RESPONSE OF THE CEREBRAL VESSELS TO NORADRENALIN DURING HYPOCAPNIA AND INHIBITION OF PROSTAGLANDIN BIOSYNTHESIS

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Hypocapnia caused by forced hyperventilation appreciably reduces the pressor action of noradrenalin on the cerebral vessels and lowers the arterial pressure. When prostaglandin biosynthesis is inhibited by indomethacin while hypocapnia continues, injection of noradrenalin into the brain vessels is accompanied by a marked increase in the cerebrovascular resistance and in the arterial pressure. It is concluded that prostaglandins play an important role in the mechanism of autoregulation of the cerebral circulation and, in particular, under conditions of adrenergic stimulation and hypocapnia.

KEY WORDS: hypocapnia; noradrenalin; prostaglandins; pressor responses; cerebral circulation.

A homeostatic role of prostaglandins (PG) in the cerebral circulation has recently been claimed [2, 3, 6, 7]. Considering the modulating role of PG in adrenergic transmission [4, 5, 11] and also the high sensitivity of the brain vessels to changes in pCO_2 of the arterial blood, in the investigation described below the effect of noradrenalin (NA) on the cerebrovascular resistance and arterial pressure was studied during hypocapnia and inhibition of PG biosynthesis.

EXPERIMENTAL METHOD

Seven cats weighing 3-4 kg, anesthetized with urethane (0.6 g/kg) and chloralose (50 mg/kg) were used. Listhenon (Chemie Linzag) was used as muscle relaxant and the animals were artificially ventilated. Changes in the resistance of the cerebral arteries in the system of the internal maxillary arteries were recorded resistographically with the aid of a peristaltic pump. At the same time the arterial pressure was recorded and the pH and pCO_2 of the arterial blood were determined by the micro-Astrup method using a Radiometer system. A solution of NA (Bayer, 5 μg/kg) was injected into the perfusion fluid. A solution of indomethacin (Polfa), made up by the method of Palmer et al. [13], was injected intravenously (1 mg/ml/min) with the aid of a specially made automatic syringe.

EXPERIMENTAL RESULTS AND DISCUSSION

During normocapnia (pCO_2 36 mm Hg) injection of NA caused the arterial pressure to rise by 44 mm Hg and the perfusion pressure by 38 mm Hg. During hypocapnia (pCO_2 16 mm Hg) marked depression of vasoconstrictor activity of NA was observed: The pressor effect with respect to arterial pressure was reduced by 63.7% and to perfusion pressure by 44.8% compared with normocapnia. During continued hypocapnia, intravenous infusion of indomethacin helped to restore the pressor effect of NA on the cerebral vessels (Fig. 1).

The combined results of all seven experiments are given in Fig. 2. During normocapnia (pCO_2 37.8 ± 2.99 mm Hg) injection of NA led to an increase of 33.00 ± 4.18 mm Hg in the arterial pressure and of 35.50 ± 4.34 mm Hg in the perfusion pressure. During hypocapnia (pCO_2 14.60 ± 1.96 mm Hg) a reduction in the pressor effect of NA on the brain vessels was

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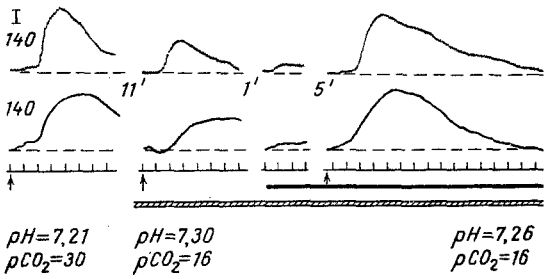

Fig. 1

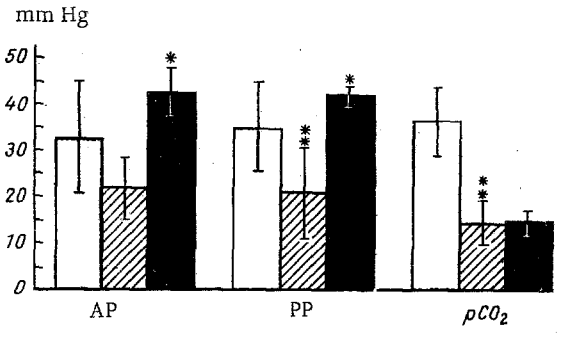

Fig. 2

Fig. 1. Effect of noradrenalin on tone of cerebral vessels and systemic arterial pressure during hypocapnia and inhibition of prostaglandin biosynthesis. From top to bottom: systemic arterial pressure, cerebrovascular resistance, time marker (17 sec); calibration 20 mm Hg. Arrows mark injections of noradrenalin (5 μg/kg); continuous line represents infusion of indomethacin (1 mg/ml/min); shaded line corresponds to hypocapnia.

Fig. 2. Effect of noradrenalin (5 μg/kg) on tone of cerebral vessels and systemic arterial pressure during hypocapnia and inhibition of prostaglandin biosynthesis (combined data). Ordinate, response of systemic arterial (AP) and perfusion (PP) pressure and of pCO_2 of arterial blood to noradrenalin during normocapnia (unshaded columns), hypocapnia (obliquely shaded columns), and hypocapnia with inhibition of prostaglandin biosynthesis (black columns). Asterisk indicates statistically significant ($P < 0.05$) change compared with effects during hypocapnia; two asterisks — the same compared with effects during normocapnia.

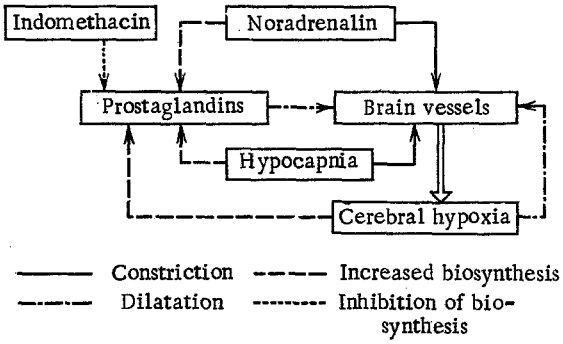

Fig. 3. Scheme of possible role of prostaglandins in the vascular effects of noradrenalin.

observed: 32% ($P > 0.05$) for the arterial pressure and 40.2% ($P < 0.05$) for the perfusion pressure compared with normocapnia. Infusion of indomethacin during continuing hypocapnia considerably increased the cerebrovascular resistance (103.7%; $P < 0.001$) and the arterial pressure (92.7%; $P < 0.001$) in response to injection of NA. If the pressor action of NA during infusion of indomethacin was compared with that during normocapnia, the increase in arterial pressure was found to be 29.7% and in the perfusion pressure 21.6%.

Hypocapnia reduces the cerebral blood flow and this effect is clearly manifested in the system of intraparenchymal vessels of the brain. Hyperventilation, leading to marked hypocapnia, can induce a hypoxic state in the brain tissue as a result of marked vasoconstriction and a reduction in the cerebral blood flow [10]. It has been shown that elevation of pCO_2 is accompanied by a linear increase in the cerebral blood flow, but during hypocapnia this increase is linear only in the initial stage. During a further decrease in pCO_2 changes in the cerebral blood flow become less marked. The limit of the decrease in the cerebral blood flow during hypocapnia does not exceed 40% [16].

According to some reports [14, 16], further intensification of cerebral hypoxia is prevented by the accumulation of metabolites (CO_2, H^+).

On the basis of the results of the present experiments the mechanism of homeostasis of the cerebral circulation can be reappraised. First, it is evident that during hypocapnia the reactivity of the brain vessels was considerably depressed (the pressor effect of NA was re-

duced). Vessels already in a state of spasm from whatever cause evidently responded weakest of all to the new constrictor agent because of the existence of powerful protective mechanisms in the body, counteracting spasm of the vessels in general and of the cerebral vessels in particular. The role of CO_2 in these processes is difficult to explain, for this antagonism between it and NA has not been found with respect to the cerebral vessels. Moreover, hypocapnia increases the vasoconstrictor action of NA on the brain vessels [8].

In the light of new data on the ability of PG to counteract the effects of NA [5, 9, 12], participation of PG in the mechanism of the changes described above can be suggested. In fact, inhibition of PG biosynthesis by indomethacin during hypocapnia, when the pressor effect of NA was considerably inhibited, not only restored it but also led to a greater increase in the cerebrovascular resistance and arterial pressure in response to NA. Hence it follows that the decrease in the pressor effect of NA could be due to accumulation of PG.

A hypothetical scheme of the role of PG in the vascular effects of NA during hypocapnia is given in Fig. 3. According to this scheme, besides causing constriction of the cerebral vessels, NA excites the system of its antagonists, namely PG [6], which limit any further constriction of the brain vessels.

Since NA quickly loses its activity in the body and its vascular effects are short-lasting, it can be postulated that the activation of biosynthesis of PG and their liberation should correspond in intensity to the vascular effects of NA. Nevertheless, as the writers' experiments [1, 6] showed, repeated injection of NA during normocapnia led to a marked increase in the PG concentration in the body, as a result of which the strength and duration of the pressor effect of NA were appreciably reduced. During forced hyperventilation, when the state of hypocapnia was prolonged in character, the liberation of PG was evidently continuous, thus preventing a possible catastrophe. Naturally, during increased production of PG, injection of NA led to a much smaller pressor effect than during normocapnia.

There is also evidence that hypoxia itself stimulates PG production [17]. It is difficult at present to say what is the relative role of hypocapnia in the stimulation of PG biosynthesis. Its effect is perhaps mediated through hypoxia, for metabolic changes induced by hyperventilation are more dependent on cerebral hypoxia than on the specific effect of a lowered pCO_2 [15]. The explanation of this problem must await further investigation.

The results described above thus suggest that PG play an important role in the mechanism of autoregulation of the cerebral circulation, especially under conditions of adrenergic stimulation and hypocapnia.

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