EFFECT OF γ-AMINOBUTYRIC ACID ON PHOSPHORYLATION COUPLED WITH OXIDATION OF α-KETOGLUTARATE, PYRUVATE, AND GLUTAMATE IN STRUCTURES OF THE SPINAL CORD

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γ-Aminobutyric acid inhibits phosphorylation coupled with oxidation of α-ketoglutarate, pyruvate, and glutamate in structures of the spinal cord (white matter) and stimulates oxidation only of α-ketoglutarate and glutamate. As a result of this, dissociation of oxidative phosphorylation is observed in the gray matter of the anterior and lateral horns, in the gray matter of the posterior horns, and in the white matter of the spinal cord.

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Among the biologically active substances playing an important role in the fine regulation and control of nerve cell metabolism an important place is occupied by γ-aminobutyric acid (GABA), which plays an active part in the regulation of the energy metabolism of the brain. Data on this question in the literature are contradictory and have been obtained mainly in studies of brain preparations [1-3, 5, 8-11, 13-15, 17-19].

The object of the investigation described below was to study the effect of GABA on energy metabolism in morphologically and functionally different parts of the lumbar division of the spinal cord, i.e., in the motor zone where motoneurons are located (the gray matter of the anterior and lateral horns); the sensory zone, where interneurons are concentrated (gray matter of the posterior horns); and the white matter, consisting of nerve fibers surrounded by glia.

EXPERIMENTAL METHOD AND RESULTS

Oxidative phosphorylation was determined in minced tissue of the spinal cord by methods described previously [4]. Glycolysis was inhibited by the addition of sodium fluoride to the incubation medium.

Oxidation substrates were used in a final concentration of 0.017 mole. GABA was added to the incubation medium in a dose of 0.017 mole per sample.

The experimental results given in Table 1 show that the intensity of phosphorylation (ΔP) coupled with oxidation (ΔO) of pyruvate, α-ketoglutarate, and glutamate in the investigated spinal cord tissues differed and depended to a large extent on the nature of the oxidation substrate. Pyruvate and glutamate were metabolized most intensively, α-ketoglutarate less intensively, and GABA least. Compared with the control, GABA activated oxygen utilization only very slightly, and only by the tissue of the gray matter of the anterior and lateral horns and the gray matter of the posterior horns. The low level of oxidation and phosphorylation when endogenous substrates were used was determined by their low concentration in the cells. This hypothesis was confirmed by the fact that substrates of the tricarboxylic acid cycle do not accumulate in large quantities in nerve cells [16]. However, large quantities of glutamate, aspartate, and glutamine [12] always are present in nerve tissue [12]. Endogenous respiration of the brain and spinal cord is associated principally with oxidation of glutamate [21]. It can be concluded from a comparison of the intensity of oxidation and of phosphorylation and the degree of their coupling in the motor, sensory, and con-

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TABLE 1. Effect of GABA on Phosphorylation Coupled with Oxidation of Different Substrates in Structures of the Spinal Cord (M ± m; number of animals in parentheses)

Substrate	Gray matter of anterior and lateral horns			Gray matter of posterior horns			White matter		
	ΔO	ΔP	P/O	ΔO	ΔP	P/O	ΔO	ΔP	P/O
Control without substrate (12)	0,69±0,05	1,15±0,07	1,70±0,13	0,66±0,02	1,00±0,09	1,49±0,11	0,27±0,04	0,37±0,03	1,38±0,12
GABA (12)	0,76±0,05	1,12±0,09	1,51±0,16	0,71±0,06	1,08±0,11	1,55±0,17	0,22±0,02	0,38±0,015	1,72±0,11
Pyruvate (12)	1,25±0,08	2,68±0,09	2,20±0,14	1,17±0,09	2,58±0,17	2,11±0,17	0,33±0,02	0,59±0,07	1,75±0,15
Pyruvate + GABA (8)	1,27±0,06	2,07±0,18	1,62±0,09	1,25±0,08	1,78±0,21	1,44±0,18	0,28±0,03	0,38±0,02	1,38±0,12
	—	P<0,01	P<0,001	—	P<0,02	P<0,05	—	P<0,02	—
α-Ketoglutarate (12)	0,73±0,07	1,72±0,07	2,42±0,23	0,74±0,03					
					1,44±0,11	1,90±0,11	0,22±0,02	0,41±0,04	1,88±0,16
α-Ketoglutarate + GABA (12)	0,91±0,03	1,05±0,07	1,08±0,065	0,96±0,06	1,13±0,115	1,16±0,09	0,30±0,02	0,30±0,02	1,05±0,11
	P<0,05	P<0,001	P<0,001	P<0,02	P<0,05	P<0,001	P<0,01	P<0,01	P<0,001
Glutamate (10)	1,30±0,06	2,14±0,19	2,12±0,05	0,91±0,04	1,90±0,13	2,08±0,12	0,30±0,01	0,66±0,05	2,06±0,17
Glutamate + GABA (12)	1,34±0,05	2,02±0,09	1,52±0,07	1,14±0,02	1,85±0,12	1,60±0,08	0,31±0,03	0,41±0,05	1,29±0,09
	P<0,01	—	P<0,001	P<0,001	—	P<0,01	—	P<0,01	P<0,01

Note. Utilization of oxygen (ΔO) and esterification of inorganic phosphorus (ΔP) calculated in μatoms/10 mg tissue.

ducting regions of the lumbar division of the spinal cord that these processes follow different courses when the same oxidation substrates are used. They take place most intensively in the gray matter of the anterior and lateral horns, less intensively in the gray matter of the posterior horns, and least intensity in the white matter.

GABA added to the incubation medium also differed in its effect on phosphorylation coupled with the oxidation of pyruvate, α-ketoglutarate, and glutamate in different structures of the spinal cord (Table 1).

GABA stimulated oxygen consumption by the gray matter of the anterior and lateral horns and the gray matter of the posterior horns when α-ketoglutarate and glutamate were used as oxidation substrates. The white matter utilized oxygen more actively only during coupled oxidation of GABA and α-ketoglutarate. When pyruvate was utilized, no increase in the oxygen consumption was observed. GABA significantly inhibited esterification of inorganic phosphorus when α-ketoglutarate and pyruvate were utilized in all regions of the spinal cord investigated, but when glutamate was oxidized, it did so only in the white matter.

In connection with these changes in oxygen consumption and in esterification of mineral phosphate, marked dissociation of oxidation and phosphorylation was observed in the motor, sensory, and conducting zones of the spinal cord when all substrates were utilized.

This was evidently associated with the fact that GABA considerably modifies membrane permeability, affects swelling of the mitochondria, and inhibits oxidation of exogenous NAD · H_2 (i.e., reduces its ability to penetrate into the mitochondria) and activates ATPase [3, 6, 7, 20]. There are indications that GABA dissociates phosphorylation coupled with oxidation of succinate [1]. The results obtained thus show that GABA exerts a considerable effect on energy metabolism in the structures of the spinal cord, although by itself it is not an active oxidation substrate for nerve tissue.

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