EFFECT OF NORADRENALIN ON ENDOGENOUS PROSTAGLANDIN E AND $F_{2\alpha}$ PRODUCTION IN CEREBRAL AND EXTRACRANIAL VESSELS OF CATS

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The production of prostaglandins (PG) E and $F_{2\alpha}$ in the isolated cerebral and extracranial vessels of cats was determined quantitatively. Basal PG production was found to be greater in the cerebral vessels, and $PGF_{2\alpha}$ exceeded PGE. On incubation of isolated vessels with noradrenalin, production of vasopressor $PGF_{2\alpha}$ was reduced, and this was accompanied by a considerable increase in the content of vasopressor PGE. The difference was particularly marked in the cerebral vessels. The level of endogenous PG production by the cerebral vessels, it can tentatively be suggested, has an important role for the local regulation of vascular tone, and a disturbance of their dynamic ratio may be one cause of the development of cerebrovascular pathology.

KEY WORDS: prostaglandins; cerebral vessels; noradrenalin.

Prostaglandins (PG) of pressor (PGF) and depressor (PGE) types are known to be synthesized in the brain of various animals, and on the basis of this and other evidence in the literature, it has been suggested that PG play a role in the regulation of the cerebral hemodynamics [9, 10, 12, 14].

Considering the connection known to exist between the adrenergic component and PG in the regulation of the cerebral circulation [3, 14], it was decided to study this interaction at the level of the cerebral vessels.

The object of this investigation was accordingly a quantitative determination of endogenous PGE and $PGF_{2\alpha}$ production in the cerebral and extracranial vessels of cats and to study its changes under the influence of noradrenalin.

EXPERIMENTAL METHOD

Acute experiments were carried out on 22 cats weighing 3-3.5 kg, anesthetized with pentobarbital (25 mg/kg, intraperitoneally). Soon after decapitation the brain was removed as a whole and placed in artificial CSF [2] at room temperature, after which the proximal part of the middle cerebral artery was isolated and removed. A segment of the external carotid artery was removed at the same time. The two segments were weighed, placed in constant-temperature 20-ml containers and suspended in artificial CSF at 37°C with the addition of 95% O_2 and 5% CO_2 by means of a Thermomix 1420 system (Hugo Sachs Elektronik). After preincubation for 1 h the time was noted and liquid draining out was collected for 1 h for subsequent extraction of PG by the method of Unger et al., [14]. Noradrenalin solution (Lederle, 0.5 μg/ml) was next added to the chamber and the hourly effluent again collected for extraction. PG were identified by the method in [6]. For their quantitative determination biological tests were carried out on a segment on the rat large intestine [4]. The significance of differences between the experimental results was assessed by the Fisher–Student test.

EXPERIMENTAL RESULTS

The experiments showed that PGE and $PGF_{2\alpha}$ are produced both in the cerebral and in the extracranial vessels; the basal level of $PGF_{2\alpha}$ production, moreover, exceeded the PGE production both in the cerebral (by 1.7 times) and in the extracranial (by 2.7 times) vessels. It was also found that the cerebral vessels produced more PG than the extracranial vessels (2.1 times more PGE and 1.3 times more $PGF_{2\alpha}$).

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TABLE 1. PGE and $PGF_{2\alpha}$ Production (in g/g wet weight of tissue/h) in Cerebral and Extracranial Vessels of Cats before and after Incubation with Noradrenalin (results of 22 experiments)

	PGE		$PGF_{2\alpha}$	
	intact vessel	incubation with noradrenalin (5 μg/ml)	intact vessel	incubation with noradrenalin (5 μg/ml)
Cerebral vessels	$2{,}33\times10^{-7}$ ($\pm0{,}49$)	$8{,}89\times10^{-7}$ ($\pm1{,}33$)	$4{,}05\times10^{-7}$ ($\pm0{,}92$)	$1{,}64\times10^{-7}$ ($\pm0{,}61$)
P		$<0{,}001$		$<0{,}05$
Extracranial vessels	$1{,}10\times10^{-7}$ ($\pm0{,}51$)	$3{,}40\times10^{-7}$ ($\pm1{,}48$)	$3{,}00\times10^{-7}$ ($\pm1{,}07$)	$1{,}28\times10^{-7}$ ($\pm0{,}35$)
P		$>0{,}05$		$>0{,}05$

The results in Table 1 show that after incubation of the cerebral and extracranial vessels for 1 h with noradrenalin PGE production in the cerebral vessels was increased considerably (by 3.8 times; $P < 0.001$) compared with the results in the absence of noradrenalin. This shift in the extracranial vessels was not statistically significant. Incubation of the cerebral and extracranial vessels with noradrenalin led to diametrically opposite changes in the $PGF_{2\alpha}$ concentration: In the cerebral vessels its production was reduced by 2.4 times ($P < 0.05$); in the extracranial vessels the reduction was not statistically significant compared with results obtained without noradrenalin.

These findings raise a number of questions which require explanation. First, the ability of the cerebral and extracranial vessels to produce certain quantities of vasoactive PG of both pressor and depressor groups spontaneously. Figures for PGE production by bovine cerebral arteries given in the literature [12] are very similar to those now obtained (2.2×10^{-7} g/g wet weight of tissue per hour). The presence of biochemical systems responsible for biosynthesis of vasoactive PG in the walls of blood vessels is evidence that PG play an active role in the mechanism of the functional organization of vascular tone.

Second, the fact that more PG are produced by the cerebral than by the extracranial vessels is interesting and may perhaps reflect the higher functional activity of the former.

Third, there is the fact that noradrenalin, a vasoconstrictor, increases the production of vasodepressor PGE and reduces that of $PGF_{2\alpha}$ in the cerebral vessels. Besides its vasodilator effect, PGE has been shown to suppress the response of blood vessels to noradrenalin [5], whereas $PGF_{2\alpha}$, which possesses vasoconstrictor properties, enhances the vasoconstrictor response to adrenalin and accelerates liberation of adrenergic mediator [7]. Consequently, increased production of PGE and reduced production of $PGF_{2\alpha}$ in the blood vessel wall under the influence of adrenalin may be an important counteracting mechanism preventing an excessive vasoconstrictor effect of noradrenalin, and this could be of great physiological importance.

In cerebrovascular disturbances accompanied by spasm of the cerebral vessels this relationship is probably disturbed and $PGF_{2\alpha}$ production is increased under the influence of adrenergic stimuli. In the case of the cerebral vessels this assumption is not unlikely if the possibility that PGE can be changed into $PGF_{2\alpha}$ by means of PGE-9-ketoreductase in vivo [8] and the increase in the $PGF_{2\alpha}$ content with a simultaneous decrease in PGE in the venous blood of patients with cerebrovascular crises [1] are borne in mind. Finally, PGE and $PGF_{2\alpha}$ production by the walls of the cerebral vessels and changes in their production in response to adrenergic stimuli indicate that the cerebral vessels are not passive effectors of extravasal impulses (nervous, humoral, etc.) and that the final state of their tone also depends on the level of endogenous production of physiologically active substances, in this case of vasoactive PG and the dynamics of the ratio between their two types, which may be disturbed under pathological conditions and cause the development of spasm of the cerebral arteries.

These observations may also help to explain the nature of local regulation of the cerebral blood flow and its disturbances.

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