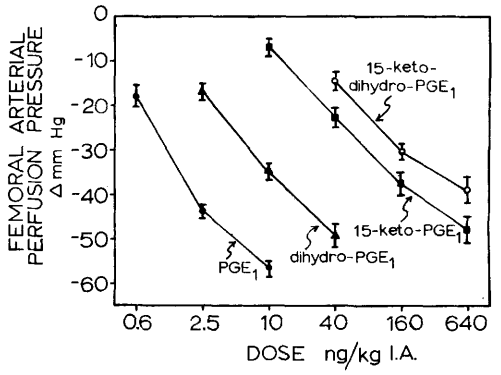

FIG. 3. Effect of the ia administration of graded doses (0.6–640 ng/kg) of PGE$_1$, dihydro-PGE$_1$, 15-keto-PGE$_1$, and 15-keto-dihydro-PGE$_1$ on femoral arterial perfusion pressure in 24 dogs, in which the femoral arterial blood flow was kept constant by a sigmamotor pump throughout a period of the experiment.

vasodilator actions of 15-keto-PGE$_1$ and 15-keto-dihydro-PGE$_1$ were qualitatively similar to that of PGE$_1$ or dihydro-PGE$_1$. As shown in Fig. 3, the vasodilator actions of dihydro-PGE$_1$, 15-keto-PGE$_1$, and 15-keto-dihydro-PGE$_1$ were approximately ¼, 1/80, and 1/100 of that of PGE$_1$ in dog hind limb preparations.

Discussion. The present data show that the three metabolites of PGE$_1$ exert qualitatively similar direct vasodilator action on the peripheral vasculature in dogs. However, the magnitude of the vasodilator action of the three metabolites is considerably smaller than that of PGE$_1$. Among the three metabolites, dihydro-PGE$_1$ is the most potent vasodilator, indicating that the saturation of Δ^{13} double bond causes little effect on the vasodilator action. In contrast, the oxidation of the secondary alcohol group at C-15 in PGE$_1$ resulted in a marked diminution of the vasodilator effect as seen with 15-keto-PGE$_1$ and 15-keto-dihydro-PGE$_1$. This indicates that the hydroxy group at C-15, as seen with all basic prostaglandins, is important in the vascular action of prostaglandins.

The present study also knows that the iv administration of 15-keto-PGE$_1$, dihydro-PGE$_1$, and 15-keto-dihydro-PGE$_1$ caused qualitatively similar hemodynamic changes to those of PGE$_1$ in dogs. However, the magnitude of the hypotensive action of the metabolites was slightly smaller than that of PGE$_1$. The results of the present study on the hypotensive action of the three metabolites in dogs are partly in agreement with the previous observations made by Änggard in guinea pigs and rabbits (6). Änggard (6) found that, compared with PGE$_1$, the hypotensive action and nonvascular smooth muscle-stimulating action of 15-keto-PGE$_1$ and 15-keto-dihydro-PGE$_1$ are negligible. In contrast, the biological effects of dihydro-PGE$_1$ differ in the species of animals and in the type of smooth muscles studied. Änggard (6) showed that dihydro-PGE$_1$ stimulates very little the nonvascular smooth muscle in rabbit duodenum and in guinea-pig ileum and uterus. On the other hand, dihydro-PGE$_1$ exerts a greater hypotensive action in guinea pig than PGE$_1$ but significantly less in rabbits. The discrepancy between the results made by Änggard and those in the present study could be due to the difference in the species of the animals studied.

In the present study, as compared with PGE$_1$, the magnitude of the biological actions of the metabolites differed markedly according to the route of the administration in dogs. The magnitude of the hypotensive action of the three metabolites was slightly less than that of PGE$_1$ when they were administered intravenously. On the other hand, the magnitude of the direct vasodilator action of the metabolites was considerably smaller than that of PGE$_1$ when they were administered directly in a femoral artery of the dogs. This difference in the magnitude of the biological actions of PGE$_1$ and its metabolites by two different routes could be explained by the efficient metabolic inactivation of PGE$_1$ in the lungs when injected intravenously. Both PGE$_1$ and dihydro-PGE$_1$ are inactivated mostly by the oxidative mechanism to 15-keto-PGE$_1$ and 15-keto-dihydro-PGE$_1$, since both compounds are found to be favorable substrates for the enzyme (5). In contrast, the products of this enzymatic reaction, 15-keto-PGE$_1$ and 15-keto-dihydro-PGE$_1$, are obviously not subjected to further degradation by this oxidative process. Hence, the majority of the intravenously administered 15-keto-PGE$_1$ and 15-keto-dihydro-PGE$_1$

would exert the vasodilator actions in various vascular beds in dogs.

Summary. The effects of PGE$_1$ and its three metabolites, 15-keto-PGE$_1$, dihydro-PGE$_1$, and 15-keto-dihydro-PGE$_1$, were studied in anesthetized dogs and in isolated dog hind limb preparations. The systemic hemodynamic effects of these three metabolites were qualitatively similar to those of PGE$_1$ in dogs, but the magnitude of the effects was smaller with these three metabolites than with PGE$_1$. Among these metabolites, dihydro-PGE$_1$ exerted the most potent hemodynamic and vasodilator actions. The present study suggests that the inactivation of PGE$_1$ in the lungs is caused, not by the saturation of the Δ^{13} durable bond of PGE$_1$, but by the oxidation of the secondary alcohol group at C-15 and probably by further degradation.

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