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Contingent Tolerance to the Anorexigenic Effects of Amphetamine[1]

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CARLTON, P. L. AND D. L. WOLGIN. *Contingent tolerance to the anorexigenic effects of amphetamine*. PHYSIOL. BEHAV. 7 (2) 221–223, 1971—Rats given pretest injections of amphetamine and post-test injections of saline develop tolerance to the anorexigenic effects of the drug. Rats given the same number of injections, but in the reverse order, fail to develop tolerance during the same period of time. Thus, the development of tolerance is contingent on the relationship between time of injection of amphetamine and eating.

Amphetamine Anorexia Tolerance Behavioral tolerance

THE TERM tolerance has been traditionally taken to mean that the initial effect of a drug may be attenuated with repeated administration. Typically, some, but not all, responsive physiological systems show tolerance. Similarly, behavioral tolerance refers to the attenuation of some, but not all, of the behavioral effects of a drug following its chronic administration. For example, the initial disruption of rats' DRL performance (differential reinforcement of low rates of responding) produced by amphetamine gradually declines with repeated injections, whereas drug-induced hyperactivity remains at a constant level during the same period of time [5]. Related effects have been reported in other studies with amphetamine [6], alcohol [2], reserpine [4] and scopolamine [1, 3]. The experiments that we report here follow from these earlier studies in two respects.

First, behavioral tolerance has been interpreted to be due to a loss of reward that occurs with the initial administration of the drug. That is, it has been postulated that, because the drug-treated animal loses reward, it somehow learns to compensate for such loss and, therefore, the initial effect of the drug wanes [6]. We were interested in determining whether this interpretation, which has been based on studies involving complex operant behaviors, would also apply to what has traditionally been termed the anorexigenic effects of amphetamine.

Second, our studies of this phenomenon involve an experimental design in which the relationship between drug injection and the measurement of food intake is varied. In particular, one group of animals is given amphetamine prior to a daily feeding session, whereas a second group is given an injection following such a session. After tolerance has developed in the first group, drug administrations for the second group are shifted so that they, too, receive amphetamine prior to the feeding session.

The rationale for this procedure is that, if the tolerance shown by the first group is a general one, then the second group, which received the same number of injections following feeding, would not show an attenuation of food intake when the drug is given prior to such feeding. If, on the other hand, the second group shows a reduction in food intake comparable to that originally seen in the first group, then the development of tolerance can not reasonably be assumed to be a general one. Rather, this result would indicate that tolerance in the first group was entirely contingent on the relationship between injection and feeding ; this kind of tolerance would thus be reflected in the differential effects on a single measure rather than in such effects on different measures (e.g. DRL performance vs motor activity). We have elected to call the phenomenon reported here contingent tolerance in order to emphasize this distinction.

Method

The animals were 40 male, Sprague–Dawley rats, weighing 190–226 g at the beginning of the experiment. Each rat was housed individually and maintained on a deprivation schedule of 2–3 Purina Lab Chow Pellets (approximately 10–15 g) and ad lib water daily. On alternate days, 30-min drinking tests were conducted in the home cages. During these tests, water bottles were replaced with graduated drinking tubes containing sweetened condensed milk diluted with water (1 part milk to 2 parts water). Intraperitoneal injections of d-amphetamine sulfate (dissolved in physiological saline), or saline only, were given 20 min before and immediately after each test (see below). Following the latter injections, water bottles were returned and the animals fed. Drug and milk were freshly prepared at least every other test day.

Three preliminary drinking tests were used to familiarize the animals with the paradigm and to establish baseline levels of intake. During these preliminary tests, each rat was

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within Group A-S were obtained as a function of dose (i.e. 2.0 vs. 3.0 mg/kg).

Inspection of Fig. 1 suggests that the S-A animals showed less of an increase on intake on Days 1–7 than did their corresponding Group S-S. Similar, but reduced, differential intake is seen in Fig. 2. However, statistical analysis of the pooled data for individual animals for Days 1–7 indicated that neither the S-A rats given 2.0 mg/kg nor those given 3.0 mg/kg differed from their respective S-S controls (two-tailed Mann–Whitney U-test). This comparison for the animals given 2.0 mg/kg did, however, fall just short of significance at the 5 per cent level.

DISCUSSION

These results clearly indicate that the development of tolerance to both doses of amphetamine is contingent on the relationship of the time of injection to the time at which food is made available. In particular, the animals given amphetamine before each test session (the A-S treatment) showed a waning of the inital effect of amphetamine; when this effect in the A-S animals had completely disappeared, animals that had received their injections after each session (the S-A treatment) showed the usual anorexic effect of amphetamine when shifted to the A-S condition. Furthermore, when pretreatment with amphetamine was continued in these animals, the initial depression of food intake waned at essentially the same rate as it had in the A-S animals. Thus, these animals showed a normal response to amphetamine; both the initial effect and the rate of recovery was normal despite the fact that the animals had received a series of injections identical to that that had led to tolerance in the A-S group. Thus, the development of such tolerance was contingent upon the relationship of amphetamine injection to food intake.

These results cannot simply be accounted for on the assumption that tolerance is a manifestation of some kind of shift in metabolism, rate of absorption or some enzymatic alteration (e.g. enzyme induction) unless such changes are assumed to be related to the aforementioned contingency in some unspecified way. In addition, these effects are uncontaminated by the effects of repeated trials because the effect of amphetamine in the animals otherwise given saline was the same during the screen as it was on test Day 19.

The most parsimonious explanation for the phenomenon of contingent tolerance to amphetamine is that it represents a form of associative learning, as has been suggested by others [6]; that is, when the drug leads to a loss of reinforcement, the animal somehow compensates for this loss and thereby becomes tolerant. Because this tolerance depends upon the loss of reinforcement and therefore upon the relationship between injection and the opportunity to eat, it may be said to be contingent.

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