EFFECT OF PROSTAGLANDIN E_1 AND NORADRENALIN ON CEREBROVASCULAR TONE AND ARTERIAL BLOOD PRESSURE

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Prostaglandin E_1 (PGE_1), in solution with ethanol, when injected into the carotid artery, increases the tone of the cerebral blood vessels and the arterial blood pressure, whereas PGE_1 without ethanol gives the opposite effect. When PG biosynthesis is blocked by indomethacin, the pressor effect of noradrenalin on the cerebral vessels was considerably increased. It is postulated that PGE_1 is an important component of the system participating in the genesis of cerebral hypertension and determining the character of its course.

KEY WORDS: Prostaglandins; noradrenalin; cerebral hypertension; systematic hypertension.

The suggestion has been made that prostaglandins of the E and F series participate on the genesis not only of hypertension [4, 9] but also of cerebral vasospasm [12].

The effect of prostaglandin E_1 (PGE_1) on the cerebrovascular resistance and the pressor effect of noradrenalin on the brain vessels during the action of PGE and during inhibition of biosynthesis of endogenous prostaglandins were studied in the investigation described below.

EXPERIMENTAL METHOD

Experiments were carried out on 25 cats weighing 3–4 kg and anesthetized with urethan (0.6 g/kg) and chloralose (50 mg/kg). The resistance in the systems of the maxillary arteries was recorded by Resistography [1–3]. The arterial blood pressure and respiration were recorded simultaneously. PGE_1 crystals (Upjohn) were dissolved by Yamamoto's method [12]. In some experiments PGE_1 was dissolved in ethanol according to instructions supplied by the Upjohn Company. Solutions of PGE_1 (10 μg/kg) and noradrenalin (Bayer 5 μg/kg) were injected into the carotid artery. A solution of indomethacin (Polfa), made up by Palmer's method [10], was injected intravenously (1 μg/ml/min).

EXPERIMENTAL RESULTS AND DISCUSSION

Depending on the way in which its crystals were dissolved, PGE_1 had opposite effects on cerebrovascular tone and the arterial pressure.

The generalized results of 10 experiments in which PGE_1 was injected are illustrated in Fig. 1. In solution with ethanol PGE_1 lowered both the arterial pressure (by 12.7%) and the tone of the cerebral vessels (by 18.4%). The duration of the hypotensive effect in the first case was 151.8 ± 4.77 sec and in the second case 273.8 ± 6.29 sec. PGE_1 without ethanol led to an increase in the arterial pressure (by 7.64%) and an increase in the resistance of the cerebral vessels (by 13.78%). The duration of the effects was 115.6 ± 3.4 and 139.4 ± 1.5 sec, respectively.

The results are in agreement with these of Yamamoto [12] who described the vascoconstrictor effect

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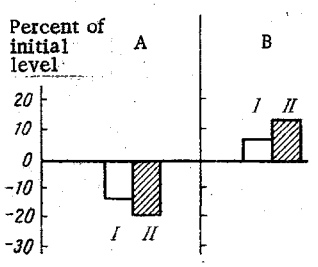

Fig. 1

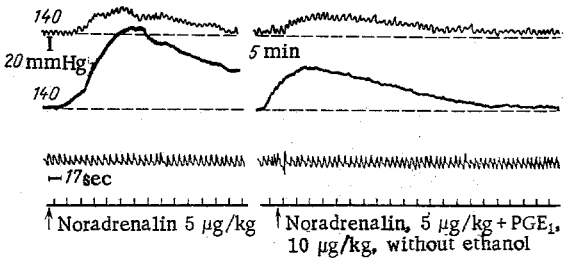

Fig. 2

Fig. 1. Effect of PGE_1 (10 μg/kg), injected with (A) and without (B) ethanol, on systemic arterial pressure (I) and cerebrovascular tone (II).

Fig. 2. Combined effect of noradrenalin and PGE_1 on systematic arterial pressure, cerebrovascular resistance, restoration, time marker.

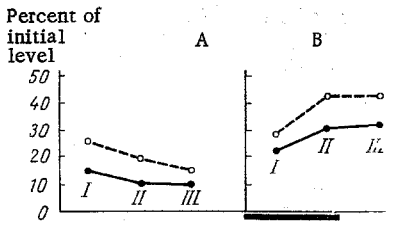

Fig. 3. Effect of noradrenalin (5 μg/kg) on cerebrovascular tone (broken line) and systemic arterial pressure (continuous line): A) without indomethacin; B) after intravenous infusion of indomethacin. I, II, III) Successive injections of noradrenalin.

of PGE_1 on the cerebral vessels, and they confirm his view that ethanol, in low concentrations, can inhibit the vasoconstrictor effect of PGE_1.

The vasodilator effect of PGE_1 described earlier [5, 7] can be explained by the presence of the ethanol in solution.

Data on the ability of PGE_1 to increase the resistance of the cerebral vessels, and also on antagonism between PG and catecholamines [6, 11], make it necessary to investigate interaction between PGE_1 and noradrenalin.

Prostaglandins are known to disappear from the blood in the course of one circulation through the body. Noradrenalin and PGE_1 were therefore injected from the same syringe. When the preparations were given in this manner the pressor effect of noradrenalin was considerably reduced. One experiment of this series is demonstrated in Fig. 2.

The results showed that an increase in the concentration of endogenous prostaglandins may be the mechanism of restriction of the effects of noradrenalin. In particular, after intraarterial injection of noradrenalin or stimulation of the sympathetic nerve, the liberation of prostaglandins from the spleen is increased [8], and prostaglandins reduce the effects of noradrenalin and of sympathetic stimulation.

In experiments in which repeated injections of the same dose of noradrenalin were given, each successive injection was accompanied by a gradual decrease in the degree of the pressor effect (Fig. 3A). The duration of the effects of noradrenalin also decreased successively (after 27 and 51 sec). Against the background of intravenous infusion (for 3 min) of indomethacin, which blocks prostaglandin synthesis, injection of noradrenalin gave a much greater pressor effect than without indomethacin (Fig. 3B). A second injection of noradrenalin after indomethacin infusion led, not to a decrease, but to a further increase in the pressor effect and in its duration (by 62 sec on the arterial pressure and 239 sec on the perfusion pressure). A third injection of noradrenalin under the same conditions caused no further increase in the pressor effect, but it lasted 2 h.

At the beginning of indomethacin infusion, before prostaglandin synthesis was completely suppressed, injection of noradrenalin was probably accompanied by the liberation of a certain quantity of prostaglandins. As the effect of indomethacin became total, noradrenalin was no longer able to excite the system of its antagonists and its pressor effect increased progressively.

On the basis of these experiments it is difficult to assess the role of PGE_1, for indomethacin blocked the synthesis of all prostaglandins. However, PGE_1 can be assumed to be an important component of the system determining the course of cerebral hypertension.

Prostaglandin deficiency in the body produced, in particular, by a disturbance of their biosynthesis, may play a decisive role in the genesis of hypertension and of cerebrovascular disturbances. Stimulation

of the biosynthesis of certain prostaglandins must evidently prevent the exhibition of vasoconstrictor responses in the body.

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