NEUROTROPIC ACTIVITY OF SUCCINIC SEMIALDEHYDE DERIVATIVES

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Experiments on mice and rabbits showed that of the derivatives of the linear form of succinic semialdehyde only those compounds with a free aldehyde group in their structure possess neurotropic activity. Activity of the cyclic derivatives is evidently connected with hydrolysis, leading to the formation of succinic semialdehyde.

Succinic semialdehyde is known to be linked metabolically with aminobutyric acid, the conjectural mediator of inhibition in the brain [7, 9-12]. The writers have shown previously [2, 13] that succinic semialdehyde possesses marked neurotropic activity.

It is therefore interesting to investigate the neurotropic properties of a series of derivatives of succinic semialdehyde on a wider scale.

EXPERIMENTAL METHOD

Derivatives of the linear form of succinic semialdehyde – aldehyde-ester IIa, aldehyde-amides IIIa and IVa, the acetals Va and the amidals VIa, Schiff bases VIIa and VIIIa, acetal-esters IXa, acetal-amides Xa and XIa, as well as the γ-substituted lactones (XIIb-XVb) which are derivatives of the cyclic form of the semialdehyde Ib (Table 1) – have been synthesized [3, 5, 6].

The most demonstrative features of the neurotropic activity of succinic semialdehyde are: a decrease in the motor activity of muscles with a characteristic "splayed-out" posture and with marked hypotonia of the hind-limb muscles; prolongation of the narcotic effect of barbiturates, and an increase in the life span of mice exposed to hypoxia [2, 13]. All 16 synthesized derivatives of succinic semialdehyde were investigated by these tests. The prolonging action was tested with thiopental sodium, which was injected into male albino mice weighing 18-24 g intravenously in a dose of 30 mg/kg 15 min after the substances to be tested. To study the antihypoxic properties of the compounds, mice were placed in chambers with a reduced (to 8 vols.%) oxygen concentration [1]. Some of the compounds were also studied by the test of conversion of a subthreshold dose of thiopental sodium (12 mg/kg) into an effective dose, by their hypothermic effect, by inhibition of the investigative reaction [8], and by their effect on the EEG (chronic experiments on rabbits with implanted cortical electrodes). These compounds were injected intraperitoneally in the experiments on mice and intravenously in those on rabbits, as 1-10% solutions.

EXPERIMENTAL RESULTS AND DISCUSSION

Of the derivatives of the linear form of succinic semialdehyde studied, evidence of neurotropic activity was discovered in the aldehyde-esters and aldehyde-amides IIa, IIIa, and IVa. These compounds led to a marked decrease of motor activity and to muscular hypotonia: they increased the duration of the

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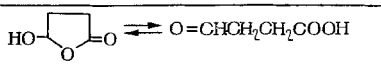
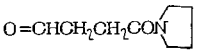
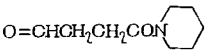
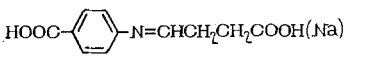
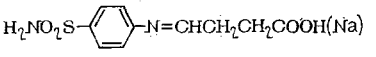
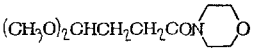
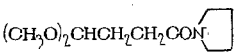
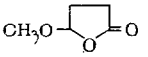
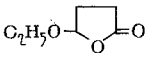
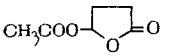
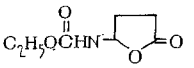
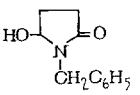
TABLE 1. Compounds Studied and Their Properties

No.	Compounds	Genl. action	Potentiation	Antihypoxic effect
Ia, b		+	+	+
IIa	$O{=}CHCH_2CH_2COOC_2H_5$	+	+	+
IIIa		+	+	+
IVa		+	+	+
Va	$(C_2H_5O)_2CHCH_2CH_2COOH$	—	—	—
VIa	$(CH_3CONH)_2CHCH_2CH_2COOH(Na)$	—	—	—
VIIa		—	—	—
VIIIa		—	—	—
IXa	$(C_2H_5O)_2CHCH_2CH_2COOC_2H_5$	—	—	—
Xa		—	—	—
XIa		—	—	—
XIIb		+	+	+
XIIIb		+	+	+
XIVb		+	+	+
XVb		+	+	+
XVIb		—	—	—

narcotic effect of thiopental sodium and slightly increased the period of survival of mice exposed to hypoxic hypoxia. However, these effects were weaker than those of succinic semialdehyde itself. The doses in which these compounds were effective in most tests ranged from 150 to 300 mg/kg, whereas LD_{50} for compounds IIa-IVa varied from 800 to 1500 mg/kg, while for Ia and Ib, LD_{50} was 1900 mg/kg.

The other derivatives of the linear form of succinic semialdehyde showed no evidence of neurotropic activity in the tests used.

Neurotropic activity was clearly exhibited by the derivatives of the cyclic form of succinic semialdehyde tested (XIIb, XIIIb, XIVb). They reduced motor activity, and in the case of γ-methoxybutyrolactone XIIb and γ-ethoxybutyrolactone XIIIb these properties began to be exhibited with doses of 150-200 mg/kg, whereas with γ-acetoxybutyrolactone XIVb the threshold dose was 300 mg/kg. All three compounds studied increased the duration of the narcotic effect of thiopental sodium. The duration of anesthesia was increased by 3 times over the control level by compound XIIb in a dose of 125 mg/kg, XIIIb in a dose of 100 mg/kg, and XIVb in a dose of 300 mg/kg. Conversion of the subthreshold dose of thiopental sodium (12 mg/kg) into effective was obtained with compounds XIIb and XIIIb in doses of 100 and 150 mg/kg, respectively, and XIVb in a dose of 300 mg/kg. These compounds (XIIb and XIIIb in doses of 200-300 mg/kg and XIVb in a dose of 350-400 mg/kg) increased the survival of the animals when exposed to hypoxia up to 50-60 min compared with 20 min in the control. All three compounds had the property of depressing the investigative reaction. Compound XIIIb showed the greatest activity in this respect: its 50% effective dose (ED_{50}) by this test was

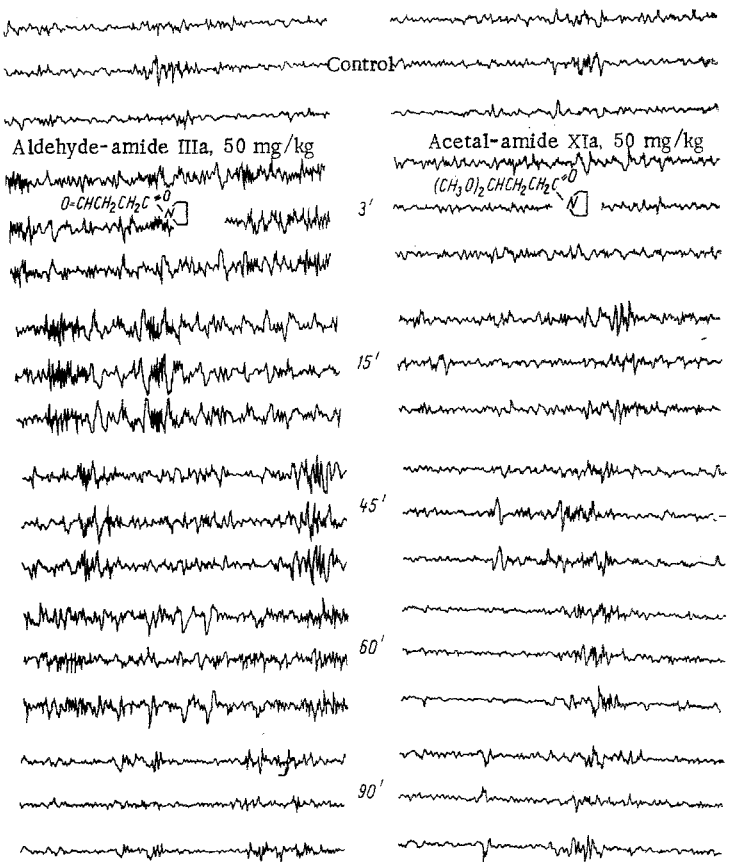


Fig. 1. Effect of succinic semialdehyde derivatives on the rabbit EEG. From top to bottom: EEG of left somatosensory, left visual, and right somatosensory areas of the cortex. Numbers denote time (in min) after injection of compounds. Experiments on rabbits with permanently implanted electrodes.

100 mg/kg, compared with 200 mg/kg for XIIb and 350 mg/kg for XIVb. By its hypothermic effect, compound XIIIb also was the most active: starting with a dose of 100 mg/kg it reduced the rectal temperature by 3-4°C. LD_{50} of these compounds varied from 1.2 to 1.9 g/kg.

By the spectrum of their pharmacological activity these compounds were similar to succinic semialdehyde [2], although their therapeutic index was somewhat narrower for most effects.

The γ-substituted lactone XVb was similar in the character of its action to lactones XIIb-XIVb, although rather weaker than them in its effect; its action, moreover, was evidently not due to the presence of a urethane group in the structure, for the compound showed a protective antihypoxic action which was not found in control experiments with urethane.

No evidence of neurotropic activity was found by means of these tests in the case of the γ-hydroxypyrrolidinone XIVb – the cyclic form of the amide of succinic semialdehyde.

These results show that of the linear derivatives of succinic semialdehyde only those compounds with a free aldehyde group in their structure (I-IVa) exhibit neurotropic activity. For instance, aldehyde-amide IIIa evoked definite synchronization of the EEG, which corresponds to its depriming action and to other tests. By contrast, the corresponding acetal-amide XIa (a compound with a hidden aldehyde group) had no synchronizing action (Fig. 1). These investigations showed that the presence of substituents on the carboxyl group has no significant effect on the neurotropic activity of the compounds.

The need for a free aldehyde group to maintain the neurotropic activity of succinic semialdehyde and its derivatives can be explained by the role of this group in the metabolism of endogenous succinic semi-

aldehyde. In fact, all three reversible conversions characteristic of succinic semialdehyde (its transamination with glutamic acid, leading to the formation of γ-aminobutyric and α-ketoglutaric acids; its oxidation leading to the formation of succinic acid; and, possibly, its reduction, leading to the formation of γ-hydroxybutyric acid) are connected with corresponding conversions in the aldehyde group itself.

The reason why derivatives of the cyclic form (XIIb-XVb) of succinic semialdehyde possess neurotropic activity is evidently because conversion into the linear form, characteristic of these compounds and the chemical experimental conditions, can perhaps take place also in vivo, possibly through the participation of hydrolytic enzymes. This "opening" of the cyclic form of succinic semialdehyde is analogous to what takes place when exogenous γ-butyrolactone is converted in vivo into γ-hydroxybutyric acid. The absence of effect of γ-hydroxypyrrolidinone XIVb is evidently explained by the fact that, unlike the γ-substituted butyrolactones XIIb-XVb, the γ-substituted pyrrolidinones are much more resistant to solvolytic fractions and do not undergo hydrolysis even in the presence of hydrolytic enzymes.

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