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Antagonism by *p*-chlorophenylalanine of late tranylcypromine toxicity

Overdoses of tranylcypromine lead to a toxic syndrome characterized clinically by hyperactivity, hyperpyrexia, seizures and other signs of marked central nervous system stimulation (Baldridge, Miller & others, 1962; Bacon, 1962; Jacobziner & Raybin, 1963; Atkinson & Ditman, 1965). At a later stage the syndrome might include psychotic behaviour (Baldridge & others, 1962). Bacon (1962) and Jacobziner & Raybin (1963) stated there is no specific antidote available; this continues to be the case. Nor is there a consensus regarding the mechanism of the toxic reactions. Thus though tranylcypromine is a very powerful and lasting monoamine oxidase (MAO) inhibitor (Pletscher, Goschke & others, 1961; Atkinson & Ditman, 1965), it has not proved possible to relate clinical changes to the effects of tranylcypromine on the metabolism of any one single amine. Moreover tranylcypromine also possesses amphetamine-like properties (Baldridge & others, 1962; Atkinson & Ditman, 1965) which tend to be most evident during an initial period after administration. Probably because of the latter, the pharmacological actions of tranylcypromine exhibit some biphasicity with respect to time. Such biphasicity has been observed by Ling (1962) in the response of the electroencephalogram (eeg) of the cat to intravenously administered tranylcypromine, an initial phase of transient and a secondary phase of intense activation being separated by a period of deactivation. We have observed a biphasicity with respect to the toxic actions of tranylcypromine in mice and have found *p*-chlorophenylalanine (*p*-CPA) to protect mice against late, but not early, tranylcypromine toxicity.

Male CWF mice (Carworth Inc., New City, N.Y.) 22–33 g, were divided into two groups, one group was administered 100 mg/kg *p*-CPA dissolved in 2% saline on three successive days, the second group 2% saline injections on the same schedule. Twenty-four h after the last injection the mice were isolated under individual 6″ diameter glass bowls inverted over a wire grid and injected in staggered fashion at 1·5 min intervals with tranylcypromine (Gessner, Soble unpublished findings).

Five doses of tranylcypromine were used, equal numbers of *p*-CPA and saline pretreated animals being injected any given dose. The animals were checked to determine whether they were still alive at 2, 4, 8, 16 and 32 h from the time of the tranylcypromine injection, death being defined as a silent ecg tracing. The cumulative results obtained are given in Table 1, expressed as a function of dose. When these results are expressed in terms of the mortality observed during given time period among the animals alive at the beginning of that period (Fig. 1), the biphasic nature of tranylcypromine toxicity becomes apparent. Moreover upon inspection of Fig. 1, it can be seen that while *p*-CPA pretreatment has no effect on early mortality following tranylcypromine administration, it does appear to have protected the mice from late tranylcypromine mortality. Statistical analysis indicates that the 32 h mortality among those animals surviving tranylcypromine administration by 4 or 8 h and the 16 h mortality among the

animals surviving tranylcypromine administration by 8 h were all very significantly lower ($P < 0{\cdot}001$ in each instance) in *p*-CPA pretreated mice than in controls. The 8 h mortality of those animals surviving tranylcypromine administration by 4 h, on the other hand, was not significantly ($P > 0{\cdot}05$) affected by *p*-CPA pretreatment. It can be concluded therefore that *p*-CPA pretreatment significantly protects mice which have survived tranylcypromine administration by 8 h against further tranylcypromine toxicity.

Table 1. *Effect of pretreatment of mice with* p-*chlorophenylalanine on mortality due to tranylcypromine.*

Tranylcypromine Dose mg/kg	Pretreatment*	N†	Cumulative mortality 2	4	8	16	32 h
135	Saline	9	3	3	5	7	9
	PCPA	9	1	1	3	3	3
153	Saline	17	6	6	11	16	17
	PCPA	17	9	9	9	10	13
171	Saline	14	8	11	12	14	14
	PCPA	14	8	8	11	11	12
189	Saline	5	5	5	5	5	5
	PCPA	5	5	5	5	5	5
207	Saline	5	5	5	5	5	5
	PCPA	5	4	4	4	4	4

* PCPA = *p*-chlorophenylalanine 100 mg/kg at 72, 48 and 24 h before tranylcypromine administration. Controls were administered saline using the same time schedule.

† Number of animals tested.

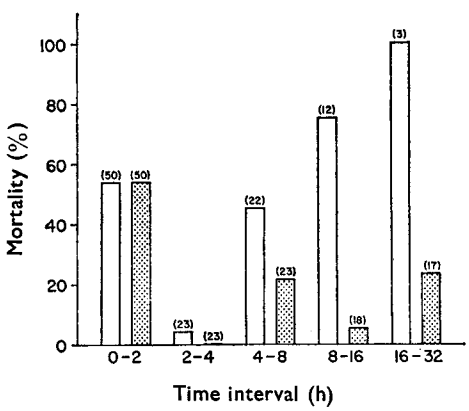

FIG. 1. Mortality of *p*-chlorophenylalanine (PCPA) and saline pretreated mice during various time intervals following tranylcypromine administration. Mortality expressed in percent of animals alive at beginning of time interval. The absolute number of animals alive at beginning of time interval is given in parentheses. Open columns: saline. Stippled columns: PCPA.

p-CPA is an inhibitor of tryptophan hydroxylase (Jequier, Lovenberg & Sjoerdsma, 1967) and its administration results in markedly lower 5-HT brain levels (Koe & Weissman, 1966). Accordingly it has been widely used in the study of serotonergic mechanisms (Sulser & Sanders-Bush, 1971). *p*-CPA administration can lead also to significantly lower brain noradrenaline and dopamine levels (Welch & Welch, 1967), though not in mice when the dosing times are similar to those employed in this study (Frey & Magnussen, 1968; Volicer, 1969). Tranylcypromine, like other MAO inhibitors, is known to lead to increases in monoamine levels, however, it appears to have more marked effects on 5-HT levels than on the levels of catecholamines. Thus Valzelli & Garattini (1968) have reported that in rats tranylcypromine leads to greater proportional increase of brain 5-HT than of brain noradrenaline or dopamine; moreover (Green, Sawyer & others, 1962) have shown that repeated administration of tranylcypromine has a cumulative effect on brain 5-HT but not brain noradrenaline levels. Baldridge & others (1962) observed a marked increase in blood 5-HT though not noradrenaline levels in a patient who attempted suicide by ingestion of tranylcypromine. Finally, Rogers & Thornton (1969) determined mouse brain 5-HT, noradrenaline and dopamine levels 4 h after tranylcypromine administration and found brain 5-HT levels to increase as a function of the dose while brain noradrenaline and dopamine levels failed to do so at any but the lowest doses. These observations coupled with our finding that *p*-CPA pretreatment protects mice against late tranylcypromine toxicity suggests that this toxicity is mediated by a serotonergic mechanism. The clear failure of *p*-CPA to protect mice against early tranylcypromine toxicity underlies the biphasic nature of the pharmacological action of this agent.

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