ACCELERATION OF COMPENSATION AND REPAIR PROCESSES BY SODIUM HYDROXYBUTYRATE AND PYRACETAM* AFTER CORTICAL BRAIN DAMAGE IN RATS

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Brain trauma and extirpation of regions of the cerebral cortex during neurosurgical operations lead to severe disturbances of CNS function. The pathophysiological mechanisms of these disturbances, and also the development of compensatory and adaptive processes in the CNS after brain trauma and ways of stimulating them have not been adequately studied. Yet we know that the nootropic drug pyracetam* is effective in the treatment of the acute phase of traumatic lesions of the brain [5]. If pyracetam is used in the postoperative period after neurosurgical operations on the brain the time course of recovery of memory functions is improved and the frequency of postoperative complications in CNS activity is reduced [9]. It has been shown that sodium hydroxybutyrate possesses nootropic activity: the severity of postconvulsive retrograde amnesia is reduced [4]. However, the role of nootropic drugs in the development of compensation and adaptation in the brain has so far received little study.

The aim of this investigation was to compare the effects of sodium hydroxybutyrate and pyracetam, as the standard nootropic drug, on the development of compensation and adaptation in the CNS after extirpation of the frontal cortex in rats.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 54 noninbred male albino rats weighing 180-200 g. Bilateral conditioned avoidance reflexes (BCAR) were formed in all the animals in a shuttle box. The conditioned stimulus was a flashing light, at the 6th second of action of which an electric shock was applied through the floor of the chamber. The intervals between combinations measured 30 sec. The criterion of successful conditioning was 10 consecutive avoidances. Preservation of BCAR was tested 7 days after its formation. Next, the frontal cortex of the trained animals of groups 2, 3, and 4 was extirpated, under pentobarbital anesthesia (50 mg/kg, intravenously). Rats of group 1 underwent a mock operation. On the 4th and 9th days after the operation, preservation of the conditioned reflexes formed previously was tested by determination of the coefficient of preservation $K = N_1 - N_2/N_1 \cdot 100\%$ (where N_1 and N_2 denotes the number of combinations required to reach the criterion of successful conditioning in the initial experiment and during testing of preservation of BCAR respectively). The nootropic drugs were injected daily into the rats starting with the day after the operation, and thereafter throughout the experiment: rats of group 3 received pyracetam (200 mg/kg), rats of group 4 received sodium hydroxybutyrate (50 mg/kg). Isotonic NaCl solution was injected into the control animals of group 2 with the same cortical lesion. All compounds were injected intraperitonally. The results were subjected to statistical analysis by Student's method.

EXPERIMENTAL RESULTS

Extirpation of the frontal cortex of rats in which BCAR had been formed beforehand was followed by considerable disturbances of conditioned-reflex activity. On the 9th day after extirpation of the cortex the coefficient of preservation was considerably reduced (to 3%)

*Soviet α-pyrrolidone derivative.

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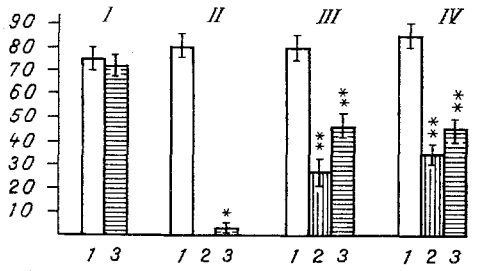

Fig. 1. Effect of extirpation of frontal cortex followed by administration of sodium hydroxybutyrate and pyracetam on preservation of bilateral conditioned avoidance reflex. Ordinate, coefficient of preservation of conditioned reflex (in %). I) Mock operation (n = 15); II) bilateral extirpation of frontal cortex followed by administration of isotonic NaCl solution (n = 12); III) the same operation followed by administration of pyracetam (n = 12); IV) the same operation followed by administration of sodium hydroxybutyrate (n = 15). 1) Preservation of reflexes before operation; 2) on 4th day, 3) on 9th day after operation. *$P \leq 0.01$, **$P \leq 0.05$ compared with before operation.

compared with that in rats undergoing the mock operation (70%), which was virtually the same as the level of preservation of the reflex in these same animals before the mock operation (75%, Fig. 1). After administration of sodium hydroxybutyrate for 9 days (group 3) the BCAR formed before the operation were restored sooner, and reached a higher level of preservation than in the animals of group 2, which underwent the same operation but were treated with isotonic NaCl solution. In rats of group 3, for instance, the coefficient of preservation of BCAR on the 4th day after the operation was 35%, rising to 45% on the 9th day. Pyracetam (group 4) also had a similar action on development of compensatory and repair processes, as reflected in the parameters of BCAR.

The results are evidence that sodium hydroxybutyrate, like pyracetam, stimulates compensation and repair processes in the brain after damage (extirpation of the frontal lobes). The writers showed previously that extirpation of the frontal cortex was accompanied by a disturbance of GAPA metabolism and by a fall in the concentration of this amino acid in different parts of the cortex and deep brain structures [1]. Meanwhile, we know that GABA increases aminoacyl-t-RNA-synthetase activity [7], thereby stimulating the amino-acid transport system and, consequently, leading to acceleration of protein biosynthesis. There is evidence of the activating action of GABA on transcription processes through the aid of cAMP [2], and an increase in the rate of leucine uptake into hypothalamic proteins under its influence [3]. This fall of the GABA level in brain structures after extirpation of the frontal cortex may therefore lead to inhibition of protein synthesis. Since γ-hydroxybutyric acid can be converted in brain tissue into GABA [8] it can be tentatively suggested that sodium hydroxybutyrate activates protein synthesis indirectly through GABA. Meanwhile the ability of pyracetam to stimulate RNA and protein synthesis has been described [6]. The leading role of informational macromolecules in CNS function is no longer disputed. It can be postulated that one mechanism of stimulation of compensatory and repair processes in the CNS may be the activation of protein and nucleic acid synthesis by sodium hydroxybutyrate and pyracetam. The antihypoxic properties of these drugs may also be of some importance for the restoration of higher integrative functions, disturbed by extirpation of the frontal lobes, although this is less essential. This is shown by the fact that pyracetam can restore BCAR in postoperative rats to the same degree as sodium hydroxybutyrate, whereas the antihypoxic effect of pyracetam is weaker than that of sodium hydroxybutyrate [4].

It can be concluded from these results that sodium hydroxybutyrate, like pyracetam, accelerates repair processes in the CNS after extirpation of the frontal cortex. Consequently, the question of the introduction of sodium hydroxybutyrate into the therapeutic program for patients after neurosurgical operations in order to accelerate recovery of the disturbed brain functions is therefore worth considering.

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ELECTROPHYSIOLOGICAL AND BIOCHEMICAL MECHANISMS OF THE ANTICONVULSANT ACTION OF A 3-HYDROXYPYRIDINE DERIVATIVE

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A promising class of antioxidants, among which some biologically active compounds have been synthesized, is that consisting of 3-hydroxypyridine derivatives (3-HPD) [8, 9]. 3-HPD have a broad spectrum of psychotropic effects, the most important of which are anxiolytic, antistressor, and antihypoxic [1, 7]. It has been shown, in particular, that 3-HPD prevent the development of convulsions induced by metrazol, strychnine, bicuculline, thiosemicarbazide, and maximal electric shock, and can reduce epileptiform activity (EPA) in experimental cobalt and penicillin epilepsy [1, 3, 6, 7].

The mechanism of the anticonvulsant effect of these antioxidants is not yet clear. Accordingly, the aim of this investigation was to study the mechanisms of the anticonvulsant action of 3-HPD from electrophysiological and biochemical aspects.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 180-220 g. Primary generalized EPA was induced by intramuscular injection of various doses of bemegride. In the experiments of series I rats with chronically implanted electrodes were used. Electrical activity was studied in the sensomotor cortex, dorsal hippocampus, and lateral hypothalamus. Methods of electrode implantation and of EEG recording were described previously [5]. The EEG was recorded in unrestrained animals on a "Neurograph" electroencephalograph and the data were processed on a BAS-161 neurocomputer (O.T.E. Biomedica, Italy). The animals were divided into three groups: 1) 3-HPD (50 mg/kg) were injected 15 min after bemegride (10 mg/kg) in the presence of frank EPA; 2) 3-HPD in the same dose were given 30-40 min before injection of bemegride; 3) control — only bemegride was given.

In the experiments of series II the effect of 3-HPD on lipid peroxidation (LPO) in the animal brain was studied on a model of primary generalized EPA. In the experiments of this series bemegride was injected intramuscularly in a dose of 25 mg/kg. To assess the convulsions the latent period (LP) of the first twitch of single muscles and LP of the first generalized fit, arising after injection of bemegride, were recorded. The state of LPO in the animals'

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