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Bait-shyness acquisition and resistance to extinction as functions of US exposure prior to conditioning*

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Cyclophosphamide-induced aversions to saccharin-flavored tap water were observed in normal control rats, in rats subjected to varying numbers of cyclophosphamide injections prior to conditioning, and in rats similarly subjected to preconditioning saline injections. Both initial magnitude and resistance to extinction of a conditioned flavor aversion were found to be inverse functions of preconditioning familiarity with drug-induced illness. Six preconditioning cyclophosphamide injections markedly reduced both initial aversion magnitude and resistance to extinction. In contrast, three such injections failed to affect initial aversion magnitude and resulted in a small acceleration of extinction rate, while one preconditioning cyclophosphamide injection produced no observable effects. These findings depict preconditioning familiarity with illness as one important variable modulating the strength of conditioned flavor aversions and emphasize the importance of viewing resistance to extinction as one indicator of aversion strength.

Bait-shyness, the learned avoidance of a substance whose consumption is followed by a case of nonlethal poisoning, is conveniently studied in laboratory rats by following the ingestion of a palatable flavor with illness induced by toxic injection or exposure to ionizing radiation (cf. Garcia & Koelling, 1967; Revusky & Garcia, 1970). Flavor familiarity prior to conditioning is one important variable influencing the strength of these conditioned aversions. Numerous studies have shown that preconditioning flavor familiarity reduces the strength of both radiation and drug-induced flavor aversions (Ahlers & Best, 1971; Domjan, 1972; Elkins, 1973a; Farley, McLaurin, Scarborough, & Rawlings, 1964; Revusky & Bedarf, 1967; Vogel & Clody, 1972; Wittlin & Brookshire, 1968). A related problem, which has received less attention, involves familiarity with illness prior to conditioning. Brookshire and Brackbill (1971) reported that 10 preconditioning injections of apomorphine hydrochloride blocked the development of an apomorphine-induced flavor aversion. Apomorphine hydrochloride induces nausea and vomiting in humans and has been used in aversion therapy for alcoholism. However, Lemere and Voegtlin (1950), who treated over 4,000 alcoholics with "conditioned reflex therapy," a procedure based on repeated pairings of alcohol ingestion with chemically induced illness, advised against apomorphine as a conditioning agent because their results suggested its effectiveness was to some extent negated by its sedative action. Similarly, the aversion attenuation reported by Brookshire and Brackbill (1971) might be, in part, a function of narcotic effects as opposed to preconditioning familiarity with illness. Further study with nonnarcotic agents such as cyclophosphamide (Cytoxan^{R}, Mead Johnson Laboratories) is, therefore, indicated. Since functional relationships between bait-shyness and differing amounts of preconditioning toxic illnesses are unknown, this experiment also investigated the effects of different numbers of preconditioning cyclophosphamide injections on bait-shyness acquisition and resistance to extinction.

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METHOD

Sprague-Dawley-derived rats were randomly assigned to six groups containing five Ss each. Ss of three groups received 6, 3, or 1 preconditioning cyclophosphamide injections over a 2-week period. Injections were 12.5 mg/kg each, were given intraperitoneally, and were scheduled on Mondays, Wednesdays, and Fridays to allow ample time for recovery from each incidence of drug-induced illness. Ss of one of the three remaining groups received six isotonic saline injections, while the others were simply maintained during this preconditioning period. Ss receiving less than six injections were phased into the injection sequence during the second week so that final preconditioning injections were all given on the same day. Injections were given at approximately 11:00 a.m., a period normally associated with reduced rat activity, including minimal feeding and drinking.

Two days after this preconditioning phase all Ss were subjected to 24 h of fluid deprivation. They were then presented with standard drinking bottles containing a novel 0.1% solution of sodium saccharin in tap water. Each S had access to this fluid for a minimum of 10 min and for 5 min after the onset of drinking. Five minutes after saccharin removal, previously injected Ss again received their standard cyclophosphamide or saline injection. Ss of one of the two previously uninjected groups also received cyclophosphamide, while those of the other group were maintained as normal controls. The overall design, therefore, included a normal control group, a saline control group, and four conditioning groups that had been subjected to 6, 3, 1, or 0 preconditioning cyclophosphamide injections, respectively.

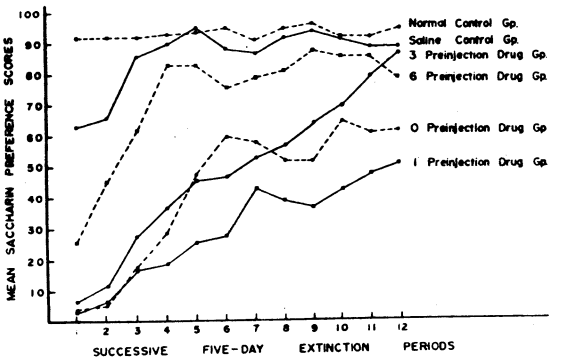

Fig. 1. Mean saccharin preference scores averaged over successive 5-day extinction periods.

Extinction testing began on the day after conditioning. During the 60 days of extinction testing, each S had free access to both the saccharin solution and plain tap water which were available in separate bottles. Bottles were weighed daily, refilled as required, and interchanged in a nonsystematic manner to control position habits. Preference scores comprised the percentage of total daily fluid consumption accounted for by ingestion of the saccharin solution.

RESULTS AND DISCUSSION

Present results depict an inverse relationship between frequency of preconditioning exposure to toxic illness and both initial aversion magnitude and resistance to extinction of cyclophospamide-induced flavor aversions. Bait-shyness magnitude and resistance to extinction were both reduced by six preconditioning cyclophosphamide injections. This finding, apparent graphically in Fig. 1, is statistically reliable. An analysis of variance test (ANOVA) performed on an arcsin transformation (Winer, 1962) of preference score data revealed differences between groups to be highly significant ($F = 12.66$, $df = 5/24$, $p < .01$). Differences over extinction periods ($F = 44.63$, $df = 11/264$, $p < .01$) were similarly significant. Separate ANOVA tests performed on the data of several individual extinction periods invariably produced between-group effects significant at the .01 level and provided error terms necessary for a more precise determination of group differences through Duncan's multiple range tests (Bruning & Kintz, 1968). A Duncan's test of group differences within Extinction Period 1 showed the 6-preinjection drug group to have generated a higher mean preference score ($p < .02$) than the 0-, 1-, and 3-preinjection drug groups (which failed to differ from each other), and a lower mean preference score than either the saline injected or normal control groups ($p < .01$). Additional applications of Duncan's test also confirmed that the 6-preinjection drug group extinguished more rapidly than the 0-, 1-, or 3-preinjection drug groups. An additional finding of interest concerns differential extinction results of the 0-, 1-, and 3-preinjection drug groups. These three groups failed to differ initially, but the 3-preinjection drug group extinguished completely over 60 days of postconditioning flavor exposure, while the 0- and 1-preinjection drug groups maintained statistical equivalence[1] and some degree of saccharin rejection over this entire extinction period. A Duncan's test confirmed that during Extinction Period 12, the 3-preinjection drug group failed to differ from the 6-preinjection drug group, the normal control group, or the saline control group, but had a significantly higher mean preference score than either the 0-preinjection drug group ($p < .05$) or the 1-preinjection drug group ($p < .01$). This finding of equivalent initial aversion magnitude, but differential resistance to extinction, complements prior observations (Elkins, 1973a, b) and emphasizes the need to view resistance to extinction as one important indicator of aversion strength. As suggested by the Revusky and Garcia (1970) discussion of floor effects, the value of initial aversion magnitude as an index of aversion strength may be reduced or eliminated when strong aversions approaching the maximum obtainable attenuate differences between groups. Under such conditions, resistance to extinction may be the most appropriate test of differential aversion strength.

Considered as a whole, these results support and extend prior apomorphine findings of Brookshire and Brackbill (1971) by demonstrating narcotic-free decrements in bait-shyness magnitude and resistance to extinction as inverse functions of differing amounts of drug-induced illness prior to conditioning. They also complement the Elkins's (1973a) finding of an orderly inverse relationship between preconditioning familiarity with a saccharin-flavored solution and the strength of a conditioned aversion to that flavor. However, present findings do not clarify the mechanisms through which preconditioning exposure to toxic illness weakens subsequent aversion formation. For example, additional research is needed to determine if aversion formation is weakened through habituation to illness or because repeated instances of illness unrelated to specific consumatory responses reduce the information value of a single flavor-illness conditioning trial.

An alternate interpretation of present findings also merits consideration. It can be argued that the inverse relationship between aversion strength and preconditioning toxic illness might have resulted from cumulative toxic effects. In other words, preinjected Ss might have been so sick at the time of conditioning that an additional cyclophosphamide injection had little or no effect. While such lingering illness is an empirical possibility meriting further investigation, it is thought to be an unlikely explanation of present results because relatively small cyclophosphamide doses were used (12.5 mg/kg) and no more than three injections were given in any 7-day period. Also, conditioning followed final preexposure injections by 3 days. In addition, careful observation during conditioning failed to suggest any gross behavioral differences which might have been

associated with lingering illness. Considered alone, such observations can constitute no more than suggestive evidence. However, they are also consistent with the results of a recent study of radiation-induced flavor aversions. Chernovetz (1973) used a design similar to that of the present experiment and supported its findings by discovering that irradiation-induced flavor aversions in rats are also progressively weakened by increasing amounts of X-ray exposure prior to conditioning. Radiation exposures were scheduled at 5-day intervals and analyses of food and water intake revealed that they were at baseline levels prior to any given radiation exposure. These radiation results therefore minimized the possibility of lingering illness, thus supporting the conclusion that aversion formation is weakened by familiarity with illness prior to conditioning.

Bait-shyness has been advanced as a convenient animal model, having important implications for aversion therapy approaches to the treatment of alcoholism (Elkins, 1974a). Since a long history of alcohol-induced illness is common in most alcoholics, aversion attenuation through familiarity with illness appears to question the efficacy of alcoholism treatment based on nausea. Similarly, such aversion therapy might also appear contraindicated by previous findings of aversion decrement as a function of flavor familiarity prior to conditioning. Such concern is probably unwarranted because well-conceived aversion therapy typically involves multiple conditioning trials and discrimination training (cf. Elkins, 1974a). In contrast, a single pairing of the target flavor with either radiation exposure or toxic injection has characterized relevant bait-shyness experiments. A discrimination learning perspective suggests that repeated episodes of illness restricted to intervals following ingestion of a familiar flavor should result in aversion development even in Ss previously exposed to many instances of illness unrelated to ingestion of the target flavor. This prediction, currently under investigation in additional bait-shyness experiments, is consistent with numerous reports that alcoholics are capable of developing strong conditioned aversions to alcoholic beverages. It also derives support from a recent demonstration that aversion attenuation resulting from preconditioning familiarity with the CS flavor is readily overcome by repeated conditioning trials and discrimination training. Specifically, Elkins (1974b) used such techniques to establish strong and long-lasting aversions to a highly familiar and relatively bland substance, laboratory tap water. The strength of these water aversions is indicated by the fact that some Ss, exposed to 60 days of continuous two-bottle preference testing following conditioning, persisted in the rejection of tap water and consumed, instead, a normally aversive quinine solution.

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NOTE

1. Statistical equivalence means that the 0- and 1-preinjection drug groups failed to differ at the conventional .05 level of statistical significance. They are therefore assumed to be equivalent in this report. However, the consistent pattern apparent in Fig. 1, suggesting retarded extinction in the 1-preinjection group, leaves open the possibility that additional research with larger groups might detect a reliable potentiation of aversion formation following a single instance of preconditioning toxicosis, thereby modifying the inverse relationship of this experiment.

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