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Enhanced toxicity of imipramine and desipramine in aggregated mice

SIR,—From experiments with amphetamine (Cohen & Lal, 1964) and cocaine (Lal & Chessick, 1965), it was postulated that the enhanced toxicity of these drugs in aggregated mice was related to their common property by which they inhibit tissue uptake of catecholamines. Recently, imipramine and desipramine were found to block tissue uptake of noradrenaline *in vitro* (Iversen, 1965) and *in vivo* (Glowinski & Axelrod, 1964). The present work shows that aggregation of mice enhanced the toxicity of both drugs.

Swiss albino random-bred male mice of 22–28 g were placed in stainless steel cages (7 × 9·5 × 7 inches), 10 to a cage, 2 hr or more before the intraperitoneal administration of the drugs. Immediately after injection the animals were returned to the same cages, one mouse to a cage for isolation and 10 mice to a cage for aggregation. To maintain group size during the experiment, any dead mouse was replaced by another living animal.

Data summarized in Fig. 1 show that aggregation enhanced the acute lethality of imipramine and desipramine. Imipramine was less toxic than desipramine. Table 1 shows that the onset of clonic convulsions or death after a large dose of desipramine was significantly sooner after aggregation.

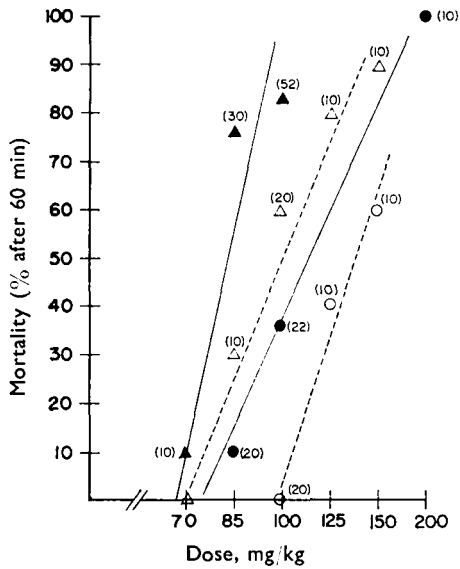

FIG. 1. Toxicity of imipramine and desipramine (doses as mg/kg) in aggregated and isolated mice. —▲— Desipramine aggregated. —●— Desipramine isolated. - - -△- - - Imipramine aggregated. - - -○- - - Imipramine isolated.

TABLE 1. ENHANCEMENT OF DESIPRAMINE*–INDUCED CONVULSIONS AND LETHALITY BY AGGREGATION

	Mean latency (min) ± s.e.		
	Isolated	Aggregated	P
Convulsions	5·4 ± 0·37	3·5 ± 0·37	<0·01
Death	8·0 ± 0·50	5·1 ± 0·34	<0·01

* 200 mg/kg injected intraperitoneally into 10 mice in each group produced convulsions and death in all of the animals. Time of first clonic convulsion is given.

Imipramine and desipramine were more toxic to aggregated mice than to isolated mice. Previous experiments with amphetamine (Cohen & Lal, 1964; Lal, Ginnochio & Shefner, 1963; Mennear & Rudzik, 1966) and cocaine (Lal & Chessick, 1965) suggested that the toxicity of these compounds was related to the tissue catecholamines. Recently, dependence of desipramine toxicity on tissue catecholamines was reported (Lal & Brown, 1968). Thus, amphetamine, cocaine, and desipramine are not lethal in the animals depleted of catecholamines. It is speculated that the aggregation provides excessive sensory stimulation which causes release of central and peripheral catecholamines. Inactivation of these physiologically active amines by "reuptake" mechanisms (Kopin, 1964) is prevented by amphetamine (Axelrod & Tomchick, 1960; Carlsson, Dahlstrom & others, 1965; Glowinski, Iversen & Axelrod, 1966), cocaine (Macmillan, 1959; Whitby, Hertting & Axelrod, 1960), and imipramine-like drugs (Iversen, 1965). This can be expected to enhance and prolong the potent actions of the released catecholamines on target tissues, thereby increasing susceptibility of the animals to the toxicity of certain drugs. Enhancement of desipramine toxicity by noradrenaline has recently been reported by Jori (1966).

Acknowledgement. This work was supported at the University of Kansas by NASA Grant NSG 298, Supl. 3.

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April 8, 1968

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