Reports from the Research Laboratories

of the

Department of Psychiatry

University of Minnesota

Adventitious Taste Aversion Conditioning:

Contaminant of Psychopharmacological Research

by

RICHARD W. POHL

Report Number PR-77-2

May 17, 1977

Adventitious Taste Aversion Conditioning: Contaminant of Psychopharmacological Research.[1]

Richard W. Pohl[2]

University of Minnesota

May 17, 1977

PP-77-2

[1]Thanks to many people; in particular, Dick Meisch.

[2]Predoctoral trainee under Psychopharmacology Training Grant (U.S. Public Health Service #MH-08565). Research in this paper was supported by Ethanol Self-administration Grant (AA-00299)

Abstract

Theories on a range of subjects (e.g., alcoholism, specific hungers) are based, in part, on experiments involving drug-induced changes in eating or drinking. In many cases, however, these drug-induced changes appear to be caused by taste aversion conditioning. The occurrence of unplanned taste aversions is suggested by long term selective decreases in ethanol drinking produced by the drug, pCPA (para-Chlorophenylalanine): at present, all existing evidence suggests that pCPA-induced reductions in ethanol drinking are taste aversions. This demonstration of unplanned taste aversion forces a re-evaluation of a theory of alcoholism based on pCPA-ethanol studies, and supports suggestions that other areas of research are contaminated by taste aversion conditioning. Implications of unplanned taste aversions are discussed, and suggestions are offered for future research.

Taste aversion conditioning, a crucial process to learning theorists, has recently attained a second, unforseen type of importance: suggestions have been made that broad classes of drug-behavior research are contaminated by taste aversion conditioning. In this paper, one of these suggestions is evaluated, and problems caused by adventitious taste aversions are discussed. Emphasis is on taste aversion conditioning as an explanatory principle; taste aversion is defined and described (viz., in section entitled "Taste Aversion Conditioning") only to facilitate explanation.

Because of this emphasis and because intended readers may be unfamiliar with taste aversion conditioning, areas of agreement are stressed and areas of controversy avoided. The taste aversion literature contains over 400 sources (Riley & Baril, 1976). Behavioral scientists, who are solely concerned with taste aversion as a contaminant of research, are unlikely to have the time to read a literature of this size. In the following pages, implications of taste aversion experiments are discussed.

Planned Taste Aversions

Taste aversion conditioning has been widely studied particularly during the last decade. Taste aversion experiments have provided material for a number of major reviews (Garcia & Ervin, 1968; Garcia, Hankins, & Rusiniak, 1974; McFarland, 1973; Rozin & Kalat, 1971).

In a number of respects, these studies and reviews have established the generality of taste aversion conditioning. Riley and Baril list more than 60 CS[1], more than 90 UCS[2], and more than 10 species. Nonetheless, in one respect the generality of taste aversion conditioning has not been widely appreciated. Comparatively, little attention has been paid to the range of conditions under which taste aversion can occur. A common view is that taste aversions occur when an animal ingests a novel substance and is then

made very ill. If this view is correct, taste aversions are unlikely to occur in drug-behavior research. In most drug-behavior experiments, the ingested substance is familiar and the drug does not produce observable illness.

Unplanned Taste Aversions

If taste aversion conditioning is more than a sharply restricted phenomenon, it must occur in situations other than taste aversion experiments. Table 1 lists areas of literature, other than taste aversion experiments, where changes in behavior have been attributed to taste aversion conditioning. The most widely studied area of unplanned taste aversion conditioning is the specific hungers literature. Agreement exists that some of the changes in behavior initially attributed to specific hungers (e.g., specific hunger for thiamine) were actually caused by taste aversion conditioning (McFarland, 1973; Rozin, 1967; Rozin & Kalat, 1971).

Additionally, recent evidence suggests that unplanned taste aversions have also occurred in drug-ethanol[3] experiments (Holman, Hoyland, & Shillito, 1975; Nachman, Lester & Le Magnen, 1970; Opitz, 1972; Parker & Radow, 1976). Although an inspection of results suggests that unplanned taste aversions have occurred in all areas of drug-ethanol research, interest has focused on pCPA-ethanol experiments. Here, existing evidence suggests that pCPA--induced decreases in ethanol drinking were, at least in part, caused by taste aversion conditioning. These unplanned taste aversions provide support for the view that taste aversion conditioning is a factor in psychopharmacological research. Additionally, developments in this area illustrate problems caused by failure to recognize and control variables involved in taste aversion conditioning. Therefore, the series of pCPA-ethanol studies will be discussed

Table 1

Changes in Behavior Attributed to Taste Aversion Conditioning

Area of the literature	References
Poisoning of rats	Rzoska, 1953; Rozin and Kalat, 1971
Specific hungers	Rozin, 1967; McFarland, 1973
Effects of drugs on ethanol drinking	Myers and Veale, 1968; Nachman et al., 1970
Effects of diabetes on saccharin drinking	Kakolewski and Valenstein, 1969; Brookshire, 1974a; Brookshire, 1974b
Effects of formalin on sodium appetite	Krieckhaus and Wolf, 1968; Woods, Weisinger, and Wald, 1971
Effects of hormones on eating	King and Cox, 1976
Effects of drugs on learning	Berger, 1972; Booth and Simson, 1973
Psychopharmacological studies using Δ9-THC	Elsmore and Fletcher, 1972; Cappell et al., 1973
Chemical aversion treatment of alcoholics	Lemere and Voegtlin, 1950; Elkins, 1974a

Note: The references in Table 1 either include experiments in which unplanned taste aversions may have occurred, or discuss the possibility that unplanned taste aversions have occurred. It should not be assumed, however, that all references favor the occurrence of unplanned taste aversions. For example, Brookshire (1974a, 1974b) presents data that suggests that alloxan-induced decreases in saccharin drinking are not entirely caused by taste aversion conditioning.

in depth. Before discussing these studies, however, it is necessary to discuss taste aversion conditioning.

Taste Aversion Conditioning

Defining Characteristics

A conditioned taste aversion is a reduction in the amount of a substance consumed following a pairing of the substance with a consequence

(i.e., UCS). The major types of consequences are drugs and radiation. As the definition implies, conditioned taste aversions are caused by the pairing between the substance (i.e., CS) and the consequence. Taste aversion experiments usually include a group administered the UCS alone to provide an assessment of the effects of the UCS not dependent on the pairing.

Taste aversion conditioning should only be used to describe changes in behavior after four defining requirements have been met.

CS requirement. A stimulus that can be tasted or smelled must have been presented to the organism (Garcia & Koelling, 1966; Martin & Ellinwood, 1974; Smith & Balagura, 1969). A possible exception exists when birds are used as subjects: for birds, visual stimuli may be adequate conditioned stimuli.

UCS requirement. Taste aversion conditioning should only be invoked when an adequate UCS has been presented. Riley and Baril's UCS list includes histidine-free diets, thiamine deficiency and rotaional stimulation. Doses of drugs that have been self-administered in other situations can also condition taste aversion (Cappell & Le Blanc, 1973; Wise et al., 1976). Therefore, this requirement is easily met.

Pairing requirement. Taste aversion conditioning should only be invoked when a pairing has occurred between the CS and UCS. The need for this requirement is demonstrated by the controls used in a taste aversion experiment. Three groups are included in these studies: (a) a control group administered the UCS alone, (b) a control group provided the CS but not the UCS, (c) a group provided with a CS-UCS pairing. The presentation of the UCS alone provides an assessment of the effects of the UCS not dependent on the pairing.

Future reduction requirement. A reduction in the consumption of the CS must occur following the CS-UCS pairing (i.e., in the future). An

extremely important feature of conditioned taste aversions is that future reductions often persist for long periods of time during extinction (i.e., following the CS-UCS pairing). For example, Elkins (1974b) reported that 60 days free access to saccharin with water also freely available, did not extinguish a taste aversion conditioned by a single saccharin-cyclophosphamide (12.5 mg/kg) pairing. This slow extinction suggests that taste aversion conditioning could have produced the long term post-drug reductions in ethanol drinking (e.g., Veale & Meyers, 1970-91 days) observed in drug-ethanol studies.

Non-defining Characteristics: Variables Determining the Extent of Taste Aversion Conditioning

Although other variables also control the extent of taste aversion conditioning, five are discussed in this section. Subsequently, responsiveness to these variables is used to determine if pCPA-induced reductions in ethanol drinking are taste aversions. These variables include: (a) prior exposure to the UCS, (b) prior exposure to the CS (i.e., novelty), (c) number of CS-UCS pairings, (d) magnitude of the UCS, (e) temporal relationship of the CS and UCS.

Prior exposure to the UCS. Presenting the UCS alone (i.e., the drug or radiation), before pairing it with the CS, can attenuate taste aversion conditioning (Berman & Cannon, 1974; Cannon, Baker, Berman, & Atkinson,1975; Cappell & Le Blanc, 1975; Elkins, 1974b; Goudie & Thornton, 1975; Goudie, Thornton, & Wheeler, 1976; Le Blanc & Cappell, 1974; Revusky & Taukulis, 1975; Riley, Jacobs, & Lo Lordo, 1976). Often, this attenuation can be attributed to tolerance occurring at a lower level of analysis (e.g., metabolic tolerance, cellular tolerance, homeostatic tolerance). There are reports, however, of attenuation occurring in the absence of observable

tolerance at lower levels of analysis (Bravemen, 1975; Cannon et al., 1975; Cappell, Le Blanc, & Herling, 1975) Cannon et al. explain attenuation in the absence of evidence for tolerance at lower levels of analysis as a conditioning phenomenon:

> a function of the differential probability of the UCS following the presence or absence of the CS...For animals given a preconditioning UCS...the occurrence of the illness is treated as not much more probable following the CS than it is at other times (p. 282).

Prior exposure to the CS. Novelty of the flavored substance (i.e., CS) is a second variable (Revusky & Bedarf, 1967; Rozin & Kalat, 1971; Wittlin & Bookshire, 1968). There have been few attempts to condition taste aversions after more than 30 exposures to the CS. It is not known if unlimited prior exposure to the CS could entirely eliminate taste aversion conditioning. There are indications, however, that familiarity alone can not eliminate taste aversion conditioning. For example, Elkins (1974a) conditioned taste aversions to tap water after 70 days of prior exposure.

Number of CS-UCS pairings. Multiple CS-UCS pairings have been reported to: (a) override prior exposure to the CS (Elkins, 1974a; Fenwick, Mikulka, & Klein, 1975; Jacquet, 1973), (b) override prior exposure to the UCS (Berman & Cannon, 1974; Cappell & Le Blanc, 1975; Le Blanc & Cappell, 1974), (c) increase taste aversion when small amounts of the drug serve as the UCS (Cappell & Le Blanc, 1973; Cappell, Le Blanc, & Endrenyi, 1973; Eckardt, Skurdal, & Brown, 1974; Le Blanc & Cappell, 1974), and (d) reverse an initial flavor preference (Woods, 1971).

Magnitude of the UCS. Under some conditions, the extent of taste aversion conditioning is directly related to the amount of drug administered (Berger, 1972; Berman & Cannon, 1974; Cappell et al., 1973; Le Blanc &

& Cappell, 1974, 1975; Revusky & Gorry, 1973). There are indications that taste aversions can be conditioned by doses of drugs that are self-administered (Cappell & Le Blanc, 1973; Pickens & Harris, 1968; Wise et al, 1976) or experimenter administered in psychopharmacological research (Cappell et al., 1973).

Temporal relationship of the CS and UCS. The time of administration of the UCS is a crucial variable. Taste aversions can be conditioned when the UCS is presented prior to the CS (Barker & Smith, 1974; Barker, Suarez, & Grey, 1974; Berger, 1972; Boland, 1973; Brookshire, 1974b). There are few reports, however, of taste aversions being conditioned when a drug (i.e., UCS) was administered more than 60 minutes prior to the consumption of a flavored substance. Taste aversion conditioning can occur over much longer delays when the CS is presented prior to the UCS (e.g., 7 hours, Revusky, 1968).

Taste Aversion Conditioning in PCPA-Ethanol Experiments

In this section, defining and non-defining characteristics of taste aversion conditioning are used to assess pCPA-induced reductions in ethanol drinking. The possibility that these reductions are conditioned taste aversions is analyzed from three perspectives: (a) the design used to examine the effects of pCPA on ethanol drinking, (b) experiments that evaluate the role of taste aversion conditioning in pCPA-ethanol research, (c) results of pCPA-ethanol studies.

Experiments in which pCPA has been administered to animals drinking ethanol have had either of two goals:

1. PCPA reduces CNS and peripheral levels of serotonin (Koe & Weissman, 1966). Additionally, pCPA reduces CNS levels of 5-HIAA, the principal

metabolite of serotonin (Koe and Weissman, 1966). These reductions in 5-HIAA levels suggest that pCPA reduces the amount of serotonin available at CNS serotonergic receptors. One goal of pCPA-ethanol studies has been to link changes in ethanol drinking to depletion of serotonin in the CNS (Cicero & Hill, 1970; Frey, Magnussen, & Nielsen, 1970; Geller, 1973; Hill & Goldstein, 1974; Myers, 1972; Myers & Martin, 1972; Myers & Tytell, 1972; Myers & Veale, 1968; Sanders, Collins, & Wesley, 1976; Veale & Myers, 1970). These studies are summarized in Table 2.

2. Four studies, discussed in the section entitled "PCPA-Ethanol Taste Aversion Experiments," have attempted to determine the range of situations in which pCPA can condition taste aversions to ethanol (Holman, Hoyland, & Shillito, 1975; Nachman, Lester, & Le Magnen, 1970; Opitz, 1972; Parker & Radow, 1976).

Table 2

Effects of pCPA (UCS) on Ethanol Drinking

Independent Variables					Dependent Variables		Ref.
Dose mg/kg	Design	Prior CS Exposure	Prior UCS exposure	Number of Pairings	Ethanol Intake During UCS	Ethanol Intake Post-UCS	
Simple exposure to ethanol							
300	A-P	11 days	0	11	SD	D-50 days	Myers & Veale, 1968
300	A-P	11 days	0	11	SD	D-91 days	Veale & Myers
300	A-P	77 days	0	11	SD	D-12 days	Veale & Myers
300	A-P	14 days	0	15	SD	NS	Frey et al.,
200	A-P	6 days	4	6	D[a]	NS	Cicero & Hill

Table 2 Continued

200	A-P	6 days	4	6	NC[b]	NS	Cicero & Hill
75-200	A-P	70 days	0	11-27	I	NC	Geller
316	A-P	6 days	3	6	NC	NC	Hill & Goldstein
250, 300	P	11 days	0	8	NC	NC	Sanders et al.,
316	A-P	8 days	1	1 or 2	NC	NC	Holman et al.,
Exposure to a flavored ethanol solution							
300	A-P	20 days	0	10	SD	SD-11 days	Myers & Tytell,
Exposure to ethanol combined with intra-ventricular infusions							
300	A-P[c]	22 days	0	5	SD	SD-11 days	Myers et al.,
300	A-P[d]	22 days	0	5	NC	NC	Myers et al.
300	A-P[e]	22 days	0	5	I	I	Myers et al.,
Exposure to ethanol and presentation of unavoidable shocks							
116, 300	P	64 days	0	5	D	D-5 days	Myers & Tytell,
300	A-P	17 days	0	10	NC	SD-53 days	Myers & Cicero, 1969
316	A-P	6 days	3	6	I	SD-36 days	Hill & Goldstein,

Note: Abbreviations include: A-P, ascending-preference (i.e., the design used by Myers and Veale); CS, conditioned stimulus (i.e., ethanol); D, decrease; I, increase; NC, no change; NS, not stated; P, preference (similar to the design used by Myers and Veale except that the concentration of the ethanol solution is held constant); Ref., reference; SD, significant decrease; SI, significant increase; UCS, unconditioned stimulus (i.e., pCPA).

[a]Ethanol solutions were prepared from absolute ethanol.

[b]Ethanol solutions were prepared from 95% ethanol.

[c]Ethanol, acetaldehyde, or 5HTOL solutions were infused into the cerebral ventricles during the ascending-preference series.

[d]Paraldehyde infused rats.

[e]5HTP infused rats.

Role of Serotonin in Ethanol Self-Administration

In the first pCPA-ethanol experiment, Myers and Veale (1968) attempted to link a change in ethanol drinking to a change in serotonin metabolism. The design and the results of this experiment are typical of studies pursuing this goal. Therefore, the Myers and Veale experiment is discussed at length.

In 1968, Myers and Veale published the first of what was to become a series of experiments on the role of serotonin in ethanol drinking. There were a number of justifications for this research. Earlier investigations had indicated that repeated infusion of small amounts of ethanol into the cerebral ventricles increased ethanol drinking. This led Myers and Veale (1968) to suggest:

> metabolic systems, in the limbic-forebrain structures lining the ventricles, are directly affected by the presence of alcohol, and the biochemical state of these systems may underlie aberrant drinking patterns observed in the chronic alcoholic. (p. 1469)

A second justification was the discovery of a new pharmacological tool, pCPA. Koe and Weissman (1966) found that pCPA produced a long lasting depletion of serotonin in the central nervous system. This depletion of serotonin occurred without concommittant changes in two other systems of neurotransmitters.

Myers and Veale reasoned that pCPA could be used to examine the role played by serotonergic neurons of the limbic forebrain in ethanol drinking. To accomplish this, Long-Evans rats were initially placed in cages where food and water were freely available. The experiment began when a gradually increasing series of ethanol solutions was made freely available over an 11 day period. Each concentration was available for 1 day; the concentration of the ethanol solution was increased daily. Food and water were also freely available during this, as well as all other periods of ethanol availability.

The rats were exposed to a second series of ethanol solutions beginning 1 day after the completion of the first. During the second series, the rats were administered pCPA (300 mg/kg/day) or saline intragastrically. Rats administered pCPA, consumed less ethanol during the second series than during the first. Food and water intake were not reported during this series.

A third series was begun 1 day after the second, pCPA was not adminstered during the third series. Ethanol drinking was even lower during this series. Reductions in serotonin levels persist for nearly two weeks after termination of pCPA treatment (Koe & Weissman, 1966). Reductions in ethanol drinking during the third series may have been caused by long term depletion of serotonin.

Myers and Veale conducted an additional series with the same rats one month after termination of pCPA. Serotonin should have returned to control levels by this time (Koe and Weissmsn, 1966). Therefore, it was even more surprising that ethanol drinking remained depressed during this series, 40-50 days after termination of pCPA. Conditioned taste aversions, however, have been reported to persist for even longer periods during extinction (Elkins, 1974b).

Additionally, the defining requirements of taste aversion conditioning were met:

1. Ethanol can be tasted and smelled, and therefore represents a potential CS.

2. PCPA represents a potential UCS.

3. PCPA was administered during periods of access to ethanol and therefore was paired with ethanol.

4. Reductions in ethanol drinking were observed following pCPA-ethanol pairings.

Myers and Veale noted the lack of correlation between reductions in ethanol drinking and depletion of serotonin, and commented that, "an entirely different biochemical system" (Myers & Veale, 1968, p. 1470) was involved in post-pCPA reductions in ethanol drinking. Subsequent developments (i.e., research on pCPA-induced taste aversions) have made this a prophetic remark.

Temporal relationship of the CS and the UCS. The rats in Myers and Veale's experiment were allowed free access to ethanol. The temporal relations between ethanol drinking (i.e., the presentation of the CS) and pCPA administration (i.e., presentation of the UCS) are crucial in determining the extent of taste aversion conditioning. It is difficult with most UCS, excluding radiation, to condition taste aversions when the UCS precedes the CS by more than 1-hr. Taste aversions can occur with much longer temporal delays (e.g., 6-hr) when the UCS is presented after the CS. Since Myers and Veale did not control the time of ethanol drinking, it is likely that the broad temporal requirements for taste aversion were met.

Amount of prior exposure to the CS. Myers and Veale did not report changing the food or liquid (i.e., water) available, when ethanol was first

presented to the rats. It is likely that food and water were much more familiar than ethanol, at the time of pCPA administration. Myers and Veale observed selective reductions in ethanol drinking during post-pCPA series: taste aversions can occur selectively to novel tastes (Revusky & Bedarf, 1967; Wittlin & Brookshire, 1968).

Additionally, Myers and Veale allowed only 11 days exposure to ethanol prior to ethanol-pCPA pairings. Taste aversions have been conditioned after much greater amounts of prior exposure (Elkins, 1974a; Fenwick, Mikulka, & Klein, 1975; Revusky & Taukulis, 1975).

Magnitude of the UCS. Under some conditions, taste aversion conditioning is directly related to the magnitude of the UCS (i.e., dose of the drug). The amounts of pCPA (300 mg/kg/day) administered by Myers and Veale are sufficient to condition taste aversions. Nachman, Lester, and Le Magnen (1970) conditioned taste aversions to ethanol (CS) following a single administration of pCPA (200 mg/kg). Panksepp and Nance (1974) reported that daily administration of pCPA (100 mg/kg) produced a 25-50% reduction in food consumption and a 75% reduction in water intake. The amounts of pCPA administered by Myers and Veale (300 mg/kg/day) could be expected to produce even more profound disruptions: again, this suggests that the magnitude of the UCS in the Myers and Veale experiment was sufficient to condition taste aversions.

Number of CS-UCS pairings. Under some conditions, taste aversion varies directly with the number of CS-UCS pairings. Myers and Veale administered pCPA daily for 11 days. It is possible that as many as 11 CS-UCS pairings may have occurred. Many studies have reported conditioning aversions with a single CS-UCS pairings (e.g., Nachman et al., 1970; Opitz, 1972). Elkins (1974a) reported conditioning taste aversions to a very

familiar substance (i.e., tap water) with only 9 pairings. The 11 pairings provided by Myers and Veale favor the development of taste aversions.

Summary. Consideration of variables controlling the extent of taste aversion conditioning suggests that the reductions in ethanol drinking observed by Myers and Veale were taste aversions. Taste aversions have occurred to flavors far more familiar than the potential CS (i.e., ethanol). The time of ethanol drinking was not controlled and suitable temporal relations for taste aversion conditioning could easily have existed.

As stated earlier, all other studies, attempting to link a change in ethanol drinking to a change in serotonin metabolism, used designs similar to Myers and Veale's: in general, these studies observed similar results. Post-drug (i.e., UCS) reduction in CS (i.e., ethanol) consumption is one of the defining characteristics of taste aversion conditioning: when pCPA decreased ethanol drinking, and post-pCPA ethanol drinking was reported, ethanol drinking remained decreased without exception.

PCPA-Ethanol Taste Aversion Experiments

Four experiments have assessed the role of taste aversion conditioning in pCPA-induced reductions in ethanol drinking. These studies have established that pCPA can condition taste aversions to ethanol. Additionally, these studies have established that the ability of pCPA to reduce ethanol drinking, under conditions existing in the Myers and Veale experiment, can be altered by manipulating variables involved in taste aversion conditioning.

Nachman, Lester, and Le Magnen (1970). Nachman et al. were the first to intentionally condition taste aversions to ethanol (CS) using pCPA (UCS). Nachman et al. used a design commonly employed to condition and study taste aversions. Wistar rats' access to fluids was restricted to daily 10 min

drinking tests for 4 days. On the fifth day, either ethanol (CS) or saccharin (CS), rather than water was available for 10 minutes. PCPA (200 mg/kg)or saline was administered 5 minutes after the session. The restriction of fluid access continued, and water drinking tests were conducted on days 6 and 7. On day 8, however, ethanol was again available to rats consuming ethanol on day 5: saccharin was again available to rats consuming saccharin on day 5. Rats administered pCPA (UCS) after consuming ethanol or saccharin on day 5, consumed less of the flavored solution on day 8. The reduced saccharin consumption on day 8, demonstrated that the reductions were not specific to ethanol.

Nachman et al. demonstrated that the reductions observed on day 8 were dependent on the pairing between ethanol or saccharin, and pCPA. Two groups of rats were injected with pCPA on day 5 but were not provided drinking tests. The amount of ethanol or saccharin consumed by these rats on day 8 did not differ significantly from other ethanol or saccharin groups respectively, prior to pCPA administration.

Nachman et al. described the reductions as "nonspecific learned aversions" (p. 1245) and commented:

> In studies on the influence of a drug on ethanol intake, the ethanol intake has usually been measured before, during and after drug administration. However, the finding of reduced selection of ethanol during or after drug administration may be mistakenly interpreted to be a result of a specific interaction of the drug with ethanol. A major difficulty of this interpretation is that rats readily learn to avoid ingesting any distinctive substance that has been associated with toxic effects, and if a

> rat becomes progressively sicker while ingesting a particular dietary substance, the rat will develop a strong aversion to that substance. Because the rat learns food aversions associated with toxic effects, it may be that drugs that have been shown to result in decreased ethanol intake actually produced a nonspecific aversion to ethanol because ethanol intake was associated with the unpleasant effects of the drug. (p. 1245)

The demonstration that pCPA can condition taste aversions to ethanol does not mean that the reductions observed by Myers and Veale were taste aversions. The Nachman et al. experiment was designed to condition taste aversions. The rats were not given prior exposure to ethanol. In contrast, Myers and Veale's rats were given 11 days prior exposure. Nachman et al. controlled the temporal relationship of pCPA and ethanol to facilitate taste aversion conditioning: Myers and Veale did not control the temporal relations and they may have deviated from those required for taste aversion conditioning. Nonetheless, the Nachman et al. results suggest that Myers and Veale's reductions were taste aversions.

Opitz (1972). Opitz repeated the Nachman et al. experiment and obtained identical results.

Holman, Hoyland, and Shillito (1975). Holman et al. used the same design as Myers and Veale except that pCPA was administered alone 2 days prior to being paired with ethanol. Prior exposure to the UCS attenuates taste aversion conditioning.

Holman et al. obtained baseline levels of ethanol (3-30% V/V) and water intake over an 8 day period. Ethanol, food, and water were freely available during this period. After the initial 8 day period, ethanol was

removed, and only food and water were available for the next 3 days. On the second day of the no ethanol period, pCPA (316 mg/kg) or saline was administered IP. A second 8 day series was initiated after the end of the no ethanol period. During the second series, rats were again administered pCPA (100 mg/kg once or 316 mg/kg twice) or saline. PCPA-rats consumed slightly more ethanol during the second series than did saline-rats. Holman et al. had determined earlier that the larger doses of pCPA (316 mg/kg x 3) lowered rats' CNS serotonin levels to the same degree expected after the amount of pCPA administered by Myers and Veale. This suggests that differences in results between the two experiments were not caused by differences in serotonin depletion.

The Holman et al. experiment differed from the Myers and Veale experiment in respect to two variables involved in taste aversion conditioning, both differences favored the development of taste aversions in the Myers and Veale experiment.

One difference was the number of pairings (i.e., ethanol-pCPA pairings). Taste aversion has been found to vary directly with the number of pairings. Holman et al. provided only two pairings, Myers and Veale provided 11. This difference made taste aversion more probable in the Myers and Veale experiment.

A second variable was prior exposure to the UCS (i.e., pCPA). Holman et al. administered pCPA 2 days prior to pairing it with ethanol, whereas Myers and Veale did not administer pCPA before pairing it with ethanol. This favored the development of taste aversions in the Myers and Veale experiment.

Holman et al. discussed their results in terms of taste aversion conditioning and explained the reductions observed by Myers and Veale as, "the

'conditioned aversion' that occurs when an unpleasant stimulus becomes associated with a rewarding condition." (p. 303)

Parker and Radow (1976). Parker and Radow used the same design as Myers and Veale except that a saccharin solution (0.23% W/V) was substituted for ethanol. Baseline levels of saccharin or water drinking were obtained during an initial 11 day period. Saccharin, water, and food were freely available throughout this period. PCPA (300 mg/kg/day) or saline was injected during a second 11 day preference test. During the second test, rats administered pCPA consumed a smaller percentage of the saccharin solution than was consumed by control rats.

A third preference test, which was conducted without pCPA, was initiated 1 day after the end of the second. PCPA-rats consumed less saccharin during the first 4 days of the third test. Parker and Radow did not include a control group administered pCPA without access to saccharin: therefore, it is not certain that the reductions observed during the third series were dependent on pCPA-saccharin pairing (i.e., caused by taste aversion conditioning). Nonetheless, these results suggest that the reductions observed by Myers and Veale were non-specific taste aversions.

A second Parker and Radow experiment replicated the Myers and Veale experiment except that the taste of ethanol was not paired with pCPA. Ethanol was unavailable during the 11 day period of pCPA administration and during the 16 day period following termination of pCPA treatment. Baseline levels of ethanol and water intake by pCPA-naive rats were obtained over an 11 day period. Ethanol was removed from the home cages at the end of the baseline period. An 11 day period of pCPA treatment began 1 day after the removal of ethanol. Drug treatment included: (a) pCPA (300 mg/kg/day), (b) pCPA (300 mg/kg/day) + ethanol (4g/kg/day IP), (c) ethanol (4g/kg/day IP),

or (d) vehicle. The rats were exposed to a second 11 day preference test beginning 16 days after the final injection. In all four groups, ethanol intake during the second series was similar to ethanol intake during the first series. Again, this suggests that the long term reductions (e.g., Veale & Myers, 1970; 91 days) in ethanol drinking produced by pCPA were taste aversions.

Summary. In summary, four experiments have experimentally assessed the role of taste aversion conditioning in pCPA-ethanol research. All four suggest that pCPA-induced reductions in ethanol drinking are taste aversions.

Table 3

Effects of Drugs on Ethanol Drinking

Independent Variables						Dependent Variables		Ref.
Drug	Dose mg/kg	Design	Prior CS Exposure	Prior UCS Exposure	Number of Pairings	Ethanol Intake During UCS	Ethanol Intake Post-UCS	
Drug which effect serotonin								
pCA	4	A-P	20 days	0	15	D	D-14 days	Frey et al.,
pCA	4	P	40 days	0	15	NC	NC	Frey et al.,
pCA	2,4	P	20 days	0	15	NC	NC	Frey et al.,
pCA	4	P	10 days	0	14	SD	NS	Frey et al,
pCA	4	P	0 days	0	12	NC	NS	Frey et al.,
5,6-DHT	75µg[a]	P	6 days	0	1	SI	NS	Ho et al.,
5,6-DHT	50µg[a]	A-P	6 days	1	1	SI	NS	Myers & Melchior, 1975b

Tryp-tophan	NS	A-P	11 days	12 days	NS	SI	NC	Myers & Melchior, 1975a
Tryp-tophan	NS	A-P	11 days	12 days	NS	SI	NC	Myers & Melchior, 1975a
Tryp-tophan	NS	A-P	11 or 12 days	11 or 12 days	NS	NC	NC	Myers & Melchior, 1975a
5-HTP	440µg[a] /day	A-P	11 days	0	11 days	D	NS	Myers et al.,
5-HTP	150	A-P	11 days	0	11	D	D-83 days	Myers et al.,
5-HTP	100	P	5 or 6 days	0	4-6	D	D-3-7 days	Geller et al.,
5-HTP	50, 100	P	70 days	0	1-6	D	D-14 days	Geller, 1973
5-HT	25-100 µg	R	1 day	0	3	D	NS	Hill, 1974
mela-tonin	0.2-1.5	P	14 days	0	14-28	I	NS	Geller, 1971
mela-tonin	1	P	56 days	0	1	NC	NC	Blum et al., 1973a
mela-tonin	NS	P	NS	0	1	NC	NS	Blum et al., 1973b
mela-tonin	1mg[a] /day	P	NS	0	1	NC	NS	Blum et al., 1973b
mela-tonin	0.5-2.5	P	49 days	0	NS	SI	NS	Burke & Kramer,
5-HTOL	192 µg[a] /day	A-P	11 days	0	11 days	I	NS	Myers et al.,
			Drugs which effect catecholamines					
aMpT	200	A-P	11 days	0	11	D	NC	Myers & Veale, 1968
6-OHDA	200 µg[a]	A-P	12 days	1	1	D	NS	Myers & Melchior, 1975b

6-OHDA	NS	P	28 days	0	1	SI	NS	Kiianmaa et al.,
Drugs which effect acetylcholine								
Carbachol	0.7 µg[a]	--[b]	0 days	2	1	NC	NC	Cicero & Myers,
THP	1.5-3.0	SIP	11 days	0	3	D	NC	Keehn,
NVP	5	P	11 days	0	4	D	D-1 day	Ho et al.,
Stimulants								
d-Amphetamine	1	A-P	20 days	0	15	D	NC	Frey et al.,
Sedative-Hypnotics								
Paraldehyde	--[c]	A-P	9 days	5 days	9 days	I	NS	Myers & Veale, 1969
Paraldehyde	--[c]	A-P	11 days	0	11 days	I	NS	Myers & Veale, 1969
Phenobarb	20-80	R	NS	0	1	I	NS	Kachanoff,
Phenobarb	20-50	R	4 days	0	3	I	D-3 days	Rondeau et al,
Minor tranquilizers								
CDZ	3-12	R	NS	0	1	NC	NS	Kachanoff,
CDZ	1-17	SIP	55 days	0	10	I	NS	Barrett & Weinberg
Tybamate	20, 40	P	48 days	0	7	NC	NC	Myers & Cicero, 1968
Pargyline	50	P	11 days	0	11	SD	D-9 days	Sanders et al.,

Narcotics								
Morphine	30	P	1 or 32 days	0	1	D	D-8 days	Sinclair,
Morphine	60	P	141 days	0	1	D	D-9 days	Sinclair et al.,
Morphine	60	P	200 days	0	1	D	D-10 days	Sinclair et al.,
Morphine	79	P	81 days	2	0	---	D-NS	Sinclair et al.,
Morphine	5	P	36 days	3	0	---	D-NS	Sinclair et al.,
Morphine	NS	R	67 days	6	0	---	D-NS	Sinclair et al.,
Compounds related to the metabolism of ethanol								
Methanol	--[c]	A-P	11 days	5 days	11 days	I	NS	Myers & Veale, 1969
Acetaldehyde	--[c]	A-P	11 days	5 days	11 days	I	NS	Myers & Veale, 1969
Acetaldehyde	--[c]	A-P	0 days	11 days	11 days	I	NS	Myers & Veale, 1969
MMTC	50-150	P	7 days	0	4-6	D	NC	Geller et al.,
6-MTHD	10-50	P	NS	0	4	D	D-7 days	Geller & Purdy,
THD	10-50	P	NS	0	4	D	D-7 days	Geller & Purdy,
NLN	10-50	P	NS	0	4	D	D-7 days	Geller & Purdy,

Compounds which interfere with ethanol metabolism								
TETD	NS	P	NS	0	NS	D	NS	Harkness et al.,
TMTD	NS	P	NS	0	NS	D	NS	Harkness et al.,
TITD	NS	P	NS	0	NS	D	NS	Harkness et al.,
SDTC	NS	P	NS	0	NS	D	NS	Harkness et al.,
BAO	NS	P	6 days	0	NS	D	D-75 days	Koe & Tenen,
Amino acids								
Glut-amine	100	P	55 days	0	26	D	NS	Rogers et al., 1955
Glut-amine	100	P	55 days	0	26	D	NS	Rogers et al., 1955
Glut-amine	100	P	94 days	0	42	SD	NS	Rogers et al., 1956
GA	100	P	94 days	0	42	NC	NC	Rogers et al., 1956
Gluta-mate	100	P	94 days	0	NS	NC	NC	Rogers et al., 1956
As-para-gine	100	P	94 days	0	NS	NC	NC	Rogers et al., 1956
Gly-cine	100	P	94 days	0	NS	NC	NC	Rogers et al., 1956

Note: Abbreviations include: A-P, ascending-preference (i.e., the design used by Myers and Veale); BAO, Butryaldoxime; pCA, p-Chloroamphetamine; CDZ, Chlordiazepoxide; CS, conditioned stimulus (i.e., ethanol); D, decrease; 5,6-DHT, 5,6-Dihydroxytryptamine; GA, Glutamic acid; 5HT, serotonin; 5HTOL, 5-Hydroxytrytophol; 5HTP, 5-Hydroxytryptamine; I, increase; MMTC, 1-Methyl-6-methoxy-1,2,3,4,-tetrahydro -2-carboline; aMpT, a-Methyl-p-tyrosine; MTHD, 6-Methoxytetrahydroharman; NC, no change; NS, not stated; NLN, Norleagnine; NVP, 4-(1-naphthylvinyl) Pyridine; 6-OHDA, 6-Hydroxydopamine; P, preference (same as the design used by Myers and Veale except that the concentration of the ethanol solution is held constant); R, restricted access to fluids; Ref., reference; SD, significant decrease; SDTC, Sodium diethyldithiocarbamate; SI,

significant increase; SIP, schedule induced polydipsia; TETD, tetraethylthiuram disulfide (i.e., Antabuse); THD, Tetrahydroharman; THP, Trihexyphenidyl; TITD, Tetraisobutylthiuramdisulfide; TMTD, Tetramethylthiuramdisulfide; UCS, unconditioned stimulus.

[a]The quantity of drug listed was administered to each animal, regardless of its weight.

[b]Non-fluid deprived rats were administered carbachol and given access to water. Rats, consuming water after carbachol, were then given access to an ethanol solution after carbachol.

[c]Each rat was administered 192 µl of a 0.5% solution per day.

Taste Aversion: Contaminant of Drug-Ethanol Research

Taste aversions have been conditioned by many drugs. If taste aversion conditioning was responsible for the decreased ethanol drinking observed in pCPA-ethanol experiments, than similar decreases should have occurred in other drug-ethanol experiments.

A major portion of the drug-ethanol literature is reviewed in Table 3. The majority (i.e., over 65%) of experiments reporting changes in ethanol drinking upon treatment with a second drug, reported that the change was a decrease. Twenty-two publications reporting decreased ethanol drinking during drug treatment, also reported post-drug ethanol drinking; nineteen of these publications reported that ethanol drinking was also reduced after termination of drug treatment. Post-drug (i.e., UCS) reduction in CS (e.g., ethanol) consumption is a defining characteristic of taste aversion conditioning. Therefore, the post-drug reductions strongly suggest that these experiments were confounded by unplanned taste aversions.

Prior exposure to the UCS can attenuate taste aversion conditioning. In 16 of the studies summarized in Table 4, animals were given exposure to the drug (UCS) prior to drug-ethanol pairing. Reduced ethanol drinking was reported in only two of these studies. When animals were not given

prior expusure to the UCS, the percentage of studies reporting reductions was much greater.

Table 4

Effect of Prior Exposure to the UCS

Amount of prior exposure	Number of studies	Reports of decreases in ethanol drinking	
		During drug	Post-drug
No prior UCS exposure	65	33	23
Prior UCS exposure	16	1	1

Note: UCS refers to the experimenter administered drug. Ethanol is the CS.

Although not mutually exclusive, two explanations have been offered for the attenuation observed after prior exposure to the UCS:

1. A conditioning phenomenon (viz., discussed in the section entitled "Prior exposure to the UCS") related to the extent to which ingestion of ethanol predicts the presence or absence of drug-induced illness.

2. Tolerance caused by increased metabolism of the drug to inactive compounds, homeostatic adjustments, or changes at cellular sites of drug action.

Many forms of tolerance would attenuate both drug-induced increases and drug-induced decreases in ethanol drinking. The conditioning phenomenon would attenuate only drug-induced decreases in ethanol drinking. As Table 5 indicates, prior exposure to the UCS did not alter the probability of drug--induced increases in ethanol drinking. Again, this suggests taste aversion.

Table 5

Effect of Prior Exposure to the UCS

Amount of prior exposure	Number of studies	Reports of increases in ethanol drinking	
		During drug	Post-drug
No prior UCS exposure	8	8	1
Prior UCS exposure	9	8	1

Note: UCS refers to the experimenter administered drug. Ethanol is the CS.

Summary

The possibility that pCPA-induced decreases in ethanol drinking are taste aversions is suggested by three types of evidence:

1. An analysis of four variables (i.e., magnitude of the UCS, prior exposure to the CS, number of CS-UCS pairings, CS-UCS temporal relations) suggests that taste aversion conditioning could easily have occurred in pCPA-ethanol studies.

2. All four pCPA-ethanol taste aversion experiments suggest that pCPA-induced reductions in ethanol drinking are taste aversions.

3. An analysis of a large portion of the drug-ethanol literature suggests that pCPA-induced reductions in ethanol drinking are taste aversions.

Implications of Unplanned Taste Aversions

One theory generated by pCPA-ethanol experiments is that ethanol and pCPA both deplete serotonin in the CNS. Myers and Veale (1968) expressed

this theory in the comment:

> There is some evidence that alcohol reduces the content of serotonin in brain tissue but this idea is not yet firmly established...Since pCPA depletes serotonin, and if alcohol has a similar effect, the pCPA rats may have rejected alcohol because its intake would have only further lowered already-depeleted levels of serotonin. Thus the aversion to alcohol may have reflected the animal's attempts to conserve remaining stores of serotonin (p. 1470)

The demonstration that pCPA-induced decreases in ethanol drinking are taste aversions does not rule out Myers and Veale's hypothesis. PCPA could have produced taste aversions to ethanol because both ethanol and pCPA depleted serotonin. The selective taste aversions to ethanol, observed by Myers and Veale, could even be used to suggest that pCPA and ethanol are interacting on serotonin in the CNS. Although taste aversion does not rule out Myers and Veale's theory, it does suggest the need for caution in interpreting behavioral evidence (e.g., pCPA-ethanol studies). Several comments illustrate this need:

1. Taste aversions can be conditioned with UCS's (e.g., pCPA, d--amphetamine, scopolamine methyl nitrate, monosodium glutamate) with no other apparent common properties. It has not been demonstrated, and appears very unlikely that all effective UCS (see Riley & Baril, 1976 for a list of 90 UCS) deplete serotonin. Therefore, it can not be concluded that every instance of taste aversion conditioning was caused by serotonin depletion.

2. PCPA has other effects than depleting serotonin in the CNS (e.g., a peripheral serotonin-like action, Marley & Whelan, 1976). PCPA-

-induced taste aversions could have been caused by these effects.

3. Taste aversions can be conditioned to many different substances (e.g., tap water, saccharin, thiamine-deficient food). It has not been demonstrated that all these substances directly deplete serotonin in the CNS. Domjan and Wilson (1972) conditioned taste aversions without allowing the CS to be ingested: the CS, in this case, could hardly have depleted serotonin in the CNS.

Theories of Alcoholism

The demonstration of unplanned taste aversions clouds the interpretation of pCPA-ethanol experiments: this difficulty with interpretation applies to drug-ethanol data used to support other theories of alcoholism. These theories include:

1. The Genetotrophic Hypothesis, a theory which stressed the role of vitamin and nutritional deficiencies in alcoholism (Beerstecher, Sutton, Kirby-Berry, Brown, Reed, Rich, Berry, & Williams, 1950; Brady & Westerfeld, 1947; Mardones, 1951, 1954, 1960; Mardones, Segovia & Hederra, 1952; Mardones, Segovia, & Onfray, 1946; Purdy & Lee, 1962; Rogers & Pelton, 1958; Rogers, Pelton, & Williams, 1955, 1956, 1957; Westerfeld & Lawrow, 1953; Williams, 1946, 1954; Williams & Beerstecher, 1950; Williams, Berry, & Beerstecher, 1949a, 1949b, 1950). The literature in this area displays the same pattern observed in pCPA-ethanol studies: initial reports of impressive long term reductions in ethanol drinking, followed by puzzling inconsistencies and failures at replication.

2. Alcoholism as a result of hormone imbalance (Prieto, Varelo, & Mardones, 1958; Richter, 1956, 1957; Zarrow, Aduss, & Denison, 1960).

3. Relations between addiction to ethanol and addiction to narcotics (Sinclair, 1974; Sinclair, Adkins, & Walker, 1973).

Experiments examining these theories used designs similar to those used in pCPA-ethanol experiments; the results were also similar. Drug--induced decreases in ethanol drinking were almost invariably followed by post-drug decreases. This does not, however, mean that these reductions are taste aversions: it does suggest the need for controlling variables involved in taste aversion conditioning when designing drug-ethanol research.

Taste Aversion Conditioning as an Explanatory Principle

In previous sections of this paper, taste aversion conditioning was offered as a possible explanation for many drug-induced reductions in eating and drinking. A detailed analysis of the drug-ethanol literature was used to support this possibility.

There are, however, at least two reasons to question the existence of unplanned taste aversions: (a) in most experiments, subjects received prior exposure to flavored substance (i.e., the CS), (b) in most experiments, the amount of the drug administered (i.e., magnitude of the UCS) would not be expected to induce illness. The prominence of these reasons appears related to the postulated evolutionary role of taste aversion conditioning.

Rozin and Kalat (1971) reasonably argue that taste aversion conditioning represents an adaptive specialization of learning:

> some basic features of learning and memory as applied to food selection in the rat are strikingly different from features characterizing the rat's learning in more traditional laboratory situations, that these differences make sense in terms of evolutionary adaptation, and that an understanding of the role of

> learning and memory in food selection involves an elucidation of specifically adapted learning mechanisms and an integration of these with genetically determined behavior patterns. (p. 460)

Rozin and Kalat's view suggests that conditioned taste aversions occur when a free living animal ingests a novel substance, and is then made very ill. This view of taste aversion conditioning was buttressed by the situations that first suggested the existence of conditioned taste aversions.

The existence of taste aversion conditioning was first suggested, in part, by poison experiments (Rzoska, 1953) and by radiation experiments. In both types of studies, rats were exposed to a noxious stimulus (i.e., the UCS, in these experiments, was poison or radiation) after consuming a novel substance. This origin appears to have influenced the terms used to describe taste aversion conditioning.

UCS Magnitude Required for Taste Aversion Conditioning

Table 6 lists terms used to describe UCS, in three major reviews of taste aversion conditioning. Poison, toxin, sickness (i.e., examples of terms used to describe the UCS) imply that taste aversion conditioning occurs only when an animal is debilitated by a UCS. Gross debilitation, however, is not required for taste aversion conditioning (Cappell and Le Blanc, 1973; Revusky and Gorry, 1973; Wise, Yokel, and De Wit, 1976).

Cappell and Le Blanc (1973) conditioned a taste aversion to a saccharin solution by following its consumption with amphetamine (0.25, 0.50, or 1.0 mg/kg) administration. These doses of amphetamine (0.25-1.0 mg/kg/infusion) have also been self-administered by rats (Pickens and Harris, 1968). Revusky and Gorry (1973) conditioned taste aversions with doses of lithium chloride, emetine, and apomorphine comparable to recommended human doses. Wise et al.

Table 6

Terms Used to Describe the UCS

UCS term	Reference
Toxin, illness, malaise, poisoned bait	Garcia et al., 1974
Nausea, poison, malaise, toxic food, sickness	Rozin and Kalat, 1971
Poison, toxic effects, sickness	McFarland, 1973

(1976) trained rats to self-administer amphetamine by following lever presses with IV infusions of amphetamine. After responding stabilized, amphetamine was replaced by apomorphine (0.5 mg/kg/infusion). The rats had consumed a novel saccharin solution immediately prior to apomorphine substitution. Saccharin (i.e., the CS) intake was lower during subsequent access periods. Apomorphine appeared to be serving as a reinforcer for at least some of the rats on the initial apomorphine day. These studies suggest that doses of drugs that are conventionally administered to humans, and to animals in psychopharmacological research, can condition taste aversions.

PreCS Novelty Required for Taste Aversion Conditioning

Many authors have stressed the importance of preCS (i.e., the flavored substance prior to taste aversion conditioning) novelty. For example, Rozin and Kalat (1971) comment in their major review:

> Rats learn aversions much more readily to novel then to familiar solutions, even when the familiar solution is drunk after the novel solution...In these experiments, familiarization occurred over a period of days, but in

> fact, a 20-minute exposure to a solution followed by neutral consequences will produce virtually the same effect, for such a solution is quite resistant to association with poisoning...This minimal (single) experience can have occurred three weeks before poisoning without a significant attenuation of the effect. (p. 471)

Again, the stress on preCS novelty is displayed by Revusky and Bedarf (1967):

> A poisoned food is bound to be novel; otherwise the rat would probably already be dead. (p. 219)

Novelty, however, is not crucial. Taste aversions have been conditioned to quite familiar tastes (Elkins, 1974a; Fenwick et al., 1975; Peacock and Watson, 1963; Revusky and Taukulis, 1975).

Peacock and Watson (1963) were able to condition taste aversions to a familiar flavor following a single CS-UCS pairing. Initially, C57BL/Cum mice were restricted to 10% ethanol for 14 days. Ethanol and water were simultaneously available for two 4-hr periods on each of the next 9 days. On the tenth day, the mice were allowed access to ethanol only, and were simultaneously irradiated (12 R/hr) throughout the session. Despite 24 days prior exposure to ethanol, the irradiated mice displayed taste aversions to ethanol for 6 days after the conditioning session.

Elkins (1974a) conditioned a taste aversion to tap water (CS) after at least 70 days of prior exposure. Elkins commented:

> The successful induction of strong aversions to familiar tap water as a consequence of repeated conditioning trials and discrimination training clearly

> demonstrates the transient nature of the aversion attenuation resulting from preconditioning flavor familiarity. (p. 413-414)

Summary

Two factors (i.e., lack of preCS novelty; insufficient magnitude of the UCS) question the existence of unplanned taste aversions; a consideration of these factors, however, suggests that neither would eliminate unplanned taste aversions.

Suggestions for Future Research

The preceding discussion has illustrated problems caused by failure to control variables involved in taste aversion conditioning. The reductions in ethanol drinking observed following pCPA administration generated a theory about the role of the serotonergic system in ethanol drinking. In retrospect, the results of existing pCPA-ethanol studies can not be used to support this theory.

Problems with unplanned taste aversions are not limited to pCPA-ethanol experiments. The comments in preceding sections are likely to apply to other areas of drug ethanol research, and to toally independent areas (e.g., research on specific hungers). Because of the problems caused by unplanned taste aversions, experiments should be designed to control or eliminate taste aversion conditioning. This can be accomplished by controlling variables involved in taste aversion conditioning.

Prior Exposure to the Flavor

Prior exposure can attenuate taste aversion conditioning. At present, however, it can't be concluded that prior exposure eliminates taste aversion

conditioning. The attenuation, obtained by increasing prior exposure, may not always justify the expenditure of time.

Magnitude of the UCS

Since taste aversions have occurred after administration of doses conventionally administered in psychopharmacological research (e.g., Myers and Veale, 1968; Elsmore and Fletcher, 1972) it is advisable to begin administering small amounts of the drug. The dose can be increased gradually until behavioral effects are observed.

Prior Exposure to the UCS

Taste aversion conditioning can be attenuated by administering the UCS alone, prior to pairing it with the CS. The most reasonable time to begin administering the UCS, is 1-2 days prior to pairing.

Number of CS-UCS Pairings

Under some conditions, more pairings yield greater taste aversions. In many experiments, (e.g., Myers and Veale, 1968) the UCS was administered on consecutive days. When the UCS is administered on consecutive days, post-drug decreases in CS consumption can only be observed following multiple CS-UCS pairings. To minimize taste aversion conditioning, administer the drug (UCS) once, and wait until intake of the flavored substance has returned to normal, before administering the UCS again.

CS-UCS Temporal Relations

The most important of the five variables is the temporal relationship of the CS and the UCS. The vast majority of post-drug reductions (i.e., possible adventitious taste aversions) have occurred in experiments which did not control this variable. To control CS-UCS temporal relations, it is necessary to control the time of eating or drinking (i.e., CS presentation). Three methods of controlling the time of CS presentation are discussed in the following paragraphs.

Liquid deprivation. Experimental subjects could first be liquid deprived, then allowed brief periods of access to ethanol solutions. This method affords a great deal of experimental control over the time of ethanol drinking. Results obtained from liquid deprived subjects, however, are unlikely to generalize widely (e.g., to non-liquid deprived alcoholics).

Restriction on access to ethanol. A second way to control CS-UCS temporal relations is to allow free access to ethanol. The design used in pCPA-ethanol experiments could be modified: free access to food and water could be continued, but access to ethanol restricted to shorter periods (e.g., 6-hr/day). The drug (UCS) could be administered at selected intervals prior to the ethanol access period. Although this procedure would insure that the UCS (e.g., pCPA) was presented prior to the CS, control over CS--UCS temporal relations would not be very exact. Restricting ethanol access would not insure that ethanol drinking began at the start of the ethanol access period.

Establishment of ethanol as a reinforcer. A third alternative is to establish ethanol as a reinforcer. This can be accomplished by at least three procedures (Meisch, 1976). When ethanol is serving as a reinforcer, ethanol drinking generally begins at the start of the ethanol access period (Anderson and Thompson, 1974; Meisch, 1976; Meisch and Beardsley, 1975). This allows precise control over the temporal relations of the CS (e.g., ethanol) and the UCS (e.g., pCPA) in the absence of fluid deprivation (Anderson and Thompson, 1974).

Figure 1 depicts results of a pCPA-ethanol experiment in which ethanol was serving as a reinforcer (Pohl, unpublished data). In this experiment, pCPA (37.5, 75, 150, and 300 mg/kg) produced reliable reductions in ethanol

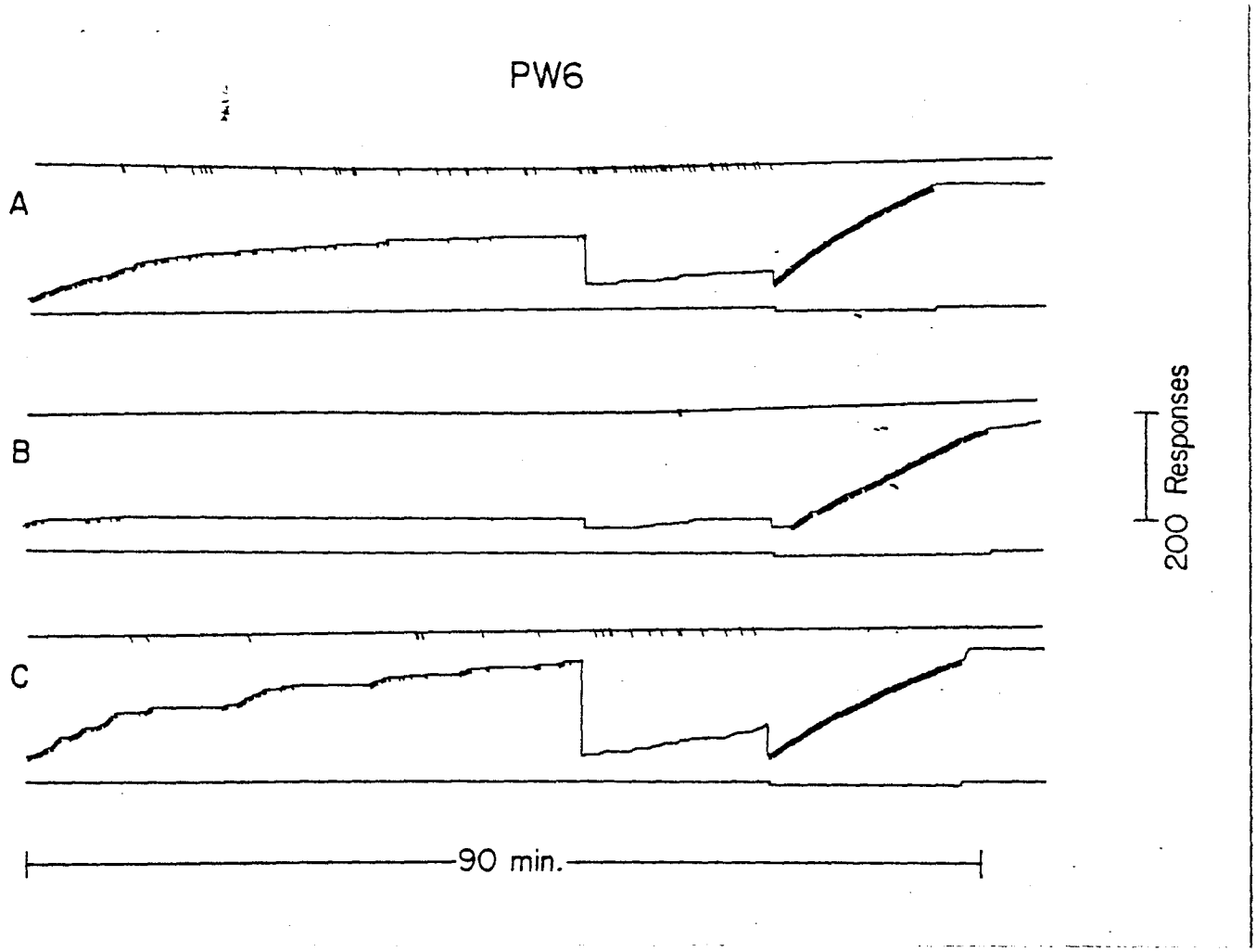

Figure 1 includes three representative cumulative records of rat PW6. These records were obtained on three consecutive days and depict performance of PW6 before, during, and after administration of pCPA (75 mg/kg). A: a representative baseline session. B: pCPA (75 mg/kg) was administered 3 hours prior to the session. C: session conducted on the day after session depicted in B.

Each session (i.e., A,B, and C) consists of three components. The pen, marking the middle trace, reset twice: (a) at the end of initial (i.e., ethanol) component and, (b) at the end of the second (i.e., time--out) component. Pips on the upper trace in A,B, and C during the ethanol and food components represent water deliveries. Pips on the upper trace during the time-out component represent responses on the water manipulandum that were not followed by water deliveries. The middle trace in each record represents: (a) ethanol responding (vertical displacement) and presentations of an ethanol filled dipper (pips), (b) time-out responding on the ethanol-food lever, (c) food responding (vertical displacement) and presentations of food pellets (pips). The lower trace in each record represents the period of food availability (downward deflection).

drinking: pCPA (viz., doses of 75 and 150 mg/kg) sharply reduced ethanol drinking without producing observable changes in food or fluid consumption. Taste aversion conditioning can not be the cause of these reductions because:

1. Future reductions in ethanol drinking were not observed (see part C of Figure 1): ethanol drinking was reduced only on the days of pCPA administration, and not on subsequent days.

2. PCPA was administered 3 hours prior to periods of access to ethanol: there are no reports of conditioned taste aversions with drug-UCS under these conditions.

Conclusion

Defining and non-defining characteristics of taste aversion conditioning were used to evaluate pCPA-induced reductions in ethanol drinking. In summary, pCPA-induced reductions in ethanol drinking were caused, at least in part, by taste aversion conditioning. Inspection of results suggested that experiments throughout the drug-ethanol literature were also contaminated by taste aversion. The demonstration of adventitious taste aversion conditioning was used: (a) to support the need for re--evaluation of drug-ethanol research, (b) to design experiments free of adventitious taste aversions, and (c) to extend the generality of taste aversion conditioning.

PCPA-induced reductions in ethanol drinking observed in home cage experiments (i.e., the design used by Myers & Veale) were caused, at least in part, by taste aversion conditioning. PCPA, however, can also induce reductions in ethanol drinking that can not be described as conditioned taste aversions (Pohl, unpublished data; discussed in section entitled

"Establishment of ethanol as a reinforcer"). This suggests a broader point, made in a comment by A. Charles Catania:

> In any study of drugs it is difficult if not impossible to ignore the fundamental pharmacologic principle that no drug has a single action. The principle is important not only because it is relevant to specific experimental problems but because it so precisely parallels a principle of overriding importance in the analysis of behavior: no stimulus has a single action. We ordinarily speak of this behavioral principle in terms of the multiple functions of stimuli, and it is illustrated in any experiment concerned controlling relationships between stimuli and responses. For example, an experiment that deals with an elicitation relationship must be carefully designed to avoid confounding elicitation with the potential reinforcing or discriminative effects of the eliciting stimulus. (Thompson & Pickens, 1971, p. 149)

In view of the problems caused by adventitious taste aversion the final sentence of Catania's comment could be rephrased:

> an experiment that deals with...[an effect of a drug on ethanol drinking]...must be designed carefully to avoid confounding...[changes in ethanol drinking caused by taste aversion conditioning with unconditioned effects of a drug]. (p. 149)

References

Anderson, W.W., & Thompson, T. Ethanol self-administration in water satiated rats. Pharmacology Biochemistry and Behavior, 1974, 2, 447-454.

Barker, L.M., & Smith, J.C. A comparison of taste aversions induced by radiation and lithium chloride in CS-US and US-CS paradigms. Journal of Comparative and Physiological Psychology, 1974, 87, 644-654.

Barkers, L.M., Suarez, M., & Gray, D. Backward conditioning of taste aversions in rats using cyclophosphamide as the US. Physiological Psychology, 1974, 2, 117-119.

Barrett, J.E., & Weinberg, E.S. Effects of chlordiazepoxide on schedule--induced water and alcohol consumption in the squirrel monkey. Psychopharmacologia, 1975, 40, 319-328.

Beerstecher, E., Sutton, E.H., Kirby-Berry, H., Brown, W.D., Reed, J., Rich, G.B., Berry, J.L., & Williams, R.J. Biochemical individuality. V. Explorations with respect to the metabolic patterns of compulsive drinkers. Archives of Biochemistry, 1950, 29, 27-40.

Berger, B.D. Conditioning of food aversions by injections of psychoactive drugs. Journal of Comparative and Physiological Psychology, 1972, 81, 21-26.

Berman, R.F., & Cannon, D.S. The effect of prior ethanol experience on ethanol-induced saccharin aversions. Physiology and Behavior, 1974, 12, 1041-1044.

Blum, K., Merritt, J.H., Reiter, R.J., & Wallace, J.E. A possible relationship between the pineal gland and ethanol preference in the rat. Current Therapeutic Research, 1973a, 15, 25-30.

Blum, K., Reiter, R.J., Merritt, J.H., & Wallace, J.E. Ethanol preference as a function of the pineal gland. Federation Proceedings, 1973b, 82, 730.

Boland, F.J. Saccharin aversions induced by lithium chloride toxicosis in a backward conditioning paradigm. Animal Learning and Behavior, 1973, 1, 3-4.

Booth, D.A., & Simson, P.C. Aversion to a cue acquired by its association with the effects of an antibiotic in the rat. Journal of Comparative and Physiological Psychology, 1973, 84, 319-323.

Brady, R.A. & Westerfeld, W.W. The effect of B-complex vitamins on the voluntary consumption of alcohol by rats. Quarterly Journal of Studies on Alcohol, 1947, 7, 499-505.

Bravemen, N.S. Formation of taste aversions in rats following prior exposure to sickness. Learning and Motivation, 1975, 6, 512-534.

Brookshire, K.H. Changes in the rat's preference for saccharin and sodium chloride solutions following injection of alloxan monohydrate. Journal of Comparative and Physiological Psychology, 1974a, 87, 1061-1068.

Brookshire, K.H. Function of the "Onset of Illness" in the preference changes of alloxan-diabetic rats. Journal of Comparative and Physiological Psychology, 1974b, 87, 1069-1072.

Burke, L.P., & Kramer, S.Z. Effects of photoperiod, melatonin and pinealectomy on ethanol consumption in rats. Pharmacology Biochemistry and Behavior, 1974, 2, 459-463.

Cannon, D.S., Berman, R.F., Baker, T.B., & Atkinson, C.A. Effect of pre-conditioning unconditioned stimulus experience on learned taste aversions. Journal of Experimental Psychology: Animal Behavior Processes, 1975, 104, 270-284.

Cappell, H., & Le Blanc, A.C. Punishment of saccharin drinking by amphetamine in rats and its reversal by chlordiazepoxide. Journal of Comparative and Physiological Psychology, 1973, 85, 97-104.

Cappell, H., & Le Blanc, A.E. Conditioned aversion by amphetamine: Rates of acquisition and loss of the attenuating effects of prior exposure. Psychopharmacologia, 1975, 43, 157-162.

Cappell, H., Le Blanc, A.E., & Endrenyi, L. Aversive conditioning by psychoactive drugs: Effects of morphine, alcohol, and chlordiazepoxide. Psychopharmacologia, 1973, 29, 239-246.

Cappell, H., Le Blanc, A.E., & Herling, S. Modification of the punishing effects of psychoactive drugs by previous drug experience. Journal of Comparative and Physiological Psychology, 1975, 89, 347-356.

Cicero, T.J., & Hill, S.Y. Ethanol self-selection in rats: A distinction between absolute and 95 percent ethanol. Physiology and Behavior, 1970, 5, 787-791.

Cicero, T.J., & Myers, R.D. Preference-aversion functions for alcohol after cholinergic stimulation of the brain and fluid deprivation. Physiology and Behavior, 1969, 4, 559-562.

Domjan, M., & Wilson, N.E. Contribution of ingestive behaviors to taste aversion learning in the rat. Journal of Comparative and Physiological Psychology, 1972, 80, 403-412.

Eckardt, M.J., Skurdal, A.J., & Brown, J.S. Conditioned taste aversion produced by low doses of alcohol. Physiological Psychology, 1974, 2, 89-92.

Elkins, R.L. Conditioned flavor aversions to familiar tap water in rats: An adjustment with implications for aversion therapy treatments of alcoholism and obesity. Journal of Abnormal Psychology, 1974a, 83, 411-417.

Elkins, R.L. Bait-shyness acquisition and resistance to extinction as functions of US exposure prior to conditioning. Physiological Psychology, 1974b, 2, 341-343.

Elsmore, T.F., & Fletcher, G.V. Δ9-Tetrahydrocannabinol: Aversive effects in rats at high doses. Science, 1972, 175, 911-912.

Fenwick, S., Mikulka, P.J., & Klein, S.B. The effect of different levels of pre-exposure to sucrose on the acquisition and extinction of conditioned aversion. Behavioral Biology, 1975, 14, 231-235.

Frey, H.H., Magnussen, M.P., and Nielsen, C.K. The effect of p-Chloroamphetamine on the consumption of ethanol by rats. Archives Internationales De Pharmacodynamie, 1970, 183, 165-172.

Garcia, J., & Ervin, F.R. Gustatory-visceral and telereceptor-cutaneous conditioning: Adaptation in the internal and external milieus. Communications in Behavioral Biology, 1968, 1, 389-415.

Garcia, J. The faddy rat and us. New Scientist and Science Journal, 1971, 49, 254-256.

Garcia, J., Hankins, W.G., & Rusiniak, K.W. Behavioral regulation of the Milieu interne in man and rat. Science, 1974, 185, 824-831.

Garcia, J., Kimeldorf, D.J., & Koelling, R.A. Conditioned aversion to saccharin resulting from exposure to gamma radiation. Science, 1955, 122, 157-158.

Garcia, J., & Koelling, R.A. Relation of cue to consequence in avoidance learning. Psychonomic Science, 1966, 4, 123-124.

Geller, I. Ethanol preference in the rat as a function of photoperiod. Science, 1971, 173, 456.

Geller, I. Effects of para-chlorophenylalanine and 5-hydroxytryptophan on alcohol intake in the rat. Pharmacology Biochemistry and Behavior, 1973, 1, 361-365.

Geller, I. & Purdy, R. Alteration of ethanol preference in rats: Effects of B-carbolines. In M.M. Gross (Ed.), Advances in Experimental Medicine and Biology (Vol. 59). New York: Plenum Press, 1975.

Geller, I., Purdy, R., & Merritt, J.H. Alteration in ethanol preference in the rat: The role of brain biogenic amines. In F.A. Seixas & S. Eggleston, (Eds.), Annals of the New York Academy of Sciences (Vol. 215). New York: New York Academy of Sciences, 1973.

Goudie, A.J., & Thornton, E.W. Effects of drug experience on drug induced conditioned taste aversions: Studies with amphetamine and fenfluramine. Psychopharmacologia, 1975, 44, 77-82.

Goudie, A.J., Thornton, E.W., & Wheeler, T.J. Drug pretreatment effects in drug induced taste aversions: Effects of dose and duration of pretreatment. Pharmacology Biochemistry and Behavior, 1976, 4, 629--633.

Harkness, W.D., Johnston, C.D., & Woodard, G. Methods to evaluate in rats the antipathy to alcohol produced by antabuse and related compounds. Federation Proceedings, 1953, 12, 328-329.

Hill, S.Y. Intraventricular injection of 5-hydroxytryptamine and alcohol consumption in rats. Biological Psychiatry, 1974, 8, 151-158.

Hill, S.Y., & Goldstein, R. Effect of p-chlorophenylalanine and stress on alcohol consumption by rats. Quarterly Journal of Studies on Alcohol, 1974, 35A, 34-41.

Holman, R.B., Hoyland, V., & Shillito, E.E. The failure of p-chlorophenylalanine to affect voluntary alcohol consumption in rats. British Journal of Pharmacology, 1975, 53, 299-304.

Ho, A.K.S., Tsai, C.S., Chen, R.C.A., Begleiter, H. and Kissen, B. Experimental studies on alcohol preference by 5,6-dihydroxytryptamine and brain acetylcholine. Psychopharmacologia, 1974, 40, 101-107.

Jacquet, Y.F. Conditioned aversion during morphine maintenance in mice and rats. Physiology and Behavior, 1973, 11, 527-541.

Kachanoff, R. The effect of phenobarbital and chlordiazepoxide on water and alochol intake. (Doctoral dissertation, Arizona State University, 1969). Dissertation Abstracts International, 1970, 31, 415B.

Kakolewski, J.W., & Valenstein, E.S. Glucose and saccharin preference in alloxan diabetic rats. Journal of Comparative and Physiological Psychology, 1969, 68, 31-37.

Keehn, J.D. Effects of trihexyphenidyl on schedule-induced alcohol drinking by rats. Psychonomic Science, 1972, 29, 20-22.

Kiianmaa, K., Fuxe, K., Jonsson, G., & Ahtee, L. Evidence for involvement of central NA neurons in alcohol intake. Alcohol consumption after degeneration of the NA pathway to the cortex cerebri. Neuroscience Letters, 1975, 1, 41-45.

King, J.M., & Cox, V.C. Effects of ergocorine and CI-628 on food intake and taste preferences. Physiology and Behavior, 1976, 16, 111-113.

Koe, B.K., & Tenen, S.S. Inhibiting action of n-butraldoxime on ethanol metabolism and on natural ethanol preference of C57BL mice. Journal of Pharmacology and Experimental Therapeutics, 1970, 174, 434-449.

Koe, B.K., & Weissman, A. p-Chlorophenylalanine: A specific depletor of brain serotonin. Journal of Pharmacology and Experimental Therapeutics, 1966, 154, 499-516.

Krieckhaus, E.E., & Wolf, G. Acquisition of sodium by rats: Interaction of innate mechanisms and latent learning. Journal of Comparative and Physiological Psychology, 1968, 65, 197-201.

Le Blanc, A.E., & Cappell, H. Attenuation of punishing effects of morphine and amphetamine by chronic prior treatment. Journal of Comparative and Physiological Psychology, 1974, 87, 691-698.

Lemere, F., & Voegtlin, W.L. An evaluation of the aversion treatment of alcoholism. Quarterly Journal of Studies on Alcohol, 1950, 11, 199-204.

Mardones, R.J. On the relationship between deficiency of B-vitamins and alcohol intake in rats. Quarterly Journal of Studies on Alcohol, 1951, 12, 563-575.

Mardones, J. Metabolic and nutritional patterns in alcoholism. In R.W. Miner (Ed.), Annals of the New York Academy of Sciences (Vol. 57). New York: New York Academy of Sciences, 1954.

Mardones, J. Changes in free selection of ethanol. International Review of Neurobiology, 1960, 2, 41-76.

Mardones, J., Segovia, M.N., & Hederra, D.A. Failure of vitamin B_{12} to reduce alcohol intake in N_1 deprived rats. Acta Physiologica Latino Americana, 1952, 2, 43-47.

Mardones, J., Segovia, N., & Onfray, E. Relationship between the dose of factor N and the alcohol intake of rats under self-selection conditions. Archives of Biochemistry, 1946, 9, 401-406.

Marley, E., & Whelan, J.F. Some pharmacological effects of p-chlorophenylalanine unrelated to tryptophan hydroxylation. British Journal of Pharmacology, 1976, 56, 133-144.

Martin, J.C., & Ellenwood, E.H. Conditioned aversion in spatial paradigms following methamphetamine injection. Psychopharmacologia, 1974, 36, 323-335.

McFarland, D.J. Stimulus Relavance and Homeostasis. In R.A. Hinde & J. Stevenson-Hinde (Eds.), Constraints on Learning. London: Academic Press, 1973.

Meisch, R.A. The function of schedule-induced polydipsia in establishing ethanol as a positive reinforcer. Pharmacological Reviews, 1976, 27, 465-473.

Meisch, R.A., & Beardsley, P.A. Ethanol as a reinforcer for rats: Effects of concurrent access to water and alternate positions of water and ethanol. Psychopharmacologia, 1975, 43, 19-23.

Myers, R.D. Brain mechanisms involved in volitional intake of ethanol in animals. In O. Forsander, & K. Eriksson (Eds.), Biological Aspects of alcohol consumption. Helsinki: The Finnish Foundation for Alcohol Studies, 1972.

Myers, R.D., & Cicero, T.J. Effects of tybamate on ethanol intake in rats during psychological stress in an avoidance task. Archives Internationales de Pharmacodynamie et de Therapie, 1968, 175, 440-446.

Myers, R.D., & Cicero, T.J. Effects of serotonin depletion on the volitional alcohol intake of rats during a condition of psychological stress. Psychopharmacologia, 1969, 15, 373-381.

Myers, R.D., Evans, J.E., & Yaksh, T.L. Ethanol preference in the rat: Interactions between brain serotonin and ethanol, acetaldehyde, paraldehyde, 5-HTP and 5-HTOL. Neuropharmacology, 1972, 11, 539-549.

Myers, R.D., & Martin, G.E. The role of cerebral serotonin in the ethanol preference of animals. In F.A. Sexias & S. Eggleston (Eds.), Annals of the New York Academy of Sciences (Vol. 215). New York: New York Academy of Sciences, 1972.

Myers, R.D., & Melchior, C.L. Dietary tryptophan and the selection of ethyl alcohol in different strains of rats. Psychopharmacologia, 1975a, 42, 109-115.

Myers, R.D., & Melchior, C.L. Alcohol drinking in the rat after destruction of serotonergic and catecholaminergic neurons in the brain. Research in Chemical Pathology and Pharmacology, 1975b, 10, 363-378.

Myers, R.D., & Tytell, M. Volitional consumption of flavored ethanol solution by rats: The effects of pCPA and the absence of tolerance. Physiology and Behavior, 1972, 8, 403-408.

Myers, R.D., & Veale, W.L. Alcohol preference in the rat: Reduction following depletion of brain serotonin. Science, 1968, 160, 1469-1471.

Myers, R.D., & Veale, W.L. Alterations in volitional alcohol intake produced in rats by chronic intraventricular infusions of acetaldehyde, paraldehyde, or methanol. Archives Internationales de Pharacodynamie et de Therapie, 1969, 180, 100-113.

Nachman, M., Lester, D., & Le Magnen, J. Alcohol aversion in the rat: Behavioral assessment of noxious drug effects. Science, 1970, 163, 1244-1246.

Opitz, K. Effect of fenfluramine on alcohol and saccharin consumption in the rat. South African Medical Journal, 1972, 46, 742-744.

Panksepp, J., & Nance, D.M. Effects of para-chlorophenylalanine on food intake in rats. Physiological Psychology, 1974, 2, 360-364.

Parker, L.F., & Radow, B.L. Effects of parachlorophenylalanine on ethanol self-selection in the rat. Pharmacology Biochemistry and Behavior, 1976, 4, 535-540.

Peacock, L.J., & Watson, J.A. Radiation-induced aversion to alcohol. Science, 1964, 143, 1462-1463.

Pickens, R., & Harris, W.C. Self-administration of d-amphetamine by rats. Psychopharmacologia, 1968, 12, 158-163.

Prieto, R., Varelo, A., & Mardones, J. Influence of oral administration of thyroid powder on voluntary alcohol intake by rats. Acta Physiologica Latino Americana, 1958, 8, 203.

Purdy, M.B., & Lee, J.G. The effect of restricted food intake, thiamin deficiency and riboflavin deficiency on voluntary consumption of ethanol by the albino rat. Quarterly Journal Studies on Alcohol, 1962, 23, 549-556.

Revusky, S.H. Aversion to sucrose produced by contingent x-irradiation: Temporal and dosage parameters. Journal of Comparative and Physiological Psychology, 1968, 65, 17-22.

Revusky, S.H., & Bedarf, E.W. Association of illness with prior ingestion of novel foods. Science, 1967, 155, 219-220.

Revusky, S.H., & Gorry, T. Flavor aversions produced by contingent drug injection: Relative effectiveness of apomorphine, emetine, and lithium. Behavior Research and Therapy, 1973, 11, 403-409.

Revusky, S.H., & Taukulis, H. Effects of alcohol and lithium habituation on the development of alcohol aversions through contingent lithium injections. Behavior Research and Therapy, 1975, 13, 163-166.

Richter, C.P. Loss of appetite for alcohol and alcoholic beverages produced in rats by treatment with thyroid preparations. Endocrinology, 1956, 59, 474-478.

Richter, C.P. Decreased appetite for alcohol and alcoholic beverages produced in rats by thyroid treatment. In H.H. Hoagland (Ed.), Hormones, Brain Function, and Behavior. New York: Academic Press, 1957.

Riley, A.L., & Baril, L.L. Conditioned taste aversions: A bibliography. Animal Learning and Behavior, 1976, 4:1B, 1S-13S.

Riley, A.L., Jacobs, W.W., & LoLordo, V.M. Drug exposure and the acquisition and retention of a conditioned taste aversion. Journal of Comparative and Physiological Psychology, 1976, 90, 799-807.

Rogers, L.L., & Pelton, B.B. Effect of behavior-altering drugs on alcohol consumption by rats. Texas Reports on Biology and Medicine, 1958, 16, 133-136.

Rogers, L.L., Pelton, R.B., & Williams, R.J. Voluntary alcohol consumption by rats following administration of glutamine. Journal of Biological Chemistry, 1955, 214, 503-506.

Rogers, L.L., Pelton, R.B., & Williams, R.J. Amino acid supplementation and voluntary alcohol consumption by rats. Journal of Biological Chemistry, 1956, 220, 321-323.

Rogers, L.L., Pelton, R.B., & Williams, R.J. Effect of some glutamine antagonists on alcohol consumption by rats. Federation Proceedings, 1957, 16, 238-239.

Rondeau, D.B., Jolicoeur, F.B., Kachanoff, R., Scherzer, P., & Wayner, M.J. Effects of phenobarbital on ethanol intake in fluid deprived rats. Pharmacology Biochemistry and Behavior, 1975, 3, 493-497.

Rozin, P. Thiamine specific hunger. In C.F. Code & W. Heidel (Eds.), Handbook of Physiology (Vol. 6). Baltimore: Williams and Wilkins, 1967.

Rozin, P. & Kalat, J.W. Specific hungers and poison avoidance as adaptive specializations of learning. Psychological Review, 1971, 78, 459-486.

Rzoska, J. Bait shyness, a study in rat behaviour. The British Journal of Animal Behaviour, 1953, 1, 128-135.

Sanders, B., Collins, A.C., & Wesley, V.H. Reduction of alcohol selection by pargyline in mice. Psychopharmacologia, 1976, 46, 159-162.

Seligman, M.E.P. On the generality of the laws of learning. Psychological Review, 1970, 77, 406-418.

Sinclair, J.D. Morphine suppresses alcohol drinking regardless of prior alcohol access duration. Pharmacology Biochemistry and Behavior, 1974, 2, 409-412.

Sinclair, J.D., Adkins, J., & Walker, S. Morphine-induced suppression of voluntary alcohol drinking in rats. Nature, 1973, 246, 425-427.

Smith, D.F., Balagura, S. Role of oropharyngeal factors in LiCL aversion. Journal of Comparative and Physiological Psychology, 1969, 69, 308-310.

Veale, W.L., & Myers, R.D. Decrease in ethanol intake in rats following administration of p-chlorophenylalanine. Neuropharmacology, 1970, 9, 317-326.

Westerfeld, W.W., & Lawrow, J. The effect of caloric restriction and thiamin deficiency on voluntary consumption of alcohol by rats. Quarterly Journal of Studies on Alcohol, 1953, 14, 378-384.

Williams, R.J. The etiology of alcoholism: A working hypothesis involving the interplay of hereditary and environmental factors. Quarterly Journal of Studies on Alcohol, 1946, 7, 567-587.

Williams, R.J. The genetotrophic concept-nutritional deficiencies and alcoholism. In R.W. Miner (Ed.), Annals of the New York Academy of Sciences (Vol. 57). New York: Academy of Sciences, 1954.

Williams, R.J., & Beerstecher, E. The concept of genetotrophic disease. Lancet, 1950, 258, 287-289.

Williams, R.J., Berry, J.L., & Beerstecher, E. Biochemical individuality. III. Genetotrophic factors in etiology of alcoholism. Archives of Biochemistry, 1949a, 23, 275-290.

Williams, R.J., Berry, J.L., & Beerstecher, E. Individual metabolic patterns, alcoholism, genetotrophic diseases. National Academy of Science Proceedings, 1949b, 35, 265-271.

Williams, R.J., Berry, J.L., & Beerstecher, E. Genetotrophic diseases: Alcoholism. Texas Reports on Biology and Medicine, 1950, 8, 238-256.

Wise, R.A., Yokel, R.A., & De Wit, H. Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. Science, 1976, 191, 1273-1275.

Wittlin, W.A., & Brookshire, K.H. Apomorphine-induced conditioned aversion to a novel food. Psychonomic Science, 1968, 12, 217-218.

Woods, S.C., Weisinger, R.S., & Wald, B.A. Conditioned aversions produced by subcutaneous injections of formalin in rats. Journal of Comparative and Physiological Psychology, 1971, 77, 410-415.

Zarrow, M.X., Aduss, H., & Denison, M. Failure of the endocrine system to influence alcohol choice in rats. Quarterly Journal of Studies on Alcohol, 1960, 21, 400-413.

Footnotes

[1]CS (i.e., conditioned stimulus or conditional stimulus) is a stimulus whose ability to elicit a response is dependent on a pairing with a UCS. In taste aversion conditioning, the elicited response is a decrease in consumption of the flavored solution.

[2]UCS (i.e., unconditioned stimulus or unconditional stimulus) is a stimulus (e.g., drug) which elicits an unconditioned response. The ability of a UCS to elicit a response is not dependent on a pairing with a second stimulus.

[3]Drug-ethanol experiments are studies in which a second drug was administered to animals during periods of access to ethanol. The primary dependent variable in these studies is alcohol consumption.