Amphetamine toxicity in genetically aggressive and non-aggressive mice

Amphetamine and isoprenaline in high doses produce a fatal myocardial necrosis in mice and rats (Chappel, Rona & others, 1959; Halpern, Drudi-Baracco & Bessirard, 1962). This susceptibility is increased by rearing the animals in isolation, or by grouping the animals while under the influence of the drugs during the experiment, as the LD50 for these drugs shows (Balazs, Murphy & Grice, 1962; Consolo, Garattini & Valzelli, 1965; Welch & Welch, 1966; Moore, 1968). Isolation of mice also renders them more aggressive (Allee, 1942; Scott & Fredericson, 1951), and aggressiveness has been associated with increased amphetamine toxicity (Consolo & others, 1965; Welch & Welch, 1966).

Whether increased amphetamine toxicity is invariably associated with aggressiveness, or whether it is an outcome of isolation only, and thus not a necessary condition of aggressiveness, has now been tested with strains of mice selectively bred for aggressiveness or non-aggressiveness (Lagerspetz, 1961, 1964, 1969).

Male mice from the 16th–19th generations of offspring from selective breeding for aggressiveness (strain TA) or non-aggressiveness (strain TNA), about 30 g, had (+)-amphetamine sulphate intraperitoneally in doses ranging from 29 to 85 mg/kg calculated as (+)-amphetamine. Mice of the 16th to 18th generations were isolated after weaning, and reared in isolation for 5 to 6 months, save for occasional aggressiveness tests, the last of which was made in the 16th generation not later than 3 weeks before the experiment, in the 17th generation 3 days before it, and in the 18th generation 3 months earlier. The mice of the 19th generation had lived together with their male siblings in groups of at least 5 animals for 6 months after weaning. During the experiment, which lasted for 24 h, the animals were kept in isolation at 23°. Altogether, 65 isolated TA mice and 81 isolated TNA mice were used, as well as 20 of each strain that had been living grouped.

The aggressiveness of the test mice had been earlier measured using the 7-point rating scale for aggressiveness in male mice (Lagerspetz, 1961, 1964). The mean aggressiveness scores for the isolated TA and TNA mice were 6·0 and 3·2, respectively. This difference is significant at the level of $P < 0{\cdot}002$ (Mann-Whitney U-test; Siegel, 1956). The aggressiveness scores of the grouped mice were low (1·5) and equal in both strains.

The LD50-values for (+)-amphetamine were 58 and 59 mg/kg for the isolated animals of the two strains and 69 and 68 mg/kg for the grouped animals. The values did not differ significantly from each other, but did differ between isolated and grouped animals.

In the non-aggressive strain, in each generation there appear a few individuals with a high aggressiveness score (Lagerspetz, 1961, 1964). The survival times of these individuals after the administration of lethal doses of (+)-amphetamine, and the doses after which they survived were not different from those of the TNA animals with a low aggressiveness score.

The genetically aggressive and non-aggressive mice show no overt aggressive behaviour and an equal amphetamine toxicity when reared in groups. When reared in isolation, the aggressiveness is increased much more in mice of the aggressive strain, but the amphetamine toxicity is increased to the same degree in both strains. Thus, high amphetamine toxicity is not invariably linked with high aggressiveness in mice. It seems more probable that increased amphetamine toxicity is associated with changes in other variables than aggressiveness, produced by isolation.

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Some effects of butoxamine on glycolysis in the mouse brain

N-t-Butylmethoxamine (butoxamine) prevents the rise in blood free fatty acids, glucose and lactate after the administration of adrenaline or isoprenaline (Burns & Lemberger, 1965; Salvador & April, 1965). The drug also produces a selective blockade of some, but not all, β-adrenergic receptor sites in the anaesthetized dog (Levy, 1966) and can therefore be clearly distinguished from such β-adrenoceptor blocking drugs as dichloroisoprenaline and pronethalol (Pilkington, Lowe & others, 1962) and propranolol (Salvador, April & Lemberger, 1967).

The effects of butoxamine on brain glycolysis are now reported.

Groups of 5 specific pathogen free mice (18–22 g) of either sex and of the Alderley Park strain were given the drug intraperitoneally and the animals transferred to a room maintained at $38 \pm 1°$. At different times after injection, groups were killed by total immersion into liquid nitrogen. The brains were removed while still frozen and triturated with cold 10% trichloracetic acid. "Bound" glycogen was estimated in the acid insoluble material by the method of Russell & Bloom (1958). Lactate, pyruvate, glucose and "free" glycogen were estimated in aliquots of the acid soluble fraction by enzymatic methods (Leonard, 1971).

The relation between the effect on some parameters of brain glycolysis are shown in Fig. 1. At 20 mg/kg, butoxamine produced a significant decrease in glucose and "free" glycogen and a significant rise in "bound" glycogen and pyruvate. Brain lactate did not change appreciably. Doses of butoxamine lower than 20 mg/kg did not produce any noticeable change in the concentrations of these substances. The changes produced were not correlated with any change in behaviour; the mice were not unduly affected by this dose of drug compared with those given physiological saline alone.