ROLE OF THE ENDOGENOUS OPIOID SYSTEM IN THE ANALGESIC EFFECT OF α-TOCOPHEROL IN DYSMENORRHEA

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UDC 618.174-06:616.8-009.7-085.356:577.161.3]-036.8:[616-008.939.5:547.943

KEY WORDS: opioid system, α-tocopherol, dysmenorrhea

In dysmenorrhea there are repeated cycles of emotional–painful stress (EPS). This state is accompanied, as we know, by intensification of lipid peroxidation (LPO) [1, 2]. It was accordingly decided to use α-tocopherol acetate (vitamin E), which is a powerful natural antioxidant, for the treatment of dysmenorrhea. A rapid analgesic effect of the compound was observed, being exhibited as early as within 15-20 min after intramuscular injection (100 mg). Such a rapid onset of the analgesic action of vitamin E is difficult to explain purely by its antioxidant properties. The participation of endogenous opioid peptides in this process may be postulated.

The facts described above served as the basis for the present investigation, whose aim was to study the possible connection between the analgesic effect of vitamin E and mobilization of β-endorphin from the pituitary in patients with dysmenorrhea.

It has been shown that repeated stress leads to the accumulation of opioid peptides in the brain [3], and their reserves can increase the resistance of the body to subsequent exposures to stress [4, 5]. Meanwhile the effect of endorphin release from the adenohypophysis is closely linked with oxidized metabolites of arachidonic acid [6].

EXPERIMENTAL METHOD

Seven patients with dysmenorrhea were investigated: six had essential dysmenorrhea, and in the other case the dysmenorrhea was a symptom of internal congenital endometriosis. The patient's ages were between 20 and 35 years and the duration of the dysmenorrhea was more than 10 years in five patients and more than 15 years in two patients. All the patients had a history of some previous disturbance, a late onset of menstruation, or a relevant family history (of a sister or mother with dysmenorrhea). Six patients had primary dysmenorrhea and four had primary infertility. The patients with essential dysmenorrhea had no other gynecologic diseases.

β-Endorphin-like immunoreactivity was investigated at the height of the pain during menstruation and 15 min after an injection of vitamin E. Vitamin E (2.0 ml of a 50% solution) was injected intramuscularly immediately after the first blood sample was taken. Blood (10 ml) was taken from the cubital vein in the morning before breakfast, centrifuged for 15 min at 1000 g and at 4°C, the plasma was separated, and kept at −40° C until required for assay. β-Endorphin-like immunoreactivity was estimated by radioimmunoassay, using a commercial kit for β-endorphin determination in plasma (Cat. No. 4600, Immuno Nuclear Corporation, USA) by the method in [7].

In addition to this, the opioid peptide antagonist naloxone was given to nine patients with dysmenorrhea (five with primary, four with secondary). As regards their clinical characteristics, the groups were homogeneous. The underlying disease of the patients with secondary dysmenorrhea also was internal genital endometriosis, the duration of which did not exceed five years.

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 0007-4888/88/0002-0162$12.50

Naloxone hydrochloride (Narcan, USA), 0.4 mg/ml, was injected intramuscularly in a dose of 2.0 ml into patients with spontaneously disappearing menstrual pain in the morning before breakfast. To relieve any pain which may arise, vitamin E (2.0 ml of a 50% solution) was injected, also intramuscularly, immediately after the appearance of painful sensations.

The intensity of the pain was assessed in points: severe pain — 3 points, moderately severe — 2 points, dull, aching pain — 1 point.

EXPERIMENTAL RESULTS

A significant increase in β-endorphin-like immunoreactivity was observed in all six patients with essential dysmenorrhea after injection of vitamin E. At the height of the pain, for instance, the value of this parameter was 2.53 ± 0.22 pM, rising to 5.36 ± 0.89 pM after injection of α-tocopherol.

In a patient with secondary dysmenorrhea, on the other hand, the endorphin-like immunoreactivity declined after injection of the vitamin. Clinically, in all patients with primary dysmenorrhea, by the 15th minute after injection of α-tocopherol acetate, reduction of the pain was observed: in 5 women from 3 points to 1 point, in one from 3 to 2 points, whereas in the patient with secondary dysmenorrhea the intensity of the pain remained virtually unchanged during this period of time.

In three patients with primary dysmenorrhea treated with naloxone, intense pain identical with that usually experienced during menstruation developed, literally in "at the tip of the needle." Injection of 2.0 ml of a 50% solution of vitamin E from the time of appearance of the pain had no significant effect on its character or intensity. The pain was relieved toward the end of the second day after injection of anloxone; administration of vitamin E throughout this period in a total dose of 300-400 mg proved ineffective.

Injection of 2.0 ml naloxone into four women with secondary dysmenorrhea likewise led to the appearance of a menstrual-like pain immediately after the injection, but the pain was short-lasting and less severe than usually (during menstruation), sometimes appearing only 4-5 h after injection of the drug, and spontaneously disappearing after 20-30 min. If, however, on the appearance of the pain, vitamin E was given in the abovementioned dose, the pain was relieved in the course of 10-15 min.

Naloxone also was given to two patients with primary dysmenorrhea in whom vitamin E, given therapeutically during menstruation for 2 menstrual cycles in a total dose of 500-600 mg (in the duration of one menstrual cycle) had a lasting analgesic effect, i.e., during 6 months after witholding the drug, menstruation was painless. After injection of naloxone on the first day of menstruation, which was painless, no painful sensations appeared.

The results are thus evidence that one possible mechanism of a rapid analgesic action of vitamin E in dysmenorrhea is activation of a rapid analgesic system and, in particular, mobilization of β-endorphin from pituitry gland. This effect may be potentiated in the brain by administration of α-tocopherol. Evidence of involvement of the endogenous opioid system in the analgesic effect is given by the onset of a pan syndrome after injection of naloxone — an antagonist of morphine and of endogenous opioid peptides. It is interesting to note that the effect of naloxone may be long-lasting and intensive, and unable to be corrected by α-tocopherol: it continued for two days, and injection of α-tocopherol during this period had no analgesic effect. Meanwhile, the analgesic effect of α-tocopherol in dysmenorrhea may be very prolonged. As the investigation showed, administration of α-tocopherol during two menstrual cycles abolished the pain for 6 months (and we have had cases whose pain did not recur for one year after discontinuation of the preparation). The effects of α-tocopherol in secondary dysmenorrhea are not so consistent, and this may be attributed to the polymorphism of the pathogenesis of this pathological state.

It must be emphasized that the realization of the analgesic effect of α-tocopherol acetate in dysmenorrhea through activation of the endogenous opioid system is a newly discovered fact. It may be of more than usual interest for the study of the mechanism of analgesic effects and of the activity of the antinociceptive system.

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DEPENDENCE OF SKELETAL MUSCULAR FATIGUE ON MEMBRANE POLARIZATION OF DIFFERENT TYPES OF MUSCLE FIBERS IN TOURNIQUET SHOCK

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UDC 616.748-008.615-02:616-617.58-005.4-008.66

KEY WORDS: tourniquet shock, types of muscle fibers, fatigue

Tourniquet shock develops after restoration of the circulation in the ischemic limbs and it is accompanied by the release of breakdown products and toxic substances into the blood stream, causing a reduction in the circulating blood volume, retention of blood in depots, reduced polarization of muscle fibers, and so on [2, 11, 12]. The earliest microcirculatory and metabolic disorders in these forms of shock are found in muscle tissue [1, 3, 7]. In this period weakness of contractions of the skeletal muscles is observed [8] and death in endotoxic shock is considered to take place as a result of acute fatigue of the respiratory muscles [8]. However, it is not yet clear whether weakening of contractility of skeletal muscles in tourniquet shock is connected with a change in the membrane potentials of different types of muscle fibers and with the degree of their motor activity.

The aim of the present investigation was to study changes in the resting membrane potential (RMP) level of different types of fibers of skeletal muscles functioning periodically or continuously, and to determine the degree of their fatigue at different stages of development of tourniquet shock.

EXPERIMENTAL METHOD

Experiments were carried out on 60 noninbred albino rats of both sexes weighing 180-200 g. A tourniquet (standard rubber tourniquet, 8 turns) was applied to both hind limbs of the rats under ether anesthesia. The tourniquets were removed 6 h after being applied and postischemic arterial pyperemia of the skin of the feet was observed. Intact animals served as the control. The fast muscle of the forelimb (m. flexor carpi radialis) and a mouth-opening muscle (the anterior belly of the digastric muscle) were investigated. Contractility, fatigue, and RMP of the myocytes of flexor carpi radialis were determined 30 min, 1 h, and 1.5 h later, and parameters of membrane excitability of fibers of the digastric muscle were investigated 3, 6, and 12 h after removal of the tourniquet. Contractility and fatigue were evaluated by the standard method with periodic direct stimulation of the carpal flexor by pulses of current with a frequency of 60 Hz and duration 0.2 msec for 1 sec with intervals of 30, 60, and 120 sec. RMP and parameters of excitability of the myocytes (action potential, critical depolarization level, rheobase currents) were recorded by intracellular glass microelectrodes, using a standard amplification technique (UPT dc amplifier, FOR-2 camera). The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Since the dynamic characteristics, excitability, and contractility of skeletal muscles are determined by the composition of the muscle fibers [3], we studied RMP of myocytes at

Department of Pathological Physiology, N. A. Semashko Moscow Medical Stomatologic Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR, A. D. Ado.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 105, No. 2, pp. 150-152, February, 1988. Original article submitted June 16, 1987.

 0007-4888/88/0002-0164$12.50