CATECHOLAMINE METABOLISM AND AMPHETAMINE EFFECTS ON SENSITIVE AND INSENSITIVE MICE

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IT HAS been found that amphetamine elicits in mice a strain-dependent symptomatology (WEAVER and KERLEY, 1962; BROWN, 1965). C_3H mice have been previously reported to be considerably less sensitive than other strains to the stimulating activity of amphetamine (DOLFINI *et al.*, 1969a, 1969b; DOLFINI *et al.*, 1970). The data presented summarise some differences and similarities between C_3H and NMRI mice in the action of *d*-amphetamine (Table 1).

DIFFERENCES IN THE ACTION OF *d*-AMPHETAMINE IN THE TWO STRAINS

(1) *d*-Amphetamine neither increases the spontaneous motility, nor, does it induce the stereotyped behaviour and grouping effect in C_3H mice as do the doses active in NMRI mice.

(2) *d*-Amphetamine does not significantly increase the body temperature of C_3H mice, while it elicits a dose-dependent hyperthermia in NMRI mice (3·75–30 mg/kg i.p.). On the contrary, at low doses, it decreases the body temperature in C_3H mice (CACCIA *et al.*, 1973).

(3) *d*-Amphetamine decreases noradrenaline (NE) in the brain-stem and increases homovanillic acid (HVA) in the striatum, but it only slightly affects noradrenaline and does not modify HVA concentrations of C_3H mice (CACCIA *et al.*, 1973).

SIMILARITIES IN THE ACTION OF *d*-AMPHETAMINE IN THE TWO STRAINS

(1) The distribution of amphetamine is similar in C_3H and NMRI mice. No differences were observed between the two strains in the concentration of amphetamine in whole brain and in specific areas such as striatum and brain-stem at various times after administration of the drug.

(2) The anorexigenic effect of *d*-amphetamine seems to be similar in C_3H and in NMRI mice.

(3) *d*-Amphetamine increases plasma FFA to a similar extent in C_3H and in NMRI mice.

(4) *d*-Amphetamine elicits a clear dose-dependent hyperthermic effect in reserpinised mice of both strains. These data are in sharp contrast with the lack of hyperthermic activity in normal untreated C_3H mice.

The thermic response to amphetamine in normal untreated mice is probably a polygenically-inherited trait. This hypothesis is supported by the results of pharmacogenetic experiments conducted in our Institute involving the cross mating of C_3H and NMRI mice (Fig. 1); (JORI and PRICE-EVANS, unpublished results). In an attempt to understand this genetically determined different reactivity to amphetamine, the basal brain concentrations of the biogenic amines and of their metabolites were compared

TABLE 1

No. determinations	Effects of amphetamine	Strain	
		C_3H	NMRI
72	Hypermotility	NO	YES
72	Stereotyped behaviour	NO	YES
18	Hyperthermia (°C)	−0·7 ± 0·1	+2·5 ± 0·1‡
8	NE decrease (ng/g)	−60 ± 15	−150 ± 20‡
4	HVA increase (ng/g)	−14 ± 20	+224 ± 15‡
5	Brain Amphetamine (μg/g)	5·2 ± 0·1	5·5 ± 0·2
3	Food intake * (g/2 hr/6 mice)	0 ± 1‡	2 ± 1‡
5	Plasma-FFA increase (mequiv/l.)	+715‡ ± 35	+727‡ ± 39
18	Hyperthermia in reserpinised mice* (°C)	+3·9‡ ± 0·4	+3·5‡ ± 0·2

‡ $P < 0{\cdot}01$ vs untreated mice. Mice were caged in groups of 6 and were given *d*-amphetamine-sulphate at a dose of 7·5 mg/kg i.p. or* 5 mg/kg i.p. Temperature and biochemical determinations were performed 30 or 60 min after treatment. Food intake of control mice was 11 g ± 0.5

in the two strains (Table 2). No differences were noted for the brain serotonin (5HT) and 5-hydroxyindolacetic acid (5HIAA), for NE in the brain-stem, and for

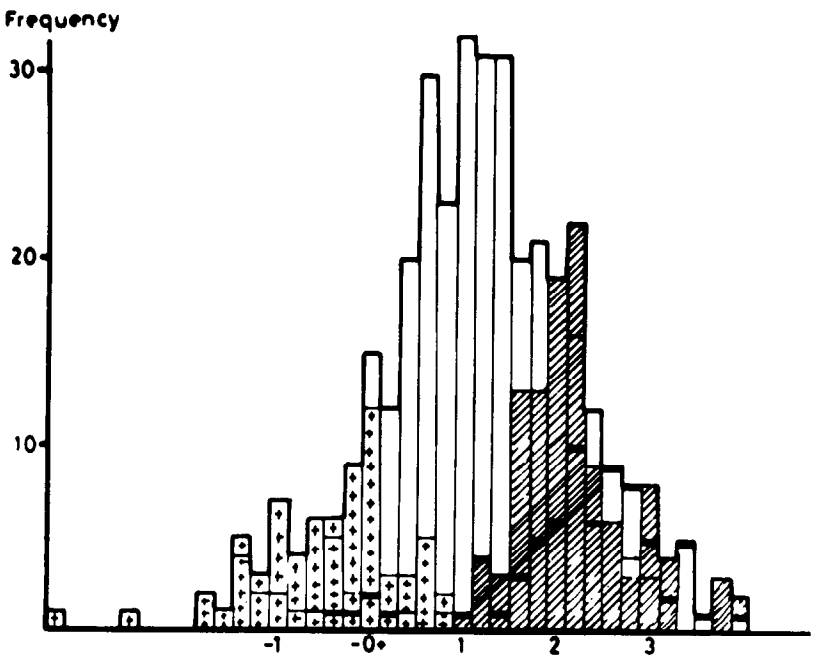

FIG. 1.—Frequency distribution of temperature changes 30 min after *d*-amphetamine sulphate (7·5 mg/kg/i.p.), in the various groups of mice. (312 mice were used.)

NMRI mice
C_3H mice
F_1 mice
F_2 mice

dopamine (DA) and HVA in the striatum However a basic difference in the striatum dopamine metabolism was suggested by determination of DA disappearance after blocking catecholamine synthesis with α-methyltyrosine and of the HVA accumulation after blocking its active transport with probenecid. These experiments demonstrated

TABLE 2

No. determinations	Biochemical parameters	Strain	
		C_3H	NMRI
		(ng/g ± S.E.)	
8	Brain 5HT	285 ± 25	250 ± 20
8	Brain 5HIAA	490 ± 10	480 ± 10
8	Brain Stem NE	570 ± 20	540 ± 20
6	Striatum DA	4280 ± 160	4260 ± 200
4	Striatum HVA	279 ± 15	240 ± 15
4	Striatum HVA after Probenecid*	389 ± 8‡	630 ± 36
	Rate constant of DA loss after αMTyrosine K (hr^{-1})†	0·136 ± 0·017‡	0·188 ± 0·021

‡ $P < 0{\cdot}01$ versus NMRI mice. * Probenecid was given at a dose of 200 mg/kg i.p. HVA was determined 90 min after Probenecid. † K represents the slope × 2·3 of the curve obtained by plotting the log-concentrations (μg/g) of dopamine at 0, 1, 2 and 3 hr after the administration of α-methyltyrosine (αMT) (500 mg/kg/ i.p.).

a lower DA turnover rate in C_3H than in NMRI mice. These last data are preliminary and other experiments are in progress. We consider that the comparative use of genetically insensitive and sensitive strains, can provide a useful model for the understanding of the mechanism of the action of amphetamine and the factors responsible for its tolerance and its abuse.

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