

The highlight for February is from Chris Cunningham of the Department of Behavioral Neuroscience at the Oregon Health & Science University. In Dr. Cunningham's highlight, he describes his initial introduction to the general field of taste aversion learning and the specific direction he has taken over the past 30 years. As he describes, the majority of his work on aversion learning has focused on alcohol. This focus has been within the context of assessing its rewarding and aversive motivational effects in taste and place conditioning preparations. For example, in the late 80's Dr. Cunningham and his colleagues provided convincing evidence for the role of hypothermia in alcohol-induced taste aversions. This was one of the first assessments of the basis for the aversive effects of alcohol or for that matter any aversion-inducing agent. His demonstration of the role of hypothermia in alcohol's ability to induce taste aversions stands out as one of the few such demonstrations, as the bases of the aversive effects of most drugs still elude us. Shortly thereafter, he turned his attention to another interesting aspect of alcohol, i.e., its ability to condition both taste aversions and place preferences (in mice), an effect reported with a variety of other drugs of abuse. In this analysis, he has assessed the interaction or relationship of these different motivational properties using a variety of genetic techniques and models (quantitative trait loci, inbred strains and selective breeding). For example, he has reported that inbred mice strains show an interesting relationship between taste aversion learning (with alcohol) and alcohol withdrawal and/or the free consumption of alcohol. These assessments clearly support the position that the tendency to acquire strong alcohol-induced taste aversions is correlated in the very same mice with a tendency to display intense withdrawal from alcohol and to avoid its free consumption, suggesting that the aversive effects of the drug may be important to the likelihood of its use and abuse. In more recent work (using selective breeding techniques), taste aversion acquisition was again shown to be negatively correlated with alcohol consumption and preference, although unrelated to the induction of alcohol-induced place preferences, suggesting a genetic dissociation between these two conditioned phenomena. For the past 30 years, Dr. Cunningham has provided a creative and impressive series of investigations into alcohol's aversive and rewarding effects. His highlight reflects these creative contributions that have increased not only our understanding of the motivational effects of alcohol but also the potential role of aversion learning to drug use and abuse.

**If You Want To Understand Alcohol Abuse,
You Must Also Understand Taste Aversion Conditioning**

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Pre-Exposure to CTA

Although I had heard and read about John Garcia's seminal taste conditioning studies as an undergraduate, I did not fully appreciate their widespread implications until a fellow graduate student, Michael Eckardt, decided to study conditioned taste aversions (CTAs) produced in rats by repeated low-dose alcohol injections. We were both students with Judson Brown, who had just moved his laboratory from the University of Iowa to the University of Oregon Medical School in order to assume a leadership role in a new training program on the biological and behavioral bases of alcoholism. A recently published paper (Nachman et al., 1970) had shown that very high doses of injected alcohol would induce CTAs to paired flavors. However, Mike was convinced that relatively low alcohol doses, which did not produce overt signs of intoxication, were also capable of producing CTA in a multi-trial procedure. In an elegant series

of studies conducted for his dissertation, he provided several demonstrations that rats would learn to avoid flavors paired with low doses of alcohol given by injection or mixed in with the flavor solution (Eckardt, 1975a, 1975b, 1976; Eckardt et al., 1974). An important implication of these studies (which I probably did not grasp at the time) was that animals trained to self-administer low doses of alcohol orally in their home cage or in operant chambers might also be expected to develop CTAs. More about this later.

While some of Jud's students, like Mike, were developing alcohol research projects, others (like me) were pursuing topics more traditionally studied in Jud's lab, including avoidance learning, fear conditioning and self-punitive behavior. However, as a result of several years of lab meetings that included discussion of projects like Mike's, I apparently learned a good deal about alcohol research and even learned (from Mike) how to give IP injections to rats. That skill turned out to be quite useful when I later conducted my first CTA study as a postdoctoral fellow in Bob Rescorla's lab at Yale (Rescorla & Cunningham, 1978), especially since I taught Bob the injection technique I had learned in Oregon. In this study, we used lithium-chloride (LiCl) induced CTA as a tool to reveal development of associations between the elements of compound flavor stimuli ("within compound" associations). The experimental design was generally modeled after that used in sensory preconditioning studies conducted with non-gustatory stimuli. In the first phase, rats were separately exposed to each of two two-flavor compounds, which presumably provided the opportunity to form an association between the elements of each compound. In the second phase, one of the flavors from one compound was presented separately and paired with LiCl injection while one of the flavors from the other compound was paired separately with a vehicle injection. In the final phase, rats had access to the other flavors from each compound in a choice test. Reduced intake of the flavor that had originally been presented in compound with the LiCl-paired flavor provided support for the notion that a within-compound association between the flavor elements had been established during the first phase. This finding has interesting implications for the way we think about the learning that occurs within multi-featured taste stimuli, and Bob conducted several other studies on this issue after I left the lab.

Establishing a Lab

After completing my postdoctoral fellowship, I returned to Oregon as a junior faculty member who was expected to participate in the same alcohol-training program that originally brought Jud Brown to Oregon. Because my startup was rather meager (\$0) and CTA studies do not require much in the way of equipment, I decided to begin my alcohol research program by studying alcohol's effect on the extinction of LiCl-induced CTAs. This project allowed me to combine my interest in Pavlovian extinction (developed during my postdoctoral year) with the study of a potentially interesting effect of alcohol. At the time, several studies had suggested that alcohol might retard extinction and I began by attempting to replicate the observation that pre-trial injections of alcohol given during the extinction of a saccharin-LiCl aversion would slow CTA extinction (Cappell et al., 1972). Because I did not have ready access to saccharin, I decided to use (very inexpensive) table sugar and salt to create my flavor solutions. This choice of flavors was fortuitous. Contrary to the findings of Cappell and colleagues, I found no effect of alcohol pretreatment on extinction of the sucrose aversion and the exact opposite effect on extinction of the salt aversion (Cunningham, 1978). That is, alcohol pretreatment *facilitated* extinction of the salt CTA. Additional studies suggested that the nature of the taste stimulus was critical in determining the direction of the alcohol effect. With a bitter taste (quinine), extinction was *retarded* (as originally shown with saccharin by Cappell et al.), but there was no effect on extinction of CTA conditioned to a sour taste (hydrochloric acid). Thus, I was able to obtain all possible outcomes depending on which flavor I used. Although intriguing, the overall pattern of results clearly suggested that I was not studying a general pharmacological effect of alcohol on associative extinction.

In subsequent studies conducted with the help of Jim Linakis, we provided support for the hypothesis that these CTA extinction effects were produced by a peripheral interaction between

the CS taste and the taste of alcohol, which was presumably produced intravascularly and/or via expiration from the lungs after IP injection of alcohol (Cunningham & Linakis, 1980). We did this by showing that pairings of an IP alcohol injection with an IP LiCl injection significantly reduced intake of a weak (4.8% v/v) oral solution of alcohol. While conducting these studies, we unknowingly replicated the Avfail phenomenon, which was concurrently under investigation by Sam Revusky and colleagues (Revusky et al., 1979). In our version of this phenomenon, we found that alcohol's ability to induce CTA to a novel saccharin solution was paradoxically reduced by prior exposure to alcohol-LiCl pairings. Linakis and I interpreted our Avfail finding in terms of associative blocking (by handling and taste cues that had been paired with LiCl during the first phase), an interpretation that was somewhat at odds with the one favored by Revusky and his students (Martin, 1982). My most delightful memory about this project comes from a visit by Sam (and Bow Tong Lett) to my lab in the early 1980s while he was on a trip along the west coast. Although Sam was willing to concede the possibility that IP alcohol might produce an internal taste that was a factor in my Avfail studies, he felt pretty strongly that pentobarbital (which had been used most often in his studies) had no distinctive taste. As well-trained experimental psychologists, we decided the only way to settle this issue was by dripping pentobarbital on our tongues while leaning over a sink in the lab. My vindication came in observing Sam's vocalizations and aversive orofacial responses to this rather bitter tasting drug.

The Preference-Aversion Paradox: Part 1

After discovering that my alcohol-extinction project had gone in a less interesting direction than I had initially hoped, I decided to focus on a problem that would eventually capture a substantial portion of my research efforts. More specifically, I became interested in the observation that many abused drugs appeared to have both positive and negative motivational effects. As a devotee of Pavlovian conditioning, I was especially intrigued by Reicher and Holman's (1977) finding that the same injection of amphetamine appeared simultaneously (and paradoxically) to be able to condition a preference for a paired flavor but an aversion for a paired spatial location. Given my knowledge of alcohol-induced CTAs (based on Mike Eckardt's work) and a single study that had shown alcohol-induced conditioned place preference (CPP) in rats (Black et al., 1973), I set out to replicate the Reicher and Holman finding in rats using alcohol instead of amphetamine. Much to my surprise (and disappointment), instead of finding opposite effects of alcohol on the conditioning of taste and spatial location cues, I found only conditioned aversion to both cues, despite several efforts to replicate the previous finding of alcohol-induced CPP (Cunningham, 1979, 1981). After several unsuccessful attempts to convince study sections that a better understanding of both forms of aversive conditioning might have important implications for understanding the development and elimination of alcohol-seeking behavior, I decided to drop this line of research. As it turned out, I would return to the preference-aversion paradox again many years later.

Role of Hypothermia in Alcohol's Aversive Effects

Fortunately, even though my own early alcohol projects were hitting dead ends, my first Ph.D. student (James Guy Mansfield) was quite successful in providing one of the first demonstrations of the acquisition and extinction of conditioned compensatory responses involved in mediating conditioned tolerance to alcohol's hypothermic effect in rats (Mansfield & Cunningham, 1980). Inspired by Guy's studies, I devoted much of the next 15 years to studying various forms of learning induced by alcohol and morphine, with a special emphasis on conditioned responses that altered unconditioned drug effects (i.e., conditioned tolerance and conditioned sensitization). Much of this research has been summarized previously (Cunningham, 1998). Although this research was generally relevant to taste-drug learning, only a handful of these studies actually involved taste CSs. Interestingly, they suggested that taste cues were unable to control conditioned tolerance (Cunningham & Hallett, 1991).

Following in the footsteps of many others, we focused on development of tolerance to the hypothermia induced by experimenter-administered injections of alcohol (Cunningham et al., 1984). Although alcohol-induced change in body temperature was well accepted as a model system for studying tolerance, I was initially at a loss to explain specifically how body temperature change might be related to the motivational processes thought to underlie alcohol-seeking behavior. However, while conducting studies designed to examine tolerance induced by self-administered alcohol, we made an unexpected observation that suggested an interesting hypothesis. Specifically, we found that rats self-administering alcohol in daily operant training sessions not only failed to develop tolerance to alcohol hypothermia, but they also rarely consumed enough alcohol to experience an acute hypothermic response. Examination of cumulative records suggested the rats might have been regulating their intake so as to avoid a drop in body temperature, i.e., drinking enough to obtain some desired effect but stopping before they experienced an aversive effect. To test this idea, we manipulated the magnitude of the hypothermic response to injected alcohol by moving half of the animals to a warm (32° C) room immediately after saccharin-alcohol pairings (Cunningham et al., 1988). The hypothermia experienced in the high ambient temperature environment was significantly reduced compared to that seen in rats maintained at normal room temperature (21-23° C). Moreover, CTA was reduced in the group that showed a reduced hypothermic response, supporting our idea that alcohol hypothermia caused or was positively correlated with an aversive alcohol effect that contributed to alcohol CTA and limited oral intake of alcohol in rats. Later studies replicated and extended these findings by also showing that a post-injection decrease in ambient temperature (to 5° C), which enhanced alcohol hypothermia, produced an increase in alcohol-induced CTA (Cunningham et al., 1992). Control studies with LiCl and morphine sulfate showed no effect of post-injection alterations in ambient temperature, confirming that the effect was specific to alcohol. Another study provided more direct support for the suggestion that the hypothermia experienced after oral ingestion of alcohol limited alcohol intake through a CTA-like process (Cunningham & D. Niehus, 1989). Eventually, we also extended our studies to the place conditioning procedure, demonstrating that exposure to an elevated ambient temperature reduced the conditioned place aversion (CPA) normally produced by alcohol injection in rats (Cunningham & J. Niehus, 1993).

Genetic Influences on Rewarding and Aversive Drug Effects: Paradox Revisited

In the late 1980s, with advice, encouragement and mice provided by my behavior genetics colleagues John Crabbe and John Belknap, my lab began to conduct studies designed to study genetic influences on the rewarding and aversive effects of several abused drugs using mice in both the taste and place conditioning procedures. At the time, there were only a few published reports of such conditioning in mice, and we invested a fair amount of time translating rat-based procedures into protocols that would work with mice. In one of the lab's first mouse projects, which examined alcohol drinking, place conditioning and taste conditioning in Crabbe's selectively bred HOT and COLD mice, we made the unexpected discovery that alcohol readily induced CPP in mice at the same doses that produced CTA (Cunningham et al., 1991). Subsequent studies confirmed this observation in other mouse strains (e.g., Cunningham et al., 1992; Risinger & Cunningham, 1992). Thus, a decade after abandoning the preference-aversion paradox based on my rat studies, it suddenly re-emerged and re-captured my interest.

In the years since then, my lab has devoted significant effort to using genetic strategies to help understand the mechanisms underlying alcohol's rewarding and aversive effects and their potential roles in determining alcohol drinking. With substantial assistance from Fred Risinger and Julie Broadbent, we have conducted several studies of alcohol-induced CTA in many different inbred strains (e.g., Broadbent et al., 1996, 2002; Risinger & Cunningham, 1995, 1998) and selectively bred mouse lines (e.g., Chester et al., 1998; Cunningham et al., 1991; Risinger et al., 1994). Two large-scale projects are of particular interest because we continue to pursue various implications. The first project was a dose-response study of alcohol-induced CTA in 20 of the BXD recombinant inbred strains (Risinger & Cunningham, 1998). The BXD strains,

which were developed by inbreeding the F2 cross of two common inbred strains (C57BL/6 and DBA/2), were selected because of their potential utility for identifying important genes using “quantitative trait locus” (QTL) mapping procedures (see Phillips et al., 2002, for a recent overview). Saccharin was paired with alcohol (0, 2 or 4 g/kg IP) several times and a behavioral index of taste conditioning was statistically correlated with genetic marker information available in public databases. These QTL analyses revealed that CTA was significantly associated with genetic markers on nine chromosomes. Moreover, our QTLs were located near several interesting candidate genes. However, the proximity of QTLs to candidate genes does not provide definitive evidence that the candidate gene actually influences the behavioral phenotype. Much more work is needed to identify and characterize the specific genes that influence alcohol CTA. That effort is ongoing.

Our other large-scale project examined alcohol-induced CTA in 15 standard inbred strains (Broadbent et al., 2002). In this case, our primary interest was in using the statistical power provided by using a large number of strains to study genetic correlations. This approach relies on the fact that all individuals within an inbred strain are genetically identical. Assuming constant environmental conditions, differences among strain means are thought primarily to reflect differences in genotype. Thus, by examining correlations between strain means for different behavioral phenotypes, we can gain a better understanding of potential commonalities in the underlying biological mechanisms (see Crabbe et al., 1990, for a more complete discussion of the genetic correlational strategy). In our study, sodium chloride was paired with alcohol (0, 2 or 4 g/kg) several times in each strain. Significant genetic correlations were obtained between CTA and several alcohol-related behaviors measured in the same strains in previously published studies. Two of these correlations were of particular interest because of their potential implications for understanding the role of alcohol CTA in alcohol-seeking behavior. Specifically, we found that strains showing strong CTA tended to show higher severity of withdrawal after chronic alcohol exposure (Crabbe et al., 1983) but a lower preference for 10% alcohol in a home cage two-bottle choice test (Belknap et al., 1993). The latter finding is of particular interest because it contradicts the predictions of Grigson’s (1997) reward comparison hypothesis, at least in the case of alcohol.

Genetic correlations can also be studied by selectively breeding for a trait of interest and then comparing the selected lines for other interesting traits. We recently reported an example of this strategy in a collaborative project (with Tamara Phillips) that involved selectively breeding mice for high (HTA) and low (LTA) alcohol CTA (Phillips et al., 2005). We began by testing a large number of F2 mice in a standard saccharin-alcohol CTA procedure. Mice showing extremely high or low levels of CTA were then mated with mice showing a similar phenotype to create the first selected generation. This process was repeated to create the second selected generation. The response to selection was quite rapid, reflecting the relatively high heritability of alcohol CTA. We then compared the selected lines for their response in several different procedures. Consistent with the conclusions from our 15-strain study, we found that HTA mice drank less alcohol and had a lower preference for alcohol, confirming the suggestion that sensitivity to alcohol CTA normally limits voluntary intake of alcohol. Moreover, there was no difference between HTA and LTA mice in magnitude of alcohol-induced CPP, suggesting there is little or no overlap between the genetic mechanisms underlying alcohol’s aversive effects (as indexed by CTA) and its rewarding effects (as indexed by CPP).

Alcohol Self-Infusion and CTA

Thanks to the heroic efforts of Tara Fidler and several others in my lab, we have recently established a model of intragastric (IG) self-infusion of alcohol in both rats (Fidler et al., in press) and mice (Cunningham et al., 2005). This model, which was derived from procedures originally described by Deutsch and colleagues (e.g., Deutsch & Cannis, 1980), involves two main phases. In the first phase, experimental animals are passively infused with alcohol several times a day through a surgically implanted gastric cannula. Control animals are infused with

water. During the second (self-infusion) phase, all animals are given access to two drinking tubes containing different flavored solutions. Licks on one tube (S+) consistently result in small IG infusions of alcohol, whereas licks on the other tube (S-) produce only IG infusions of water. The consistent result of this procedure is that experimental animals self-infuse alcohol in greater volumes than control animals.

Our primary interest in establishing this model was to be able to study excessive alcohol intake in animals with a high level of tolerance and/or dependence induced during the period of passive alcohol exposure. By administering alcohol via the IG route, we are able to avoid the unlearned oral aversion that most rats and mice have for the highly concentrated alcohol solutions that are needed to achieve high blood alcohol levels. However, as students of CTA will readily note, our procedure does not eliminate the possibility of CTA to the S+ flavor. In fact, during several years of using this procedure, we have typically found that manipulation of variables known to affect alcohol CTA also affect self-infusion. Based on data collected thus far, we believe that greater self-infusion in animals that have previously received chronic passive alcohol exposure is most easily explained as the result of developing tolerance to aversive pharmacological effects that would otherwise induce CTA to the S+ (i.e., a US-pre-exposure effect).

Epilogue

In the process of writing this CTA autobiography, I decided it should have a title and composed one that expresses my strong belief that our understanding of alcohol-seeking behavior has been improved by learning more about the conditioning of alcohol's aversive properties. Although I have never thought of myself as someone who was interested in CTA *per se*, it turns out that I have done a lot of CTA studies over the years. Most of these studies were done with the goal of better understanding how the multivalent effects of abused drugs might interact to promote or prevent excessive use of these drugs. As reflected in the studies described in earlier sections, I remain convinced that CTA is an important piece of this complicated puzzle.

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