INTERACTIONS BETWEEN RESERPINE AND ANTICONVULSANTS ON CONVULSION PARAMETERS

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Summary: Reserpine lowered the MET and this lowering of MET was antagonized by chlordiazepoxide but not by acetazoleamide and phenytoin. With increasing doses of reserpine the extension time in an MES test was increased and this was antagonised by all anticonvulsants tested namely acetazolamide, chlordiazepoxide, phenytoin and propranolol. High doses of reserpine abolished flexion component and this was restored by propranolol, phenytoin, atropine, chlordiazepoxide and acetazolamide.

Keywords: reserpine MET anticonvulsants antagonism

INTRODUCTION

Reserpine has always been a paradox. Thus even though it is a central nervous system depressant, and increases barbiturate sleeping time (14), it facilitates convulsions.

Ever since Chen *et al.* (2) reported that reserpine lowered the threshold for electroshock seizure in mice, a large number of papers have appeared confirming this particular property of reserpine (3,4,18). A number of papers also have appeared on the antagonism of anticonvulsants by reserpine. The ED50 of anticonvulsants for protection against maximal electroshock seizure (MES) is raised in reserpinized animals. The antagonism of reserpine by acetazolamide and phenytoin has been studied in particular. Amine depleting agents and false transmitters were widely used to elucidate the mechanisms in the convulsive methods used for these experiments (12,13).

Almost always MES tests were used to study the antagonism of anticonvulsants by reserpine. The other aspects of electroshock for example, minimal electroshock seizure threasold (MET) were not given much importance. Even in the case of MES most of the studies have been confined to anticonvulsant activity as evidenced by abolition of extension phase of the convulsion. Other aspects of convulsions, for example, the presence or absence of flexion (F), duration of extension time (E), F/E ratio have almost always been overlooked. It is quite possible that the machanism of convulsion facilitating action of reserpine may be better understood when these other parameters are also taken into account. The present study concerns itself with the other aspects of convulsions.

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MATERIALS AND METHODS

Effect of reserpine on MET:

Male albino rats weighing between 180-200 g were used for the present experiments. Shocks were delivered by Techno Model Convulsiometer (Model C) and the method originally introduced by Swinyard *et al.* (15), as quoted by Bapat *et al.* (1) was employed for the measurement of MET. The effect of various drugs on MET in the presence of reserpine was studied by the same method.

MES seizures were produced by giving shock of 150 mA for 0.2 second through ear clip electrodes. The presence or absence of flexion was noted and duration of extension was also noted with a stop watch.

The effect of various anticonvulsants on the presence or absence of flexion and the duration of extension were also studied.

Reserpine dissolved in a drop of glacial acetic acid and diluted with normal saline to the required volume, was given intraperitoneally in a volume of approximately 0.1 *ml* 5 hr prior to shock. Controls received the same volume of normal saline, intraperitoneally.

Alpha-methyl dopa was administered 24 hr prior to shock and all other drugs 30 min prior to shock.

RESULTS

Reserpine lowered MET and this lowering effect was dose-related (Table I).

TABLE I: Effect of reserpine on MET.

Reserpine dose in mg/kg	*Number of animals*	*Mean threshold (mA±SEM)*	*'P' value*
0	40	16.5±0.002	—
0.5	8	16±0.01	<0.05
1.0	8	15±0.08	<0.01
2.0	8	14±0.1	<0.01
8.0	8	12.17±0.06	<0.01
12.0	8	9.7±0.12	<0.01

Alpha methyl-dopa *per se* had no action on MET but prevented this action of reserpine (Table II). Chlordiazepoxide and acetazolamide elevated MET (Table II). Phenytoin had no effect on MET (Table II). Phenytoin and acetazolamide had no effect on MET reducing action of reserpine whereas chlordiazepoxide antagonized this action of reserpine (Table II).

TABLE II: Effect of some drugs on MET in reserpinized rats.
Mean threshold (mA ± SEM)

Drug	*Control*	*Reserpine alone*	*Reserpine + drug*	*Drug alone*
Alpha-methyl dopa	(40) 16.5±.002	(16) 12.17±.06 P<.01	(8) 15.9±.12 P<0.1	(8) 16.2±.08 P<.05 NS
Phenytoin	(40) 16.5±.002	(16) 12.17±.06 P<.01	(8) 11.25±.06 P>.05 NS	(8) 16.45±.09 P>.05 NS
Acetazolmide	(40) 16.5±.002	(16) 12.17±.05 P<.01	(8) 12.25±.09 P>.05 NS	(8) 17.5±.08 P<.02
Chlordiazepoxide	(40) 16.5±.002	(16) 12.17±.06 P<.01	(8) 17.8±.09 P<.01	(8) 19.5±0.06 P<.01

Reserpine 8 *mg/kg*, Alpha-methyl-dopa 800 *mg/kg*, Phenytoin 20 *mg/kg*, Acetazolamide 10 *mg/kg*, Chlordiazepoxide 10 *mg/kg*.
Figures in parentheses indicate the number of animals.

The extension time increased with increasing doses of reserpine (Table III).

TABLE III: Effect of reserpine on extension time of hind limb in rats.

Reserpine dose in mg/kg	*Number of animals*	*Flexion*	*Mean extension time sec ±SEM*	*'P' value*
0	8	Present	3.4±0.012	—
2	8	Present	3.7±0.02	<0.01
4	8	Present	4.4±0.022	<0.01
8	8	Present	4.9±0.016	<0.01
10	8	Absent	5.1±0.08	<0.01

Reserpine given in graded doses ip 5 hr before shock.

The flexion component of the convulsion was restored by all the anticonvulsants (Table IV). The extension time was also diminished by all the anticonvulsants tested (Table IV).

TABLE IV: Effect of reserpine and some drugs on extension time of hind limb in rats.

	Number of animals	*Flexion*	*Mean extension time sec±SEM*	*'P' value*
Control	15	Present	3.45±0.002	—
Reserpine	10	Absent	5.1 ±0.06	<0.01
Reserpine + Propronalol	10	Present	3.2 ±0.02	<0.01
Reserpine + Phenytoin	10	Present	2.6 ±0.08	<0.01
Reserpine + Chlordiazepoxide	10	Present	2.8 ±0.09	<0.01
Reserpine + Acetazolamide	10	Present	3.1 ±0.06	<0.01
Reserpine + Atropine	10	Present	3.3 ±0.06	<0.01

Reserpine 10 *mg/kg*, Propranalol 4 *mg/kg*, Phenytoin 4 *mg/kg*, Chlordiazepoxide 10 *mg/kg*, Acetazolamide 10 *mg/kg*, Atropine 5 *mg /kg*.

DISCUSSION

Reserpine facilitated convulsions i.e., the convulsive threshold was lowered. In higher doses it abolished the flexion component of convulsion as previously reported by other workers (11). When stimulus intensity increases the extension time increases (17). Thus the severity of convulsion is proportional to extension time. The dose-related effect of reserpine may be explained in the light of this observation.

Phenytoin did not elevate MET, but chlordiazepoxide and acetazolamide raised MET. Other workers have also reported that acetazolamide raised MET (10). However, chlordiazepoxide elevated MET lowered by reserpine but acetazolamide did not. Phenytoin reported to restore MET previously reduced by cortisone, thyroxine and hyponatraemia to normal (19) was ineffective in restoring the MET lowered by reserpine. Acetazolamide is also ineffective against M.E.S. seizures in the presence of reserpine (5,13). It appears that in the presence of reserpine the anticonvulsant actions of acetazolamide either to elevate MET or prevent MES do not operate and that intact amine stores should be present for acetazolamide to exert its anticonvulsant effect measured by MES test (7). This possibility may apply to the effect of acetazolamide on MET also.

The anticonvulsant activity of propranolol is well documented. Furthermore antagonism of propranolol to reserpine appears to be more specific (9). The present study showed that propranolol diminished the time of extension component of convulsion in reserpinised rats. Like the other anticonvulsants, propranolol also restored the flexion component of convulsion when abolished by reserpine.

Atropine has anticonvulsant activity (20). Besides atropine is specific in antagonising another action of reserpine, namely, antiavoidance effect (8). Hence its antagonism to the convulsion facilitating effect of reserpine was investigated. Atropine diminished the extension time and also restored flexion when abolished by reserpine.

Alpha-methyl dopa is converted into the methylated compounds, namely, methyladrenaline and methylnoradrenaline. Prior administration of alpha-methyl dopa protects rats against the convulsion facilitating effect of reserpine as measured by the MES test (6). It is possible that the protective effect of alpha-methyl dopa (antagonism of the MET lowering effect of reserpine) is related to the fact that the methylated amines are not substrates for depletion by reserpine.

All anticonvulsants diminish extension time (11). In the presence of reserpine the extension time is still reduced by these anticonvulsant drugs. Hence we conclude that the effect on convulsion is the net result of two opposing actions, one a facilitation of spread of convulsion by reserpine and the other the prevention of such spread by anticonvulsants. The flexion component when abolished by high doses of reserpine is restored by anticonvulsants.

Koslow and Roth (11) have argued that the abolition of flexion, extension still persisting, produced by high doses of reserpine represents an anticonvulsant action produced by reserpine in high doses and argued in favour of a competitive antagonism between reserpine and acetazolamide. This argument is erroneous for the following reasons. The appearance of extension as a result of MES stimulus is considered as further facilitation of spread of seizure (11). One of the fundamental principles of drug action is that the function which is last to develop is the first to be abolished with drugs. Hence an anticonvulsant effect will be first manifested as an abolition of extension first and all anticonvulsant drugs produce an abolition of extension and not abolition of flexion. Phenytoin in increasing doses diminish extension time, increases flexion time and ultimately abolish extension (17). Tomich has also pointed out that with increasing doses of anticonvulsant drug, the extension phase of the tonic convulsion is abolished first and then the flexion phase (16). Since all anticonvulsant drugs restore the flexion component, this restoration of flexion should be considered as an anticonvulsant effect.

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