Amphetamine toxicity and brain amphetamine concentrations in adult and developing mice

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Amphetamine toxicity in mice is age dependent, the susceptibility to amphetamine increasing with age (Alhava, 1971). The low concentrations of brain catecholamines in young mice may be associated with this phenomenon (Alhava, 1971). The dose-mortality curve for amphetamine given to mice is polyphasic (Gardocki, Schuler & Goldstein, 1966) and it can be reproduced in all age groups of mice. Since differences in the distribution of amphetamine might also play a role in its lower toxicity in developing mice, the amphetamine concentrations in the brain and heart were investigated.

Adult male NMRI strain mice (21–26 g) and developing mice of either sex aged 3–5 days (2·0–4·4 g) or 32–35 days (10·0–18·0 g) were injected intraperitoneally with 50 mg/kg of DL-amphetamine sulphate, kept in groups of three to four in opaque plastic cages, and killed by decapitation at various times after injection. The brain and heart amphetamine concentrations was measured (Axelrod, 1954) and all values were corrected for respective recoveries. The room temperature was 24·5±0·5° C.

As shown in Table 1, the highest concentrations of amphetamine were reached within 15 min after injection in the adult brain and heart. The concentrations then steadily declined, the brain amphetamine being 45% and heart amphetamine 32% of the peak level 120 min after injection. In mice aged 32–35 days the peak amphetamine concentration in brain was higher ($P<0·02$) and was reached within 30 min, and its decline was rapid. In contrast, in mice aged 3–5 days, the brain amphetamine concentration was lower than that measured in adult mice at 30 min ($P<0·001$) and continued to rise with time, the concentration measured at 120 min after injection being 235% of that recorded at 15 minutes. In this age group, the heart amphetamine concentration was slightly higher than brain amphetamine 15 and 30 min after injection, and did not change significantly up to 120 minutes.

It appears that the low concentrations of brain amphetamine in the youngest age group and the delay in reaching the peak may well contribute to the relative resistance

TABLE 1. *Tissue content of DL-amphetamine in developing and adult mice after administration of amphetamine (50 mg/kg i.p.)*

Age	DL-amphetamine (μg/g), mean ± S.E.				
	Time after administration (min)				
	15	30	60	90	120
3–5 days					
Brain	25±1·7 (6)	33±3·0 (5)	41±2·5 (12)	55±5·4 (6)	58±5·1 (6)
Heart	31±6·5 (6)	41±6·8 (5)	32±1·8 (10)	30±3·8 (10)	33±4·9 (6)
32–35 days					
Brain	96±4·9 (8)	103±4·2 (8)	80±3·0 (8)	55±1·7 (8)	
Heart	37±3·1 (8)	38±2·4 (8)	33±2·7 (8)	19±1·4 (8)	
Adult					
Brain	91±2·6 (7)	89±2·6 (5)	56±4·6 (4)	56±3·9 (7)	41±3·2 (7)
Heart	62±3·9 (7)	54±2·8 (5)	40±6·9 (4)	30±2·3 (7)	20±3·9 (7)

The number of experiments is given in parentheses.

of these animals to amphetamine. The concentrations of brain amphetamine and the effects of amphetamine may be modified by the morphological immaturity of the cerebral cortex in the youngest mice (Kobayashi, Inman, Buno & Himwich, 1963).

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Inability of antidepressants and morphine to reverse reserpine-induced hypothermia in adrenalectomized mice

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The interaction between imipramine-like compounds and reserpine on body temperature in rats may be mediated through the central sympathetic system (Bernardi, Paglialunga & Jori, 1968). In mice, however, Somerville & Whittle (1967) have proposed that the hypothermic action of reserpine may be peripheral rather than central. Since the reversal of reserpine-induced hypothermia by desmethylimipramine is enhanced rather than abolished in immunosympathectomized mice (Greenwood & Somerville, 1970) the possibility remains that the adrenal gland plays an important part in this response.

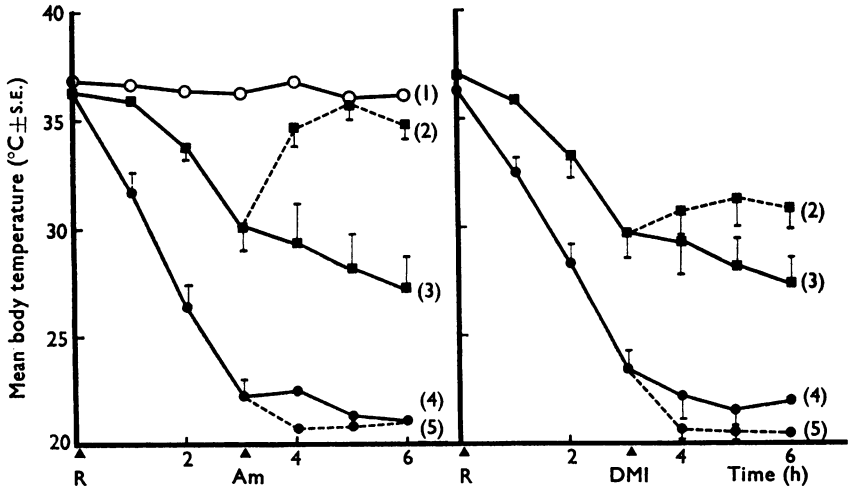

FIG. 1. Lack of antagonism by oral amphetamine (left) and desmethylimipramine (DMI) (right) of the hypothermic effect of reserpine (R) (2 mg/kg, s.c.) in groups of six adrenalectomized mice (ADX). (1) ADX+saline+saline. (2) Sham operated mice+reserpine+amphetamine (10 mg/kg) or DMI (10 mg/kg). (3) Sham operated mice+reserpine+saline. (4) ADX+reserpine+saline. (5) ADX+reserpine+amphetamine (10 mg/kg) or DMI (10 mg/kg).