Effects of Prostaglandins E_2 and $F_{2\alpha}$ on the Carotid Arterial Blood Flow, Cerebrospinal Fluid Pressure and Intraocular Pressure in Dogs[1] (36569)

J. NAKANO, A. C. K. CHANG, AND R. G. FISHER

Departments of Pharmacology, Medicine and Neurosurgery, University of Oklahoma College of Medicine, Oklahoma City, Oklahoma 73190

It is known that significant quantities of prostaglandins (PG) are biosynthesized in the central nervous system (CNS), and released by neuronal stimulation or by a variety of drugs (1–4). Horton (5, 6) showed that the intravenous (iv) administration of prostaglandins exert a variety of stimulatory and inhibitory actions on the CNS in cats and chickens. In addition, PG were found to cause increased intraocular pressure (IOP) and miosis in animals (7–10). Thus, it has been postulated that PG may play physiological and pathophysiological roles in the CNS and in the eye of animals and humans (3, 4, 6). The present study was undertaken to investigate the effects of an iv infusion of prostaglandins E_2 (PGE_2) and $F_{2\alpha}$ ($PGF_{2\alpha}$) on the carotid arterial pressure, IOP and cerebrospinal fluid pressure (CSFP) in anesthetized dogs.

Methods. Mongrel dogs weighing between 20 and 28 kg were anesthetized by the intravenous (iv) administration of sodium pentobarbital (30 mg/kg). Endotracheal intubation was performed, and the animals were allowed to breathe spontaneously. Systemic arterial pressure was measured continuously with a Statham pressure transducer (P23AA) connected to a polyethylene catheter (PE 160) placed in a femoral artery. The CSFP and IOP were measured continuously with Statham pressure transducers (P23BB) connected, respectively, to a size 20 spinal needle inserted percutaneously into the cisterna magna, and to a size 24 needle inserted directly into the anterior chamber of an eye. Common carotid arterial blood flow was measured continuously with a Biotronics Laboratories (Silver Spring, MD) electromagnetic flowmeter (Model 310) using a Micron Industries (Los Angeles, CA) electromagnetic flowmeter probe (Model MQ 4035) applied around the right common carotid artery. Heart rate was measured using a Sanborn electrocardiograph (Model 1500A). All of the parameters measured except for heart rate were recorded continuously with a Sanborn recorder (Model 771K-04A).

The effects of a continuous intravenous infusion of PGE_2 (1 μg/kg/min) or $PGF_{2\alpha}$ (2 μg/kg/min) were studied in dogs using a Harvard Infusion Pump (Model 600-910). Each prostaglandin was dissolved in 95% ethanol (10 mg/ml) and further diluted with 0.9% NaCl solution to make a 100 μg/ml solution prior to infusion into the dog. Previously, the magnitude of the changes in the superior vena caval pressure induced by PGE_2 or $PGF_{2\alpha}$ was found to be very small as compared with that in the systemic arterial pressure (11). Hence, carotid arterial peripheral resistance (peripheral resistance unit) was computed by dividing mean systemic arterial pressure (mm Hg) by carotid arterial blood flow (ml/min). The data in this paper were evaluated statistically, employing the *t* test (12).

Results. The effects of a continuous iv infusion of PGE_2 or $PGF_{2\alpha}$ on the heart rate, mean systemic arterial pressure, carotid arterial blood flow, IOP and CSFP were studied in 16 anesthetized dogs. The results of the study are summarized in Figs. 1 and 2. The iv administration of PGE_2 (1 μg/kg/min) significantly increased heart rate, carotid arterial blood flow, IOP and CSFP as mean systemic arterial pressure and carotid

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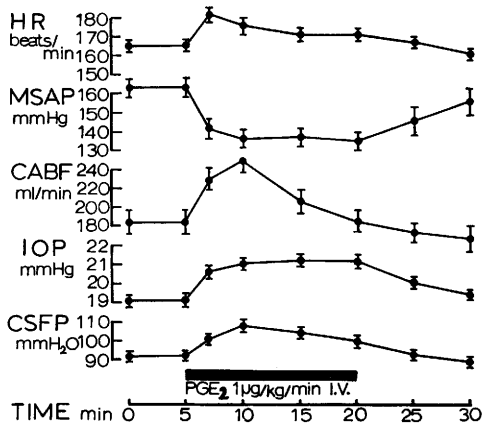

FIG. 1. Effect of the continuous iv infusion of PGE_2 (1 µg/kg/min) on heart rate (HR), mean systemic arterial pressure (MSAP), carotid arterial blood flow (CABF), intraocular pressure (IOP) and cerebrospinal fluid pressure (CSFP) in 8 dogs. Each point represents the mean values of the parameters. The vertical bars denote the standard errors of the means.

arterial peripheral resistance fell markedly. Initially, mean systemic arterial pressure fell and IOP rose rather rapidly, but these two parameters became stabilized during the period of the infusion. On the other hand, after their initial marked increases, heart rate, carotid arterial blood flow and CSFP returned toward or to control levels in spite of the continued infusion of PGE_2 at a constant rate. Following the cessation of the PGE_2 infusion, all parameters gradually returned toward control values except for carotid arterial blood flow which further decreased slightly below control after the infusion had ended. Otherwise, approximately 15–20 min elapsed before the complete return to control parameters.

The iv infusion of $PGF_{2\alpha}$ (2 µg/kg/min) decreased heart rate, carotid arterial blood flow and CSFP as carotid arterial peripheral resistance increased markedly. Thereafter, these parameters became stabilized during the period of the infusion. In 4 out of 8 dogs $PGF_{2\alpha}$ infusion initially increased slightly both mean systemic arterial pressure and IOP, but these increments are statistically insignificant. After a slight rise, IOP decreased to levels significantly below control as the infusion continued. On discontinuation of this infusion, all the parameters measured gradually returned to or toward control values. Approximately 15–20 min elapsed before their complete return.

Discussion. From the results of the present study, it is evident that the iv infusion of PGE_2 increases heart rate, carotid arterial blood flow, IOP and CSFP as systemic arterial pressure falls significantly. On the other hand, the infusion of $PGF_{2\alpha}$ decreases heart rate, carotid arterial blood flow, IOP and CSFP without producing any significant change in systemic arterial pressure.

The hemodynamic changes induced by PGE_2 and $PGF_{2\alpha}$ in this study are essentially in agreement with the observations made previously in this laboratory (4, 14–16) and by others (17–20). The hemodynamic effects of PGE_2 are mostly due to its direct vasodilator action on the carotid arteries and other regional vascular beds in dogs. It should be noted that the PGE_2 infusion initially increases the carotid arterial blood flow markedly as carotid arterial peripheral resistance decreases. However, the carotid arterial blood flow gradually decreases thereafter, and carotid arterial peripheral resistance increases toward control values in spite of the

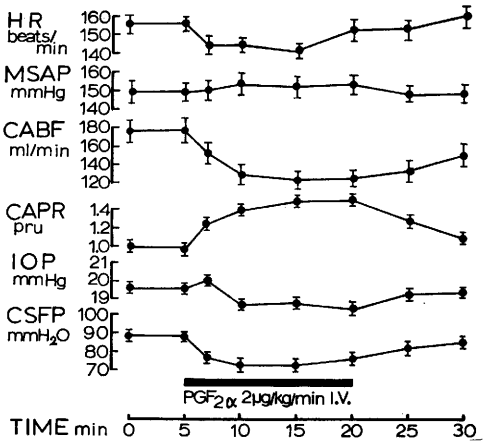

FIG. 2. Effect of the continuous iv infusion $PGF_{2\alpha}$ (2 µg/kg/min) on heart rate (HR), mean systemic arterial pressure (MSAP), carotid arterial blood flow (CABF), carotid arterial peripheral resistance (CAPR), intraocular pressure (IOP) and cerebrospinal fluid pressure (CSFP) in 8 dogs. PRU represents peripheral resistance unit (mm Hg/ml/min).

continuous constant infusion of PGE_2. From previous observations in this laboratory (unpublished data), it appears that a continuous iv infusion of PGE_1 or PGE_2 initially decreases total peripheral resistance and increases cardiac output markedly (4, 11). Thereafter, these PG increase total peripheral capacitance, hence reducing systemic venous return and subsequently the cardiac output due to the sequestration of blood in the splanchnic circulation.

$PGF_{2\alpha}$ infusion decreases the carotid arterial blood flow as the carotid arterial peripheral resistance increases markedly. Previously, $PGF_{2\alpha}$ was found to increase cardiac output and systemic arterial pressure together with the increase in total peripheral vascular resistance although systemic venous return and regional blood flow decreased significantly (14, 16). A single injection of $PGF_{2\alpha}$ increases systemic arterial pressure (14, 16) whereas, as seen in this study and in others (20), a continuous infusion of $PFG_{2\alpha}$ does not change it significantly. It appears that a continous iv infusion of $PGF_{2\alpha}$ gradually decreases systemic venous return and cardiac output, which offset the pressor effect of $PGF_{2\alpha}$ caused by an increase in total peripheral resistance.

In addition to the marked hemodynamic effects of PGE_2 and $PGF_{2\alpha}$, the present study shows that a PGE_2 infusion increases and a $PGF_{2\alpha}$ infusion decreases IOP and CSFP in dogs. There appear to be multiple factors influencing both IOP and CSFP, including the ocular or cerebral blood flow, the rate of production and absorption of the aqueous humor or cerebrospinal fluid, arterial and venous pressures and other factors (22). Previously, it was found that an intracameral injection of PGE_1, PGE_2 and $PGF_{1\alpha}$ causes miosis and increases IOP in the rabbit (7–10). The present study shows that an iv infusion of PGE_2 increases and that of $PGF_{2\alpha}$ decreases IOP and CSFP in dogs. The changes in the IOP and CSFP appear to be due not only to the direct effect of these substances on the eye but also to their indirect effect on carotid arterial blood flow and on the subsequent change in the formation of the aqueous humor. Hence, the results obtained in the present study on the effects of an iv infusion of PGE_2 upon IOP in dogs are essentially in agreement with those reported previously by others in the rabbit (7–10). In contrast, in the present study, the iv $PGF_{2\alpha}$ infusion decreases both IOP and CSFP as carotid arterial blood flow decreases markedly. This observation does not seem to be in accordance with that reported by Beitch and Eakins (9) after the intracameral injection of $PGF_{2\alpha}$ in the rabbit. In their study, $PGF_{2\alpha}$ might not have reduced the carotid arterial blood flow simply because of the intracameral injection. In contrast, in the previous study, the marked decrease in carotid arterial blood flow caused by an iv infusion of $PGF_{2\alpha}$ may decrease the rate of production of the aqueous humor so markedly that the IOP decreases significantly. Probably, a similar mechanism may have been operant for the production of the CSF, thus resulting in the reduction of CSFP. Recently, both PGE_2 and $PGF_{2\alpha}$ have been used rather extensively for the induction of natural labor and therapeutic abortion as well as for contraception (22, 23). A question has been raised as to whether a continuous infusion of PGE_2 and $PGF_{2\alpha}$ would cause glaucoma or worsen the eye symptoms of the patient with glaucoma (23). This study indicates that this could occur with a PGE_2 infusion but not with a $PGF_{2\alpha}$ infusion.

Summary. The effects of PGE_2 and $PGF_{2\alpha}$ on carotid arterial blood flow, IOP and CSFP were studied in anesthetized dogs. It was found that an iv infusion of PGE_2 decreases systemic arterial pressure, and increases heart rate, carotid arterial blood flow, IOP and CSFP. During the period of infusion, however, after an initial increase, carotid arterial flow gradually decreases to control levels. In contrast, an iv infusion of $PGF_{2\alpha}$ decreases heart rate, carotid arterial blood flow, IOP and CSFP, as mean systemic arterial pressure remains essentially unchanged. This study suggests that the changes in IOP induced by PGE_2 or $PGF_{2\alpha}$ are not only due to their direct effect on the eye but also due to their effect on carotid arterial blood flow. In contrast, the changes in the CSFP are most likely due only to the effects of PGE_2 and

$PGF_{2\alpha}$ on carotid arterial blood flow.

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