ANALYSIS OF THE DEPRESSANT ACTION OF D,L- AND D-CYCLOSERINE ON THE CENTRAL NERVOUS SYSTEM

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 55, No. 3, pp. 60-62, March 1963
Original article submitted June 23, 1961

A previous study of the effect of cycloserine on the convulsant action of metrazol, strychnine, and caffeine showed that D,L-cycloserine and, to a lesser extent, D-cycloserine increase the threshold of "metrazol" and "strychnine" convulsions [1]. The results of this research, and reports by other workers [2, 7, 8] of the depressant action of L-cycloserine, prompted our further study of the effect of D,L- and D-cycloserine on the central nervous system by combining them with certain drugs depressing the nervous system.

EXPERIMENTAL METHOD

Experiments were carried out on 200 albino mice weighing 18-20 g. The drugs selected as depressants of the central nervous system were chloral hydrate and the barbiturates: luminal (a long-acting drug), ethaminal (moderate duration of action), and thiopental (short-acting drug). These substances were injected intraperitoneally in starch mucilage in doses causing a marked depressant action. Cycloserine was given by mouth in a dose of 50 mg/kg 2 h before injection of the chloral hydrate and barbiturates. The duration and depth of the depressant action were estimated in control animals and after the preliminary injection of cycloserine. The criteria used were the time of onset and the duration of the lateral position, and the loss of pain sensitivity by the animals. The pain reaction was determined by Hesse's method [4], by compressing the base of the tail with a Dieffenbach's clamp. The control animals immediately turned their head towards their tail and bit the clamp, attempting to get rid of it. The absence of this reaction was a sign of the loss of pain sensitivity. The numerical results were treated statistically, and the standard error and the confidence limits of the arithmetical mean ($P = 0.05$) are shown in the tables.

EXPERIMENTAL RESULTS

It may be seen in Table 1 that D,L-cycloserine potentiated the depressant action of luminal, as shown by the earlier onset of the lateral position and the earlier loss of pain sensitivity in the larger number of animals than in the controls. After the preliminary administration of D-cycloserine, only a slight tendency towards potentiation of the depressant action of luminal was observed.

The effect of D,L- and D-cycloserine on the action of ethaminal, thiopental, and chloral hydrate was assessed from the duration of the lateral position (Table 2) and the loss of pain sensitivity. It was found that D,L-cycloserine increased the duration of the lateral position in mice caused by administration of ethaminal, thiopental, and chloral hydrate. This was most marked in respect to thiopental and least so in respect to the action of chloral hydrate. The effect on pain sensitivity was similar. The dextrorotatory isomer of cycloserine had a much weaker potentiating effect than D,L-cycloserine on the action of thiopental and ethaminal, and it had no effect on the action of chloral hydrate.

Similar results were obtained from the study of the effect of cycloserine on the depressant action of ethyl alcohol. These particular experiments were carried out because when cycloserine is used in clinical practice complications affecting the central nervous system are most frequently observed in alcoholics [3, 5, 6]. It was found that D,L-cycloserine increased the duration of the lateral position in mice caused by the intraperitoneal injection of a 15% solution of ethyl alcohol to 115 min compared with 5 min in the control animals. The dextrorotatory isomer had no such effect.

TABLE 1. Effect of Cycloserine on the Depressant Action of Luminal

Drug and dose (in mg/kg)			No. of animals	Time of assuming lateral position (in min)	Loss of pain sensitivity	
D,L-cycloserine	D-cycloserine	Luminal			absolute	%
–	–	100	30	34 ± 2.1 (30 – 38.4)	1	3.3
50	–	100	30	18 ± 1.2 (15.5 – 20.5)	17	56.6
–	50	100	20	30 ± 2.3 (25.2 – 34.8)	2	10.0

TABLE 2. Effect of Cycloserine on the Depressant Action of Ethaminal, Thipental, and Chloral Hydrate

Drug and dose (in mg/kg)		Sedative	(in mg/kg)	No. of animals	Duration of lateral position (in min)
D,L-cycloserine	D-cycloserine				
–	–	Ethaminal	20	11	6 ± 2.2 (1.1 – 10.9)
50	–	Ethaminal	20	14	43 ± 6.0 (30 – 56)
–	50	Ethaminal	20	11	13 ± 3.9 (4.3 – 21.7)
–	–	Thiopental	50	10	5 ± 0.96 (2.8 – 7.2)
50	–	Thiopental	50	10	165 ± 36.8 (81 – 249)
–	50	Thiopental	50	10	9 ± 1.2 (6.2 – 11.8)
–	–	Chloral hydrate	300	10	31 ± 4.1 (21.7 – 40.3)
50	–	Chloral hydrate	300	10	64 ± 7.7 (46.6 – 81.4)
–	50	Chloral hydrate	300	10	32 ± 4.6 (21.4 – 42.6)

Hence, D,L-cycloserine potentiated the action of luminal, ethaminal, thiopental, chloral hydrate, and ethyl alcohol. The action of D-cycloserine, when it was observed (ethaminal, thiopental), was much weaker. These results, in conjunction with the previous findings indicating that D,L-cycloserine possesses stronger anticonvulsant properties than D-cycloserine [1], suggest that the greater depressant action of D,L-cycloserine is evidently due to the presence of the L-isomer in the racemate, for according to Italian workers [2, 7, 8] this isomer possesses a depressant action. The potentiating effect of D,L-cycloserine is less marked in respect to chloral hydrate and more marked in relation to barbiturates. In addition to their cortical action, the latter compounds also have a considerable effect on the brain stem. The results contribute towards our understanding of the mechanism of the action of cycloserine on the central nervous system.

SUMMARY

A study was made of the influence of D,L- and D-cycloserine on the depressive action of chloral hydrate, ethyl alcohol, and barbiturates (luminal, ethaminal, and thiopental). It was established that D,L-cycloserine potentiates the action of the mentioned substances. The potentiating effect of D-cycloserine was observed only in respect to ethaminal and thiopental and was much weaker.

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