α-TOCOPHEROL-INDUCED ACTIVATION OF THE ENDOGENOUS OPIOID SYSTEM

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It was shown previously that intramuscular injection of α-tocopherol with the aim of relieving the pain syndrome of dysmenorrhea has a rapid analgesic effect (after 10-15 min), accompanied by elevation of the β-endorphin-like immunoreactivity level in the venous blood [1].

The aim of this investigation was to study possible mechanisms of action of α-tocopherol in the opioid system, including its binding with opioid receptors and its effect on the content of opioid peptides in the adenohypophysis.

EXPERIMENTAL METHOD

Thirty Wistar rats were decapitated, their brains removed, the pituitary gland isolated at 25°C and the posterior lobe removed. The adenohypophyses were incubated in watch glasses in 0.5 ml of medium 199 (pH 7.4) in an atmosphere of 5% CO_2 and 95% O_2. After preincubation for 30 min, α-tocopherol was added to the medium (final concentration in the sample 10^{-5} M). Incubation was carried out for 30, 60, and 120 min. At each time the concentration of β-endorphins in the medium was studied; their concentration in the adenohypophyseal tissue was determined after 120 min of incubation. The study of the effect of α-tocopherol on binding of ligands of opioid receptors by brain membranes was carried out as in [4]; the membranes were isolated as described in [5]. A concentration of opioid peptides was expressed in β-endorphin units.

μ-Receptors were labeled with the special selective ligand (^{3}H/D-Ala^2) MePhe^4, Glyol^5-enkephalin (^{3}H-DAGO); Δ-receptors by the relatively selective ligand (^{3}H/D-Ala^2, D-Leu^5-enkephalin; ^{3}H-DADL) in the presence of 50 μM DAGO, which blocks μ-receptors; κ-receptors with ^{3}H-ethylcyclazocin, in the presence of DAGO and DADL, masking μ- and Δ-receptors; and γ-receptors by the selective ligand (+)(−)^{3}H/SKF 10047.

EXPERIMENTAL RESULTS

In a system in vitro α-tocopherol had no effect on opioid receptors. On the addition of α-tocopherol in concentrations of up to 10^{-4} M (final concentrations in the sample) to the incubation medium binding of ligands of opioid receptors with the brain membranes was unchanged. Thus α-tocopherol itself does not bind with opioid receptors and is not an opioid receptor agonist.

Addition of α-tocopherol (final concentration 10^{-5} M) to the medium during incubation of the adenohypophyses induced a marked rise in the β-endorphin content in the tissues of the adenohypophysis (Fig. 1) The β-endorphin level in the incubation medium after incubation for 60 min was significantly higher than values for the control group (Fig. 2).

The authors showed previously that termination of the pain syndrome after administration of α-tocopherol could be abolished in some patients by giving them naloxone [1]. These observations point to a role of the opioid system in suppression of the pain syndrome associated with dysmenorrhea. Repeated administration of α-tocopherol to patients in whom naloxone caused provocation of the pain syndrome had no analgesic effect. Another fact deserving at-

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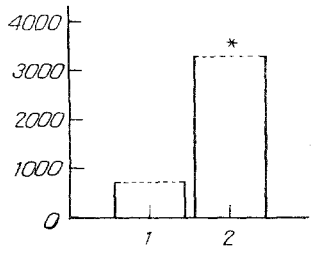

Fig. 1

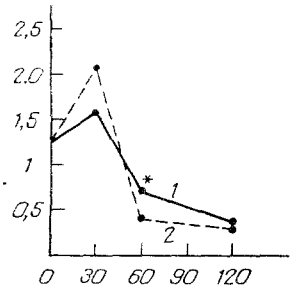

Fig. 2

Fig. 1. Changes in β-endorphin concentration in adenohypophyses of rats under the influence of α-tocopherol. Abscissa: 1) before addition of α-tocopherol; 2) after addition. Ordinate: β-endorphin concentration (in relative units). *$p < 0.05$ compared with 1.

Fig. 2. Dynamics of changes in β-endorphin concentration in incubation medium under the influence of α-tocopherol. Abscissa, incubation time (in min); ordinate, β-endorphin concentration (in conventional units). 1) α-Tocopherol; 2) control. *$p < 0.05$ compared with control.

tention is that after administration of α-tocopherol for 3 months for dymenorrhea, if naloxone was given to the treated women on the 1st day of the menstrual cycle, it did not give rise to painful sensations [1, 3]. These data suggest that as a result of long-term administration of α-tocopherol, comparatively persistent activation of the antinociceptive system develops.

It can thus be concluded from the results of previous [1, 2] and the present investigations, considered together, that α-tocopherol causes activation of the opioid system. The analgesic effect achieved in dysmenorrhea with the aid of α-tocopherol is therefore connected not only with its effect on the prostaglandin system [2], but also with its effect on the endogenous opioid system. These results raise the question of whether α-tocopherol can exert the effect described above in pain syndromes of other genesis.

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