EFFECT OF CERVICAL SYMPATHECTOMY AND CIRCULATORY HYPOXIA ON TIME COURSE OF PROSTAGLANDIN CONCENTRATION IN BRAIN TISSUES

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The mechanisms of regulatory and adaptive changes during hypoxia and the ways of correction of ischemic injuries to brain tissue are among the most urgent problems in present-day biology and medicine. Nevertheless the relations between adrenergic and cholinergic mechanisms of adaptation and the role of the sympathetic nervous system in the regulation of brain metabolism and in the regulation of cerebrovascular tone, including under hypoxic conditions, are problems which have received little study. One possible component of the chain of regulatory and compensatory changes in the metabolism and circulation of the brain during circulatory hypoxia is the prostaglandins (PG).

There is at present no doubt about the role of PG in the formation of the cellular response to extracellular hormonal regulation [4, 7, 10]. However, the possibility cannot be ruled out that endogenous PG exert their action intracellularly also, before secretion, i.e., that they play the role of intracellular "messengers," with a direct influence on cell metabolism.

Experiments in recent years have demonstrated conclusively the important role of PG in activity of the nervous system. A topical yet one of the least studied aspects of these investigations is the elucidation of the mechanisms of PG participation in synaptic transmission processes. It has been suggested that PG are formed by an effector cell in response to the action of a neuromediator and that they regulate the process of synaptic transmission at the level of the pre- or postsynaptic membrane. PGF and PGE are probably competitive modulators of noradrenalin secretion [9].

It has been suggested that PG perform the role of local self-regulated mechanism, based on the negative feedback principle, preventing excessive activation of the sympathetic nervous system [12, 14].

An influence of PG on tone of the vascular wall has been established. PG of the A and E groups are known as vasodepressors and they differ only in the intensity of their vasodilator action on different animals. Injection of PGE weakens vasoconstriction induced by noradrenalin. The action of $PGE_{2\alpha}$ is dose-dependent and biphasic in character. Weeks [16] characterizes $PGE_{2}\alpha$ as a cerebral vasoconstrictor.

On the basis of the facts described above an investigation of the role of PG in responses of adaptation to cerebral ischemia and also the dependence of these processes on integrity of the sympathetic innervation of the cerebral vessels is undoubtedly interesting. The aim of the investigation described below was to determine the effect of cervical sympathectomy (CSE) on the time course of changes in PG(E + A) and $PGE_{2\alpha}$ under conditions of normoxia and circulatory hyposia.

EXPERIMENTAL METHOD

Albino rats weighing 150-180 g were used. CSE was performed by bilateral removal of the superior cervical ganglia 1, 7, 14, and 40 days before the main determinations. Circulatory

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hypoxia was produced by ligation of both common carotid arteries (for 15 and 120 min). The operation was performed under superficial ether anesthesia. A mock operation was done on the control animals. PG were determined in the brain tissue by a radioimmunologic method using the kit of reagents from Clinical Assay (USA). The radioactivity of the samples was determined on a Mark-III Nuclear Chicago (USA) scintillation counter. The numerical data were subjected to statistical analysis and the significance of differences from the control determined at the $P \leqslant 0.05$ level.

EXPERIMENTAL RESULTS

Biphasic changes in the PG(E + A) level were found in the sympathectomized rats (Table 1, Fig. 1). An increase in the PG(E + A) concentration was found on the 1st and 7th days, normalization on the 14th day, and a fresh increase in the PG concentration on the 40th day after CSE. The $PGE_{2\alpha}$ concentration rose sharply on the 7th day after CSE, then returned to the control level. It can be tentatively suggested that the changes observed in the PG concentration are connected with changes in the catecholamine level in the brain tissue after CSE and changes in the sensitivity of the brain tissues to blood catecholamines [2]. Changes in the PG level on the 1st day after removal of the superior cervical ganglia were probably connected with activation of the sympathico-adrenal system as a result of operative stress. The effects of desympathization itself appeared on the 7th day after CSE. The increase in the PG level, especially $PGE_{2\alpha}$, at this period was probably a manifestation of adaptive responses. Unlike PGE, PGF are known to potentiate the effects of sympathetic stimulation and to increase the sensitivity of adrenoreceptors. The facilitation of adrenergic transmission caused by PGF is found in particular in smooth-muscle cells of the vascular wall [1, 9]. Later, probably, the sensitivity of the brain tissues to the blood catecholamines increases and the deficit of sympathico-adrenal regulation is thereby made good.

Some workers [8, 11, 15] suggest a possible "transmembrane" role of PG in the nervous system. The trend of PG biosynthesis in the nervous system can be changed depending on its functional state. In the period of rest PGE synthesis predominates, whereas stimulation evokes an increase in the PGE concentration [9]. Low concentrations of PGE_1, PGE_2, and $PGF_{2\alpha}$ (from 3 mM to 0.3 μM) inhibit Ca-dependent noradrenalin secretion in response to electrical stimulation of the sympathetic nerves; inhibitors of PG synthesis potentiate evoked noradrenalin secretion [13]. Noradrenalin stimulates PG biosynthesis [5].

Differences in the action of PG are determined by specific interaction between individual PG and the various receptors of the plasma membranes of nerve cells and also with particular systems of cyclic nucleotides. PGE have been shown to be connected mainly with adrenergic, and PGF with cholinergic mediator processes [6]. The results of the present experiments probably reflect the time course of changes in activity of the adrenergic and cholinergic systems after removal of the superior cervical ganglia and interruption of the sympathetic nerve chain.

Maximal changes in the concentration of PG of both groups were observed on the 7th day after CSE. At the same time an increase in the liability of the tissues to bleed during the operation and during application of ligatures on the carotid arteries and maximal mortality of the animals exposed to circulatory hypoxia were observed (80% of rats died during ischemia 7 days after CSE). Cerebral ischemia led to a mortality of only 25% of the animals in the course of 1 day when the sympathetic nerve chain was intact.

Cerebral ischemia led to an increase in the concentrations of PG(E + A) and, in particular, $PGF_{2\alpha}$ in the cerebral cortex of the rats (Table 1; Figs. 2 and 3). The results showing a sharp increase in the concentrations of $PGF_{2\alpha}$ and PG(E + A) in the initial hours of cerebral ischemia are in agreement with data in the literature on the time course of changes in the blood PG levels in myocardial infarction. An increase in the concentrations of PGE and $PGF_{2\alpha}$ was found on the 1st day of the disease; later the PG levels in the blood plasma and myocardium depended on the severity of the course of myocardial infarction. If the outcome was favorable, a tendency toward its normalization was noted [3].

Cerebral ischemia against the background of CSE led, in turn, to fresh disturbances of the PG level. Circulatory hypoxia 1 day after CSE was accompanied by a fall in the PG(E + A) level to control values. Cerebral ischemia 7 to 40 days after CSE led to a fall in the PG(E + A) level, whereas after circulatory hypoxia for 2 h a second increase was observed in the PG(E + A) concentration although, admittedly, it was less than that at the same time after

TABLE 1. Effect of CSE and Circulatory Hypoxia on PG Level in Cerebral Hemispheres of Rats (M ± m)

Duration of action of hypoxia, min	PG (E+A)					PG $F_{2\alpha}$				
	Time after CSE, days									
	control	1	7	14	40	control	1	7	14	40
Control	128,4±2,5 n=8 (4,8)	181,4±6,1* n=12 (6,4)	202,8±8,5* n=9 (1,5)	150,4±3,1 n=10 (4,8)	240,1±2,8* n=7 (7,4)	27,0±1,5 n=8	28,5±2,1 n=10	135,7±4,7† n=10	31,3±1,9 n=10	32,4±1,5 n=8
15	233,4±4,3† n=9 (2,2)	114,4±1,9 n=7 (2,3)	142,8±2,6 n=8 (1,1)	94,4±2,3* n=10 (2,7)	118,9±2,3 n=6 (1,1)	107,5±3,7† n=10	51,8±1,8† n=7	124,6±3,9† n=12	34,2±2,1 n=11	117,7±3,8† n=8
120	327,8±9,7† n=11 (2,1)	122,9±1,9 n=12 (3,1)	182,8±5,0* n=9 (1,5)	173,0±2,7* n=9 (2,1)	159,3±3,5 n=7 (2,5)	156,1±4,1† n=10	39,9±1,6* n=10	128,6±3,5† n=9	82,7±2,5† n=9	62,7±3,1† n=10

Legend. n) Number of animals; ratio of concentration of PG(E + A) to total PG concentration given in parentheses. *) $P \leq 0.05$, †) $P \leq 0.01$.

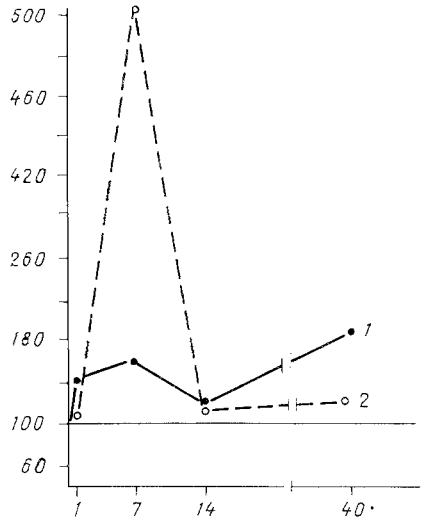

Fig. 1

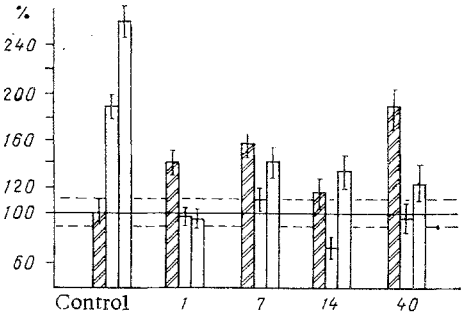

Fig. 2

Fig. 1. Effect of CSE on PG(E + A) (1) and $PGF_{2\alpha}$ (2) levels in tissues of rat cerebral hemispheres. Here and in Figs. 2 and 3: abscissa, time after CSE (in days); ordinate, changes in PG concentration (in %).

Fig. 2. Effect of CSE and circulatory hypoxia on PG(E + A) concentration in tissues of rat cerebral hemispheres. Here and in Fig. 3: first columns represent control or CSE, second columns — circulatory hypoxia for 15 min, third columns — circulatory hypoxia for 120 min.

CSE alone. If the increase in the PG(E + A) level during ischemia is regarded as a protective reaction, it must be admitted that no increase took place 1 day after CSE, and it was considerably weakened 7-40 days after CSE.

The concentration of $PGF_{2\alpha}$, which has a vasoconstrictor action on the cerebral vessels, was increased during ischemia 1, 14, and 40 days after CSE compared with its level at the same time after CSE alone. A sharp rise in the $PGF_{2\alpha}$ concentration was observed 7 days after CSE. The effect of cerebral ischemia was virtually indistinguishable from the action of CSE itself. It will be noted that when the sympathetic innervation was intact, the effect of circulatory hypoxia of the brain was much greater than the effect observed against the background of CSE.

It can be postulated that with the form of circulatory hypoxia used (one of the most widely used models) generalized activation of the sympathico-adrenal system takes place when the carotid arteries are compressed. Consequently, the increase in the PG level observed in the present experiments during circulatory hypoxia may be due to two factors: cerebral ischemia and activation of the sympathico-adrenal system.

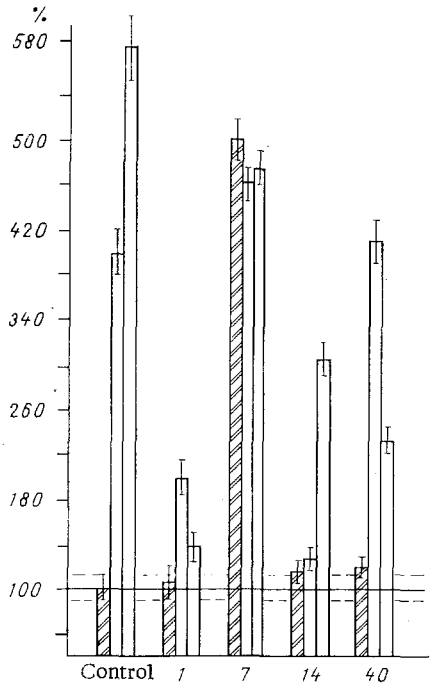

Fig. 3. Effect of CSE and circulatory hypoxia on $PGF_{2\alpha}$ concentration in tissues of rat cerebral hemispheres.

Preliminary CSE thus led to a definite reduction in the amplitude of changes in PG(E + A) caused by cerebral ischemia. It can be tentatively suggested that $PGF_{2\alpha}$ plays the main role in the regulation of tone of the vascular wall and in the regulation of metabolism under conditions of ischemia when the sympathetic regulation is disturbed.

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