PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Implication of the Hippocampus in the Development of a Pain Syndrome in Rats Following Sciatic Nerve Damage

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UDC 616.833.58-001.3-092.9-06:616.8-009.7-092-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 118, № 8, pp. 120-122, August, 1994
Original article submitted November 21, 1993

Local destruction or electrostimulation of the hippocampus did not affect pain sensitivity thresholds in rats with intact sciatic nerve. In rats with transected sciatic nerve, local hippocampal damage accelerated the development of a pain syndrome considerably, while hippocampal electrostimulation delayed it so that 80% of the test rats did not appear to have been experiencing pain throughout the 45-day observation period.

Key Words: *hippocampus; pathological algetic system; neurogenic pain syndrome*

Clinical and experimental studies have shown that limbic structures are involved not only in mediating physiological pain [1,9,11] but also in the development of pain syndromes [7,10,15,16]. It is not clear, however, what role in the mechanisms of physiological and pathological pains is played by the hippocampus, one of the central structures of the limbic system.

The purpose of the present study was to examine how destruction and electrostimulation of the hippocampus might influence thresholds of physiological pain and the development of a neurogenic pain syndrome which arises in rats after transection of the sciatic nerve.

MATERIALS AND METHODS

For the experiments, 110 male Wistar rats weighing 180-200 g were used. To elicit a neurogenic pain syndrome, the sciatic nerve was transected under Hexenal anesthesia (30 mg/kg intraperitoneally) below the site of its ligation, and the central portion of the nerve was placed in a polyethylene capsule to prevent its regeneration. The animals were considered to have developed a pain syndrome when their behavior was altered, autotomies were observed on the operated hind paw, and pain sensitivity thresholds were lowered [3]. The severity of the syndrome was rated in points from 1 to 11 using our modification of a previously proposed scoring scale [12]. Autotomic damage to one claw was assigned 1 point; to 2-5 claws, 2-5 points, respectively; to a phalanx on one digit, 6 points; to phalanges on 2-5 digits, 7 to 10 points, respectively; and damage to metatarsal bones, 11 points. Pain sensitivity thresholds were estimated by the hot plate and tail flick tests: licking the hind paws in response to the application of a hot (55°C) plate and flicking of the tail in response to focused radiant heat. The hippocampus was stimulated electrically and damaged locally on the side contralateral to sciatic nerve transection. Local hippocampal damage (areas CA1-CA3) was produced electrolytically - by passing a direct an-

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0007-4888/94/0008-0806$12.50

ode current (2 mA) for 1 min via a monopolar electrode insulated throughout its length except for the tip. The electrode was inserted into the hippocampus stereotactically 2.8 mm caudal to the bregma and 1 cm lateral to the midline, to a depth of 3.2 mm from the brain surface. The hippocampus was stimulated by square pulses (duration 0.1 msec; frequency 50 Hz) through bipolar Nichrome electrodes implanted according to the same stereotactic coordinates as above. Electrostimulation was started on the day following electrode implantation and continued for 2 weeks - a total of 14 daily 5-min sessions of intermittent stimulation (exposures of 10 sec each interrupted by 10-sec pauses) were administered. The intensity of the stimulating current was selected individually and its strength was not increased further when the rat began to exhibit a strongly marked orientative reaction and signs of the "wet dog" syndrome. The mean amplitude of the current was 8.6±4 V. The hippocampus was damaged or implanted with stimulating electrodes either one week before sciatic nerve transection or on the day of this operation.

There were four test groups, 20 rats in each. In group 1 the hippocampus was damaged one week before sciatic nerve transection and in group 2 on the same day. In group 3 the nerve was transected after the hippocampus had been stimulated as described above. In group 4, hippocampal electrostimulation was started on the day of nerve transection. Controls (n=15) for test groups 1 and 2 were rats in which the hippocampus was damaged, after sciatic nerve transection, by inserting and removing a monopolar electrode without delivering electric current. Rats (n=15) with divided sciatic nerve and with bipolar electrodes implanted into the hippocampus without subsequent electrostimulation served as controls for test groups 3 and 4. In test groups 1 and 3, the impact of hippocampal damage or electrostimulation on pain sensitivity thresholds was studied additionally under conditions of free behavior prior to sciatic nerve transection.

The results were treated statistically by methods of nonparametric statistics. When all tests were completed, the brains of the animals were removed to verify the sites of electrode placement and hippocampal damage.

RESULTS

In group 1 rats, the local hippocampal damage prior to sciatic nerve transection did not lead to any visible alterations in behavior, and these rats showed no significant changes in pain sensitivity thresholds, as judged by the tail flick (tf) and hot plate (hp) tests (tf=4.3±0.4 and hp=11.5±0.8 sec before hippocampal damage vs. 3.3±0.2 and 13.5±±1.2 sec, respectively, after it). In group 3 rats, hippocampal electrostimulation before sciatic nerve transection resulted in enhanced orientative-exploratory reactions, and the "wet dog" syndrome was observed when the stimulation intensity was increased; neither vocalization nor aversive reactions were noted throughout the electrostimulation session. Hippocampal stimulation (or damage) did not significantly alter pain sensitivity thresholds (tf = 5.4±0.2 and hp = 9.8±0.6 sec before stimulation and 6.1±0.2 and 11.8±1.3 sec, respectively, immediately after it).

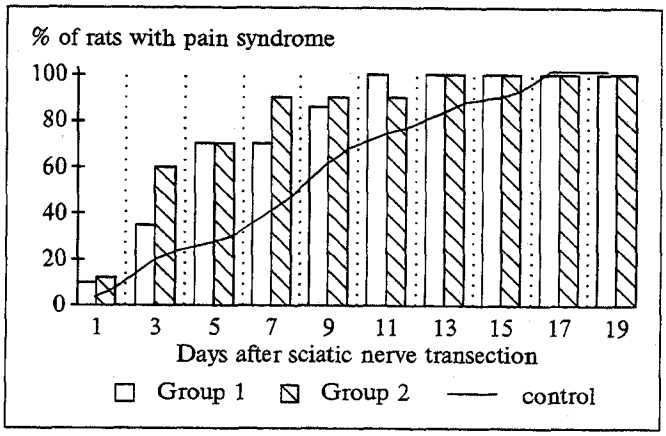

Fig. 1. Effect of hippocampal damage on temporal evolution of the pain syndrome in rats after sciatic nerve transection.

After sciatic nerve transection, however, both hippocampal damage and stimulation had a significant effect on the development of a neurogenic pain syndrome. Local hippocampal damage either before or at the time of sciatic nerve transection led to a more rapid onset and greater severity of this syndrome than in the respective control group

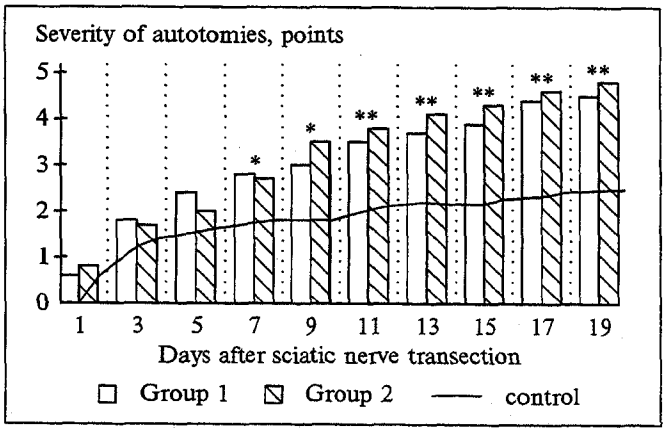

Fig. 2. Effect of hippocampal damage on pain syndrome severity in rats after sciatic nerve transection. One asterisk: p<0.05; two asterisks: p<0.01.

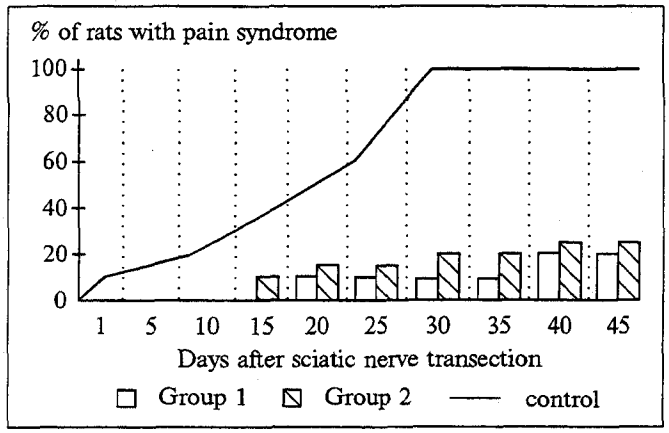

Fig. 3. Effect of hippocampal electrostimulation on temporal evolution of the pain syndrome in rats after sciatic nerve transection. Dark bars: control rats; light bars: test rats (groups 3 and 4).

(Figs. 1 and 2). In groups 3 and 4, on the contrary, hippocampal stimulation either delayed the onset of autotomies or, in most animals, prevented their occurrence throughout the 45-day observation period (Fig. 3).

The observed failure of local hippocampal damage to affect appreciably pain thresholds agrees with reports that removal of the hippocampus in human patients does not alter thresholds of tactile and pain sensitivity [6]. The absence of aversive reactions in rats during hippocampal stimulation is in accord with clinical observations: a temporary loss of contact with the patient (as a result of mental confusion and absence of any emotional reactions) is usually the most conspicuous symptom [8,13]. In addition to the absence of aversive reactions, no changes in pain sensitivity were recorded during hippocampal stimulation. This is at variance with the results of other researchers authors [14], who found that rats show increased pain thresholds without displaying aversive behavior during hippocampal stimulation. In our view, this seeming contradiction between our results and theirs is attributable to procedural differences: in our study the hippocampus was stimulated with pulses of direct current and the rats were allowed to move freely in the cage during stimulation, whereas in the study cited above [14] alternating sinusoidal current was used and the rats were restrained by hand during stimulation, which could have stressed them and increased their pain thresholds.

The findings that hippocampal damage and electrostimulation both substantially alter the time course of a neurogenic pain syndrome in animals with divided sciatic nerve but not in those with the intact nerve indicate that the hippocampus interferes with the mechanisms of pain sensitivity regulation only when pathological reactions develop in nociceptive structures of the brain. Such interference may involve a tonic inhibitory influence of the hippocampus on those nonspecific reticular structures of the brainstem and mesencephalon which are activated when the hippocampus is damaged and inhibited when it is stimulated [1]. Since neurogenic pain syndromes spring from the formation, in structures of the pain sensitivity system, of generators of enhanced excitation and the development of a new pathodynamic entity, namely, of a pathological algetic system (PAS) [5] whose activity involves nonspecific structures of the brainstem and mesencephalon [2], it may be deduced that hippocampal injury leads to accelerated formation of a PAS and to clinical manifestations of the pain syndrome, whereas hippocampal stimulation inhibits PAS formation and prevents pain development. Also, it may be inferred from what is known about the role the hippocampus plays in the isolation of new information, in the comparison of this information with that contained in the long-term memory, and in the retrieval of information from the memory in various emotional-motivational states [1,7], that when a new pathodynamic system is being formed, the hippocampus becomes actively involved in the reaction and acts as an additional controlling structure whose activity is directed at preventing PAS development. The inhibitory influence of the hippocampus on PAS formation in animals with divided sciatic nerve is most likely to result from its influence on plastic processes that go on in the central nervous system and cause some of the abnormal nociceptive afferent signals emanating from the damaged nerve to be redistributed to symmetrical structures of the "healthy" hemisphere, thereby preventing the generation of stable pathological hyperactivity in nociceptive structures of the central nervous system [4,5].

The study reported here warrants the conclusion that the formation of a PAS depends to a large extent on the functional state of the hippocampus - a structure whose main activity is associated with memory processes [1,7].

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Effects of α-Tocopherol in Rats with a Neuropathic Pain Syndrome

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UDC 616.8-009.7-02:615.356:577.161.3]-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 118, № 8, pp. 123-125, August, 1994
Original article submitted November 24, 1993

The rat model of a neuropathic pain syndrome (transection of the sciatic nerve with encapsulation of its central end) was used to evaluate the efficacy of the antioxidant α-tocopherol in such syndromes. It was found that administration of α-tocopherol 3 days before nerve transection and then for 3 weeks thereafter it delayed the development of the pain syndrome, which subsequently tended to subside. In contrast, a 3-week α-tocopherol treatment started when the pain syndrome had already set in failed to influence its evolution. α-Tocopherol markedly reduced manifestations of inflammatory and degenerative processes in the denervated limb.

Key Words: *generator of pathologically enhanced excitation; neuropathic pain syndrome; α-tocopherol; lipid peroxidation*

Damage to peripheral nerves and the consequent hyperactivity of central neurons in the system of pain sensitivity lead to the development of pain syndromes. It has been shown that the formation of a generator of pathologically enhanced excitation (GPEE) [1,2] and the establishment of a pathological algetic system (PAS) are of key importance in the pathogenesis of these syndromes [4, 16]. When the neurons have become hyperactive, the regulation of free-radical lipid peroxidation (LPO) is impaired, and this leads to substantial changes in cellular metabolism [9,17,18]. Agents that prevent or diminish imbalance of the LPO-regulating system, in particular antioxidants, delay the pathological process [6,9,10] and promote suppression of neuronal activity [8].

The present work was undertaken to study how the antioxidant α-tocopherol might influence the time course of the neuropathic pain syndrome arising after transection of the sciatic nerve [5,6].

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MATERIALS AND METHODS

A total of 56 random-bred male rats weighing 180-200 g were used. In all rats, the sciatic nerve was

0007-4888/94/0008-0809$12.50