EFFECT OF LEUKOTRIENE E_4 ON THE CENTRAL HEMODYNAMICS AND ON VASCULAR CONTRACTILITY

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The discovery of a new group of arachidonic acid metabolites, the leukotrienes (LT), has significantly broadened our ideas on the physiological role of eicosanoids including their participation in regulation of cardiovascular function. It has now been shown that LTC_4 and LTD_4 raise arterial pressure (BP) and induce spasm of the blood vessels of the brain and heart, with disturbances of the regional circulation [6, 10, 11]. Much less attention has been paid to the study of LTE_4, from this point of view, and the mechanisms of its action on the vascular wall has not been explained. The aim of the present investigation was accordingly to study the effect of LTE_4 on parameters of the central hemodynamics and the mechanisms of its action on the cerebral and coronary vessels.

EXPERIMENTAL METHOD

The dimethyl ester of LTE_4, obtained by the method described previously [4, 5] and purified by high performance liquid chromatography on a DuPont 8800 instrument, was used. Experiments were carried out on mature Wistar rats weighing 150-200 g. BP was measured in the carotid artery with an electromanometer and recorded on a K-201 automatic writing potentiometer (East Germany). The stroke volume of the heart (SV) was determined by tetrapolar chest rheography, as described by Ismailov et al. [3], on the PKhCh-02 polygraph (USSR). The ECG was recorded in lead II on an EK-6-01 electrocardiograph (USSR). Contractility was studied on spiral strips of rat aorta and of the human basilar, middle cerebral, and anterior coronary arteries. The vessels were obtained 4-8 h after death, and vessels showing no evidence of atherosclerotic involvement were used in the experiments. We know that such vessels remain functionally completely normal, and respond adequately to vasoactive agents, and so on [1, 12, 13]. Contractions were recorded by means of an HSE Elekt isotonic transducer (West Germany). The investigations were conducted with observation of the recommendations of Karaki and Weiss [9]. The data were analyzed by the nonparametric Wilcoxon–Mann–Whitney test.

EXPERIMENTAL RESULTS

Under the influence of LTE_4 BP rose — by 18.2 ± 1.7% with a dose of 2 μg/kg and by 22.3 ± 2.4% with a dose of 4 μg/kg ($P < 0.05$). A further increase in the dose of the preparation injected did not lead to any increase in the pressor effect but, on the contrary, it was reduced. After injection of LTE_4 in a dose of 16 μg/kg BP rose by only 18.3%. In its pressor effect LTE_4 was weaker than noradrenalin in analogous doses, but the duration of the rise of BP produced by it was longer. The duration of hypertension after injection of LTE_4 in a dose of 4 μg/kg was 4-6 min, and in a dose of 8 μg/kg it was 5-12 min.

Analysis of the effect of LTE_4 on the central hemodynamics showed that its effect on BP is the result of two opposite actions. It was found that under the influence of LTE_4 a marked disturbance of the pumping function of the heart developed, with a fall of SV and of the cardiac output (CO). Conversely, the peripheral vascular resistance (PVR) increased (Fig. 1). Consequently, LTE_4 induces spasm of peripheral resistive vessels, which accounts for its pressor effect, the degree of which, however, is counterbalanced by a parallel fall of cardiac

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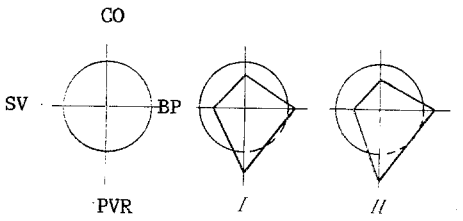

Fig. 1. Effect of LTE_4 in a dose of 2 (I) and 4 μg/kg (II) on the central hemodynamics.

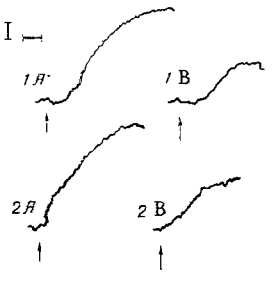

Fig. 2

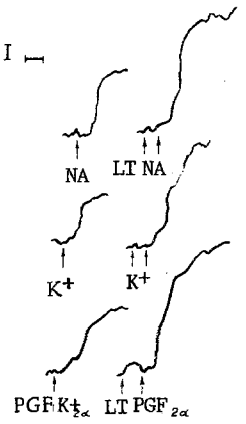

Fig. 3

Fig. 2. Effect of LTE_4 ($2 \cdot 10^{-6}$ M) on spiral strips of basilar (1) and anterior coronary (2) arteries. A) Intact vessels, B) after administration of verapamil (10^{-4} M).

Fig. 3. Effect of LTE_4 (10^{-7} M) on contractile effect of noradrenalin (NA), of potassium depolarization (K^+), and of $PGF_{2\alpha}$.

output. With an increase in the dose of LTE_4 the ability of this substance to depress CO rises sharply, and for that reason, when it is given in larger doses, its pressor effect is not increased, but reduced.

The experiments showed that under the influence of LTE_4 peripheral angiospasm may develop, and for that reason a more detailed investigation of this effect is interesting. Experiments showed that LTE_4 had no effect on the rat aorta, but caused contraction of spiral strips of the human cerebral and coronary arteries (Fig. 2). In the presence of verapamil, which blocks calcium channels, the contractile effect of LTE_4 was weakened, but still remained quite distinct (Fig. 2). Contraction of strips of arteries could be observed under the influence of LTE_4 in calcium-free medium also, in which it amounted to 30-50% of the maximal contraction. These facts are evidence that LTE_4 induces contraction of blood vessels through its influence on the entry of Ca^{++} into the myoplasm of the smooth-muscle cells of arteries both from the external medium and from intracellular depots.

LTE_4 was active on isolated preparations of blood vessels in concentrations of under 10^{-7} M. In a concentration of 10^{-7} M its effect was not significant, but under these conditions, it potentiated by 49.7 ± 2.9% contractions evoked by potassium depolarization (60 mM KCl, $P < 0.05$), and by 56.2 ± 0.2%, contractions evoked by noradrenalin ($P < 0.01$, Fig. 3). It is a particularly interesting fact that LTE_4, under these conditions, increased the contractile effect of $PGF_{2\alpha}$ by 50.9 ± 3.4% ($P < 0.01$, Fig. 3). There are grounds for the suggestion that the effect of $PGF_{2\alpha}$ is realized through the same receptor structures as that of thromboxane A_2 [2]. On the basis of the facts described above it can therefore be postulated that LTE_4 and thromboxane behave as synergists in their vascular effect.

Conversely, prostacycline (PGI_2) depresses the vasoconstrictor effect of LTE_4. Higgs et al. [8] showed that the constrictor action of LTC_4 and LTD_4 on smooth muscle is effectively inhibited by PGI_2. Our investigations showed that this applies also to LTE_4. It was found that the addition of PGI_2 ($5 \cdot 10^{-8}$ M) to the perfusion fluid reduced the contractile effect of LTE_4 by 68.8 ± 4.2% ($P < 0.01$).

The present investigation thus showed that LTE_4 is a vasoconstrictor, capable of exerting a pressor effect and of inducing spasm of the coronary and cerebral vessels. This corresponds to the action of LTC_4 and LTG_4, and confirms the concept of LT as systemic vasoconstrictor substances [10]. Under these circumstances, since LTE_4, like other LT, depresses CO, an increase in its plasma concentration can be regarded as an important risk factor for circulatory disorders in shock, for example, the hemodynamics during which also is characterized by disturbances of the pumping function of the heart with a sharp increase in peripheral resistance.

On the other hand, the marked effect of LTE_4 on the coronary and cerebral vessels presupposes its participation in the development of regional circulatory disturbances and, in particular, in the development of angiospasm. Even low concentrations of LTE_4 may lead to disturbances of the regional circulation on account both of its direct action on the vascular wall and, in particular, its sensitization to other vasotropic agents. Under these circumstances LTE_4 may modulate the vasoconstrictor effect of thromboxane, which increases still more the importance of its role in the pathogenesis of angiospasm, especially under conditions of defective prostacycline control of vascular tone and reactivity. All these considerations make the search for methods of pharmacologic regulation of the vascular effects of LT very important, and this is particularly true of the discovery of natural and synthetic antagonists of LT, which may be of great interest for the treatment of disturbances of the systemic and regional circulation.

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