Effect of Sodium Hydroxybutyrate in Pain Syndromes

E. I. Danilova, V. N. Grafova, R. U. Ostrovskaya, and V. K. Reshetnyak

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It is shown that sodium hydroxybutyrate exerts a preventive and therapeutic effect on models of neuropathic pain syndrome and adjuvant arthritis. The effects of sodium hydroxybutyrate are correlated with its ability to reduce hyperactivity of the neurons that are generators of pathologically enhanced excitation and to inhibit the pathological algetic system.

Key Words: *generator of pathologically enhanced excitation; pathological algetic system; neuropathic pain syndrome; adjuvant arthritis*

The pathophysiological basis of pain in various pain syndromes is the formation of a generator of pathologically enhanced excitation (GPEE) in the algetic system, the appearance and functioning of which stems from the insufficiency of inhibitory control of the neuronal population in this generator [2]. Hence, the pathological algetic system (PAS) is constructed from functionally interconnected units of pain sensitivity. Conceivable causes of the appearance of the generator and PAS formation are damage to the peripheral nerves in neuropathic pain syndrome and joint inflammation in adjuvant arthritis. This heightens the excitability of the nociceptive neurons in the dorsal horns of the spinal cord, the thalamic nuclei, and the brain cortex [3,9]. Inhibition or attenuation of the pain syndrome may be achieved with the aid of agents that depress GPEE activity and the impulse traffic produced by it. Sodium hydroxybutyrate (sodium salt of γ-hydroxybutyric acid — GHBA) is a neurotropic agent possessing a generally depressive effect on the spinal reflex apparatus [1] and blocking excitation at the thalamic level [6]. GHBA activates various monoaminergic systems, which is suggestive of its influence on the different PAS elements. The aim of the present investigation was to study the effect of GHBA in neuropathic pain syndrome and adjuvant arthritis.

Research Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences; Research Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow (Presented by G. N. Kryzhanovskii, Member of the Russian Academy of Medical Sciences)

MATERIALS AND METHODS

Experiments were carried out on 60 outbred albino rats weighing 180-200 g; 10 rats made up each experimental series. To create a neuropathic pain syndrome in the rats the sciatic nerve was cut under ether anesthesia at the level of the popliteal fossa. The proximal end was encapsulated in a polyethylene tube with a soldered tip and left *in situ* in the sutured wound. The pain syndrome was evaluated according to the appearance of autotomy of the denervated paw on an 11-point scale as follows: 1 point indicates injury to one claw; 2, 3, 4, and 5 injury to 2, 3, 4, and 5 claws, respectively; 6 points reflects amputation of a toe phalanx; 7, 8, 9, and 10 amputation of 2, 3, 4, and 5 toes, respectively; 11 points corresponds to amputation of a paw at the level of the tarsal joint. Adjuvant arthritis was induced by administration of 0.1 ml of Freund's adjuvant to the pad of the left hind limb. The severity of the process was assessed by the index of limb edema according to the formula: $(A-B)/B \times 100$, where A is the diameter of the joint after adjuvant administration, mm; B is the diameter prior to adjuvant injection, mm. GHBA was administered intramuscularly in a dose of 150 mg/kg twice a day

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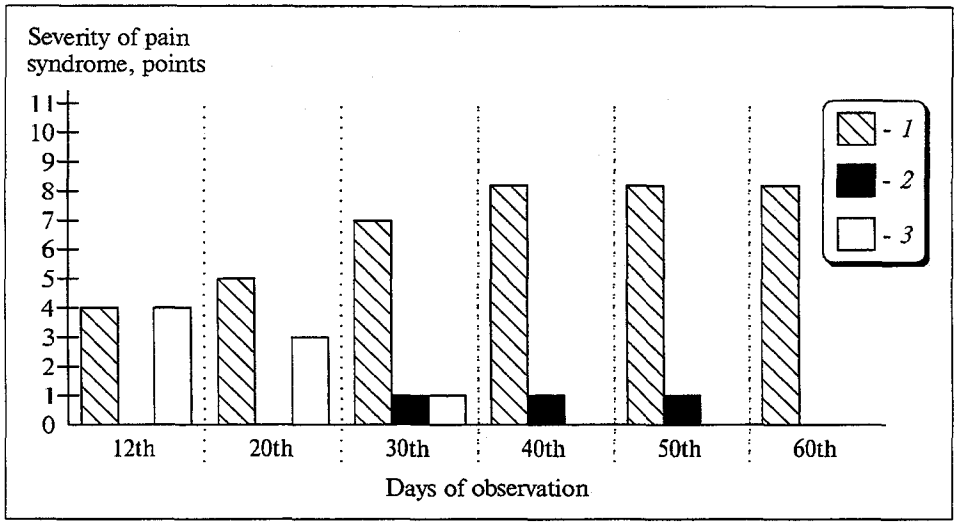

Fig. 1. Effects of GHBA in neuropathic pain syndrome. Control group (*1*); GHBA administered from the 1st (*2*) and 12th (*3*) day postoperation.

during 1 month prophylactically (from the 1st day postoperation in neuropathic pain syndrome and 3 days prior to adjuvant injection) and for therapeutic purposes (from the 12th day postoperation in neuropathic pain syndrome and 3 days after adjuvant injection). The "hot plate" test was used for a study of the dynamics of the pain sensitivity thresholds in response to a thermal stimulus. For this purpose the animals were placed on the metal plate at 55°C and the time of appearance of the paw-licking reaction (in sec) was recorded.

Statistical treatment was performed according to the Student test.

RESULTS

Within 5-7 days after nerve transection autotomies of magnitude 2-3 appeared in 3 of the 10 control animals. The rats became anxious, groomed themselves often and for a long time, and exhibited a prolonged scratching reflex and biting of the toe tips on the paw in which the nerve had been cut. By the 12th day the pain syndrome achieved a rating of 4 points in 6 animals. In the succeeding days the strength of the pain syndrome and the number of afflicted animals increased, until by the 40th day the rating had risen to 7-9 points in 9 animals (Fig. 1). If GHBA was administered from the 1st day postoperation the pain syndrome did not manifest itself during 20-25 days. Toward the 30th day a pain syndrome with a magnitude of 1 developed in 2 of the 10 animals. No further boost of the pain syndrome or increase of the number of afflicted animals was noted (Fig. 1). When GHBA was administered against the background of a developed pain syndrome (12 days postoperation), all subsequent elevation of

TABLE 1. Change of Pain Sensitivity (According to Paw-Licking Reaction) under the Influence of GHBA

Days of observation	Neuropathic pain syndrome			Adjuvant arthritis		
	control group	GHBA from the 1st day of sickness	GHBA from the 12th day of sickness	control group	GHBA 3 days before infection	GHBA 3 days after infection
Prior to operation (neuropathic pain syndrome)	9.0±0.8	9.0±0.7	9.2±1.0	9.1±0.8	9.2±1.2	9.0±0.9
Prior to infection (adjuvant arthritis):						
3rd	9.1±1.0	10.6±1.0	8.3±0.8	9.0±0.9	12.9±1.0	9.1±0.8
7th	8.8±1.1	10.4±1.2	8.4±0.9	8.7±1.0	18.0±1.4	14.4±1.4
12th	7.4±0.9	12.7±1.2	7.6±0.9	7.7±0.7	17.4±1.5	17.9±1.6
20th	6.3±0.7	12.0±0.9	14.9±1.3	7.4±0.9	16.3±0.9	17.6±1.1
30th	6.0±1.2	10.8±0.9	14.4±1.2	7.6±0.9	14.6±1.4	16.2±0.9
40th	6.1±0.9	9.7±1.1	13.6±0.9	8.5±1.1	12.1±0.8	14.1±1.0
50th	6.3±1.0	9.2±1.0	12.3±1.4	9.0±1.1	10.8±0.9	12.2±0.9
60th	6.4±0.8	9.1±0.8	11.7±0.7	9.0±1.2	10.6±1.0	11.9±1.1

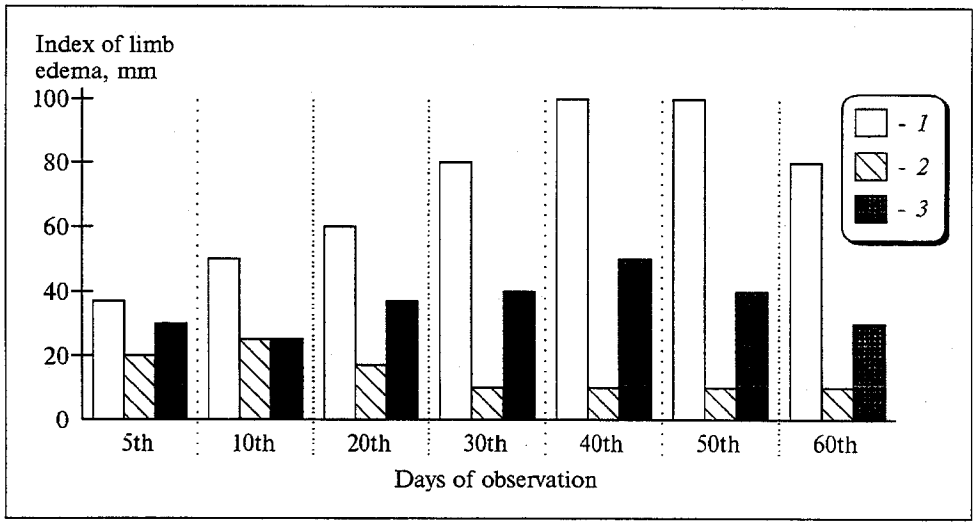

Fig. 2. Effects of GHBA in adjuvant arthritis. Control group (*1*); GHBA administered 3 days before (*2*) and 3 days after (*3*) adjuvant injection.

the pain syndrome ceased. By the 20th day the pain syndrome had diminished to 3 points, and by day 40 the claws on the damaged paw had entirely grown back (Fig. 1). During the GHBA treatment and the succeeding days of observation the animals became calm and the scratching reflex normalized. Sedative effect was not noted. A relapse did not occur after the abolishment of treatment (Fig. 1) and pain sensitivity decreased in the "hot plate" test (according to the reaction of paw licking) (Table 1).

Within 8-10 h after the administration of Freund's adjuvant hyperemia and mild paw edema which increased over 1.5 months to an index of 100 (10 is normal) (Fig. 2) were observed in the animals. After 12-14 days the process became manifest on the contralateral hind limb in 60% of animals. Arthritis developed on the two hind extremities (indexes of 60 and 50) in all animals 18-21 days later. Thereafter the inflammatory process spread to the tail and forelimbs. Ulcers appeared on the hind limbs. The animals dragged themselves about with difficulty, lost weight, and became aggressive. Preliminary administration of GHBA did not prevent the inflammatory process, which developed during the first 10 days, attaining an index of 30 (Fig. 2). From the 15th-17th day the inflammation and limb edema tapered off, disappearing altogether by the 28th-30th day (Fig. 2). The inflammation did not spread to the opposite side, ulcers were absent in the skin, and the animals did not lose weight. If GHBA was administered against the background of arthritis (3 days after adjuvant injection), after a brief amelioration (during 7-10 days) the inflammatory process increased, achieving an index of 45-50 by the 40th day (Fig. 2). In 30% of cases the arthritis transferred to the contralateral hind limb (edema index 30), ulcers did not appear on the skin of the damaged paws, and the animals maintained their weight. Subsequently the arthritis gradually subsided (Fig. 2) and pain sensitivity decreased according to the "hot plate" test (reaction of paw licking) (Table 1).

The results attest to the preventive and therapeutic effect of GHBA in neuropathic pain syndrome. γ-Hydroxybutyric acid does not prevent, but does significantly attenuate, the development and shorten the duration of adjuvant arthritis after preliminary administration, and it lessens the degree of progression of adjuvant arthritis when the preparation is used against the background of a developed pathological process.

As result of damage to the sciatic nerve or the appearance of inflammation in the joints of the hind extremities, a powerful nociceptive impulse traffic reaches the spinal cord, leading to depolarization of the nociceptive neurons, their hyperactivity, and GPEE formation in the algetic system due to these disturbances [2]. Presynaptic, reciprocal, and descending inhibition of the segmental apparatus in the spinal cord is boosted by GHBA [1], bringing about a decrease of GPEE activity. In the first hours of development of the pathological process GHBA prevents increased release of norepinephrine and conserves a large depot of this transmitter [5]; it also boosts the synthesis and release of norepinephrine and serotonin, thereby enhancing descending monoaminergic inhibition [4,8,12]. During the development of a pain syndrome, after an initial compensatory elevation of opioids disadaptive processes evolve in the spinal cord, causing a drop of the level of opioid peptides in it [7]; GHBA increases the level of dinorphin and β-endorphin in various brain regions, and boosts the synthesis and hastens the release of opioids [10]. GHBA exerts an antihypoxic effect and reduces energy consumption by normalizing oxidative metabolism in the cells, protect-

ing them from destruction in extreme situations [11]. GHBA blocks excitation at the thalamic level, inhibits conduction in the spinothalamic tract, and enhances the synthesis of monoamines, especially dopamine, a drop of which results in a boost of the pain syndrome [10]. All of the above makes for a preventive effect of GHBA in neuropathic pain syndrome and a considerable weakening and shortening of the duration of the inflammatory process in adjuvant arthritis.

The effects of GHBA mentioned above may be attributed to the inhibition of GPEE in the spinal cord and the decline of PAS activity.

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