The investigation thus showed that during prolonged disturbance of the filtration function of the kidney as a result of a reduction in the blood flow the MC become capable of producing renin and they can be regarded as reserve cells of the JGA.

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BIOSYNTHESIS OF RENAL PROSTAGLANDINS IN SPONTANEOUSLY HYPERTENSIVE RATS

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The biosynthesis of prostaglandins (PG) E_2 and $F_{2\alpha}$ from [^{14}C]arachidonic acid by renal medullary tissue of rats with spontaneous hypertension and of normotensive Wistar rats was investigated at different ages (1.5 and 3.5 months). In animals with spontaneous hypertension the synthesis of PG E_2 from arachidonic acid was at a much lower level than in Wistar rats. The biosynthesis of PG $F_{2\alpha}$ in these animals was virtually indistinguishable from normal. No age differences were found in PG formation by the kidneys of rats with spontaneous hypertension, whereas in Wistar rats PG E_2 biosynthesis was depressed at the age of 3.5 months.

KEY WORDS: prostaglandins; hypertension.

Considerable attention has recently been paid to the prostaglandins (PG), biologically active substances of lipid nature [3]. It has now been shown that PG play an important role in arterial hypertension [3, 5, 8, 9, 11], but the mechanisms of their participation in this process have not yet been explained. The question of ontogenetic variations in the biosynthesis of renal PG both under normal conditions and in arterial hypertension likewise has not been settled.

It was accordingly decided to study the biosynthesis of PG E_2 and $F_{2\alpha}$ in the renal medulla of rats with spontaneous hypertension (SHR) from exogenous [^{14}C]arachidonic acid during ontogenetic development.

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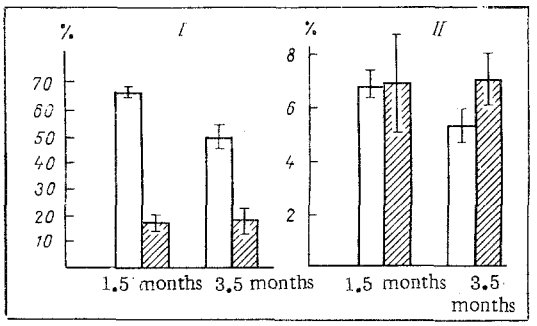

Fig. 1. Biosynthesis of PG E_2 (I) and PG $F_{2\alpha}$ (II) in Wistar and SHR rats. Unshaded columns – Wistar rats; shaded columns – SHR rats. Ordinate, degree of PG biosynthesis (in percentage of total radioactivity of arachidonic acid incorporation).

EXPERIMENTAL METHOD

Experiments were carried out on 14 Wistar rats aged 1.5 and 3.5 months and 15 male rats of the same age of the Okamoto-Aoki strain with spontaneous hypertension (SHR), nowadays regarded as one of the best experimental models of human essential hypertension.

After decapitation of the rats 25 mg of renal medulla was homogenized with 1 ml of phosphate buffer, pH 7.4, containing 20 mM EDTA, 0.57 μg/ml hydroquinone, and 56 μg/ml reduced glutathione. The homogenate was incubated with 0.01 μCi of [^{14}C]arachidonic acid (Radiochemical Centre, Amersham, England) for 1 h at 37°C in an atmosphere of carbogen. Biosynthesis was stopped with 9 vol of 96% ethanol. The extract was evaporated to water, the pH adjusted to 1.0, the product extracted three times with ether, evaporated to dryness, and subjected to thin-layer chromatography on "Silufol" (Avalier, Czechoslovakia) plates in a system of chloroform:methanol:acetic acid:water (90:9:0.65:1). Regions corresponding to PG E_2, PG $F_{2\alpha}$ (Upjohn Company, USA), and arachidonic acid (Merck) were cut out and their radioactivity was determined with a SL-30 liquid scintillation counter (Intertechnique, France). The degree of biosynthesis was expressed as a percentage of the total radioactivity.

EXPERIMENTAL RESULTS

The blood pressure of the SHR rats was 160-200 mm Hg and of the control Wistar rats between 100 and 125 mm Hg.

As Fig. 1 shows, PG E_2 biosynthesis in the Wistar rats depended on age. The highest level of biosynthesis (per unit weight of medulla) was found in young rats aged 1.5 months (66.4 ± 1.4%) and it decreased with age (to 49.5 ± 3.6%; $P < 0.001$). It is interesting to note that the formation of PG $F_{2\alpha}$ did not change significantly with age (6.9 ± 0.5 and 5.2 ± 0.6%, respectively).

Comparison of PG formation in Wistar and SHR rats showed that in animals with spontaneous hypertension PG E_2 synthesis from arachidonic acid was at a much lower level than in the control (16.9 ± 3.2% at 1.5 months; 17.5 ± 5.0% at 3.5 months; $P < 0.001$). As regards PG $F_{2\alpha}$, no such difference was discovered (6.8 ± 1.8% at 1.5 months; 7.0 ± 0.9% at 3.5 months). No age changes in PG biosynthesis were found in the SHR rats.

In normal Wistar rats a considerable age difference is thus observed in PG biosynthesis: The production of the principal renal depressor prostaglandin E_2 falls with age, whereas the formation of the sole pressor prostaglandin $F_{2\alpha}$ is unchanged. Considering that arterial hypertension develops more often in old age, one factor contributing to this result could evidently be the observed decrease in the relative proportion of the depressor component of the kidney.

As yet there has been only one investigation of age differences in the production and metabolism of renal PG [12], in which PG biosynthesis remained unchanged at different stages of postnatal development (in rats aged 19 and 24 days and adult rats), despite a marked difference in the activity of the enzymes metabolizing PG in the kidneys. This could be connected with the fact that when the author cited studied biosynthesis in young rats, in some samples he used homogenates of whole kidneys, as a result of which some of the newly formed PG could be rapidly metabolized by enzymes present in the renal cortex.

The physiological role of increased PG formation in the young animal may be to stimulate the blood supply to the growing, developing kidneys (PG are known to increase the renal blood flow). On the other hand, it has been shown that in young infants the concentrating power of the kidneys is considerably reduced [2]. This has been explained as a result of reduced formation of antidiuretic hormone (ADH). It may be that PG, which are diuretic agents and prevent the reabsorption of water, participate in this process. This could explain the increased PG biosynthesis in young rats aged 1.5 months, for competitive relations between PG and ADH have been described and they are known to have opposite effects on the cyclic AMP system.

Although a role of PG in the regulation of the arterial blood pressure is now accepted [8, 9, 15], the mechanisms of their participation in this process are by no means explained. Information on the content of renal PG in animals with experimental hypertension is limited in amount and contradictory in nature. A decrease in the size of the lipid granules in the interstitial cells of the kidney has been demonstrated in deoxycorticosterone (DOC)–salt hypertension [17], and it was interpreted initially as an indication of a decrease in PG biosynthesis. However, it has now been discovered that lipid granules are most probably the storehouse for precursors of renal PG, in particular, for arachidonic acid; a decrease in the granularity of the interstitial cells thus most probably reflects an increased demand of the substrate for PG synthesis and, consequently, an increase in their production. It has in fact been shown [18] that an incubated renal papilla from rats with post-salt hypertension secretes more PG E_2 than a papilla from normotensive rats. An investigation on rabbits [1] and another in the writers' laboratory on rats [4] demonstrated a fall in the renal PG concentration in animals during DOC + NaCl loading, which does not necessarily reflect the rate of their biosynthesis but could be the result of the more rapid utilization of PG for the excretion of large amounts of salt. This is a matter for further research.

Investigations with ischemia of the kidney showed that a decrease in the renal blood flow causes the liberation of PG into the renal venous blood in dogs [10] and in patients with renal hypertension [16]. Some workers have observed an increased PG content in the ischemic kidney [7, 15]. In other investigations a decrease in the concentration of renal PG was observed in vasorenal hypertension [6, 13, 14]. It is impossible on the basis of these data to draw any firm conclusions regarding changes in the prostaglandin system of the kidney in vasorenal hypertension.

The data at present available reveal changes only in the PG concentration in the kidney or blood. Any conclusions regarding the intensity of PG biosynthesis in hypertension must therefore be drawn with great caution. Other possibilities leading to changes in the PG concentration in the kidney cannot be ruled out. They may include the more rapid utilization of PG in connection with changes in the state of the kidney function and disturbances of the metabolism of these substances. For example, a fall in the PG concentration in the kidney could be the result of, first, a decrease in their biosynthesis (through a decrease in the activity of PG synthetase or as a result of a fall in the amount of available substrate – arachidonic acid); second, it could be due to increased "demand" for vasodilator or sodium-excreting agents and, consequently, their more rapid utilization. Finally, an increase in the intensity of PG metabolism could take place, and if biosynthesis remained unchanged this must also lead to a reduction in their concentration. The importance of the direct study of the production of renal PG in hypertension will thus be evident. Practically no such investigations have as yet been carried out. The writers showed that even in young rats with spontaneous hypertension the PG E_2 formation in the renal medulla is considerably reduced, most probably as a result of a decrease in PG synthetase activity. It is difficult at present to say why this should be so. It may perhaps be the result of inborn defects or of hemodynamic changes in the kidney. Whatever the reason, there is no doubt that this disturbance of the formation of renal PG must be a significant factor maintaining the high level of the blood pressure in these animals.

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POSSIBLE ROLE OF PROSTAGLANDINS A_1 AND B_1 IN SPASM OF THE INTERNAL CAROTID ARTERIES

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Experiments were carried out on the internal carotid artery of a dog, isolated from the rest of the circulation and continuously perfused in situ with oxygenated Ringer–Krebs bicarbonate solution. Prostaglandins A_1 and B_1 (PGA_1 and PGB_1) cause contraction of the artery. The effect of both prostaglandins was much less, but more prolonged, than the effect of the same doses of serotonin. The following facts are evidence of a possible role of prostaglandins in the development of angiospasm: a) In response to the repeated action of PGA_1 and PGB_1 their effect is unchanged and it therefore ought probably not to be reduced during the prolonged action of these prostaglandins on the vessel wall; b) PGA_1 and PGB_1 potentiate the constrictor effect of both serotonin and noradrenalin.
KEY WORDS: angiospasm; prostaglandins; internal carotid artery; serotonin; smooth muscles of blood vessels.

Although they were discovered more than 40 years ago the prostaglandins (PG) first attracted attention as physiologically active substances only in the 1960s. Unlike hormones produced by the glands of internal secretion, PG are formed in the cells of various tissues and they are regarded as "cell hormones." It has been suggested that PG are synthesized and broken down comparatively quickly and that their physiological effect is mainly local [1, 2]. Most PG (A_1, B_1, E_2, $F_{2\alpha}$) have a vasoconstrictor action, but some (mainly E_1, and inconstantly) have a vasodilator action [2, 12]. The constrictor effect of PG (A_1, E_2, and $F_{2\alpha}$) has also been demonstrated on the cerebral vessels; they were dilated by PGE_1 [3, 10, 11].

The object of this investigation was to study the action of PGA_1 and PGB_1 on the internal carotid artery which, if the behavior of different parts of the arterial system of the brain and the physiological mechanisms controlled by them [4] are taken into account, must be the most typical site of origin of angiospasm in the brain [5, 9].

EXPERIMENTAL METHOD

Experiments were carried out on 19 dogs in which the internal carotid artery was isolated from the rest of the circulation. The artery, remaining in situ and with its innervation intact, was perfused continuously with oxygenated Ringer–Krebs bicarbonate solution through a constant-output pump. The dynamics of the perfusion pressure thus reflected changes in the tone of the artery. Fuller details of the method were

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