POSSIBLE COMMON MECHANISMS OF THE CONVULSANT EFFECT OF THIOSEMICARBAZIDE AND AMINOHYDROXYACETIC ACID

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A protective effect of the semialdehyde of succinic acid and of sodium γ-hydroxybutyrate against convulsions induced by thiosemicarbazide (TSC) and aminohydroxyacetic acid (AHA) was demonstrated in experiments on mice. In addition, in TSC convulsions the lipophilic derivative of GABA (its cetyl ester) also proved effective. It is postulated that despite differences in the primary localization of action of TSC and AHA with respect to enzymes of the "GABA shunt" both these compounds can induce similar secondary changes: deficient formation of the semialdehyde of succinic acid and sodium γ-hydroxybutyrate. It is emphasized that for the normal excitability of the brain to be preserved the normal level not only of GABA, but also of the two next metabolites of the shunt, must be maintained.

Thiosemicarbazide (TSC) is known to inhibit the decarboxylase of glutamic acid [9]. The deficiency of γ-aminobutyric acid (GABA) formation [6] and the disturbance of its compartmentalization [13] thus arising lead to increased readiness of the brain to produce convulsions; this fact can be fully explained from the standpoint of the participation of GABA in inhibition. It is paradoxical, however, that aminohydroxy acetic acid (AHA), a substance inducing the accumulation of GABA in the brain [15], and consequently, increasing the threshold of the electroconvulsive fit [10], itself induces convulsions [3, 14]. The question thus arises whether other mechanisms not directly connected with GABA formation may be involved in the development of the convulsant effects of TSC and AHA: in particular, a disturbance of the reactions of the "Roberts' cycle," leading to the formation of the semialdehyde of succinic acid [12] and sodium γ-hydroxybutyrate [7].

To shed light on the validity of this hypothesis, the effect of succinic acid semialdehyde and sodium γ-hydroxybutyrate on the convulsant effects of TSC and AHA was studied.

EXPERIMENTAL METHOD

Experiments were carried out on male albino mice weighing 18-22 g. TSC and AHA* were injected in doses of 15 and 150 mg/kg, respectively, inducing convulsions in 95% of mice, while succinic acid semialdehyde and γ-hydroxybutyrate† were injected in a dose of 500 mg/kg. TSC was injected subcutaneously and the other compounds intraperitoneally.

EXPERIMENTAL RESULTS AND DISCUSSION

When equieffective (95% of the convulsant) doses of TSC and AHA were used, the latent period of the

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†Both substances were synthesized in the Department of Organic Synthesis, Institute of Pharmacology, Academy of Medical Sciences of the USSR [1, 5].

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clonico-tonic convulsions in the first case was 88-100 min and in the second 10.8-12.2 min. Even in a 100% lethal dose (25 mg/kg) CSC induced convulsions with a latent period of not less than 50 min; a decrease in the dose of AHA led to a decrease in the frequency of onset of the convulsions, but in animals in which convulsions were observed their latent period did not exceed 20 min. Convulsions induced by TSC occurred against the background of normal or even slightly increased motor activity, while convulsions induced by AHA appeared against a background of depressed motor activity and catalepsy. This depression, characteristic of the action of small doses of AHA (15-30 mg/kg), persisted after administration of large doses (125-150 mg/kg); the difference was that in the latter case clonic convulsions developed against the background of depression.

Succinic semialdehyde lengthened the latent period of convulsions induced by TSC from 88-100 to 173-199 min. If injected before AHA it completely prevented the development of convulsions in 85% of mice, while in the rest it increased the latent period to 36-44 min. Sodium γ-hydroxybutyrate also lengthened the latent period of convulsions induced by TSC (to 173-245 min). If injected before AHA, γ-hydroxybutyrate completely prevented convulsions in 70% of mice, while in 30% it lengthened the latent period to 35 min.

In a dose of 500 mg/kg, GABA prevented none of the types of convulsions studied, evidently because of its poor power of penetration into the brain. A lipophilic derivative of GABA, its cetyl ester, with distinct neurotropic activity when administered by extracerebral routes [4], had a protective action against convulsions induced by TSC: no convulsions occured in 50% of mice, while in the rest the latent period was lengthened to 105-153 min. However, the cetyl ester of GABA was absolutely ineffective against convulsions induced by AHA.

The effect of derivatives of the GABA shunt described above was evidently not due to their muscle-relaxant action; muscular hypotonia of the same degree produced by chlorphromazine (4 mg/kg) did not prevent the development of these convulsions.

Both TSC and AHA are known to depress different stages of the GABA shunt: the former depresses the reaction leading to GABA formation while the second depresses the reaction responsible for its subsequent conversions. As a result, TSC leads to a deficiency while AHA leads to the accumulation of GABA. This fact evidently explains the protective action of the cetyl ester of GABA against convulsions induced by TSC, analogous to the action of GABA when injected into the brain. This same effect against convulsions induced by TSC was also characteristic of AHA when injected in small doses, under the influence of which GABA begins to accumulate. Possibly, however, with an increase in the dose of AHA, the results of blocking of the transamination of α-ketoglutarate with GABA were added to this effect; the deficient formation of glutamic acid and of the semialdehyde of succinic acid.

Glutamic acid deficiency could hardly be the cause of the convulsions, for glutamic acid excites unit activity [8]. In the present experiments, glutamic acid injected parenterally did not reduce the convulsant effect of large doses of AHA. However, succinic acid semialdehyde proved highly effective in preventing these convulsions. Since mutual conversion of succinic semialdehyde and γ-hydroxybutyrate takes place in the brain [7], if the formation of the semialdehyde of succinic acid was blocked by AHA, the formation of γ-hydroxybutyrate would be disturbed. This evidently explained the ability of γ-hydroxybutyrate to diminish the convulsant effect of AHA. When injected extracerebrally, succinic acid semialdehyde and γ-hydroxybutyrate showed a clearly defined neurotropic action [2, 11], suggesting that they penetrate freely into the brain. Presumably their protective action against convulsions induced by AHA is based on compensation of the deficiency of endogenous formation of these brain metabolites by the corresponding exogenous substance. The presence of the protective effect of succinic acid semialdehyde and γ-hydroxybutyrate against TSC convulsions suggest that the deficiency of the metabolites may also arise under the influence of TSC. In fact, by blocking GABA formation, TSC may thereby reduce the quantity of products of the further conversion of this compound, namely succinic acid semialdehyde and γ-hydroxybutyrate.

The protective effect of these substances against TSC and convulsions was evidently not due to the accumulation of GABA through a shift in the reversible transamination reaction toward GABA formation, for in biochemical experiments no accumulation of GABA was found after administration of these products. Meanwhile, after administration of, for example, γ-hydroxybutyrate endogenous metabolites of GABA accumulate [7].

These results are evidence that the preservation of a certain level of GABA in the brain is not sufficient to ensure maintenance of its normal excitability; the subsequent products of the shunt – succinic acid semialdehyde and γ-hydroxybutyrate – must also be formed in adequate amounts.

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