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EFFECT OF TYPE E PROSTAGLANDINS ON CHANGES IN CEREBROVASCULAR RESISTANCE AND ARTERIAL PRESSURE PRODUCED BY TYRAMINE

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Investigation of the cerebrovascular resistance and arterial blood pressure by resistography showed that type E prostaglandins inhibit the pressor action of tyramine on the cerebral vessels and on the blood pressure. Indomethacin, which inhibits prostaglandin biosynthesis, delayed the development of tachyphylaxis to tyramine and restored its pressor effect. Iproniazid, a monoamine oxidase inhibitor, did not affect the rate of development of tyramine tachyphylaxis following administration of indomethacin but potentiated the pressor effect of tyramine. It is suggested that the effect of indomethacin on the pressor effect of tyramine is based on increased sensitivity of the vascular adrenoreceptors.

KEY WORDS: cerebral circulation; tyramine tachyphylaxis; prostaglandins; indomethacin; monoamine oxidase inhibition.

Tyramine – a biogenic amine which exerts its action through the liberation of endogenous noradrenalin (NA) from the tissue reserves [4] – has for a long time been investigated as a potential factor in the pathogenesis of migraine [1, 7]. Meanwhile the results of recent investigations point to the ability of prostaglandins (PG) of types E and F to participate in the processes responsible for the onset of the attack of migraine [12, 13].

Many investigations of the effect of PG on adrenergic transmission in the smooth-muscle structure of the vascular wall have now been published [3, 6], but there is only scanty information in the literature on interrelations between tyramine and PG [8-10], and hardly anything at all has been published on the study of these interrelations at the level of the cerebral circulation.

The object of this investigation was to study: a) the effect of tyramine on the cerebrovascular resistance and arterial blood pressure (BP) during the action of PG of type E; b) tyramine tachyphylaxis following inhibition of PG biosynthesis by indomethacin and during inhibition of monoamine oxidase (MAO) by iproniazid.

EXPERIMENTAL METHOD

Acute experiments were carried out on 42 cats anesthetized with pentobarbital (50 mg/kg). Changes in tone of the cerebral arteries in the internal maxillary system were recorded by resistography, with the aid of

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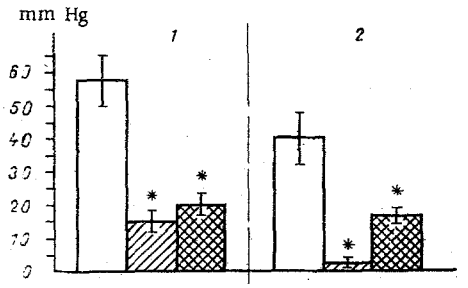

Fig. 1. Effect of tyramine on systemic BP and resistance of cerebral vessels during infusion of PGE_1 and PGE_2. 1) Responses of systemic BP; 2) responses of perfusion pressure; unshaded columns denote control effects of tyramine, obliquely shaded and cross-hatched columns show effects of tyramine during infusion of PGE_1 and PGE_2 respectively. Statistically significant results ($P < 0.001$ compared with the control) marked by an asterisk.

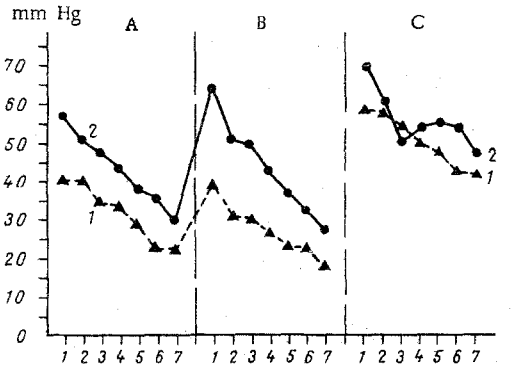

Fig. 2. Effect of repeated injection of tyramine on cerebrovascular resistance (1) and systemic BP (2) during inhibition of PG biosynthesis by indomethacin. A) Without indomethacin; B) during subsequent infusion of indomethacin; C) immediately after infusion of indomethacin. Abscissa, successive days of tyramine injections.

a peristaltic pump. The systemic BP was recorded at the same time in the femoral artery by a mercury manometer.

In the experiments (13) of series I tyramine (Ferak, 0.2 mg/kg) was injected into the carotid artery against the background of infusion of PGE_1 and PGE_2 (Upjohn, 5 μg in 1 ml during 1 min) by the same route. In the control group of animals tyramine was injected as a single dose into the carotid artery without PG. In the experiments (10) of series II the same dose of tyramine was injected intravenously on seven successive occasions. With the onset of marked tachyphylaxis, intravenous infusion of indomethacin (Polfa, 1 mg in 1 ml during 1 min) began. After 15 min, when PG biosynthesis was inhibited [14], a further seven injections of tyramine were given intravenously against the background of indomethacin. In the experiments (8) of series III the effects of repeated injection of tyramine (0.2 mg/kg, intravenously) immediately after the blocking of PG biosynthesis were studied. In the 6 experiments of series IV and the 5 experiments of series V the experiments of series II and III were repeated but after preliminary injection of the MAO inhibitor iproniazid (20 mg/kg intraperitoneally daily for 4 days). The significance of differences between the data for the experimental and control groups was estimated by the Fisher–Student criterion.

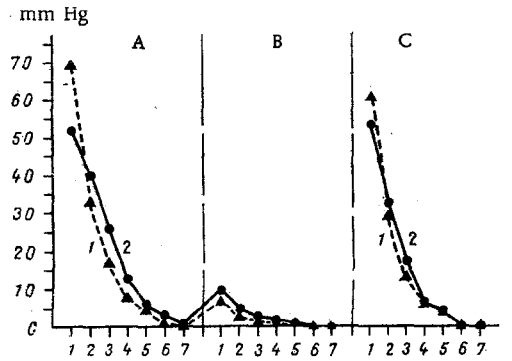

Fig. 3. Effect of repeated injections of tyramine on cerebrovascular resistance and BP during administration of indomethacin and the MAO inhibitor iproniazid. A) After iproniazid; B) injection of iproniazid followed by infusion of indomethacin; C) immediately after indomethacin and iproniazid. Remainder of legend as in Fig. 2.

EXPERIMENTAL RESULTS

The results of the experiments of series I (Fig. 1) showed that PGE_1 appreciably inhibits the pressor effect of tyramine observed in the control group. The effect of tyramine on BP was reduced in this case by 71% and on the resistance of the cerebral vessels by 93% compared with the control ($P < 0.001$). As is clear from Fig. 1, PGE_2 inhibited the pressor effect of tyramine less strongly, reducing its action on BP by 64% and on the cerebral vessels by 57% compared with the control ($P < 0.01$). Consequently PG of the E type, especially PGE_1, have the property of reducing the constrictor action of tyramine on the brain vessels.

The results of the experiments of series II (Fig. 2) showed that during seven injections the pressor effect of tyramine on the cerebral vessels gradually diminished (the effect of the last injection was inhibited by 44.1% compared with the first). The response of BP was correspondingly reduced by 47.2% (Fig. 2A). The first injection of tyramine 15 min after the beginning of intravenous infusion of indomethacin (Fig. 2B) led to a marked recovery of its pressor effect on the cerebral vessels (which was 69.5% greater than the effect of the 7th injection before infusion of indomethacin). With respect to BP, the blocking of PG biosynthesis not only restored the level of the first injection of tyramine before infusion of indomethacin, but exceeded it by 12.1%.

The blocking of PG biosynthesis thus led not only to restoration of the pressor effect of tyramine, but also to a marked decrease in the rate of development of tachyphylaxis (Fig. 2B).

A series of experiments was then carried out to study the effect of tyramine on the cerebrovascular resistance and BP during the blocking of PG biosynthesis but without the preliminary development of tachyphylaxis to tyramine, immediately after inhibition of PG biosynthesis was achieved. The results of series III (Fig. 2C) showed that under these circumstances tachyphylaxis developed much more slowly than in the previous experiments. For instance, the pressor action of the 7th injection of tyramine on BP was 31.2% less, and on the perfusion pressure 29.2% less than the action of the 1st injection.

The results of the experiments of series IV in which seven injections of tyramine were given after preliminary inhibition of MAO by iproniazid (Fig. 3) and after preliminary blocking of PG biosynthesis by indomethacin (Fig. 3B, C) showed that after MAO inhibition tachyphylaxis to tyramine developed much faster than in the absence of iproniazid (Fig. 3A). The pressor effect of tyramine at its first injection also was stronger than in the experiments without iproniazid.

Prostaglandins of type E thus inhibit the pressor action of tyramine on the cerebral vessels and BP, and PGE_1 is more active in this respect. These results agree with those obtained by other workers [9], who found a marked reduction in the vasoconstrictor activity of tyramine on peripheral vessels in dogs under the influence of PGE_1.

The ability of indomethacin to restore the pressor effect of tyramine after the onset of tachyphylaxis and to delay its onset substantially is a fact that deserves attention. Tyramine tachyphylaxis is known to be the

result of gradual exhaustion of the NA reserves in granules of axoplasm. The response of an organ to tyramine depends basically on two factors: the quantity of NA secreted and the sensitivity of the organ to it [2]. It has been shown that the heart ceases to respond to tyramine when the NA level in the myocardium is reduced to 45% of its initial value. The effects of tyramine under conditions of inhibition of PG biosynthesis can be tentatively explained either on the grounds that indomethacin enables further mobilization of the residual NA reserves or potentiates its biosynthesis, or by an increase in the sensitivity of the vascular adrenoreceptors to NA under the influence of indomethacin. It has been found [8] that PGE_2, in doses reducing NA secretion in response to stimulation of the sympathetic nerve of the spleen, did not inhibit the outflow of NA induced by tyramine. Consequently, the secretion of NA in response to stimulation of the nerve and under the influence of tyramine takes place by different mechanisms. PG have no action on NA secretion under the influence of tyramine, which is a process independent of Ca^{2+} [5]. It has also been shown [10] that NA increases the outflow of PG, whereas tyramine does not have this property. The recovery of the pressor effect of tyramine after tachyphylaxis, brought about by the blocking of PG biosynthesis, can thus hardly be connected with an increase in the liberation of NA. On the same grounds the possibility of increased biosynthesis of NA is unlikely. Indomethacin has been shown to inhibit dopa-decarboxylase activity, thereby reducing NA synthesis [15]. Hence it follows that an increase in the sensitivity of the vascular adrenoreceptors to NA is a possible mechanism of the restoration of the pressor effect of tyramine after tachyphylaxis and also of the marked decrease in the rate of its onset during blocking of PG biosynthesis. This hypothesis is confirmed by other experiments [6], which showed that repeated injection of the same dose of NA during infusion of indomethacin is accompanied by an increase in the pressor effect of NA.

It is interesting to note that under MAO inhibition conditions, depression of the pressor effect of tyramine, i.e., tachyphylaxis, develops very rapidly. Against this background the infusion of indomethacin left the response of the brain vessels to subsequent injection of tyramine almost unchanged. Only a weak pressor effect was observed, and this soon disappeared during the subsequent injections of tyramine.

During MAO inhibition the rate and character of onset of tachyphylaxis likewise remained unchanged after preliminary blocking of PG biosynthesis. This may perhaps be explained by the fact that tyramine, protected against enzymic hydrolysis, acts more aggressively on the preservation of NA and exhausts its reserves quickly. Consequently, as a result of the increased sensitivity of the vascular receptors after blocking of the PG system, the initial pressor response is stronger than when MAO is functioning, and rapid exhaustion of NA soon follows.

Data [11] indicating that MAO inhibition leads by a negative feedback mechanism to a decrease in the rate of synthesis of dopamine and NA. Naturally under these conditions hypersensitization of the vascular adrenoreceptors could hardly delay the onset of tachyphylaxis to tyramine, as was found in the experiments with intact MAO.

It can thus be concluded that inhibition of PG biosynthesis causes hypersensitivity of the vascular adrenoreceptors, which leads to restoration of the pressor response to tyramine after the development of tachyphylaxis and delays its onset.

The decrease in sensitivity of the vascular adrenoreceptors to tyramine induced by PGE_1 and PGE_2 and its increase associated with the inhibition of their biosynthesis may play a definite role in the pathogenesis of migraine.

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