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The effect of (±)-*p*-chloroamphetamine on the susceptibility to seizures and on the monoamine level in brain and heart of mice and rats

SIR,—In recent experiments we established that α-methyldopa inhibits the convulsion-facilitating effect and the brain noradrenaline-depleting effect of reserpine. The 5-hydroxytryptamine (5-HT)-depleting effect of reserpine was not influenced by α-methyldopa (Pfeifer & Galambos, 1965). We assumed that the changes in brain noradrenaline level played an important role in the susceptibility to seizures but that changes in the 5-HT level did not. Pletscher, Bartholini & others (1964) and Fuller, Hines & Mills (1965) reported the fact that *p*-chloro-*N*-methylamphetamine and *p*-chloroamphetamine lowered the 5-HT level in rat brain without lowering the concentration of noradrenaline. The compounds did not decrease the 5-HT level in the brain in mice. On the basis of these observations *p*-chloroamphetamine seemed to be a useful tool for investigating further the role of 5-HT and catecholamines in the susceptibility to seizures.

Wistar rats and Swiss mice were used in these experiments. The convulsive threshold was determined by the slow intravenous infusion of leptazol (Orloff, Williams & Pfeiffer, 1949). Noradrenaline, dopamine and 5-HT levels in brain and heart were measured by spectrophotofluorimetry (Bogdanski, Pletscher & others, 1956; Drujan, Sourkes & others, 1959).

(±)-*p*-Chloroamphetamine (10 mg/kg) much increased the convulsive threshold in mice and also in rats after 30 min, and the effect was seen even after 8 hr. There was no change in the brain 5-HT levels in mice. In rats the brain 5-HT level decreased to about 40%, and even after 18 hr when the convulsive threshold had returned to the control value, the 5-HT level was still low (Table 1). The brain noradrenaline and dopamine levels in rats and mice were unchanged.

The anticonvulsive effect of (±)-*p*-chloroamphetamine also developed in the presence of reserpine. The mice received 2·5 mg/kg reserpine intraperitoneally and 90 min later chloroamphetamine 10 mg/kg. The leptazol convulsion threshold was estimated after 30 min. In these circumstances the convulsion-facilitating effect of reserpine was not seen. When the mice were treated with chloroamphetamine 2 hr before reserpine and the convulsive threshold was

determined 2 hr after the reserpine, the anticonvulsive effect of the chloroamphetamine could be observed to an even greater extent. The phenomenon was similar to the reversal of the reserpine effect in the presence of a monoamine oxidase inhibitor.

In recent experiments we demonstrated that α-methyl-*m*-tyrosine did not influence the convulsive threshold, but in the presence of a monoamine oxidase inhibitor it greatly increased the convulsive threshold (Pfeifer & Galambos, 1967). When the mice were pretreated with the chloroamphetamine, α-methyl-*m*-tyrosine further increased the anticonvulsive action of chloroamphetamine, just as did reserpine. The chloroamphetamine did not influence the monoamine-depleting effect of reserpine, but diminished the noradrenaline- and dopamine-depleting effect of α-methyl-*m*-tyrosine in brain, but not in heart (Table 2).

TABLE 1. THE EFFECT OF (±)-*p*-CHLOROAMPHETAMINE (10 MG/KG) ON THE CONVULSIVE THRESHOLD AND ON BRAIN 5-HT LEVEL IN MICE AND RATS. Values are means with standard deviation; the number of experiments is shown in parentheses.

Time after treatment hr	Mouse		Rat	
	Convulsive threshold leptazol ml/10 g	Brain 5-HT μg/g	Convulsive threshold leptazol ml/10 g	Brain 5-HT μg/g
0	0·177 ± 0·044 (30)	0·520 ± 0·02 (3)	0·488 ± 0·186 (5)	0·525 ± 0·1 (3)
0·5	0·270 ± 0·04* (10)			
4	0·237 ± 0·073* (19)	0·465 ± 0·053* (4)	1·061 ± 0·154* (5)	0·304 ± 0·05* (4)
8	0·268 ± 0·064* (8)	0·429 ± 0·166 (3)	0·946 ± 0·126* (5)	0·212 ± 0·03* (4)
18	0·152 ± 0·054 (10)	0·468 ± 0·038 (4)	0·643 ± 0·210 (5)	0·238 ± 0·05 (3)

* Significantly different ($P < 0·01$) from control animals.

TABLE 2. THE EFFECT OF (±)-*p*-CHLOROAMPHETAMINE (10 MG/KG, I.P.) ON THE BRAIN NORADRENALINE, DOPAMINE, 5-HT LEVEL, ON THE HEART NORADRENALINE LEVEL AND ON CONVULSIVE THRESHOLD IN CONTROL MICE, IN MICE TREATED WITH RESERPINE (2·5 MG/KG I.P.) AND WITH α-METHYL-*m*-TYROSINE (50 MG/KG I.P.), RESPECTIVELY. Chloroamphetamine was given 2 hr before reserpine or α-methyl-*m*-tyrosine and the determinations were made 2 hr after. Values are means with standard deviation; the number of experiments is shown in parentheses.

Treatment	Animals not given chloroamphetamine					Animals given chloroamphetamine				
	Brain			Heart	Convulsive threshold	Brain			Heart	Convulsive threshold
	Noradrenaline μg/g	Dopamine μg/g	5-HT μg/g	Noradrenaline	leptazol ml/10 g	Noradrenaline μg/g	Dopamine μg/g	5-HT μg/g	Noradrenaline	leptazol ml/10 g
—	0·445 ± 0·08 (13)	0·997 ± 0·20 (13)	0·565 ± 0·06 (4)	0·776 ± 0·256 (7)	0·177 ± 0·044 (50)	0·514 ± 0·10 (13)	1·044 ± 0·19 (12)	0·551 ± 0·10 (4)	0·646 ± 0·147 (5)	0·237* ● 0·073 (20)
Reserpine	0·087 ± 0·03 (5)	0·134 ± 0·04 (5)	0·199 ± 0·02 (4)		0·118 ± 0·029 (20)	0·149 ± 0·07 (5)	0·178 ± 0·09 (5)	0·152 ± 0·02 (4)		0·304* ± 0·081 (20)
α-Methyl-*m*-tyrosine	0·179 ± 0·05 (8)	0·332 ± 0·07 (8)		0·244 ± 0·09 (5)	0·161 ± 0·043 (20)	0·376* ± 0·14 (7)	0·598* ± 0·04 (8)		0·318 ± 0·103 (6)	0·331* ± 0·057 (15)

* Significantly different ($P < 0·01$) from animals not given chloroamphetamine.

TABLE 3. THE EFFECT OF (±)-*p*-CHLOROAMPHETAMINE (20 MG/KG I.P.) ON THE BRAIN NORADRENALINE AND DOPAMINE LEVEL AND ON THE HEART NORADRENALINE LEVEL IN MICE. Values are means with standard deviation; the number of experiments is shown in parentheses.

Time after treatment (hr)	Brain		Heart
	Noradrenaline μg/g	Dopamine μg/g	Noradrenaline
0	0·523 ± 0·09 (12)	0·916 ± 0·172 (12)	0·633 ± 0·183 (12)
4	0·548 ± 0·132 (7)	1·190 ± 0·392 (7)	0·450 ± 0·173 (6)
26	0·408 ± 0·136 (5)	0·580 ± 0·211* (5)	0·195 ± 0·114* (5)
48	0·440 ± 0·099 (5)	0·756 ± 0·118 (5)	0·204 ± 0·07* (5)

*Significantly different ($P < 0·01$) from control animals.

Chloroamphetamine in a larger dose (20 mg/kg) decreased slightly the brain noradrenaline and dopamine level, and more so the heart noradrenaline level. The heart noradrenaline level decreased to 30% of the control, an effect which lasted more than 48 hr (Table 3).

These results support our view that changes in brain 5-HT levels do not affect the susceptibility to seizures; chloroamphetamine increases the convulsive threshold with normal brain 5-HT levels in mice and with low brain 5-HT levels in rats. As the anticonvulsive effect of chloroamphetamine took place in the presence of reserpine without affecting the low noradrenaline and dopamine level we may presume that the compound acted directly on the noradrenaline receptors. This hypothesis is supported by the fact that chloroamphetamine diminished the noradrenaline- and dopamine-depleting effect of α-methyl-*m*-tyrosine. The cause of the catecholamine-depleting effect of α-methyl-*m*-tyrosine is thought to be that metaraminol, which is formed from α-methyl-*m*-tyrosine, replaces the depleted noradrenaline stoichiometrically (Carlsson & Lindquist, 1962; Shore, Busfield & Alpers, 1964). It can be presumed that (±)-*p*-chloroamphetamine inhibits the uptake of metaraminol.

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