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Inhibitory Effects of Pre- and Posttest Drugs on Mouse-killing by Rats[1]

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GAY, P. E., R. C. LEAF AND F. B. ARBLE. *Inhibitory effects of pre- and posttest drugs on mouse-killing by rats.* PHARMAC. BIOCHEM. BEHAV. 3(1) 33–45, 1975. – Mouse-killing in rats was gradually inhibited by repeated posttest injections of *d*-amphetamine (1.5 mg/kg), *l*-amphetamine (1.5 mg/kg) or pilocarpine (7.5 mg/kg), but not by control substances. Of these drugs, only *d*-amphetamine inhibited killing when given prior to a mouse-killing test. Further experiments suggested that anorexia per se did not contribute to drug-induced inhibitory effects, but that changes in internal state were important to the development of inhibition. Pretest injections appear to inhibit predatory killing by a direct pharmacological action on some target site or sites, while posttest injections produce a learned aversion to predatory killing.

Predatory aggression Amphetamine Pilocarpine Learned aversions

EARLY studies of the effects of amphetamines on mouse-killing by rats anticipated that amphetamines might induce killing due to their activating effects. However, *d*-amphetamine did not induce killing, but blocked or delayed it. Because other basic behaviors were also disrupted at equal doses, the inhibitory effects of *d*-amphetamine seemed nonspecific, due only to its general disorienting effects [22].

Later work confirmed the inhibitory effects of amphetamines on mouse-killing, and indicated that inhibition began at systemic doses that did not produce ataxia or general debilitation [19,20]. Moreover, compounds with similar biochemical actions (e.g., increase in noradrenergic activity at the synapse) were found to have similar behavioral actions on mouse-killing when injected either systemically or directly at amygdaloid brain sites [18,25]. Analyses of these actions suggested that amphetamines block mouse-killing by a selective action on an noradrenergic inhibitory system located in the amygdaloid region.

Although the hypothesis that amphetamines block rat predatory behavior by direct pharmacological action on a specialized brain system is more tenable than the earlier view of indirect and nonspecific action, the range of behaviors modified by this brain system and the functional specificity of the inhibitory drug actions have not been delimited. It is possible that amphetamines block predation indirectly by actions on "feeding" or other "motivational" or "perceptual" mechanisms [10, 11, 12]. Several effects of feeding manipulations on mouse-killing have been identified [31, 32, 33, 43], and these findings suggest that drug-induced anorexia may underlie, at least in part, amphetamine-induced inhibition of predatory killing. Prey novelty also influences mouse-killing by rats [2] and brain lesions that block killing produce profound changes in responses to novel stimuli [13,40]. Amphetamine-induced inhibition of mouse-killing could, therefore, be an indirect consequence of drug actions on brain systems that normally function to regulate effects of stimulus novelty. In addition, the aversiveness of certain drug states can produce learned inhibition of mouse-killing by rats, though data on amphetamine has not been reported [9,27]. Learned food aversions to amphetamine have been shown [6, 7, 8], however, and these may account, at least in part, for drug-induced inhibition of mouse-killing in experiments that involve repeated drugging and testing. In sum, possible mechanisms of drug action that might account for amphetamine-induced inhibition of predatory mouse-killing by rats include, but are not limited to, changes in func-

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tional systems that control feeding, responses to novel stimulation, and association of the drug state with antecedent conditions.

This report describes a series of studies undertaken to evaluate relationships between drug-induced anorexia, novelty, learned aversion, and amphetamine-induced inhibition of mouse-killing by rats.

EXPERIMENT 1

The initial experiment compared the effects of amphetamine given prior to an opportunity to kill with those of amphetamine given after an opportunity to kill. Both *d*- and *l*-amphetamine were studied, in order to assess the probable role of central versus more peripheral actions on each type of killing inhibition. A drugged control group to evaluate the interaction of the inhibitory effects of mouse exposure [2,44] and amphetamine was also included.

METHOD

Animals

The animals were 56 male Holtzman rats (222–518 g) that killed mice spontaneously on two successive 30-min tests. The prey were adult ICR mice (20–40 g) of both sexes.

Apparatus and Procedure

Rats were individually housed in 8 X 9 3/4 X 7 in. stainless steel Wahmann cages, with solid backs and sides and hardware cloth floors and fronts, in a room which contained no mice. The cages were equipped with external pellet containers and water bottles with stainless steel tubes. Mice were group-housed, in plastic cages on Litter Green bedding or cedar shavings, in a separate room.

The experiment consisted of two phases. During Phase 1, each rat received a daily i.p. injection for 7 days. Except as noted below, each rat also had a 10 min opportunity to kill, but not eat, one mouse placed in its home cage. During Phase 2, no injections were given. Each rat, however, had two 30 min opportunities to kill, one on Day 8 (the day after the last drug injection) and one on Day 15 (8 days after the last drug injection). For this and all subsequent experiments described in this report, opportunities to kill mice are called killing tests. For each killing test, success and latency to kill were recorded. After a kill, the mouse was always immediately removed from the rat's cage. No rat was ever allowed to feed from the carcass. Animals that did not kill mice were assigned a latency score equal to the total length of the killing test.

On each test day, except as noted below, each rat was transported in its home cage to a test room in which mice were housed. Here the rats were weighed, tested for mouse-killing, and, during Phase 1, administered drug. Each animal spent approximately 2 hr per test day in this room, exposed to mouse odors.

Rats were randomly assigned to 7 groups of 8 rats each. Three groups (pretest groups) received their drug injections 90 min before their daily killing tests. Rats in one group received distilled water, rats in another group received 1.5 mg/kg *d*-amphetamine SO_4 in 1 cc/kg distilled water (*d*-amphetamine) and rats in the third group received 1.5 mg/kg *l*-amphetamine SO_4 in 1 cc/kg distilled water (*l*-amphetamine). Three additional groups (posttest groups) received daily injections of the same drugs (at the same doses), but they were injected within 1 min after either a kill or the end of the killing test, whichever came first. The seventh group provided a control for mouse-exposure. Rats in this group received a daily i.p. injection of 1.5 mg/kg *d*-amphetamine, but were not exposed to mice or mouse odors.

RESULTS

Figure 1 shows the mean number of mice killed during the drug injection trials of Phase 1. Analysis of variance of these data identified a significant drug effect, $F(2,42) = 9.81$, $p<0.01$, and a significant drug X injection time interaction, $F(2,42) = 3.74$, $p<0.05$. Of the three pretest treatments, only *d*-amphetamine significantly inhibited killing. Pretest *l*-amphetamine, at the dose given, was no more effective than the vehicle. On the other hand, both *d*- and *l*-amphetamine significantly reduced killing when given after the killing tests (based on multiple *t* tests of drug versus vehicle groups following analysis of variance, $p<0.05$ for all comparisons).

Day by day analyses indicated differences between pre- and posttest injection groups in the pattern and persistence of inhibition. Analyses of the latencies (Mann-Whitney U tests) and frequencies (Fisher Exact Probability tests) were generally in agreement, but latencies were a more sensitive measure of drug effects. These findings are illustrated in Fig. 2 and Table 1.

With pretest injections, only *d*-amphetamine inhibited mouse-killing. Latencies of killing on every Phase 1 test day were significantly lengthened ($p<0.05$ for all comparisons against both the pretest *l*-amphetamine group and the pretest vehicle group), but because 1.5 mg/kg is only the ED_{50} for blocking mouse-killing in Holtzman rats [25] and the groups in the present study were small, killing was not completely blocked on every single test day. When Phase 1 was considered as a whole, however, highly significant blocking of killing was evident (as discussed above). During Phase 2, when no drugs were administered, animals that had received pretest *d*-amphetamine during Phase 1 resumed killing immediately.

Inhibition of killing developed gradually with both *d*- and *l*-amphetamine posttest injections. The latency measures showed significant differences beginning on Day 4 and continuing throughout the remainder of Phase 1 ($p<0.05$ for all comparisons of both *d*- and *l*-amphetamine with the vehicle group). In addition, by Day 5, animals in the *d*- and *l*-amphetamine groups killed significantly fewer mice than the posttest vehicle controls ($p<0.05$). Once developed, inhibition appeared to be relatively permanent, because it persisted throughout Phase 2 ($p<0.05$ for all frequency comparisons of both *d*- and *l*-amphetamine with the vehicle group; $p<0.01$ for all similar latency comparisons). Indeed, during Phase 2, when no drugs were injected, animals previously given posttest *d*- or *l*-amphetamine killed fewer mice ($p<0.05$ for all comparisons) and had longer latencies ($p<0.05$ for all comparisons) than those in the pretest *d*- and *l*-amphetamine injection groups on both Days 8 and 15.

Mouse exposure did not contribute to amphetamine-induced inhibition of killing. Unlike results with spontaneous or pilocarpine-induced killing [2,44], pretest *d*-amphetamine animals exposed to mice did not differ from similarly drugged, but unexposed, controls.

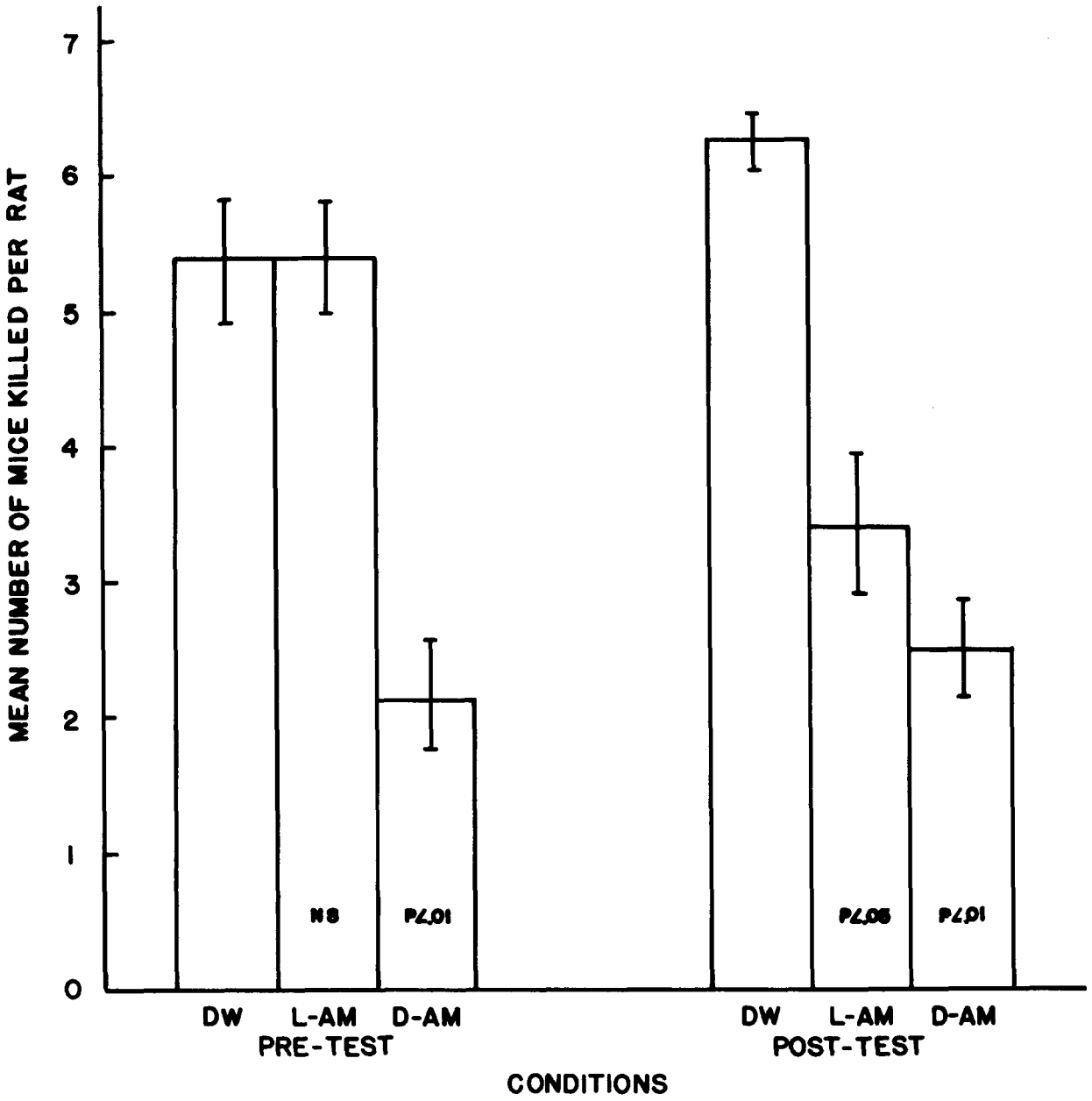

FIG. 1. Mean number of mice killed per rat during Phase 1 (Days 1–7) of Experiment 1. Vertical bars indicate standard errors of the mean. Probability levels are for statistical comparisons (*t* tests) of each group against its own distilled water control. Each rat had the opportunity to kill one mouse per day. DW = distilled water; L–AM = *l*-amphetamine; D–AM = *d*-amphetamine.

DISCUSSION

While pre- and posttest *d*-amphetamine injections both inhibit mouse-hilling, they probably do so via different physiological mechanisms. Pretest inhibition was immediate and stable during Phase 1, and did not persist when the drug was not administered, during Phase 2. It was limited to *d*-amphetamine, which unlike *l*-amphetmine increases levels of norepinephrine at central receptor sites [35,39]. These findings are consistent with the hypothesis that pretest *d*-amphetamine acts to inhibit mouse-killing by a direct pharmacological action on specific central target sites. On the other hand, posttest inhibition of mouse-killing developed gradually, persisted throughout Phase 2 (when the drugs were not given) and could be produced by both *d*- and *l*-amphetamine. Previous studies have shown that *d*-amphetamine can produce learned aversions of other behaviors [6, 7, 8]. It is, therefore, questionable whether a gradually developed, persistent, neither behavior specific nor isomer specific phenomenon is due to a direct pharmacological action on a central system for predation. Alternatively, it has been suggested that drugs which produce learned aversions may be effective because they

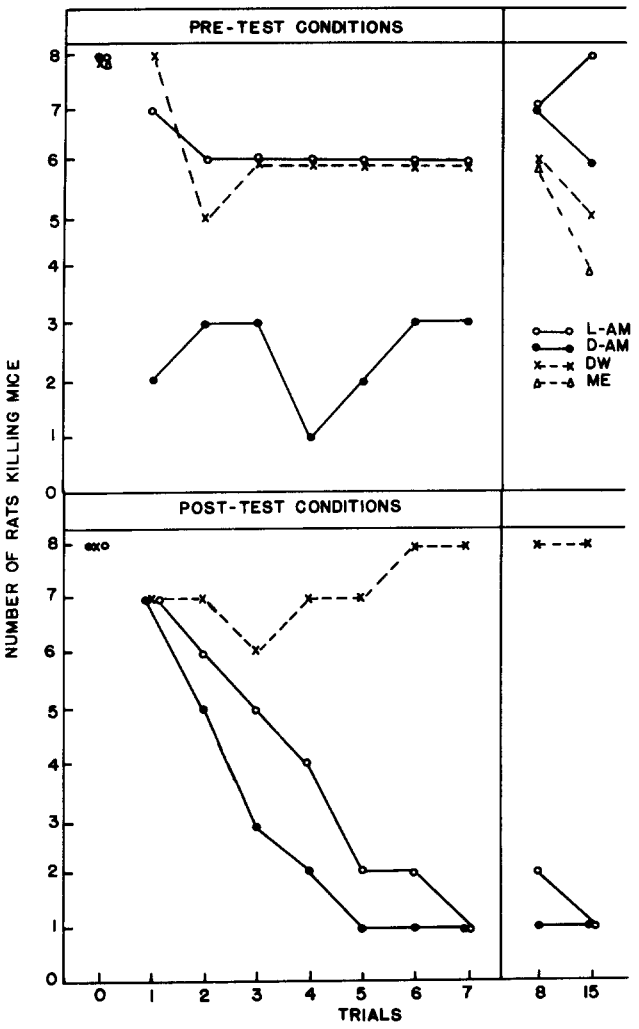

FIG. 2. Number of rats killing mice under seven conditions of repeated drug administration (Experiment 1). During Phase 1 (Trials 1–7) rats in the pretest conditions were administered 1.5 mg/kg *d*-amphetamine (D–AM), 1.5 mg/kg *l*-amphetamine (L–AM) or distilled water (DW) 90 min prior to a 10 min killing test. Rats in the posttest conditions received the same drugs, but they were administered after the killing tests. Rats in the Mouse Exposure Control Group (ME) received 1.5 mg/kg *d*-amphetamine, but were not exposed to mice or mouse odors. On Trials 8 and 15, rats in all groups were given a 30 min killing test, but were not drugged.

produce "sickness" or "malaise" [14,15]. *d*-Amphetamine does not seem to produce obvious "malaise", but it can produce a discriminable state-change [29,30], a property it has in common with other compounds known to produce learned aversions to mouse-killing. Thus, perhaps posttest *d*-amphetamine produces inhibition by producing a discriminably altered change in internal state that in some way is aversive. Because the peripheral actions of *d*- and *l*-amphetamine are more similar than their central effects [17], it seems likely that peripheral physiological changes may be critical for posttest amphetamine-induced learned aversion of killing.

EXPERIMENT 2

If learned aversion involves the production of a discriminable state-change, then many drugs which produce such changes should inhibit mouse-killing when given following a kill. This could apply even if the drugs also produce central facilitation of killing. This hypothesis was tested with repeated injections of pilocarpine, a cholinergic drug which initiates predatory killing (pilocarpine killing) when given prior to opportunities to kill [26,42], but which has marked peripheral autonomic effects.

METHOD

Animals

The animals were 24 male Holtzman rats (406–590 g) that killed mice reliably with a latency of less than 30 min. The prey were adult ICR mice of both sexes.

Apparatus and Procedure

The rats and mice were housed as in Experiment 1. General procedures of testing, drug administration, and data recording were identical to those in Experiment 1, with the following exceptions: (1) all killing tests were 30 min in duration, and (2) although rats and mice were housed in separate rooms, the rats remained in their colony room during killing tests.

Rats were randomly assigned to 4 groups of 6 rats each. Two groups (pretest groups) received i.p. drug injections 15 min before daily killing tests. Rats of one pretest group received 7.5 mg/kg pilocarpine HCl (pilocarpine) in 1 cc/kg 0.9% NaCl (saline) and rats of the other group received saline. Two additional groups (posttest groups) received daily injections of the same drugs, but they were injected immediately (less than 1 min) after either a kill or the end of the killing test, whichever came first.

RESULTS

As shown in Fig. 3 and Table 2, posttest pilocarpine gradually inhibited mouse-killing, but the effect was not highly robust. During Phase 1, animals in the posttest pilocarpine group killed significantly fewer mice than all other groups only on Day 7 (one-tailed Fisher Exact Probability Tests, $p<0.05$ for all comparisons), but had a longer latency to kill on both Days 6 and 7 (one-tailed Mann-Whitney U tests, $p<0.05$ for all comparisons). During Phase 2, the posttest pilocarpine animals continued to show an increased latency to kill (one-tailed Mann-Whitney U tests, $p<0.05$ for all comparisons), but failed to kill significantly fewer mice than animals in the other groups.

While posttest pilocarpine inhibited killing on some trials, it did not entirely eliminate attack behavior. Several rats showed approach–avoidance behavior towards mice and killing could be readily disinhibited by extraneous stimuli (*e.g.*, the increase in killing on Day 5 followed a loud, unexpected noise in the laboratory).

DISCUSSION

These data support the previous suggestion that learned aversions are primarily dependent on the production of discriminable peripheral state-changes. The central action of a drug, however, may partially determine the robustness of the phenomenon. The posttest pilocarpine animals seemed

TABLE 1

MEDIAN LATENCY TO KILL AND INTERQUARTILE RANGE (IN MIN) FOR EACH GROUP IN EXPERIMENT 1*

	Pretest Conditions			Posttest Conditions			
Test Day	D.W.	L–AM	D–AM	D.W.	L–AM	D–AM	M.E.
PHASE 1							
0	0.66 (0.29–6.30)	0.30 (0.16–2.00)	0.52 (0.16–14.63)	0.26 (0.17–4.53)	0.22 (0.14–0.64)	0.41 (0.14–1.27)	0.86 (0.24–1.73)
1	0.50 (0.08–1.02)	0.80 (0.20–1.02)	10.00‡ (0.25–10.00)	0.49 (0.10–2.30)	0.11 (0.08–0.41)	0.18 (0.10–0.34)	
2	0.24 (0.10–10.00)	0.44 (0.13–5.26)	10.00† (6.81–10.00)	0.32 (0.10–1.92)	0.21 (0.12–5.28)	2.39 (0.12–10.00)	
3	0.27 (0.06–5.35)	0.82 (0.12–5.33)	10.00† (9.47–10.00)	0.40 (0.04–8.49)	2.98 (0.37–10.00)	10.00 (0.53–10.00)	
4	0.09 (0.04–5.15)	1.08 (0.19–5.89)	10.00‡ (10.00–10.00)	0.61 (0.05–5.27)	6.50† (0.50–10.00)	10.00† (5.02–10.00)	
5	0.30 (0.07–5.36)	0.76 (0.17–5.41)	10.00† (7.31–10.00)	1.42 (0.06–9.22)	10.00† (7.07–10.00)	10.00† (10.00–10.00)	
6	0.19 (0.09–5.58)	0.76 (0.24–6.89)	10.00† (6.79–10.00)	0.80 (0.14–3.20)	10.00† (10.00–10.00)	10.00‡ (10.00–10.00)	
7	0.18 (0.13–5.23)	1.20 (0.11–10.00)	10.00† (7.57–10.00)	0.18 (0.03–1.45)	10.00‡ (10.00–10.00)	10.00‡ (10.00–10.00)	
PHASE 2							
8	0.14 (0.04–15.19)	0.44 (0.06–10.56)	5.05 (0.94–17.57)	0.36 (0.03–0.50)	30.00‡ (16.55–30.00)	30.00‡ (30.00–30.00)	0.78 (0.24–17.05)
15	3.30 (0.10–30.00)	0.60 (0.08–1.00)	3.30 (0.88–21.90)	0.66 (0.06–3.60)	30.00‡ (30.00–30.00)	30.00‡ (30.00–30.00)	21.40 (0.17–30.00)

*D.W. = distilled water; L–AM = *l*-amphetamine; D–AM = *d*-amphetamine; M.E. = mouse-exposure control group. Significance levels are for comparisons of each drug group with its own distilled water control (Mann-Whitney U).

†$p<0.05$

‡$p<0.01$

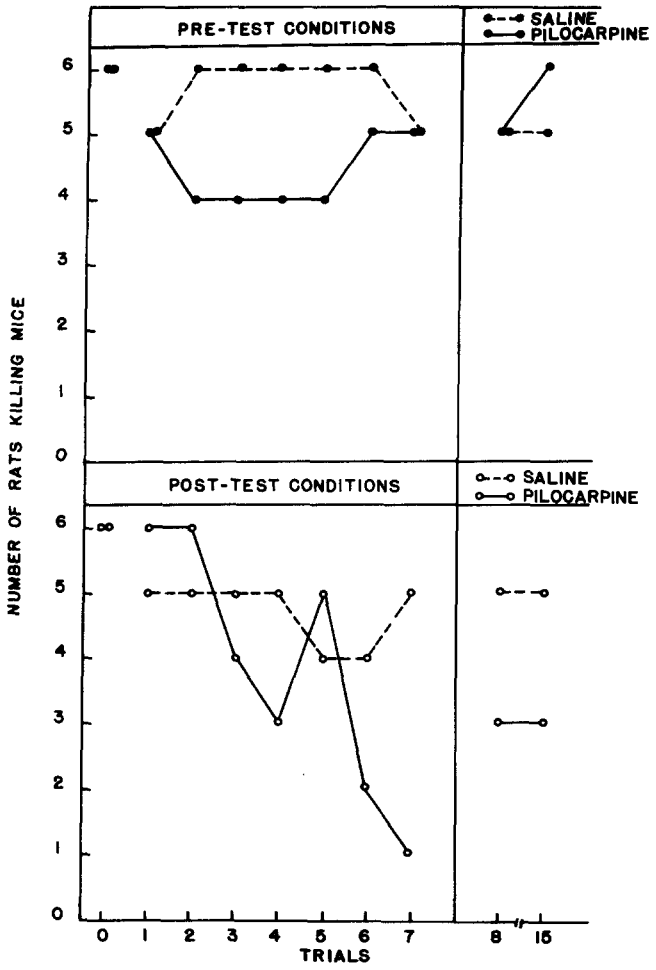

FIG. 3. Number of rats killing mice under conditions of pre- and posttest pilocarpine or saline vehicle. Rats were administered drugs on Trials 1–7, but not on Trials 8 and 15.

highly susceptible to disinhibition and showed some recovery from complete inhibition during Phase 2. These findings suggest competition between the central sensitizing effects of the drug and its inhibitory peripheral effects.

Similarly, pretest effects of drugs may depend on the competition of central and peripheral factors, but here the central effects are usually primary. In this study, pretest pilocarpine produced only a small decrease in the number of rats killing mice. In the studies of Wnek and Leaf [44], however, blocking the inhibitory peripheral actions of pilocarpine with methyl atropine produced a fairly large increase in the probability of pilocarpine killing.

EXPERIMENT 3

Experiments 1 and 2 suggested that peripheral state-changes could inhibit predation. While state-changes following a kill were most effective in producing inhibition, it seemed that state-change also contributed to pretest inhibition. It seems difficult to detect and differentiate such inhibition from the apparently more robust direct pharmacological inhibition, however. Effects of state-change might be more easily demonstrated in animals developing the killing response, and in situations where state-change is produced by a nonpharmacological method.

In view of these considerations, the following study assessed the effects of changes in feeding conditions on the development of pilocarpine killing. Pilocarpine was used because repeated injections of pilocarpine gradually increase the number of rats killing mice, and because all Holtzman rats eventually kill [41]. Changes in feeding pattern provided a convenient nonpharmacological method for inducing peripheral state-change. Moreover, this manipulation allowed further assessment of the role of feeding in the initiation of predatory killing.

METHOD

Animals

The animals were male Holtzman rats (216–400 g) that failed to kill mice on two 30 min tests of mouse-killing. Forty-two rats began the study, but due to death (N = 8) and deprivation-induced killing (N = 4), only 30 rats completed the entire study. The prey were adult ICR mice of both sexes.

Apparatus and Procedure

The rats were individually housed in stainless steel cages in a room which also housed mice. The mice were caged as in Experiments 1 and 2. All rats were allowed ad lib access to tap water except during testing.

This experiment was run in two phases. During Phase 1, feeding histories were established by randomly assigning rats to one of two food deprivation conditions. One group (N = 16) was allowed ad lib access to Purina Rat Chow, while the other group (N = 14) was given 2 pellets of chow once every 24 hr. (The 2 pellets were generally consumed within 30 min, and served to reduce and maintain the rats at approximately 85% of their freefeeding body weight.) These regimens were continued for 4 weeks. Once a week, each rat was given a 30 min killing test. Rats that killed mice were eliminated from the experiment.

During Phase 2, current feeding conditions were established and daily pilocarpine injections and killing tests were begun. Rats within each feeding history group were randomly assigned to one of two current feeding conditions. One-half of each group continued to receive the food allotment prescribed by its feeding history and the other half was switched to the alternative feeding condition. The rats were maintained on these food deprivation schedules throughout the remainder of the experiment. On the second day of Phase 2, all rats began a regimen of repeated pilocarpine administration. Each rat received a daily i.p. injection of 7.5 mg/kg pilocarpine 15 min before a 2 hr killing test. Injections were continued until a criterion of 1 successful kill was met. After each rat met criterion, it was given two more killing tests, but was not drugged. One test occurred on the day after the criterion test and the other a week later. During the intervening week, each rat was maintained on its current feeding condition.

RESULTS AND DISCUSSION

As can be seen in Fig. 4, both changes in feeding conditions delayed the appearance of pilocarpine killing. Rats maintained on a constant feeding schedule, whether it was a deprivation schedule or a schedule of ad lib intake,

TABLE 2

MEDIAN LATENCY TO KILL AND INTERQUARTILE RANGE (IN MIN) FOR EACH GROUP IN EXPERIMENT 2*

	Pretest Conditions		Posttest Conditions	
Test Day	Saline	Pilocarpine	Saline	Pilocarpine
PHASE 1				
0	0.13 (0.08–0.71)	0.30 (0.08–3.83)	0.60 (0.08–6.74)	0.39 (0.21–0.5)
1	0.28 (0.07–16.48)	0.32 (0.09–15.25)	0.38 (0.08–18.31)	0.50 (0.15–0.55)
2	0.53 (0.06–17.33)	0.62 (0.07–30.0)	0.21 (0.08–15.04)	0.50 (0.12–0.79)
3	0.26 (0.06–13.31)	0.38 (0.09–30.0)	0.59 (0.03–16.01)	0.50 (0.19–30.0)
4	0.51 (0.14–13.71)	0.32 (0.08–30.0)	0.18 (0.03–15.36)	20.16 (0.36–30.0)
5	0.52 (0.18–1.62)	0.43 (0.04–30.0)	0.57 (0.08–30.0)	1.14 (0.36–26.15)
6	0.35 (0.06–2.49)	0.39 (0.12–28.12)	0.23 (0.08–30.0)	30.0† (9.96–30.0)
7	0.59 (0.07–25.36)	0.29 (0.04–15.25)	0.56 (0.11–16.91)	30.0† (15.2–30.0)
PHASE 2				
8	0.31 (0.04–19.21)	0.35 (0.09–18.12)	0.35 (0.07–20.28)	19.45† (0.63–30.0)
15	0.12 (0.06–15.16)	0.67 (0.07–14.0)	0.27 (0.04–20.15)	15.3† (0.51–30.0)

*Significance levels are for each pilocarpine group with its own saline control (one-tailed Mann-Whitney U tests).
†$p<0.05$

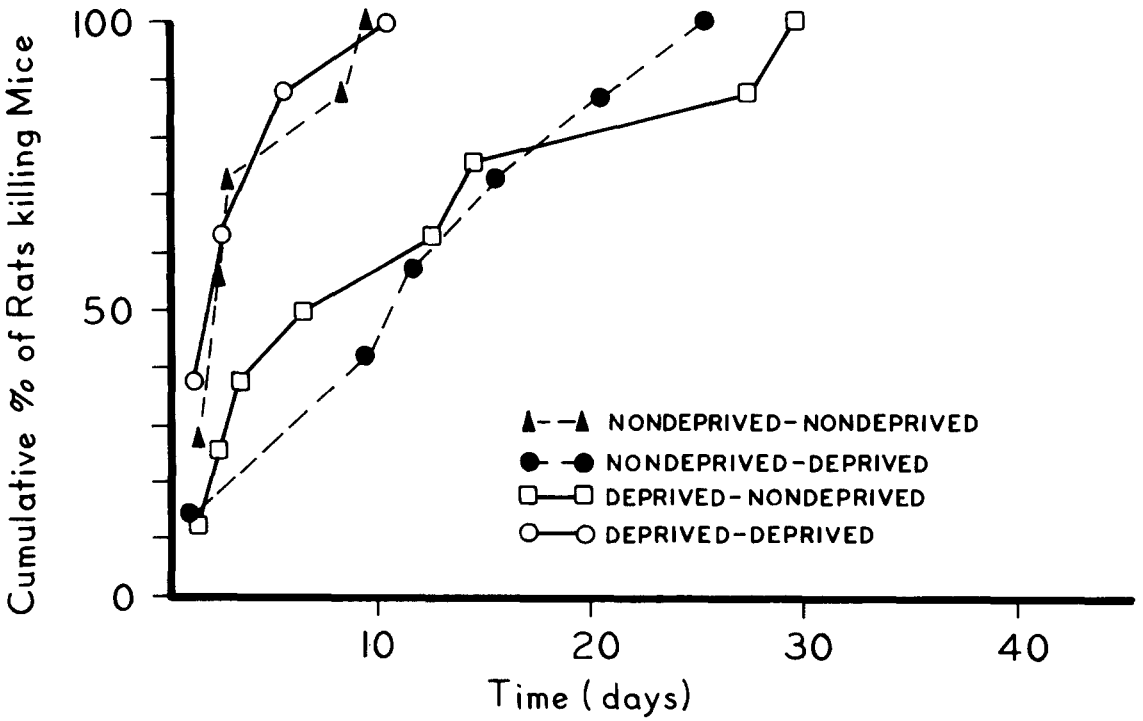

FIG. 4. Cumulative percentage of rats killing mice under pilocarpine as a function of 4 combinations of feeding history and current (test) feeding condition. Rats were maintained on ad lib or 23½ hr cyclic food deprivation for 4 weeks and then either maintained on that schedule or changed to the alternative feeding condition. Beginning at the time of schedule change, daily injections of 7.5 mg/kg pilocarpine were employed to initiate killing.

took fewer injections to initiate killing than did rats whose deprivation schedules had been changed (analysis of variance, interaction term: $F(1,26)$, = 10.60, $p<0.01$). The main effects of feeding history and current feeding condition were not significant. Thus, internal change appears to inhibit the development, as well as the maintenance, of mouse-killing (see Experiments 1 and 2). Change in food deprivation conditions also facilitates the acquisition posttest drug injection inhibition of mouse-killing [9] and disrupts (disinhibits) the retention of posttest drug injection aversion to saccharin [34], as shown in other studies.

No rat killed without a pilocarpine injection, confirming the observations of Vogel and Leaf [41] that pilocarpine killing is drug-dependent in Holtzman rats. These findings also suggest that pilocarpine, and not food deprivation, played the major role in the initiation of predatory killing during Stage 2. Deprivation without pilocarpine, however, initiated killing in 4 rats during Stage 1, confirming the findings of Paul *et al.* [32].

EXPERIMENT 4

It is interesting that food deprivation without drugs increased killing (Experiment 3 [32]), but when pilocarpine was used to produce killing, the effects of food deprivation were minimal (Experiment 3 [41]). It is possible that some aspect of the drug experience inhibits expression of the deprivation effect. Observation of pilocarpine-drugged animals and the work of Overstreet *et al.* [28] suggests that pilocarpine animals, even when deprived, may not eat. Thus, perhaps the effects of food deprivation in Experiment 3 were partially masked by some effects of pilocarpine on feeding behavior.

The following experiment was designed to determine whether pilocarpine-drugged animals show decreased food consumption and a decreased sensitivity to deprivation conditions.

METHOD

Animals

Twenty male Holtzman rats (382–514 g) were used.

Apparatus and Procedure

The rats were housed as described for Experiment 1. They all had ad lib access to tap water and Purina Rat Chow except when under test conditions.

The rats were randomly assigned to 1 of 2 food deprivation conditions (0 or 24 hr) and 1 of 2 drug conditions (7.5 mg/kg pilocarpine or saline) to form 4 independent groups of 5 rats each. All rats were given a single food consumption trial under the appropriate combination of drug and food deprivation.

The testing for each rat was as follows. After having been food deprived in the home cage for the appropriate time, each rat was removed from the cage, injected, and returned to the home cage. At this time, food bins for the 0 hr deprivation groups were removed. Thirty min later, a food dish containing 45 mg Noyes pellets was placed in each cage. A tray placed in the cage allowed for an estimation of spillage. The rats were allowed to eat for 15 min,

after which time the food dish was removed and the number of pellets eaten was counted.

RESULTS AND DISCUSSION

The feeding data are presented in Table 3. Pilocarpine-injected rats ate significantly less than the saline controls under both deprivation conditions (analysis of variance, $F(1,16) = 5.75$, $p<0.05$, confirming the observations of Overstreet *et al.* [28]. They were also less reactive to variation in deprivation conditions (interaction term: $F(1,16) = 12.25$, $p<0.01$. The difference in deprivation conditions, however, was significant, with the saline group contributing most of the variance, $F(1,16) = 8.25$, $p<0.05$. Thus, pilocarpine may have masked the effects of current feeding conditions on mouse-killing and on eating in the previous study.

TABLE 3

MEAN FOOD CONSUMPTION (Mg) FOR DRUG AND DEPRIVATION GROUPS IN EXPERIMENT 4

	Drug Conditions			
	Pilocarpine		Saline	
Deprivation condition	0 hr	24 hr	0 hr	24 hr
Mean mg food consumed	63	153	711	1584

This study also suggests a dissociation between feeding and mouse-killing. Pretest injections of pilocarpine induced killing in Experiment 3, but reduced food consumption in the present study. While other studies have also demonstrated such a separation (*e.g.*, [5, 21, 37]), cyclic food deprivation typically induces or facilitates rat predatory behavior [32, 43]. Thus, pilocarpine killing may differ from spontaneous killing in the degree to which it is facilitated by food deprivation.

EXPERIMENT 5

A second test for state-change inhibition of pilocarpine killing was carried out with posttest *d*-amphetamine injections. Because previous work on drug-induced learned aversions indicated the phenomenon could be obtained with considerable delay of reinforcement [14, 15, 36], injection-delay was included as a variable.

METHOD

Animals

Twenty male Holtzman rats (225–416 g) that failed to kill a mouse on 3 consecutive 30 min tests (1 test per day) were used. The prey were adult ICR mice of both sexes.

Apparatus and Procedure

The rats and mice were housed as in Experiment 3. Both rats and mice had ad lib access to tap water and Purina Rat Chow except during killing tests when water bottles were removed to prevent competing cholinergic drinking responses.

To obtain a killing baseline each rat was induced to kill reliably by repeated i.p. injections of 7.5 mg/kg pilocarpine. Fifteen min after injection, each rat was given a 1 hr killing test. This procedure was repeated every other day until the rat killed on 2 consecutive killing tests.

Rats were then assigned to 1 of 2 i.p. posttest injection conditions (*d*-amphetamine or saline) and one of 2 delay of injection conditions (0 min or 30 min) to form 4 groups of 5 rats each. Groups were matched on the number of pilocarpine injections to criterion. Each rat received 8 killing tests. For Tests 1–5, the dose of *d*-amphetamine was 1.5 mg/kg. Because this dose did not seem effective, for Tests 6–8 the dose was increased to 3.0 mg/kg. After the eighth test, all rats were given pilocarpine alone (without saline or *d*-amphetamine) until a criterion of one successful kill was met. Animals were injected and tested every other day.

On all test days, each rat was injected with pilocarpine and tested for killing. For rats in the 0 min delay conditions, the posttest injection (saline or *d*-amphetamine) was given immediately after removal of the mouse (after 1 hr or a successful kill). For the 30 min delay rats, the posttest injection was delayed 30 min.

RESULTS

Five injections of 1.5 mg/kg *d*-amphetamine did not significantly reduce the number of rats killing mice nor did it increase killing latencies (see Table 4 and Fig. 5, Tests +1 and +6). In fact, most animals became more proficient killers during this time.

After the dose was increased, 3 injections of 3.0 mg/kg did produce some significant changes in behavior. Latency change proved to be the most sensitive measure of amphetamine effects. Animals in the combined *d*-amphetamine groups showed a significant increase in latency (latency on Trial 9 – latency on Trial 6) when compared to the combined saline groups (one-tailed Mann-Whitney U, $p<0.05$) as did the immediate injection groups when compared to the delayed conditions ($p<0.01$). Individual group comparisons showed that the amphetamine immediately group differed significantly ($p<0.05$ for all comparisons) from all other groups, but these did not differ from one another.

Significant differences in the frequency of killing were also evident. On Trial 9 (the trial following the third 3.0 mg/kg posttest injection), significantly fewer animals in the combined *d*-amphetamine groups killed mice, when compared to the combined saline groups (one-tailed Fisher Exact Probability test, $p<0.05$).

DISCUSSION

d-Amphetamine given immediately after a kill did not completely inhibit killing, but it did significantly increase killing latencies. While the effect of posttest *d*-amphetamine was not as striking in pilocarpine killers as it was in spontaneous killers (see Experiment 1), these data indicate that such a phenomenon can be produced. Additional studies, in which this effect has been replicated, further substantiate this point [16].

Delayed *d*-amphetamine injections did not inhibit pilocarpine killing. The lack of effect may be due to a small N, a weak or masked phenomenon, and/or to previous over-

TABLE 4

MEDIAN LATENCY CHANGE AND RANGE (IN MIN) AFTER 3 POSTTEST INJECTIONS OF 3.0 mg/kg *d*-AMPHETAMINE (TRIAL 9 – TRIAL 6)*

	Saline	*d*-Amphetamine	Total
0 min delay	0‡ (−3 – +30)	+50 (+30 – +60)	+30 (−3 – +60)
30 min delay	0‡ (−55 – 0)	0‡ (0 – 0)	0‡ (−55 – 0)
Total	0† (−55 – +30)	15 (0 – +60)	0 (−55 – +60)

*Significance of the marginal totals is for combined group analyses. Other significance levels are for individual group comparisons against the *d*-amphetamine immediately group (one-tailed Mann-Whitney U tests).
†$p<0.05$
‡$p<0.01$

exposure to mice and pharmacological agents [36, 38, 41] during preliminary stages of the experiment.

The posttest dose of *d*-amphetamine required to inhibit pilocarpine killing appeared to be higher than that required to inhibit spontaneous killing. While 4 posttest injections of 1.5 mg/kg *d*-amphetamine were sufficient to produce maximum inhibition of killing in the spontaneous killers in Experiment 1, 5 injections of the same dose in this study failed to produce a significant effect. Three injections of a 3.0 mg/kg dose, however, did produce a significant effect.

It was not possible to assess whether the duration of inhibition also differed for spontaneous and pilocarpine killing because animals in the two studies had not been inhibited for comparable periods of time prior to test trials without *d*-amphetamine. In the present study, the number of trials to extinction did not differ significantly between groups, although the mean values were all in the expected direction, as can be seen in Table 5.

It was possible to block pilocarpine killing with posttest injections of *d*-amphetamine. While quantitative aspects of the phenomenon may not have been identical, the basic process of posttest injection inhibition seemed qualitatively similar with both spontaneous and pilocarpine-killing (i.e., inhibition was gradually developed).

EXPERIMENT 6

d-Amphetamine given after a kill can inhibit killing in both spontaneous and pilocarpine killers, although the dosage requirements may differ for the two populations (Experiments 1 and 5). Pretest *d*-amphetamine can also block both spontaneous killing (Experiment 1, [3, 4, 19, 20, 22, 23, 24, 25]) and pilocarpine killing [41]. The next study was designed to determine whether pretest *d*-amphetamine inhibition of pilocarpine killing required high doses, with extensive nonspecific effects, as was the case for posttest *d*-amphetamine inhibition of pilocarpine killing (Experiment 5).

METHOD

Animals

Sixteen of the rats used in Experiment 5 were used. Each rat was allowed a rest of approximately one month between the studies. The prey were adult ICR mice of both sexes.

Apparatus and Procedure

Both rats and mice were housed as in Experiment 3 and had ad lib access to tap water and Purina Rat chow, except during killing tests when water bottles were removed.

The rats were induced to kill reliably as in Experiment 5. Each rat was then tested for killing 4 times, once each with pretest saline, 0.75, 1.5, and 3.0 mg/kg *d*-amphetamine in combination with its standard 7.5 mg/kg pilocarpine injection. To obtain different amphetamine dosages, concentration was held constant (3.0 mg/cc) and injection volume was varied. The order of *d*-amphetamine doses was assigned from a 4 × 4 Latin square. Testing took place every other day.

In addition, rats were assigned to 1 of 2 pilocarpine-amphetamine injection orders to assess possible interactions due to order of administration. Group P-A received pilocarpine, followed 15 min later by *d*-amphetamine. Killing tests were begun 30 min after the *d*-amphetamine administration. Group A-P received *d*-amphetamine followed 30 min later by pilocarpine. Killing tests were begun 15 min later. All rats were permitted 1 hr to kill, beginning 45 min after the first of the two pretest injections.

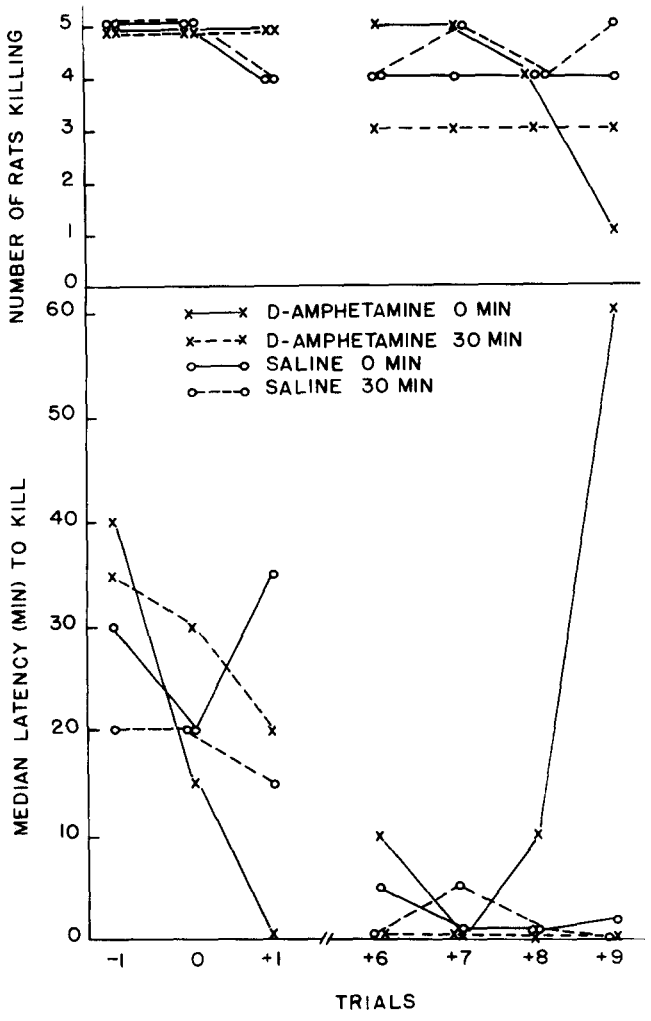

FIG. 5. Median latency to kill and number of rats killing mice under 4 conditions of posttest drug injections. All rats were pilocarpine killers. Trials −1, 0, and +1 are baseline trials preceding the first posttest injection which occurred on Day 1. Trial +6 followed 5 posttest injections of 1.5 mg/kg *d*-amphetamine (or saline) given immediately (0 min) or 30 min after a killing test. On Trials +6, +7, and +8, the *d*-amphetamine dose was increased to 3.0 mg/kg. No *d*-amphetamine or saline was administered on Trial 9.

RESULTS AND DISCUSSION

Pretest *d*-amphetamine clearly inhibited pilocarpine killing. As shown in Table 6, neither the dose order nor the drug order had a significant effect, so these variables were collapsed for calculation of the ED_{50}. The ED_{50} calculated by fitting a straight line, by eye, to a plot of percent kill by log dose, was 0.40 mg/kg *d*-amphetamine. This value is substantially less than that reported by Horovitz *et al.* [19,20] for Holtzman strain spontaneous killers (1.5 mg/kg *d*-amphetamine). Thus, pilocarpine killers may be more easily inhibited by some pretest drugs than are spontaneous killers. Additional results consistent with this hypothesis have been reported by Vogel and Leaf [41] for *d*-amphetamine and for methyl atropine.

TABLE 5

MEAN NUMBER OF TRIALS UNTIL REAPPEARANCE OF THE KILLING RESPONSE FOLLOWING DISCONTINUATION OF POSTTEST INJECTIONS

	Drug Conditions			
	d-Amphetamine		Saline	
Delay condition	0 Min	30 Min	0 Min	30 Min
Mean trials	3.00	2.60	1.20	1.00

TABLE 6

PERCENTAGE OF RATS KILLING MICE UNDER CONDITIONS OF EXPERIMENT 6

Condition		*d*-Amphetamine			
		0.0	0.75	1.5	3.0
P–A*	(N = 8)	87	25	25	0
A–P	(N = 8)	87	12	25	0
Order 1†	(N = 4)	75	50	50	0
Order 2	(N = 4)	100	25	25	0
Order 3	(N = 4)	75	0	25	0
Order 4	(N = 4)	100	0	0	0
Overall	(N = 16)	87	19	25	0

*Rats in the P–A Group received 7.5 mg/kg pilocarpine 15 min prior to the appropriate dose of *d*-amphetamine. Rats in the A–P Group received the appropriate dose of *d*-amphetamine followed 30 min later by 7.5 mg/kg pilocarpine.

†The dose order for rats in Order 1 was 0.0, 0.75, 1.5, 3.0 mg/kg *d*-amphetamine; for those in Order 2: 0.75, 1.5, 3.0, 0.0 mg/kg *d*-amphetamine; for those in Order 3: 1.5, 3.0, 0.0, 0.75 mg/kg *d*-amphetamine; for those in Order 4: 3.0, 0.0, 0.75, 1.5 mg/kg *d*-amphetamine.

The pretest dose of *d*-amphetamine required to inhibit pilocarpine killing was substantially lower than the posttest dose (approximately 3.0 mg/kg as determined in Experiment 5). Also pretest inhibition was more reliable and more easily obtained than posttest inhibition. These results support the hypothesis that pretest and posttest procedures inhibit predation by different physiological mechanisms.

GENERAL DISCUSSION

Like previous work, the present studies indicate that *d*-

amphetamine is a potent inhibitor of mouse-killing in the rat. Not only did *d*-amphetamine given prior to an opportunity to kill block killing, but so did *d*-amphetamine given after an opportunity to kill. Differences in the development of inhibition, isomer-specificity, subsequent persistence in the nondrugged state, and drug threshold, however, suggest strongly that pre- and posttest injections produce their effects by different physiological mechanisms. Pretest *d*-amphetamine injections produced immediate inhibition of predatory killing at relatively low doses and the inhibition was drug-state dependent; that is, it failed to persist subsequently in the nondrugged state, and inhibition could not readily be produced by the *l* isomer. These results support the hypothesis that pretest injections exert an inhibitory effect by direct pharmacological action on specific target sites. On the other hand, posttest injections of both *d* and *l*-amphetamine produced an inhibition which developed slowly over a period of days, but which once developed, persisted after the drug was withdrawn. Such a pattern of responding seemingly fits the characteristics of learned aversions [14, 15, 36]. Thus, *d*-amphetamine inhibition of killing can involve at least two situation-specific processes.

Both patterns of inhibition, however, may partially share a common mechanism – an altered or changed physiological state. Change itself was shown in Experiment 3 to inhibit development of killing. Because *d*-amphetamine produces a discriminably altered state [29,30], this change may be partially responsible for the inhibitory action of pretest injections of *d*-amphetamine. Inhibition in this case, however, is probably not learned. It is immediate and pronounced during the first drug experience and does not lessen with repeated dosing (as would be expected if the rats were learning to cope with aversive side effects of the drug). An altered physiological state is probably not the only mechanism involved in pretest inhibition because pretest *l*-amphetamine failed to block killing. Many drugs produce discriminable state-changes [29], but only the antidepressants, some amphetamines, and some antihistamines inhibit predatory killing when given prior to testing [3, 4, 19, 20, 22, 25].

An altered physiological state may be more necessary for the production of learned aversions to predatory killing. In this case, the altered physiological state may function as a punishment. Discriminability, but not necessarily dissociation [29], of the drug state may be important, because the already drugged pilocarpine killers (Experiment 5) required a higher posttest dose of *d*-amphetamine to inhibit killing than did the spontaneous killers (Experiment 1). The pilocarpine killers were required to discriminate a combined drug state from a single drug state, while the spontaneous killers needed only to discriminate a drug state from a nondrug state. Discriminability, however, does not seem to be invariably linked to overt side effects, because *d*- and *l*-amphetamine, with few overt peripheral effects, seemed to produce a more profound aversion to killing than did pilocarpine. While amphetamines produced inhibition of both killing and attack, pilocarpine produced a great deal of conflict behavior and did not entirely eliminate attack behavior. Typically, drugs which produce learned aversions to mouse-killing seem to affect eating of the prey first, killing second, and attack last [5,9], as was predicted by Revusky and Garcia [36]. Ineffective drugs or low doses of effective drugs inhibit terminal portions of the response sequence most easily. Pilocarpine, at the dose administered, appears to belong to such a group of weakly effective drugs.

It is possible that novelty of internal state is also a contributing factor to the aversiveness of a drug state, as has been suggested by Amit *et al.* [1]. Because the pilocarpine killers in Experiment 5 could not be pharmacologically naive, this may provide a partial explanation for the marginal quality of the posttest inhibition observed. The novelty of a drug state is difficult to assess, however. Prior experience with one drug (e.g., pentobarbital) does not necessarily block learned aversions produced with another drug (e.g., *d*-amphetamine), while previous experience with the same drug does block development of aversions to its own effects [42]. Thus, each drug state may have some different novel qualities which are separately capable of producing learned aversions.

As demonstrated by Experiments 3 and 4, anorexia is not incompatible with predatory killing. For this reason, and because the effective anorexic dose of *d*-amphetamine is lower than the effective pretest dose for inhibiting mouse-killing [10,25], it seems unlikely that the anorexic effects of *d*-amphetamine play a principal role in its inhibition of predatory killing.

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