ON AMPHETAMINE TOLERANCE AND ABSTINENCE IN RATS

TOMMY LEWANDER, GULL MOLIIS and INGER BRUS
Psychiatric Research Center, University of Uppsala, Ulleråker Hospital,
S 750 17 Uppsala, Sweden

INTRODUCTION

DEVELOPMENT of tolerance to a number of pharmacological effects of amphetamine on chronic administration of the drug has been described in animals and man (see reviews by KOSMAN and UNNA, 1968, LEWANDER, 1970, 1972, KALANT *et al.*, 1971). In rats it has been concluded that amphetamine tolerance seem to be functional rather than dispositional (LEWANDER, 1968, 1971b). The depletion of noradrenaline and incorporation of *p*-hydroxynorephedrine, a metabolite of amphetamine in rats, as a false transmittor into central and peripheral noradrenaline neurons, seem to be one mechanism of tolerance to amphetamine in rats (BRODIE *et al.*, 1969; LEWANDER, 1971b).

The present communication concerns a preliminary account of a study of some aspects of amphetamine tolerance, such as its speed of production, its extent and duration, the occurrence of carry-over of tolerance, which do not seem to have been investigated previously. In addition, the development of tolerance to the inhibitory action of amphetamine on hoarding behaviour (BLUNDELL, 1971) and the unexpected finding of an increased hoarding activity on withdrawal of chronic amphetamine administration is demonstrated.

METHODS

Male Sprague–Dawley rats, approximately 300 g body wt., were used. The rats were kept in individual cages in a temperature constant room (21°C).

In the first experiment body (colonic) temperature was measured by an electric thermometer (Ellab, Copenhagen) at hourly intervals after the morning injection for 7 hr a day for 45 days. *d*-Amphetamine, 20 mg/kg i.p., or saline was administered twice daily to two groups of 15 rats each for 15 days (day 1–15, Fig. 1a). During the following 15 days (day 16–30) all rats received saline except on day 21, 25 and 30, when two subgroups of five rats each from the chronically amphetamine and saline treated groups respectively, were tested with amphetamine. *d*-Amphetamine or saline was again given chronically for a second 15 days period (day 31–45). Food and water was freely accessible between 4.30 p.m. and 8.30 a.m.

The temperature response to amphetamine was calculated each day as the mean area limited by the time–response curves between 0 and 6 hr for amphetamine and saline respectively. For convenient presentation of the results (Fig. 1a) the daily areas were expressed as percentages of the day 1 area, which was set to 100 per cent.

Hoarding behaviour was measured as the number of food pellets (2, 6 g, Anticimex no. 214) hoarded during a 15-min trial (BLUNDELL, 1971). Twelve rats received *dl*-amphetamine sulphate, 16 mg/kg i.p. twice daily for 14 days and 12 control rats received saline. At day 18 (Fig. 1b) all rats were injected with amphetamine and from day 19 on all rats were given saline. The hoarding trials were run daily at 1, 3 and 5 hr after the morning injections; food was then freely available for 3 hr. The mean hoarding score for the 3 trials were calculated for each rat and the daily median of the hoarding scores for each group are given in Fig. 1b. During the chronic amphetamine treatment period (from day 6 through day 18), however, the hoarding trials for each time point are given separately for the amphetamine treated rats. Filled circles in Fig. 1B indicates statistically significant differences ($p < 0{\cdot}05$) between the experimental and control groups (Mann–Whitney U-test; SIEGEL, 1956).

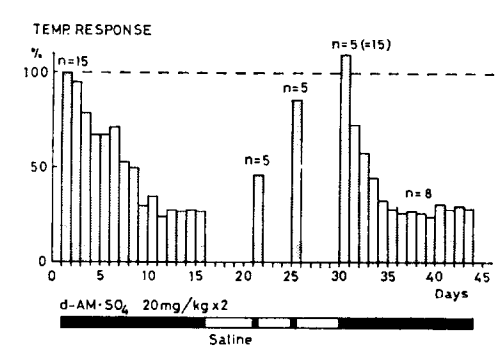

FIG. 1(a)

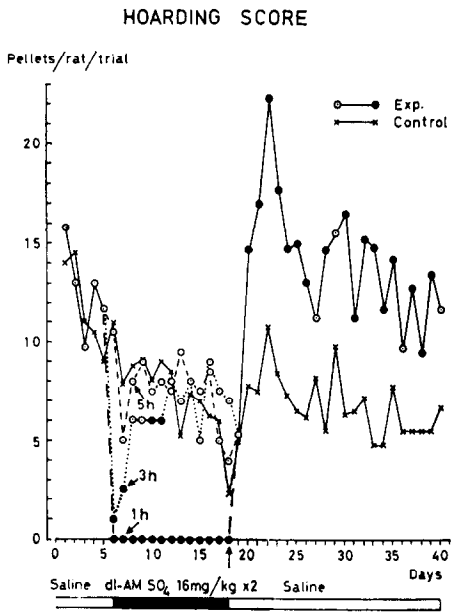

FIG. 1(b)

RESULTS AND DISCUSSION

It is concluded from the present experiment, Fig. 1a, that maximal tolerance, about 30 per cent of the initial response, to the hyperthermic effect of a high dose of amphetamine developed after 9 days of chronic treatment. The duration of tolerance was estimated to 10–15 days, when initial temperature response was reattained. The presence of the phenomenon of carry-over of amphetamine tolerance could be demonstrated, since maximal tolerance was reached already after 6 days during a second period of chronic amphetamine administration. Tolerance to the hyperthermic action of amphetamine has been related to the biochemical effects of amphetamine on noradrenaline neurons (LEWANDER, 1971b). The present results prompts a study of central and peripheral catecholamines at various time points in a similarly designed experiment in order to find explanations for the present observations.

In the second experiment, Fig. 1b, the development of tolerance to the inhibitory effect of amphetamine on hoarding behaviour was demonstrated, which was dependent on the time-point after the injection of amphetamine. At 1 hr after the amphetamine injection, the hoarding score was practically zero throughout the treatment period and at 5 hr hoarding was not significantly affected by amphetamine. At 3 hr after injection, however, the hoarding scores were initially decreased but after 7 days did not differ significantly from control scores of chronic treatment. Hoarding activity increased unexpectedly after withdrawal of the chronic amphetamine treatment. This sign of amphetamine abstinence appeared to have an initial phase for about 7 days with a maximal hoarding score on the fourth day, and a second protracted disappearance phase for at least 2 additional weeks. To the knowledge of the authors only slight sedation (LEWANDER, 1968) and a small rebound increase in food intake (TORMEY and LASAGNA, 1960) after withdrawal of amphetamine in tolerant rats

have been noticed previously. In humans an increase in rapid eye movement sleep been documented during amphetamine withdrawal in amphetamine dependent subjects (OSWALD and THACORE, 1963).

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