A STUDY OF CENTRAL NERVOUS SYSTEM STIMULANTS

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Received for publication March 17, 1958

The central nervous system stimulants are commonly categorized according to their principal site of action on the spinal cord, the medullary centers, or the cerebral cortex. In our investigation with the various CNS stimulants during the past decade, we have utilized some of their typical neuropharmacological effects for characterization and classification. This approach has been used with two purposes in mind: 1) to investigate the properties of new stimulating agents by comparison with those of reference standards and 2) to examine the neuropharmacological properties of CNS depressants by antagonism.

In this paper, the results obtained with various old and some new CNS stimulants in mice are given; the data are elucidated categorically according to seizure patterns and some other typical pharmacological effects. Studies on CNS depressants will be communicated in a subsequent report.

METHODS. Male albino mice weighing 18 to 22 gm. were used. The effective dose of each stimulant was determined in 10 animals by parenteral administration. Intravenous administration was carried out by slow infusion at the rate of 0.05 ml. per 10 seconds (Orloff, Williams and Pfeiffer, 1949) in the case of the following stimulants: picrotoxin, pentylenetetrazol, caffeine, 10-(2-dimethylaminopropyl)-9-acridone ("Acridone"), 4-methyl-4-ethylglutarimide (Megimide)[1], $\alpha,\alpha,\beta,\beta$-tetramethylsuccinimide (PM 1090) and 1-hydrazinophthalazine (hydralazine, Apresoline). The quantities of the stimulant required for producing the first clonic contracture, for the maximal tonic extension of hind limbs and for respiratory failure were recorded. Since the average body weight of 10 mice was about 20 gm., the amounts of the stimulants used were expressed in mean values of milliliters per 20-gm. mouse. In antagonism experiments where the tonic extensor seizures of some mice were abolished under the influence of a depressant, the results for such a response were given by the fraction of animals so affected.

[1] This compound was investigated by us in 1948 (Benica and Wilson, 1950).

Cocaine·HCl, desoxyephedrine, α,α-diphenyl-2-piperidinemethanol (pipradrol, Meratran), 2-phenyl-2-piperidine acetic acid methyl ester (methyl phenidate, Ritalin), lysergic acid diethylamide (LSD) and 1,4-dipyrrolidino-2-butyne (Tremorine) were administered intraperitoneally. The signs and symptoms noted were tremors, running movement, pilomotor response, salivation and lacrimation.

For some stimulants, their antiextensor seizure effects were examined by a modified procedure of Toman, Swinyard and Goodman (1946). Three groups of 10 mice each were employed for each dose of the stimulant to determine the three current strengths which would be required to produce tonic extensor seizures in 10 to 90 per cent of the animals. The 50 per cent convulsive threshold of current and standard errors were estimated from a graph relating the percentage of the convulsive animals in probit units to milliamperes of current in logarithms (Miller and Tainter, 1944).

RESULTS AND DISCUSSION. The data are presented under two main divisions on the basis of whether or not intravenous administration of the stimulants will induce tonic extensor seizures in the limbs of mice.

Tonic extensor seizure producing agents. As has been mentioned in a previous report (Chen and Bohner, 1956a), a large number of CNS stimulants can produce clonic and tonic extensor seizures in mice during slow intravenous administration administration. However, under the influence of reserpine and by antagonism with different pharmacological types of anticonvulsant agents, the convulsant properties of these stimulants may be distinctly differentiated. For instance, reserpine will facilitate the tonic extensor seizures of mice induced by pentylenetetrazol or caffeine but it does not affect those induced by strychnine. Dilantin (diphenylhydantoin), on the other hand, is effective in mice in suppressing pentylenetetrazol-induced seizures but not in suppressing strychnine- or caffeine-induced tonic extensor seizures. Under similar experimental conditions ammonium acetate and nikethamide

act like strychnine and pentylenetetrazol, respectively. Picrotoxin behaves like pentylenetetrazol against the anticonvulsant effect of Dilantin but behaves like strychnine in the presence of reserpine. A majority of the other compounds available to us for study have convulsant properties similar to those of picrotoxin or pentylenetetrazol. A comparison of four CNS stimulants, which are of current interest, with picrotoxin and pentylenetetrazol is shown by the data in table 1. It may be noticed first from the quantity of the stimulant required to produce tonic extensor seizures that the extensor seizure response of mice to pentylenetetrazol, 4-methyl-4-ethylglutarimide or PM-1090 stimulation was facilitated by reserpine but the response to picrotoxin, hydralazine or "Acridone" was not affected by reserpine. Second, the extensor seizures of the limbs induced by the six convulsants were suppressed or abolished by Dilantin. This influence of Dilantin may be prevented by reserpine. Third, there is an indication that, although phensuximide, mephenesin and barbital were almost equally effective in suppressing the convulsive seizures induced by the six convulsants, their anticonvulsant effects were antagonized by reserpine more efficiently in seizures induced by pentylenetetrazol, 4-methyl-4-ethylglutarimide or PM-1090 than in picrotoxin-, hydralazine- or "Acridone"-induced seizures. Thus, the results appear to indicate that hydralazine and "Acridone" are picrotoxin-like while 4-methyl-4-ethylglutarimide and PM-1090 are pentylenetetrazol-like convulsants.

Excitants. These CNS stimulants are so referred to here simply because they do not produce tonic extensor seizures in mice by intravenous administration. The outstanding signs and symptoms produced by the excitants are tremors, increased body movements, piloerection, salivation or lacrimation. In table 2 are listed eight compounds which may represent the principal types of excitants. The quantities given in column 1 are excitatory doses producing typical symptoms in all 10 mice. Animals receiving diphenhydramine will run or jump intermittently with slight attacks of clonic seizures but without tremors. The typical effect of cocaine is the well-known "circus" movement in which mice circle along the cage rapidly and continuously. At "noncircling" doses of cocaine, slight tremors and ruffling of hair are observable. Desoxyephedrine,

TABLE I

A comparison of the convulsant properties of certain stimulants under the influence of reserpine and different anticonvulsants in mice

Treatment	Route	Time Int.†	Picrotoxin, ml./20‡-gm. (0.15%)			Hydralazine, ml./20-gm. (1.0%)			Acridone, ml./20-gm. (0.05%)			Pentylene-tetrazol, ml./20-gm. (0.5%)			4-Methyl-4-ethyl glutarimide, ml./20-gm. (0.25%)			PM-1090, ml./20-gm. (0.1%)		
			C§	T	L	C	T	L	C	T	L	C	T	L	C	T	L	C	T	L
mgm./kgm.																				
0 (Control)			0.29	0.36	0.39	0.17	0.32	0.37	0.31	0.38	0.43	0.16	0.49	0.55	0.11	0.29	0.34	0.15	0.41	0.48
R* 8	i.p.	5 hr.	0.34	0.37	0.42	0.20	0.29	0.34	0.34	0.39	0.45	0.16	0.17‖	0.17‖	0.10	0.11‖	0.16‖	0.16	0.21‖	0.26‖
Dilantin 10	i.p.	2 hr.	0.28	—¶	0.51	0.17	7/10	0.40	0.37	6/10	0.62	0.15	—	0.87	0.11	2/10	0.49	0.15	2/10	0.64
Dilantin + R			0.36	0.55	0.60	0.20	0.32	0.42	0.37	0.44	0.53	0.19	0.21	0.22	0.11	0.17	0.22	0.16	0.27	0.35
Phensuximide 125	or.	1 hr.	0.36‖	0.53	0.58	0.34‖	0.45	0.51	0.44‖	0.51	0.60	0.20	—	0.82	0.14	0.51	0.62	0.25‖	7/10	0.72
Phensuximide + R			0.49‖	0.71	0.75	0.35‖	0.36	0.51	0.49‖	0.55	0.65	0.33‖	0.42	0.43	0.13	0.20	0.26	0.27‖	0.57	0.68
Mephenesin 125	i.p.	10 min.	0.36‖	—	0.62	0.26‖	0.39	0.44	0.46‖	5/10	0.67	0.19	—	0.97	0.10	5/10	0.52	0.20‖	—	0.82
Mephenesin + R			0.46‖	0.68	0.78	0.29‖	0.46	0.52	0.65‖	0.71	0.85	0.22‖	—	0.75	0.12	2/10	0.52	0.29‖	2/10	0.74
Barbital 100	i.p.	2 hr.	0.38‖	0.55	0.59	0.42‖	0.61	0.65	0.63‖	0.93	0.99	0.33	—	1.00	0.27‖	1.06	1.11	0.28‖	0.88	0.97
Barbital + R			0.52‖	0.78	0.85	0.44‖	0.62	0.67	0.58‖	0.97	1.02	0.44‖	0.96	0.97	0.26‖	1.09	1.14	0.39‖	1.14	1.19

* R = Reserpine.

† Time interval between injection of an antagonist and challenging the mice with a stimulant.

‡ Average quantity of the solution required to produce a typical seizure in a 20-gram mouse calculated from 10 animals.

§ C = clonic seizure, T = tonic extensor seizure; expressed in ml./20-gm. of the stimulant required or in fractions of animals whose tonic extensor seizures were abolished, L = lethal.

¶ Tonic extensor seizures abolished in all animals.

‖ Significantly different from controls at a "P" value of less than 0.01 (Simpson and Roe, 1939).

TABLE 2

The convulsant and antiextensor properties of some excitants in mice

Compound	Motor Activity (Running)	Tremor	Pilo-erection	Salivation	Antiextensor Seizure (CS_{50} ± S.E.)*			
					mgm./kgm.	Route	Time int.†	mA
mgm./kgm., i.p.								
Diphenhydramine, 40	Jerky	No	No	No	50	i.p.	¼ hr.	>200
Cocaine, 40	"Circus"	Slight	Slight	Slight	50	i.p.	½ hr.	>200
Methylphenidate, 20	Increased co-ordinated	Slight	Very slight	Slight	80	i.p.	½ hr.	71 ±5.8
Pipradrol, 10	Increased co-ordinated	Slight	Very slight	Slight	40	i.p.	½ hr.	>200
Desoxyephedrine, 5	Increased co-ordinated	Marked	Slight	Slight	20	i.p.	½ hr.	7.9 ±0.3
Ibogaine, 20	Slightly increased	Slight	No	No	80	i.p.	1 hr.	>200
LSD, 3	"Popcorn"	Very marked	Very marked	Slight	40	i.p.	½ hr.	5.4
Tremorine, 10	Slightly increased	Marked	No	Very marked	20	i.p.	½ hr.	5.5 ±0.2

* CS_{50} ± S.E. of untreated mice = 4.6 ± 0.1 mA.
† Time interval between injection of the drug and electroshock.

TABLE 3

The influence of certain excitants on clonic and tonic extensor seizures induced by strychnine, pentylenetetrazol and caffeine in mice

Compound	Time Int.	Strychnine·NO_3, ml./20-gm. (0.005%)			Pentylenetetrazol, ml./20-gm. (0.5%)			Caffeine, ml./20-gm. (1.0%)		
		C*	T	L	C	T	L	C	T	L
mgm./kgm., i.p.										
0 (Control)		0.27	0.27	0.31	0.31	0.42	0.49	0.23	0.33	0.40
Diphenhydramine 20	15′	0.29	0.29	0.37	0.12	—	0.70	0.30	0.40	0.51
Cocaine 40	15′	0.26	0.26	0.44	0.10	—	0.59	0.20	0.33	0.49
Methylphenidate 120	15′	0.24	0.24	0.31	0.11	—	0.62	0.23	0.36	0.45
Pipradrol 20	15′	0.28	0.28	0.36	0.09	—	0.53	0.24	0.36	0.46
Desoxyephedrine 5	15′	0.23	0.23	0.28	0.13	—	0.55	0.22	0.30	0.39
Ibogaine 80	15′	0.20	0.20	0.25	0.11	—	1.15	0.18	0.31	0.38
LSD 40	30′	0.21	0.21	0.27	0.12	0.32	0.37	0.21	0.32	0.37
Tremorine 20	30′	0.30	0.30	0.48	0.19	0.30	0.35	0.15	0.19	0.36

* Same notations as those used in table 1.

pipradrol and methylphenidate appear to act similarly in mice with piloerection, tremors and coordinated running movements, the pilomotor response and tremors being more marked with desoxyephedrine than with the other two agents. In the case of ibogaine, although the tremor is distinct, running activity and pilomotor reaction are less pronounced. The effects of LSD in mice are most striking in piloerection and intense tremors, without much running, giving rise to so-called "popcorn seizures." Mice given Tremorine exhibit shaking, but still, with profuse salivation and lacrimation. The latter effect of Tremorine distinguishes it from the other excitants.

Interestingly, with the exception of LSD and Tremorine, the other excitants can also suppress and abolish the tonic extensor seizures of mice in response to electrical or pentylenetetrazol stimulation (Swinyard, Jolley and Goodman, 1950;

Tanaka, 1955; Chen and Bohner, 1956b; Schneider and Sigg, 1957). However, in contrast to the effect of anticonvulsants and CNS depressants, the antiextensor seizure effect of the excitants prevails only at highly exciting dose levels. As revealed by our studies of the joint antiextensor effect of Dilantin, phenobarbital and desoxyephedrine in mice, the mode of the antiextensor action of an excitant is apparently different from that of an anticonvulsant drug (Chen, 1957). In the last column of table 2 are given the antiextensor seizure values of these excitants in terms of the current strengths required to produce tonic extensor seizures in 50 per cent of the animals. They were determined with maximal nonlethal doses at the time of their peak effect. The maximal tolerated doses were required instead of the excitatory doses (column 1), in order to obtain a definite antiextensor seizure effect of these compounds.

Their antiextensor seizure activities as determined against pentylenetetrazol-induced convulsions in mice are shown in table 3. Here are presented also data to show that they are ineffective in suppressing strychnine- or caffeine-induced extensor seizures. Therefore, the term "antiextensor" effect of this type of compound as employed by Tanaka and Kawasaki (1957) is applicable only in electrically or pentylenetetrazol-induced convulsions.

Since the electrically induced extensor seizure in animals was introduced by Toman, Swinyard and Goodman in 1946 for the evaluation of anticonvulsant drugs, the question has often been asked but unanswered as to how the extensor seizure is produced neurologically by stimulation with ocular or pinnal electrodes. From the drug antagonism studies presented here and elsewhere, it appears to be clear that the neurological mechanism involved in the tonic extension of limbs immediately following electrical stimulation is very much similar to, if not the same as, that by stimulation with pentylenetetrazol. On the other hand, different nervous structures are evidently concerned in the production of tonic extensor seizures in mice by strychnine and caffeine. They probably not only exert their convulsive action on the structures at different levels of the central nervous system, but the convulsive discharges so induced are propagated also along different nervous pathways.

SUMMARY

A number of CNS stimulants have been investigated under two main categories based on whether or not they produce tonic extensor seizures in mice.

Among the tonic extensor seizure producing agents, 10-(2-dimethylaminopropyl)-9-acridone and hydralazine are shown to be picrotoxin-like, while 4-methyl-4-ethylglutarimide and $\alpha,\alpha,\beta,\beta$-tetramethylsuccinimide are pentylenetetrazol-like convulsants.

A comparative study has been carried out with the following excitants: diphenhydramine, cocaine, methylphenidate, pipradrol, desoxyephedrine, ibogaine, lysergic acid diethylamide and 1,4-dipyrrolidino-2-butyne. They are incapable of inducing tonic extensor seizures in mice. The stimulant effects of these compounds differ by the running movements, (disorderly or coordinated), by the intensity of tremors and by the presence or absence of piloerection and salivation.

With the exception of the last two compounds, the other excitants are capable of suppressing electrically or pentylenetetrazol-induced tonic extensor seizures in mice but are ineffective in suppressing strychnine- or caffeine-induced tonic extensor seizures.

ACKNOWLEDGMENT. We are indebted to Dr. G. M. Everett, Dr. J. A. Schneider, the Ciba Pharmaceutical Products Inc., and the Wm. S. Merrell Co. for the supply of Tremorine, ibogaine, Ritalin and Apresoline, and Meratran respectively.

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