Anticonvulsant Properties of Procaine, Cocaine, Adiphenine and Related Structures.* (21979)

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In low concentrations, local anesthetics block conduction without depolarizing nerves, by stabilizing neuronal membranes(1,2); but large doses given systemically can induce convulsions. It was therefore of interest that Yasukata(3) reported that procaine exhibits anticonvulsant effects in rabbits. Among the numerous classes of chemicals capable of preventing experimentally-induced and/or clinical seizures, there are several antihistaminic agents(4-6), ethers of phenylacetic and phenylbutylic acids(7,8), and other closely related substances. For these reasons, it seemed worthwhile to attempt to disclose some effective structural denominator of anticonvulsant activity among compounds in which dialkylaminoalkyl is linked via O, H or C to an aryl or aralkyl radical. To initiate this study, procaine and adiphenine (Trasentine) were tested for anticonvulsant properties in mice and compared with certain of their chemical and pharmacological congeners, particularly cocaine. The results obtained provide the basis for this report.

Methods. Male albino mice (CF #1 strain) obtained from the Carworth Farm were used as experimental animals. They were maintained on Purina Laboratory Chow and allowed free access to food and water except during the short time they were removed from their cages for testing. Anticonvulsant potency (ED_{50}) was determined by the maximal electroshock seizure (MES) test (50 mA alternating current, 0.2-second stimulus duration, corneal electrodes), and neurotoxicity (TD_{50}) was determined on the basis of overt signs of minimal neurological deficit. The details of the MES test and the endpoints employed for determination of acute neurotoxicity in mice have been described in full elsewhere(9). In order to determine the peak time for anticonvulsant action, the estimated ED_{85} for each drug was administered intraperitoneally to several groups of 6 mice each. Each group was then subjected to the MES test after a different time interval and the number of animals protected (*i.e.*, failing to exhibit the tonic-extensor component) was recorded for each group. The results obtained were plotted on graph paper and the time of peak effect estimated from the plotted points. For the determination of the ED_{50} (or TD_{50}), groups of 10 mice were given various doses of the experimental drug and tested at the previously determined time of peak effect until at least 3 points were established between complete protection (or toxicity) and no protection (or toxicity). The results were then plotted on logarithmic probability paper and a regression line was visually fitted to the plotted points. From this plot of the data, the ED_{50} or TD_{50} was determined and 95% confidence limits were calculated by the method of Litchfield and Wilcoxon(10). The drugs subjected to the MES and neurotoxicity tests were as follows: procaine hydrochloride, cocaine hydrochloride, adiphenine (Trasentine).‡ β-(o-benzylphenoxy)-α-diethylaminoethane (No. BL 338-22)§, 2-diethylaminoethyl-1-phenylcyclopentane-1-carboxylate hydrochloride (caramiphen, Parpanit), diethylaminoethanol, and diethyl-(2-hydroxyethyl)-methylammonium bromide-α-phenylcyclohexaneglycolate (Ba 5473, oxyphenonium, Antrenyl).‡ The drugs were administered intraperitoneally as aqueous solutions. All animals were observed for the effect of the drugs on

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TABLE I. Neurotoxicity and Anti-electroshock Potency of Procaine, Cocaine, and Trasentine.*

Drug	Neurotoxicity (TD_{50}), mg/kg	Max electroshock seizure test†	
		Effective dose (ED_{50}), mg/kg	Protective index (P.I.)
Procaine	105 (98-113)	45 (42-49)	2.3 (2.1-2.5)
Cocaine	32 (29-36)	17.5 (15-23)	1.8 (1.6-2.0)
Trasentine	123 (116-131)	62 (58-67)	2.0 (1.8-2.2)

* All values in parentheses indicate 95% confidence limits.
† 50 mA, 0.2-sec. alternating current, corneal electrodes.

postictal phenomena, the details of which have been described elsewhere(11,12). In addition, the ED_{50}, as determined by the MES test, and the TD_{50}, as determined by the neurotoxicity test, for procaine hydrochloride, cocaine hydrochloride, and Trasentine were administered to groups of 5 mice each and tested for ability to prevent the tonic-extensor component of maximal seizures induced by the rapid intravenous injection of 38 mg/kg of pentylenetetrazol (Metrazol) (MMS test). The details of the MMS test have been published in full elsewhere(13).

Results. Procaine, cocaine, and Trasentine proved to possess anticonvulsant action, but their antiseizure activity appeared and disappeared very quickly. The time of peak action was estimated to be 5 minutes; by 20 minutes little if any residual effect could be observed. Therefore, all tests were performed 5 minutes after drug administration.

The neurotoxicity and anti-electroshock potency for procaine, cocaine, and Trasentine are summarized in Table I from which it may be seen that cocaine is 3 to 4 times more toxic than procaine or Trasentine. Indeed, 32 mg/kg of cocaine produced signs of minimal neurotoxicity in 50% of mice as compared to 105 mg/kg for procaine and 123 mg/kg for Trasentine. The initial signs of cocaine neurotoxicity were agitation ad increased excitability; larger doses caused ataxia and postural abnormalities. The initial signs of procaine and Trasentine neurotoxicity were postural abnormalities and abnormal gait, especially dragging of the hindlimbs; moderately intoxicated animals were unable to maintain equilibrium. Doses of procaine in excess of 120 mg/kg produced excitation.

All 3 agents were capable of preventing the hindleg tonic-extensor component of maximal electroshock seizures (MES). Cocaine was approximately 2½ times more potent than procaine in this regard, and 3½ times more potent than Trasentine. For example, 17.5 mg/kg of cocaine abolished the hindleg tonic-extensor component in 50% of mice, whereas 62 mg/kg of Trasentine were required to produce the same level of protection. Larger doses than those required to protect 50% of animals by the MES test not only abolished the tonic-flexor phase as well as the tonic-extensor phase, but also produced the "anticoma effect" in the postictal period (prevention of immediate postseizure depression). Approximately 50% of animals receiving 75, 27.5, and 80 mg/kg of procaine, cocaine, and Trasentine, respectively, manifested this anticoma effect.

The protective index, *i.e.*, the ratio between TD_{50} and ED_{50}, was remarkably similar for all 3 agents. For example, the P. I. for cocaine was 1.8, whereas that for procaine was 2.3 and that for Trasentine was intermediate to these two values. Thus, all three agents exhibited anticonvulsant activity in non-toxic doses.

The anti-Metrazol activity exerted by the TD_{50} and the ED_{50} of each of the three agents was measured by the MMS test. The results obtained are summarized in Table II from which it may be seen that all 3 agents have the ability to decrease the incidence of the

TABLE II. Anti-Metrazol Effect of Procaine, Cocaine, and Trasentine.

Drug	Dose, mg/kg	Prevention of tonic-extensor component	Mortality
Procaine	45 *	3/5	4/5
	105 †	5/5	5/5
Cocaine	17.5*	3/5	2/5
	32 †	3/5	3/5
Trasentine	62 *	2/5	4/5
	123 †	4/5	2/5

* ED_{50} as determined by MES test.
† TD_{50} " " " neurotoxicity test.

tonic-extensor component of maximal Metrazol seizures; however, the required doses frequently synergized with the convulsant drug to cause death. The clonic component of Metrazol-induced maximal seizures was not abolished even by toxic doses of the 3 agents.

Beta - (o-benzylphenoxy)-α-diethylaminoethane (No. BL 338-22) and Parpanit, the chemical structures of which comply with the prerequisites mentioned in the introduction, were also tested for neurotoxicity and for ability to modify the pattern of maximal electroshock seizures. Their time of peak anticonvulsant action was estimated to be 10 minutes; by 30 minutes little if any residual effect could be observed. Both compounds were anticonvulsant, but their protective indices were near unity. Thus, the ED_{50}s for No. BL 338-22 and Parpanit were 52 and 80 mg/kg, respectively; their P.I.s were 1.0 and 1.5, respectively. In contrast, diethylaminoethanol and Antrenyl, the chemical structures of which only partially comply with the previously described structural prerequisites, were ineffective by the MES test even in toxic doses.

Discussion. The present investigation demonstrates that anticonvulsant activity is embodied not only in procaine, as was first reported by Yasukata(3) in rabbits, but also in cocaine and Trasentine. Since procaine and cocaine in large toxic doses are convulsant, it is of particular interest that in non-toxic doses these drugs act as anticonvulsants.

The anticonvulsant action of procaine, cocaine and Trasentine is rapid in onset and brief in duration. Peak action was observed 5 minutes after drug administration; by twenty minutes all anticonvulsant effect had disappeared. This very rapid onset of anticonvulsant activity and the evanescent duration of action probably account for previous failures to demonstrate antiseizure activity in local anesthetics.

The 5 compounds which have within their chemical structure a dialkylaminoalkyl linked via O, N or C to an aryl or aralkyl radical were all found to possess anticonvulsant activity as measured by the MES test; in contrast, the diethylaminoethanol moiety alone and Antrenyl, a quaternary ammonium compound, were devoid of such activity. (The ability of prior administration of diethylaminoethanol, the hydrolytic product of procaine, to prevent procaine convulsions in experimental animals(14) is probably accounted for by competitive inhibition on the basis of similarity of chemical structure.) Although the above findings suggest that compounds within this chemical series share a common anticonvulsant nucleus, further studies will be necessary precisely to determine what specific structural elements are essential for antiseizure activity.

Procaine, cocaine, and Trasentine all exhibit anticonvulsant effects in the laboratory which are qualitatively similar to those produced by the therapeutically useful antiepileptic drugs. However, the potential clinical value of compounds of this class must be considered minimal because of the very short duration of action and relatively low protective indices. Nevertheless, the data presented suggest that a search for congeners with less fugitive action is warranted. It is of interest in this connection that Bernhard and Bohm (15) have demonstrated that intravenous injection of the local anesthetic lidocaine (Xylocaine), an aminoacyl amide, can modify electrically induced cortical discharges in cats and interrupt epileptic seizures in patients. Preliminary experiments in our laboratory indicate that this compound, in non-toxic doses, is highly effective in abolishing the tonic-extensor component of maximal electroshock seizures. Indeed, others(16) have observed that intravenous procaine paradoxically increases the threshold for electrically evoked cortical responses in rabbits, but causes repetition and increased voltage of such responses as well as widespread irradiation. Since it is likely that the small neurones in the brain are the earliest to be blocked after systemic administration of local anesthetics, the possibility exists that the seizures induced by this class of drugs may be due to selective depression of inhibitory systems(16).

Summary. Five compounds—procaine hydrochloride, cocaine hydrochloride, adiphenine (Trasentine), β-(o-benzylphenoxy)-α-diethylamino-ethane, and Parpanit—the chemical structures of which have a dialkylaminoalkyl

linked via O, N or C to an aryl or aralkyl radical, were tested in mice for neurotoxicity and for ability to modify maximal electroshock seizures. In addition, procaine, cocaine, and Trasentine were tested for ability to modify maximal Metrazol seizures and to prevent postictal depression (anticoma effect). For comparison, two compounds (diethylaminoethanol and Antrenyl), the chemical structures of which only partially comply with the above structural prerequisites, were tested only for neurotoxicity and for ability to modify maximal electroshock seizures. The results obtained may be summarized as follows: 1. Procaine, cocaine, and Trasentine prevent the tonic-extensor component of maximal electroshock seizures in non-toxic doses and exert an anticoma effect in doses near the toxic level. All 3 agents prevent the tonic-extensor component of maximal Metrazol seizures, but only in doses which frequently synergize with the convulsant to cause death. 2. All compounds tested, the chemical structure of which contains a dialkylaminoalkyl linked via O, N or C to an aryl or aralkyl radical, were found to exhibit anticonvulsant activity. In contrast, diethylaminoethanol and Antrenyl were devoid of anticonvulsant activity. 3. The data indicate that compounds within this series share a common anticonvulsant nucleus, but further studies will be necessary precisely to characterize its structural requirements. 4. The laboratory search for congeners with less transient anticonvulsant action and higher protective index is warranted.

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