EFFECT OF INTRAVENTRICULAR INJECTIONS OF ω -AMINOSULFONIC ACIDS ON THE CENTRAL NERVOUS SYSTEM OF CONSCIOUS MICE

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In the course of a survey on the physiological role of taurine (2-aminoethanesulfonic acid, C_2) and related compounds, we focused attention on the relationships between chemical structures and pharmacological effects. In earlier studies we found that intravenous administration of homotaurine (3-aminopropanesulfonic acid, C_3) produced a marked decrease in blood pressure in dogs. Both taurine and N-methyl- or side chain-derivatives of C_3 had a weaker effect than C_3 (1). These results were much the same as those obtained by Stanton and Woodhouse (2), Iino (3), Tsujioka et al. (4) and Takahashi et al. (5) with γ -aminobutyric acid (GABA) derivatives, the carboxylic analogues of C_3 .

Behavior patterns in conscious mice given aliphatic ω -aminosulfonic acids which had a carbon chain from one to six (Fig. 1), were pursued to determine if there was any evident correlation between behavior and chemical structures of the acids.

Male ddY mice, weighing 20 ± 1 g were separated into groups. Each group included 10 mice. Each amino acid was dissolved in physiological saline, neutralized with sodium hydroxide solution and the solution (5 μ l) administered directly into the cerebral lateral ventricle, according to the method of Haley and McCormick (6), with slight modifications (7).

All amino acids tested induced a similar type of dosage dependent convulsion, that is, immediately or within 1 min after injection, an extreme running convulsion was evoked, and tonic flexor to tonic extensor convulsions occurred before death. When the tonic flexor convulsion resulted in clonic convulsion, the animals survived.

FIG. 1 ω -Aminosulfonic acids and its guanylated derivative.

The dose-response curves of amino acids tested are shown in Fig. 2. Shifting of a curve to the left indicates that the tested material produced an enhanced convulsion. We classified such amino acids as excitants. As seen from Fig. 2, these were 4-aminobutanesulfonic acid (C_4), 5-aminopentanesulfonic acid (C_5), 6-aminohexanesulfonic acid (C_6), guanyl- C_3 (G- C_3), 3-guanylamino-2-hydroxypropanesulfonic acid (G-AHPS) and homocysteic acid (HCA).

On the other hand, aminomethanesulfonic acid (C_1), 3-mono-methylamino-2-hydroxypropanesulfonic acid (Me-AHPS) and 3-trimethylamino-2-hydroxypropanesulfonic acid (AHPS-betaine) written on the right side bottom in Fig. 2 had no effect on the behavior of mice even at the most elevated concentration of 2×10^{-1} M. Such were classified as inactive amino acids.

The materials of a third type had an effect even with a moderate concentration, which included C_2 , C_3 and 3-amino-2-hydroxypropanesulfonic acid (AHPS). When injected, these substances at the concentration of $2-6 \times 10^{-2}$ M, mice produced biphasic behavioral patterns, that is a temporary excitatory tendency induced by external stimuli such as touch and the sedation leading to drowsiness. Such were also observed with administration of

FIG. 2. Dose-response curves for action of ω -aminosulfonic acids and related compounds upon CNS of mice.

○---○ HCA: DL-homocysteic acid	⊙---⊙ C_3 : 3-aminopropanesulfonic acid
○---○ C_5 : 5-aminopentanesulfonic acid	+---+ 6-ACA: 6-aminocaproic acid
□---□ G- C_3 : 3-guanylamino-2-hydroxypropanesulfonic acid	●---● C_2 : taurine
●---● C_6 : 6-aminohexanesulfonic acid	▲---▲ G- C_2 : taurocyamine
⊙---⊙ C_4 : 4-aminobutanesulfonic acid	* C_1 : aminomethanesulfonic acid
■---■ G-AHPS: 3-guanylamino-2-hydroxypropane sulfonic acid	* G-GABA: γ -guanidinobutyric acid
△---△ G- β -Ala: guanyl- β -alanine	* Me-AHPS: 3-monomethylamino-2-hydroxypropanesulfonic acid
×---× AHPS: 3-amino-2-hydroxypropanesulfonic acid	* AHPS-betaine: 3-trimethylamino-2-hydroxypropanesulfonic acid

GABA to mice, as reported by Gulati and Stanton (8). We classified these amino acids as depressants.

From the above experimental results we speculated that it may be necessary to have a four to six aliphatic carbon chain between the anionic and cationic sites for demonstration of the excitement. A basic character of ω -amino group seems to be required for production of the convulsive activities, since methylation of ω -amino group of AHPS (N-monomethyl and N,N,N-trimethyl derivatives) reduced and guanlylation of AHPS or C₃ enhanced the convulsive activities, in comparison with those of the parent compounds, respectively. The acidity constant may be related to the convulsive activities since ω -aminosulfonic acids were much more potent excitants than ω -aminocarboxylic acids such as 6-aminocaproic acid (6-ACA).

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