Is Behavioral Tolerance Learned?

MURIEL VOGEL-SPROTT, PH.D.

Both scientific and anecdotal evidence indicates that social drinkers can develop resistance (i.e., behavioral tolerance) to alcohol's impairing effects over time. Although repeated exposure to alcohol is thought to explain tolerance development on a physiological level, the acquisition of behavioral tolerance appears to involve additional factors. In particular, learned associations between a drinker's behavior following alcohol consumption and the subsequent consequences may play an important role. When favorable consequences result from displaying unimpaired (i.e., tolerant) behavior after drinking, a drinker learns to develop behavioral strategies to compensate for alcohol's effects. In contrast, if a drinker does not receive a reward for unimpaired behavior—or finds that a more favorable outcome follows the display of intoxicated behavior—tolerance does not develop. Studies show that subjects also can develop behavioral tolerance to alcohol when they practice a task while impaired by factors other than alcohol or when they mentally rehearse task performance while under the influence of alcohol. *KEY WORDS: AOD tolerance; reinforcement; AOD impairment; AODE (alcohol and other drug effects); behavior; AOD intoxication; expectancies; learning; context dynamics; literature review*

The term "tolerance" refers to a reduction in the intensity of the effect of alcohol (or other drugs) over the course of repeated use. Thus, a person developing tolerance to alcohol must drink greater quantities of alcoholic beverages to produce the same effect that had been previously achieved at a lower consumption level. This phenomenon may reflect the acquisition of tolerance to alcohol's physiological effects (e.g., reduced body temperature) as well as its behavioral effects (e.g., impaired motor coordination). Researchers generally believe that the physiological actions of alcohol and other drugs contribute to tolerance by triggering the body to produce opposite physiological reactions in an effort to compensate and restore stable internal conditions (i.e., homeostasis). A compensatory response usually is assumed to become stronger each time a person uses alcohol or other drugs and to subside gradually during a period of abstinence.

Research on the effects of alcohol on cellular and neuronal functions has provided much information on where and how alcohol acts in the brain to produce its physiological effects. In contrast, no direct causal relationship has been established between any specific biological change induced by alcohol exposure and a particular behavioral response (e.g., Hunt 1993). Nonetheless, clinical observations suggest that tolerance plays an important role in alcohol abuse and addiction. For example, compared with social drinkers,[1] alcoholics have more exposure to alcohol, giving their bodies repeated opportunities to activate increasingly strong compensatory responses. In addition, alcoholics may display remarkable resistance (i.e., tolerance) to the effects of drinking alcoholic beverages in quantities that would greatly impair social drinkers.

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[1]Throughout this article, the term "social drinker" refers to a person who consumes alcohol but does not experience any alcohol-related problems and is not alcohol dependent. The terms "alcoholic" and "alcohol abuse" as used in this article encompass all levels of problem alcohol use and do not refer to a particular diagnostic system.

These observations accord with the notion that apparent sobriety after drinking or an "ability to handle one's liquor" (i.e., exhibit tolerance to alcohol's behavioral effects) may be a useful pathological diagnostic symptom (American Psychiatric Association 1994).

The transition from social to abusive drinking often occurs gradually over years of drinking sessions, however, and only in some drinkers. This finding suggests that the acquisition of behavioral tolerance to alcohol in social drinkers results from factors in addition to the extent of alcohol exposure.

One research-supported explanation involves environmental events that predict drug administration. Investigators have found that the expectation of receiving a drug can affect tolerance. For example, studies have shown that animals made tolerant to a drug through repeated administrations in a distinctive setting subsequently will display greater tolerance when the drug is administered in this same setting as opposed to a new one (see, for example, Siegel 1989). Researchers have interpreted these results in terms of associative learning: When distinctive events reliably precede drug administration, they serve as a signal that provides a basis for expecting the drug. When tolerance is established, this expectation results in anticipatory compensatory reactions to reduce the drug's effect. Consequently, "tolerance is maximally displayed following 'expected' drug administration but not following 'unexpected' drug administration" (Siegel 1989, p. 116).

People likely acquire tolerance to alcohol's behavioral effects in drinking situations where reliable cues, such as liquor bottles, signal alcohol availability. Research indicates that when alcohol is expected and received, however, a social drinker may demonstrate behavioral tolerance while performing one task but not another (see, for example, Vogel-Sprott 1979). Alcohol expectations arising from events that precede drinking therefore do not appear to fully account for the development of behavioral tolerance in social drinkers. Thus, the question remains: What additional factors in drinking situations affect the acquisition of tolerance to alcohol's behavioral effects among social drinkers?

This article focuses on an intriguing potential factor currently undergoing investigation in behavioral neuroscience research—the idea that environmental events associated with a drinker's behavior following alcohol consumption (e.g., positive or negative consequences) play a role in determining whether the drinker will develop behavioral tolerance (see box, p. 167). This research has been guided by the theory that environmental events known to affect the learning of new behavior likewise will influence behavioral tolerance to alcohol.[2] This article first presents some historical background for theories on the development of behavioral tolerance, then reviews contemporary findings and their implications. (For a more detailed discussion of this work, see Vogel-Sprott 1992.)

Historical Background

Although the view that tolerance stems from alcohol-induced compensatory reactions is prevalent in the scientific literature, other possibilities have received attention. The idea that environmental events following alcohol consumption contribute to tolerance development has roots in the 19th century, when opinion held that tolerance was largely under volitional control. For example, more than 100 years ago, MacNish penned the following observation:

> The mind exercises a considerable effect upon drunkenness, and may control it powerfully. When in the company of a superior whom we respect, or of a woman in whose presence it would be indelicate to get intoxicated, a much greater portion of liquor may be withstood than in societies where no such restraints operate (MacNish 1832, p. 45).

MacNish's notion that circumstances following drinking can affect behavioral tolerance has been advanced during the 20th century as well. Goldberg (1943) speculated that "psychic compensation" contributed to the tolerance displayed by alcoholics. A few decades later, Dews (1962) proposed that drinkers' tolerance might result from new learned behavior that compensates for alcohol's impairing effects. In addition, MacAndrew and Edgerton (1969) noted that drinking orgies in aboriginal cultures resulted in gross intoxication in some societies but tolerance in others; they attributed this variance to learned conformity to different culturally specific standards of behavior under alcohol.

Anecdotes about grossly inebriated drinkers who become sober when they believe it is important to do so also suggest that events after drinking alcohol can affect tolerance. This ability of drinkers to "sober up" apparently provided the impetus for introducing the breathalyzer to measure blood alcohol concentration (BAC) levels for forensic purposes. Before the breathalyzer was available, a medical examination of suspected intoxicated drivers was required to support the charge. Goldberg and Havard (1968) reported that these clinical assessments were completely unreliable. They noted that suspects faced with a doctor called in by the police often were capable of "pulling themselves together" to pass all the clinical tests. After the suspect satisfied the police physician and was free to leave, however, signs of intoxica-

[2]This article presents evidence that learning plays a crucial role in the acquisition and display of behavioral tolerance to alcohol in drinkers who have no alcohol-related problems. For drinkers who have become physically dependent on alcohol, however, the story may differ. Research cited in this article still leaves open the possibility that the behavioral tolerance of alcohol-dependent drinkers involves some alcohol-induced biological changes. In other words, the processes initiating behavioral tolerance to alcohol may be entirely different from those sustaining tolerance after physical dependence has been established.

tion reasserted themselves. As a result, the police frequently had to assist suspects from the station and escort them home.

Tolerance on the part of intoxicated suspects appears to depend on the expectation of a reward for sober behavior. The suspects exhibited sober behavior (i.e., tolerance) when they perceived a payoff for doing so but did not act sober in the absence of a rewarding consequence for compensating for alcohol's effect. In this respect, tolerance resembles a goal-directed (i.e., instrumental) learning response that becomes dominant when associated with a reward and extinguishes when the reward is withdrawn.

Effects of Rewarding Sober Behavior

Using simple and complex psychomotor tasks as tests, researchers have studied the effect of rewarding sober performance on the development of alcohol tolerance. Motor-skill tasks, such as tracking randomly presented visual targets, typically require eye-hand coordination of complex responses. Alcohol-induced impairment of a psychomotor skill is characterized by reduced accuracy, slower performance, or both. In studies using motor-skill tasks, groups of social drinkers learn to perform a task, then typically attend three or four weekly drinking sessions in which they receive 0.62 gram of alcohol per kilogram of body weight. (For a person weighing 154 pounds, this dose equals approximately three 12-ounce bottles of 5-percent beer.) During each 2½-hour session, the subjects perform a task at regular intervals as their BAC rises to a peak (to approximately 0.08 percent, which is the BAC limit for drivers in at least 14 States) and subsequently declines. In these types of studies, researchers determine alcohol's impairing effect by measuring how much the subjects' performance differs from their baseline proficiency on the task while sober. Each week of the study's duration, the researchers measure the subjects' average impairment under the alcohol dose and assess their development of tolerance by noting any reduction in impairment as the alcohol dose is repeated over time.

One way to reward sober behavior is to pay drinkers whenever their performance while intoxicated matches their level of achievement while sober. In studies employing this reward treatment, researchers have observed a progressive development of tolerance with repeated drinking sessions (e.g., Beirness and Vogel-Sprott 1984). In addition, they have found that no such increase in tolerance occurs under control conditions in which the reward is unrelated to sober performance. Although social drinking situations ordinarily do not pay drinkers when they act sober, such behavior might result in verbal approval from others (e.g., the comment "good"). Some studies have compared the rewards of monetary payment versus more realistic verbal approval for sober performance in terms of their tolerance-inducing effects (e.g., Sdao-Jarvie and Vogel-Sprott 1991). Interestingly, these studies have found that both forms of reward have similar efficacy. In general, a favorable outcome for sober behavior appears to enhance the development of tolerance in social drinkers, and different types of favorable outcomes can accomplish the same end (see figure 1 for the results from one study).

In contrast, behavioral tolerance disappears when the reward is withheld (Mann and Vogel-Sprott 1981; Zack and Vogel-Sprott 1993). This finding is consistent with learning studies showing that subjects trained to produce a particular response for an immediate reward will extinguish this response readily when the reward is withheld. After subjects had acquired tolerance during drinking sessions in which they were immediately rewarded for sober performance, for example, their tolerance vanished when the reward was withheld on subsequent drinking sessions, even though they continued to consume the same amount of alcohol (Mann and Vogel-Sprott 1981; Zack and Vogel-Sprott 1993).

A drinker may readily discriminate between the presence or absence of an immediate reward for sober performance, but this circumstance is unlikely to characterize social drinking situations. More commonly, behavior after drinking may result in a significant consequence or outcome only when such behavior deviates from a socially accepted standard (e.g., when behavior is obnoxious). In these situations, the consequence is likely to be negative. Therefore, the absence of an unfavorable consequence serves as a reward for displaying tolerance as sober behavior. Withdrawal of the reward, however, means that nothing happens (i.e., no unfavorable consequence ensues), even though the drinker meets the socially accepted standard of behavior. Consequently, the drinker cannot distinguish the presence of a reward from its absence, because both conditions are characterized by the lack of an aversive consequence.

Learning studies indicate that rewarding a response by withholding an aversive consequence results in the acquisition of a persistent response that is difficult to extinguish when the reward is removed. Researchers have obtained similar results using this procedure to develop behavioral tolerance through repeated doses of alcohol: In a study by Zack and Vogel-Sprott (1995), subjects performing a task received an unfavorable verbal consequence (e.g., the comment "bad") when their performance deviated from a sober standard of behavior (i.e., the subjects' alcohol-free level of proficiency on the task). The absence of this consequence served as a reward when they matched the standard. Such training encouraged the subjects to act sober (i.e., it enhanced their behavioral tolerance to repeated doses of alcohol). Furthermore, the subjects retained this tolerance well during subsequent drinking sessions in which all consequences for performance were withheld.

Taken together, evidence on the acquisition, extinction, and retention of alcohol tolerance in social drinkers

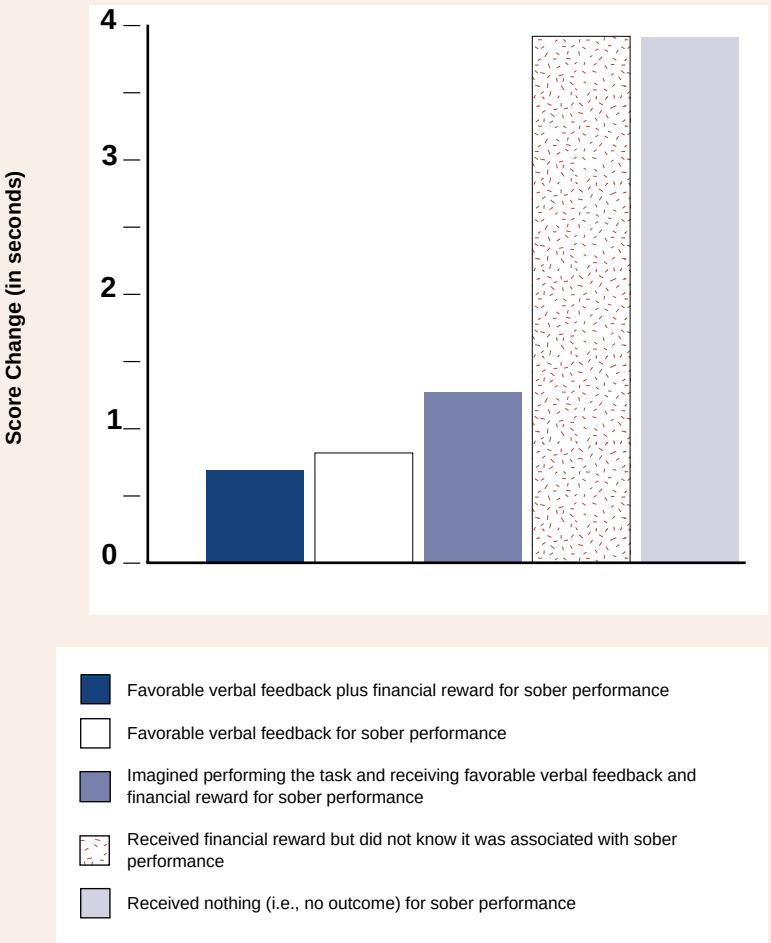

Figure 1 Alcohol-induced impairment of task performance. Completion times for subjects' sober performance of an eye-hand coordination task were obtained and used as baseline scores. Subjects then had a chance to overcome impairment (i.e., build tolerance) during three sessions of alcohol consumption followed by either performing or mentally rehearsing the task. Next, all subjects performed the task after drinking. This graph shows the difference for each group between the average time needed to complete the final task and the average baseline score. Subjects in groups receiving actual or imagined rewards during previous sessions displayed greater tolerance by achieving times closer to their sober performance (i.e., low score changes). Results indicate that actual or mental practice, when associated with a reward for unimpaired behavior, enhances behavioral tolerance.

NOTE: Zero = Sober baseline score.
SOURCE: Adapted from Sdao-Jarvie, K., and Vogel-Sprott, M. Learning alcohol tolerance by mental or physical practice. *Journal of Studies on Alcohol* 53(6):533–540, 1992. p. 538.

indicates that environmental outcomes of alcohol-induced behavior are important predictors of the degree of behavioral tolerance that social drinkers will display (see flowchart in figure 2). These results can be explained by associative learning: When a reliable association exists between a behavioral response and a particular outcome, people learn to expect the response to yield the same outcome each time. Applying this interpretation to the evidence described thus far suggests that drinkers display greater tolerance in situations in which they expect sober behavior to yield the most favorable outcome.

This conclusion also suggests that rewarding other types of behavior after drinking likewise would increase the occurrence of those behaviors. For example, a drinking situation in which flagrant intoxication is rewarded would be expected to lead to an intensification of behavioral impairment—a prediction that recently has been confirmed (Zack and Vogel-Sprott in press). In this study, a group of subjects displayed intense impairment following repeated doses of alcohol when impaired behavior was rewarded, whereas another group displayed tolerance when the same reward was given for sober behavior. Loosely speaking, whether a drinker displays tolerance or gross impairment as a result of drinking alcohol apparently depends on which behavior he or she expects will yield the more favorable outcome. This interpretation closely parallels some learning theories that attribute the ability to adapt a goal-directed response to expectancies acquired from learned associations between the response and its outcome (e.g., Bolles 1979).

Compensating for Alcohol Effects

Substantial research indicates that a compensatory response that counteracts the effects of a drug underlies tolerance. Various studies (e.g., Siegel 1989) have shown that animals that have developed tolerance may display a compensatory reaction when they receive a placebo in the presence of cues signaling drug administration (i.e., when they expect a drug but receive a placebo instead). In drinkers who display alcohol-tolerant behavior, some compensatory response also may be operating to counteract alcohol's disrupting behavioral effect. A compensatory response cannot be

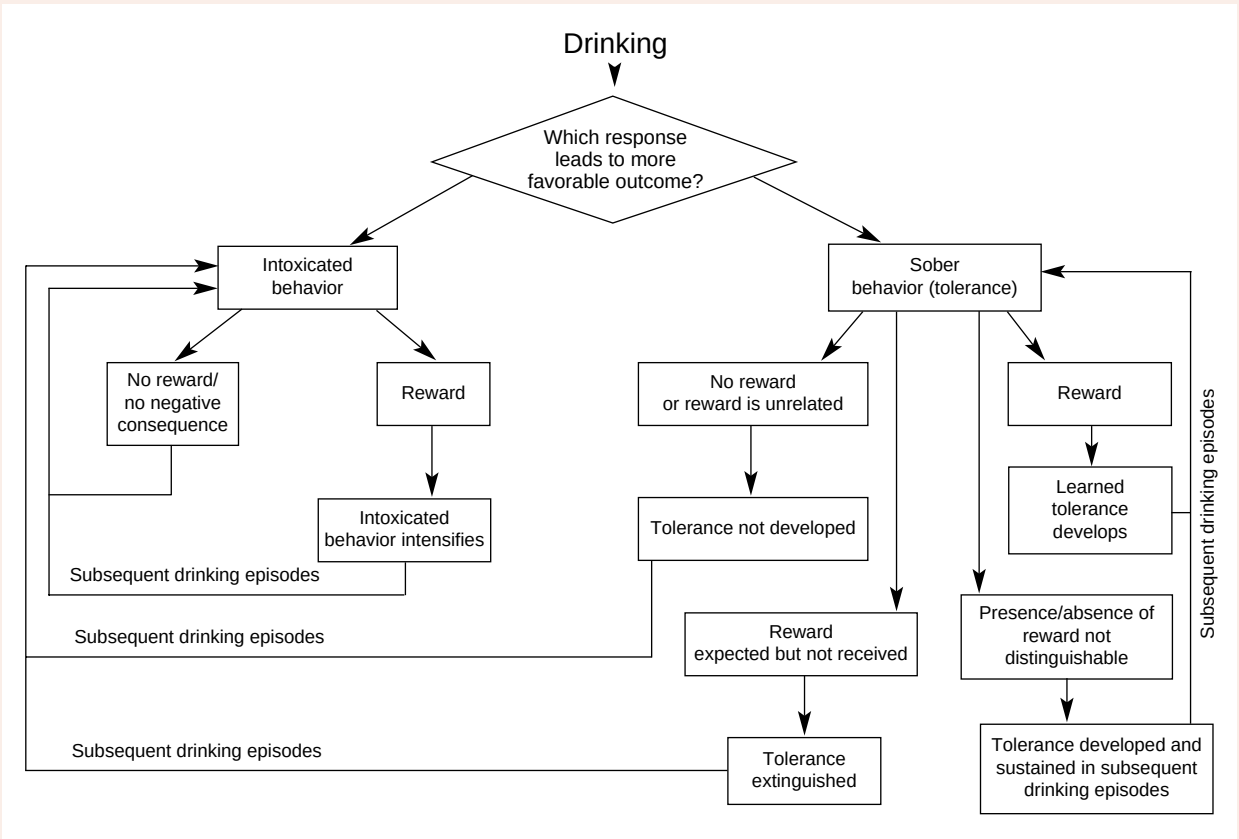

Figure 2 Current research suggests that drinkers will display intoxicated or sober (i.e., alcohol-tolerant) behavior following alcohol consumption, depending on which type of behavior they believe will lead to a more favorable outcome (i.e., a reward or positive consequence). The actual outcome will then influence the drinker's behavior following subsequent drinking episodes.

observed directly when alcohol effects are also present, but such a response theoretically should affect a drinker's behavior by shifting it in a direction opposite to that attributed to the effect of alcohol. For example, if a person performs a task more slowly after drinking alcohol, a compensatory response should speed performance.

Some researchers testing for a compensatory response have surreptitiously substituted a placebo for alcohol after a series of drinking sessions in which subjects who were rewarded for sober performance displayed tolerance and unrewarded control subjects did not (e.g., Sdao-Jarvie and Vogel-Sprott 1991). After drinking a placebo, all the subjects exhibited a compensatory response to some degree, as indicated by faster, improved task performance. Because they all had received their doses of alcohol and the placebo in the same environment, the expectation of receiving alcohol could have contributed to the compensatory response the study subjects displayed. Nevertheless, the groups that had received the reward and had shown the highest tolerance to alcohol displayed a much greater compensatory improvement in performance compared with the control groups (see figure 3 for results from one study). These findings are consistent with the theory that tolerance stems from a compensatory response. The findings also indicate that both the expectation of receiving alcohol and the expectation of a reward for sober performance will strengthen tolerance. (For a more technical learning-theory explanation of the contribution of these expectancies to tolerance development, see Bennett 1992.)

Learning To Compensate for Alcohol Effects

Why should rewarding sober behavior strengthen a compensatory response? Evidence exists that a reward provides drinkers with an opportunity to learn a new behavioral strategy to compensate for the impairing effect of alcohol.

Research on motor-skill learning indicates that rewarding efficient performance provides feedback that helps the learner identify the change in be-

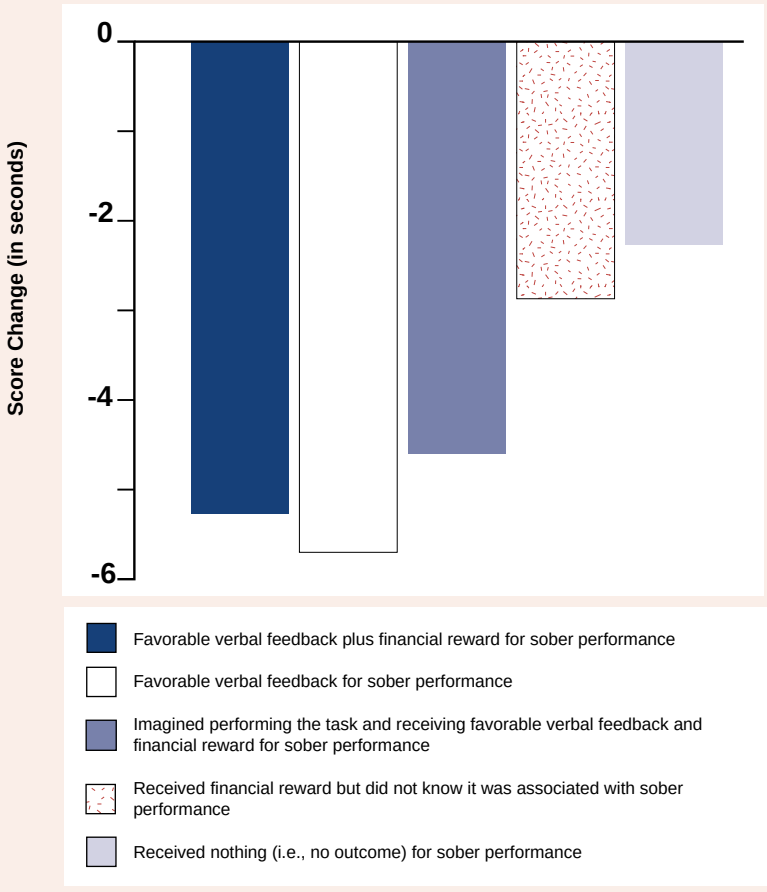

Figure 3 Compensation for alcohol effects. In four sessions, subjects performed or mentally rehearsed an eye-hand coordination task after consuming alcohol; their completion times (i.e., scores) were recorded. In a fifth session, the subjects performed the task but received a placebo instead of alcohol. The subjects' compensation for the anticipated effects of alcohol was measured by comparing their average speed at finishing the task with a score recorded earlier, when they were sober. All subjects performed faster after drinking the placebo, but those who were least impaired after drinking (i.e., had become most tolerant) displayed the strongest compensation, indicated by the greatest decrease in their scores. Results imply that tolerance to alcohol involves learning to compensate for its impairing effects.

NOTE: Zero = Sober baseline score.
SOURCE: Adapted from Sdao-Jarvie, K., and Vogel-Sprott, M. Learning alcohol tolerance by mental or physical practice. *Journal of Studies on Alcohol* 53(6):533–540, 1992. p. 538.

havior required to perform more skillfully (e.g., Schmidt 1988). The learner maintains the behavioral changes that yield a reward and discards those that do not. In a similar way, a drinker's progressive development of behavioral tolerance as alcohol doses are repeated may reflect the gradual acquisition of a behavioral strategy intended to compensate for impaired behavior and maximize reward.

If a person displaying tolerance (i.e., no impairment) in one psychomotor task has learned a new behavior to overcome alcohol's effects, the learned behavior should be transferable to a similar task performed for the first time after alcohol consumption. Research confirms such skill transfer in drinking situations that reward sober performance. When drinkers display tolerance to repeated doses of alcohol on one task, their tolerance transfers to a second task (Rawana and Vogel-Sprott 1985).

Researchers also have directly tested the idea that new learned behavior contributes to alcohol-tolerant performance. Drug-free performance of a psychomotor task can be impaired by environmental factors, such as lowered lighting or reduced visibility of a moving target. Studies have shown that behavioral tolerance to alcohol increases when subjects receive prior training to overcome impairment induced by such environmental factors (Zinatelli and Vogel-Sprott 1993; Easdon and Vogel-Sprott 1996). In these studies, all subjects first practiced a task while drug-free, although some subjects did so under environmentally induced impairment. The results showed that subjects receiving practice in overcoming environmental impairment later displayed greatly enhanced behavioral tolerance to alcohol. Apparently, practicing the task under environmentally induced impairment provided these subjects with an opportunity to learn a compensatory behavioral strategy that they could then transfer to improve their resistance to alcohol-induced impairment. These effects are analogous to cross-tolerance between two drugs; in this case, however, the cross-tolerance occurs between environmental and alcohol impairment.

Other research suggests that a technique commonly referred to as "mental rehearsal" can build tolerance as an alternative to actually performing a task after drinking alcohol (Annear and Vogel-Sprott 1985; Sdao-Jarvie and Vogel-Sprott 1986; Vogel-Sprott et al. 1984; Zinatelli and Vogel-Sprott 1990). This technique, often applied to improve motor skills in sports, involves imagining task performance before putting it into practice. To investigate the effect on

tolerance of mental rehearsal under the influence of alcohol, subjects in the cited studies drank repeated doses of alcohol and either mentally rehearsed a task with an imaginary reward for sober performance or actually practiced the task and received a reward for sober performance. After the treatments concluded and all groups performed the task after drinking alcohol, both the mental-rehearsal and the task-practice groups displayed complete tolerance (i.e., no impairment) under the influence of alcohol. Thus, behavioral tolerance to alcohol apparently can be acquired either by mentally rehearsing or actually practicing sober performance after drinking alcohol.

Conclusions and Implications

Comments and observations spanning more than a century have suggested that drinkers retain some volitional control over the behavioral effects of alcohol. Contemporary research now indicates that learned associations between alcohol-induced behavior and its environmental consequences may account for this volitional control. The important factor promoting behavioral tolerance in a drinking situation appears to be the association between the display of sober behavior and a favorable environmental outcome. Studies reviewed in this article show that drinkers acquire and display behavioral tolerance in drinking situations in which they expect sober performance to yield a positive outcome or reward. Subsequently withholding the reward so that the drinkers' expectancy is not confirmed will extinguish their tolerance, even though they continue to drink alcohol. In contrast, drinkers retain tolerance well in drinking situations that provide no clues to indicate that a rewarding outcome is removed. Thus, the endurance of behavioral tolerance appears to depend greatly on maintaining the expectation of a favorable outcome for sober performance after drinking alcohol.

Taken together, the findings indicate that behavioral tolerance is learned. This conclusion has important implications in a variety of areas, including the following:

- Understanding behavioral tolerance. The development of behavioral tolerance to alcohol can be attributed to normal learning processes. Like any learned response, behavioral tolerance is displayed when it is reliably associated with a favorable consequence. Three exposures to alcohol under such conditions are sufficient to develop behavioral tolerance in social drinkers (Sdao-Jarvie and Vogel-Sprott 1991; Sdao-Jarvie and Vogel-Sprott 1992). Therefore, the environmental outcome expected by the drinker appears to be a far more critical determinant of behavioral tolerance than a large number of alcohol exposures is. The process of learning about the relationship between behavior and outcomes in a given situation continually occurs, and the associations that will be learned can be changed by altering the environmental consequence of a response. In other words, behavioral tolerance can be controlled by controlling its environmental consequence.
- Using behavioral tolerance to assess alcohol abuse. Many people assume that drinking must cease for tolerance to subside. Although this requirement may apply to alcohol tolerance observed at cellular and neuronal levels (i.e., physiological tolerance), a period of abstinence is not needed to reduce behavioral tolerance. Despite continued alcohol use, tolerant performance displayed by drinkers will extinguish when they do not expect or do not receive a favorable outcome. This apparent adaptive flexibility of a drinker's behavioral response to alcohol implies that clinical assessments of behavioral tolerance are unlikely to be a reliable diagnostic symptom of a drinker's alcohol abuse or risk of physical dependence.

Contributors to Tolerance Development

Physiological compensation. Alcohol consumption induces physiological reactions to compensate for its effects; these reactions strengthen with repeated alcohol exposure and contribute to tolerance.

Learned expectation of receiving alcohol. Reliable repetition of specific events preceding alcohol consumption leads to the expectation of receiving alcohol; these expectations result in compensatory reactions that contribute to tolerance.

Learned expectation of behavioral consequence. Favorable events reliably associated with sober behavior lead to expectations of a positive consequence for such behavior; these expectations result in the development of behavioral strategies to overcome alcohol-induced impairment and contribute to tolerance.

- Attributing responsibility for behavior after drinking. The finding that social drinkers will display either tolerance or significant impairment, depending on which they expect to yield a more favorable consequence, suggests that these expectations also may influence other types of activities performed under the influence of alcohol, including antisocial activities. This idea has implications particularly for alcohol abusers who engage in harmful, violent, or obnoxious behavior after drinking. Like social drinkers, most alcohol abusers are not physically dependent on alcohol, and the line between the two groups can be difficult to draw. Alcohol abusers who engage in problem behavior, however, contribute to a long-standing societal problem commonly attributed to

alcohol's intoxicating chemical action. For example, in 1991 a man was acquitted on a sexual assault charge by a Quebec court judge on the grounds that the defendant probably was too intoxicated to know what he was doing when he broke into a locked home and attacked a 65-year-old, wheelchair-bound woman. Pardoning antisocial activities that occur under the influence of alcohol on the grounds that alcohol is responsible may be counterproductive, however, because it fosters the expectation of minimal or nonexistent adverse consequences for antisocial behavior. The removal of a penalizing consequence makes the expected outcome of such behavior more favorable than it would be otherwise. As a result, the undesirable behavior is potentially more likely to occur.

In summary, the research reviewed in this article suggests that the consequences drinkers learn to expect will influence their behavior. Theoretically, then, alcohol-related antisocial behavior might be reduced by cultivating the expectation that socially acceptable drinking behavior yields a more favorable outcome. This may be achieved by programs and policies that advocate responsible drinking behavior and consistently penalize antisocial behavior under the influence of alcohol. ■

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THE NEUROBIOLOGY OF ALCOHOLISM IN GENETICALLY SELECTED RAT MODELS

Robert B. Stewart, Ph.D., and Ting-Kai Li, M.D.

Rats selectively bred for their tendency to drink large or small quantities of alcohol are a useful model for investigators examining the possible neurobiological processes underlying alcoholism. Studies with the alcohol-preferring (P) and alcohol-nonpreferring (NP) and the high-alcohol-drinking (HAD) and low-alcohol-drinking (LAD) pairs of rat lines developed at Indiana University have illustrated differences in several behavioral and neurobiological characteristics associated with alcohol consumption. Specifically, compared with alcohol-avoiding rats, rats with an affinity for alcohol have a greater sensitivity to the stimulatory effects of low to moderate doses and a reduced sensitivity to the negative effects of high doses. Rats that voluntarily drink large quantities of alcohol also acquire tolerance to alcohol's aversive effects. In addition, these rats differ from their alcohol-avoiding counterparts in the levels of several chemical mediators (i.e., neurotransmitters) found in the brain, including serotonin, dopamine, gamma-aminobutyric acid (GABA), and the endogenous opioids. *KEY WORDS: animal strains; selective breeding; AOD preference; amount of AOD use; AOD tolerance; neurotransmitters; reinforcement; drug therapy; literature review*

Animal models have been critical to many areas of research, including the investigation of the behavioral and neurobiological processes that may underlie alcohol abuse and alcoholism. The use of animals, rather than humans, in research has two advantages: (1) animal models allow a high degree of experimental control not possible with human subjects (i.e., scientists can focus solely on alcohol's effects without the interference of confounding factors that may accompany alcoholism in humans, such as liver damage, poor nutrition, or psychiatric disturbances) and (2) animal models permit the use of invasive procedures. This article describes the findings of studies on rats that have been specially bred for their tendencies to drink either large or small quantities of alcohol. In particular, the article focuses on characteristics associated with high and low levels of alcohol drinking that have been investigated in the specially bred lines of rats developed at Indiana University.

TOLERANCE, DEPENDENCE, AND REINFORCEMENT

Historically, animal models of alcoholism have been used most extensively to study alcohol tolerance and physical dependence (see Kalant et al. 1971 for a seminal review in this field; see Kalant 1993 and Hoffman and Tabakoff 1996 for recent reviews on the mechanisms of tolerance and dependence). Tolerance to alcohol occurs when, following chronic consumption, higher doses of alcohol must be ingested to achieve a given effect. Consequently, researchers believe that tolerance accounts for increases in the amount of alcohol consumed over time. Physical dependence is indicated by signs of withdrawal resulting from the absence of alcohol in the body when drinking is discontinued. Because alcohol withdrawal symptoms—which range from anxiety, tremors, hypothermia, and sleep disturbances to hallucinations and seizures—are unpleasant (i.e., aversive), researchers hypothesize that physically dependent people drink to avoid or alleviate these symptoms. In fact, the development of tolerance and physical dependence are considered hallmarks of alcoholism.

These two processes, however, cannot account for the initiation of alcohol drinking or explain why relapse occurs in abstinent alcoholics long after the signs of physical dependence have disappeared. Thus, researchers continue to investigate additional behavioral and neurobiological factors that may underlie alcohol use. Recent studies have focused on a process called reinforcement. In behavioral psychology, reinforcement refers to the connection between a behavior and a stimulus whereby the chance of repeated behavior (e.g., alcohol-seeking) is enhanced if the behavior results in obtaining a reinforcing stimulus (e.g., the desirable effects of drinking an alcoholic beverage). The biological basis of alcohol and other drug reinforcement appears to involve the interaction of these substances with specific systems in the brain that regulate "natural" reinforcing and motivated activities such as eating, drinking, and sex (Wise 1980; Koob and Bloom 1988).

SELECTIVE BREEDING PROGRAMS

Animal studies of the relationship of reinforcement processes to alcoholism initially were hampered by the fact that most laboratory animals, such as rats and mice, will not voluntarily consume alcohol in quantities sufficient to produce significant pharmacological effects (Cicero 1979). To overcome this problem, researchers have found numerous environmental manipulations that increase the rates of alco-

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hol self-administration in laboratory animals (Meisch 1984; Samson et al. 1988). For example, the feeding-induced drinking procedure (Meisch 1976) involves feeding animals such as rats or mice all or part of their daily ration of dry pelleted chow either during or immediately before daily drinking sessions. This feeding results in thirst, and the animals subsequently drink considerable amounts of the fluid made available to them. Initially, the fluid is only water, but alcohol solutions are then presented in gradually increasing concentrations over several sessions. Finally, the food is no longer presented during the drinking sessions, yet the intake of the alcohol solution remains elevated.

A second environmental manipulation is called the sucrose-fading procedure (Samson 1986). In this procedure, animals are first trained to press a lever to access a sweet sucrose solution containing no alcohol. Over the course of several daily drinking sessions, the sucrose concentration is gradually reduced while alcohol is added at increasingly higher concentrations. Finally, the fluid consists of an alcohol solution with no sucrose, and high alcohol intake is maintained.

In addition to such environmental manipulations, genetic manipulation also has been an effective approach to animal studies of alcohol reinforcement, particularly the use of selective breeding programs.[1] This approach springs directly from the first experiments on rodent alcohol consumption. The oldest and most straightforward method for measuring voluntary alcohol self-administration in rats is to offer a continuous choice between an alcohol solution and water (Richter and Campbell 1940). Although widely used, this so-called two-bottle preference method has been severely criticized, because the average (i.e., mean) daily dose of alcohol consumed by groups of "normal," or stock, laboratory rats is not high enough to produce significant levels of alcohol in the blood or brain. In other words, stock rats can metabolize alcohol (i.e., break it down and eliminate it from the body) faster than they consume it. If the rate of alcohol consumption does not exceed the rate of alcohol elimination, then the amount of alcohol in the blood and brain can never achieve significant levels. Thus, it is not surprising that stock rats do not display tolerance, physical dependence, or overt intoxication with such low levels of alcohol intake. More important, researchers cannot determine whether the rats consume alcohol for its pharmacologic effects on the central nervous system (CNS) or for other reasons, such as to alleviate hunger or thirst or simply for its taste or smell.

The low mean alcohol intake by stock rats reflects the fact that most rats within a given population avoid alcohol. Much variability exists in the amount of alcohol consumed by individual rats, however. A small percentage of rats within a given population will drink relatively large amounts of alcohol, and a small percentage will drink relatively little. Selective breeding capitalizes on this variation in preference for alcohol over water and has resulted in the development of lines of rats that will consistently self-administer large or small quantities of alcohol when given continuous access to two bottles, one containing a 10-percent alcohol solution and the other containing water alone. Rats bred for their high affinity for alcohol typically consume more than 5 grams of alcohol per kilogram (g/kg) of body weight per day, whereas rats bred for a low affinity for alcohol typically ingest less than 1 g/kg per day. Several pairs of rat lines have been produced through genetic selection for alcohol preference/aversion, including the University of Chile UChA/UChB lines (Mardones and Segovia-Riquelme 1983), the Finnish Alko alcohol-preferring and alcohol-avoiding (AA/ANA) lines (Eriksson 1968), the Sardinian sP/sNP lines (Fadda et al. 1989), and the Indiana University alcohol-preferring and -nonpreferring (P/NP) lines and high- and low-alcohol-drinking (HAD/LAD) lines (Lumeng et al. 1995).

An important criterion for the scientific usefulness of these genetically selected rat lines is maintenance of the preference for (or aversion to) alcohol through successive generations. Figure 1 indicates that in the P/NP rat lines, daily alcohol consumption has been relatively stable since the eighth generation of selective breeding. The P rats, for example, consistently drink more than 5 g/kg per day, resulting in blood alcohol concentrations (BAC's) of up to 0.2 percent and the development of alcohol tolerance and physical dependence following periods of chronic alcohol self-administration (Li et al. 1988; Li and McBride 1995; Lumeng et al. 1995). Selectively bred rats, such as the P rats, satisfy Cicero's (1979) rigorous criteria for an animal model of alcoholism (see box, p. 173). In addition, rats selectively bred for alcohol preference add experimental evidence to the importance of genetic factors in determining the risk for alcoholism in humans (Cloninger 1987) and provide an opportunity to determine whether a genetic basis exists for the association between high alcohol consumption and other behavioral and neurobiological characteristics.

Characteristics Associated With High and Low Alcohol Drinking

The following survey of research findings emphasizes studies of the original pair of rat lines selectively bred at Indiana University, the P/NP rats, as well as a second pair of rat lines, the HAD/LAD rat lines, which were developed to replicate and confirm the research findings obtained with the P/NP lines. Unless otherwise noted, the research described was carried out by Li and colleagues at Indiana University. For more specific references, extensive reviews and bibliographies on these and other rat lines are provided

[1] In selective breeding programs, animals from a genetically heterogeneous population with a certain desired characteristic (e.g., a tendency to drink alcohol) are mated and their offspring are screened for that characteristic. Those offspring bearing the desired characteristic are then bred. If the characteristic is a heritable trait, the process of selection is repeated in successive generations to produce lines of animals that "breed true" for the characteristic.

by Li and colleagues (1988, 1993), Li and McBride (1995), and Lumeng and colleagues (1995).

Alcohol-Related Traits

The amount of alcohol that an animal consumes is controlled in part by two competing factors: (1) the reinforcing effects that encourage intake (e.g., euphoria or, conversely, the alleviation of dysphoria or negative emotional states, such as anxiety) and (2) the aversive effects that limit intake (e.g., unpleasant taste, motor-skills impairment, or negative physical reactions, such as dizziness or vomiting). Whether alcohol is reinforcing or aversive depends to some extent on the amount of alcohol intake. Low doses of alcohol generally are reinforcing, but high doses tend to be aversive. Numerous studies have been conducted to characterize the reinforcing and aversive effects of alcohol in the P/NP and HAD/LAD rat lines (see Lumeng et al. 1995 for a review).

Although differences in the rats' alcohol intake in the two-bottle preference test suggest that alcohol is more reinforcing for P and HAD than for NP and LAD rats, recent studies provide additional evidence for this conclusion. Rats can be trained to press a lever or perform some other work to obtain alcohol (see figure 2), a paradigm known as operant responding, and the alcohol "reward" received as a result of the rats' correct action can increase the frequency of the operant response (i.e., it is reinforcing). In both P and HAD rats, operant responding is maintained by the delivery of alcohol over a wide range of experimental conditions. For example, the period of daily alcohol availability may be limited to, say, 30 minutes (Schwarz-Stevens et al. 1991) or it may be continuous (Files et al. 1993). Several methods of initiating the operant response for alcohol have been investigated, including the feeding-induced drinking and sucrose-fading procedures (Schwarz-Stevens et al. 1991; Ritz et al. 1994). Alcohol concentrations as low as 1 percent and as high as 40 percent maintain responding in P and HAD rats. In contrast, responding by NP and LAD rats under the same conditions either is not maintained or is much lower than responding by their alcohol-preferring counterparts.

Alcohol also functions as a reinforcer by nonoral routes of administration for P, but not NP, rats. For example, P rats will learn the correct operant response that results in alcohol administration through a tube directly into the stomach (i.e., intragastric administration). Conversely, stock rats will engage in intragastric alcohol self-administration only after developing physical dependence during a period of forced alcohol infusion. P rats, but not NP rats, also will learn to perform the correct response that administers alcohol through a tube directly into the ventral tegmental area of the brain, a region implicated in reinforcement by alcohol and other drugs. By bypassing the mouth, these methods of alcohol consumption eliminate all of the behaviors and stimuli (e.g., taste) associated with oral consumption as factors that may explain the line differences in the reinforcing effects of alcohol.

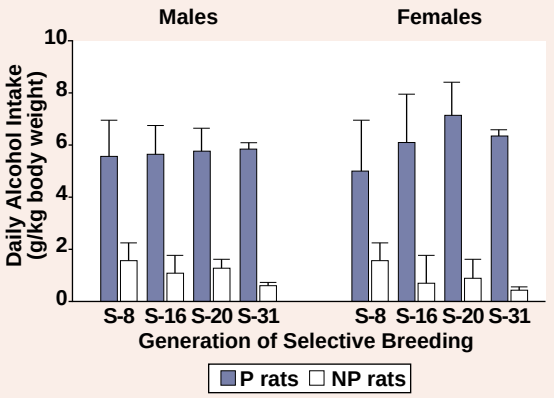

Figure 1 Mean free-choice alcohol consumption (grams of alcohol per kilogram [g/kg] of body weight per day) by recent generations of selectively bred alcohol-preferring (P) and -nonpreferring (NP) rat lines. Males and females of both lines show similar rates of alcohol consumption.

Increases in spontaneous motor activity[2] and other signs of behavioral arousal following drug administration are strongly associated with the reinforcing effects of many drug classes, including stimulants, opiates, and sedative-hypnotics. Interestingly, low doses of alcohol also produce increases in spontaneous motor activity shortly after alcohol administration in P and HAD rats, but not in NP and LAD rats. In addition, studies using techniques such as electroencephalography (EEG), a method of measuring brain electrical activity, also provide evidence that alcohol produces more arousal in P than in NP rats.

Because alcohol usually is consumed orally, it is of interest to determine whether P and HAD rats differ from NP and LAD rats in their reactions to alcohol's flavor (i.e., taste reactivity). A variance in avidity for alcohol may result from different preferences for the taste of alcohol solutions, for example. To test the taste reactivity of the selectively bred rats, Kiefer and coworkers (Bice and Kiefer 1990; Kiefer et al. 1995) placed drops of alcohol solution into the mouths of rats who had never previously consumed alcohol (i.e., alcohol-naive rats) and noted their facial responses, which were then quantified to measure how much the rats liked or disliked the flavor of the solution. The investigators did not find any differences in taste reactivity between the alcohol-preferring (P and HAD) and -nonpreferring (NP and LAD) rat lines on initial exposure. Next, the researchers gave the rats a two-bottle preference test with alcohol solution and water for 3 weeks, and pre-

[2]"Spontaneous motor activity" describes the measured amount of movement and exploration that takes place when rats are placed in an enclosure consisting of an open area or "field" surrounded by four walls.

Figure 2 A female alcohol-preferring (P) rat presses a lever in an operant chamber. Each time the lever is pressed, 0.1 milliliter of alcohol solution is delivered into a well to the right of the lever. P rats work to obtain alcohol solutions at concentrations as high as 40 percent (the typical concentration of unmixed hard liquors, such as straight whiskeys).

Photograph by Maggie Johann Stewart

dictably, the P and HAD rats consistently drank more alcohol than did the NP and LAD rats. Following the two-bottle preference test, a second taste-reactivity test was given, and results indicated that alcohol had become more palatable to the P and HAD rats (although not to the NP and LAD rats) during the period of oral alcohol consumption. The alcohol-preferring rats maintained this increase in alcohol palatability even after 1 month of alcohol abstinence. Thus, preference for the taste of alcohol is not an inherited characteristic in the alcohol-preferring rat lines; instead, this taste preference is acquired through alcohol-drinking experience.

Some of the CNS effects of alcohol, especially at high doses, are aversive or dysphoric. Rats selectively bred for high and low alcohol preference have been tested for their sensitivity to these negative effects. Among the most useful testing methods is the conditioned taste aversion procedure, wherein an animal receives a large, presumably aversive, dose of alcohol by injection at approximately the same time that it receives a particular food or other taste stimulus. In normal rats, pairing a taste stimulus and an aversive dose of alcohol will cause the rat to avoid that taste in the future. Similarly, the conditioned place aversion procedure creates aversion to a particular location by placing the rat there as it experiences the aversive effects of an alcohol injection. In both types of studies, P rats are less sensitive than NP rats to alcohol's aversive effects.

Furthermore, P rats with histories of oral alcohol consumption, compared with alcohol-naive rats, experience less motor-impairing and aversive effects from high doses of alcohol, suggesting that they developed tolerance following chronic drinking. For example, in one study, P rats were given continuous access to an alcohol solution and water for 32 days. During this period, the rats increased their alcohol consumption by about 50 percent (see figure 3), indicating the development of tolerance. Following the period of oral alcohol self-administration, these rats, along with alcohol-naive P rats serving as control subjects, underwent conditioned taste aversion trials in which they drank a sweetened fluid they had never previously tasted, then immediately received an injection of alcohol. The injected doses were sufficiently high to produce conditioned aversive effects, as indicated by the rats' avoidance of the sweetened fluid upon subsequent exposure. The alcohol-exposed P rats, however, exhibited an attenuated conditioned taste aversion relative to the alcohol-naive P control rats. Thus, P rats developed tolerance to alcohol's aversive CNS effects just as they had developed a tolerance for alcohol's flavor in the taste reactivity tests. This tolerance to aversive CNS effects could contribute, at least in part, to the rats' high alcohol intake.

In addition to the rats' acquired reduction in sensitivity to the CNS effects of alcohol (termed "neuronal" or "functional" tolerance), prolonged periods of alcohol self-administration also increase the rate of alcohol metabolism in the liver (termed "metabolic" tolerance) in P rats. Rats of the NP line do not self-administer sufficient quantities of alcohol to develop metabolic tolerance. A comparison of alcohol-naive P and NP rats, however, found no differences in the rates at which alcohol is metabolized in the liver and eliminated from the body. Consequently, when the same amount of alcohol is administered to P and NP rats, both lines achieve the same BAC levels. Thus, the divergent drinking levels and reactions to alcohol seen in P and NP rats apparently are not attributable to differences in alcohol metabolism or elimination, but to differences in neuronal sensitivity to alcohol.

A series of studies has shown that P rats can develop acute tolerance to a single sedative-hypnotic dose of alcohol more quickly and/or to a greater extent than NP rats. That is, P rats recover more quickly than NP rats on a number of tests measuring the depressant effects of alcohol, including motor impairment, lowered body temperature, and regain of righting reflex (i.e., sleep time). Using a behavioral measure of alcohol-induced motor impairment, researchers observed that the tolerance P rats develop to a single dose of alcohol can persist for as long as 10 days, whereas such tolerance in NP rats, which is weaker in the first place, dissipates within 3 days. Differences in initial sensitivity and acute tolerance also have been found in other alcohol-preferring and -nonpreferring rodent lines and strains, such as the AA/ANA rat lines (Le and Kiianmaa 1988) and the C57BL/DBA mouse strains (Tabakoff and Ritzmann 1979). This finding indicates a strong association between tolerance and high voluntary alcohol consumption.

Traits Not Directly Related to Alcohol

In addition to alcohol-related traits, researchers are interested in detecting other behavioral and biological differences between rats genetically selected for high or low alcohol preference, with the hope that such differences may provide further clues to the genesis and perpetuation of alcoholism. Thus far, however, relatively few studies of this type have been conducted.

Among existing studies, results indicate that P rats exhibit higher spontaneous motor activity than do NP rats when placed in a new environment, but no difference appears between the lines when the environment is no longer novel. These observations concur with the high novelty-seeking personality characteristic that is noted in certain types of human alcoholics (Cloninger 1987). P rats also seem to be more anxious than NP rats on a number of behavioral tests of anxiety, which accords with the notion that alcohol may be self-administered to relieve tension and anxiety.

In addition, P rats exhibit a higher preference than NP rats for oral consumption of highly palatable, nondrug solutions, such as sucrose or saccharin, but intake of plain water and of sour and bitter-flavored solutions does not differ between P and NP rats. Because a preference for sweets highly correlates with high alcohol intake in numerous rodent lines and strains, investigators have suggested that the same, or overlapping, brain mechanisms may be involved in the reinforcement mediated by some drugs (e.g., alcohol) and other palatable substances (e.g., chocolate).

NEUROBIOLOGICAL DIFFERENCES ASSOCIATED WITH HIGH AND LOW ALCOHOL DRINKING

Biological studies of the P/NP and HAD/LAD rat lines have focused on the study of chemical mediators known as neurotransmitters[3] (i.e., neurochemistry) and the identification and mapping of groups of neurons that seem to have similar functions (i.e., neuroanatomy). Neurochemical studies implicate a subset of neurotransmitters with special roles in the control of alcohol-seeking behavior: 5-hydroxytryptamine (5-HT), also called serotonin; dopamine; gamma-aminobutyric acid (GABA); and the body's own opiatelike substances, the endogenous opioids (i.e., endorphins).

The 5-HT system appears to be a key component in the regulation of food consumption and mood as well as the development of alcohol tolerance. In addition, 5-HT modulates the release of dopamine, thereby directly affecting the dopamine system. In turn, the dopamine system plays a major role in motor activity, drug reinforcement, and the motivation to engage in several other behaviors that may be considered reinforcing or rewarding, such as eating and sex. GABA differs from 5-HT and dopamine in that it is not confined to certain neurons and pathways forming a system. Rather, it is found throughout the brain, conveying inhibitory signals and perhaps interacting with dopamine and other neurotransmitter systems in alcohol reinforcement. Endogenous opioids also act as inhibitory neurotransmitters and are released in response to stresses such as injury, childbirth, and vigorous exercise. In addition, opioids play a role in eating and drinking behaviors and, like GABA, appear to interact with dopamine and other neurotransmitter systems involved in alcohol reinforcement.

Several brain structures appear to participate in a postulated brain "reward pathway," including the ventral tegmental area, raphe nuclei, lateral hypothalamus, olfactory tubercle, nucleus accumbens, and medial prefrontal cortex and other limbic areas (see glossary, pp. 177–179). The function of this neural pathway system is to regulate behaviors motivated by "natural" rewards such as food, water, and sex. Scientists believe, however, that alcohol and other drugs of abuse (e.g., cocaine and morphine) function as reinforcers by imitating, facilitating, or sometimes blocking the various neurotransmitters involved in this system. Based

CRITERIA FOR AN ANIMAL MODEL OF HUMAN ALCOHOLISM

The criteria for an animal model of human alcoholism are as follows:

- Given a choice between an alcohol solution and another solution (such as water), the animal must voluntarily consume alcohol in an amount sufficient to produce meaningful blood alcohol concentrations (BAC's). The animal should drink alcohol solely for its pharmacological effects, not for its caloric value or its taste or smell.
- Following a period of chronic alcohol consumption, the animal must develop tolerance, as demonstrated by a reduction in the effects of the same dose of alcohol and the same BAC.
- Following a period of chronic alcohol consumption, the animal must develop alcohol dependence, as demonstrated by behavioral and biological responses characteristic of acute alcohol withdrawal and confirmation of alcohol's ability to act as a reinforcer (i.e., its ability to increase the chance that alcohol-seeking behavior will occur).

SOURCE: Adapted from Cicero, T.J. A critique of animal analogues of alcoholism. In: Majchrowicz, E., and Noble, E.P., eds. *Biochemistry and Pharmacology of Ethanol.* Vol. 2. New York: Plenum Press, 1979. pp. 534–535.

[3]For definition of this and other technical terms used in this article, see central glossary, pp. 177–179

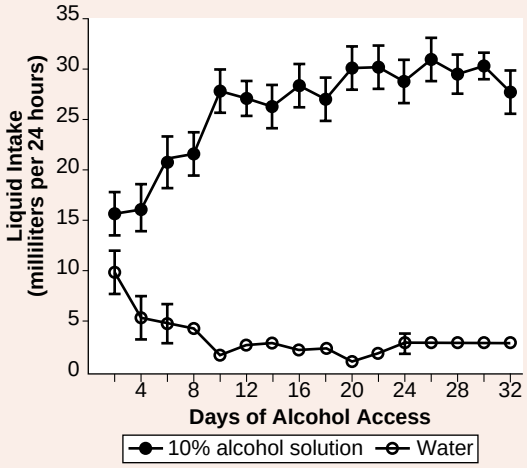

Figure 3 Volume of water (open circles) and concurrently available 10-percent alcohol solution (closed circles) consumed by 18 alcohol-preferring rats during 32 days of chronic alcohol drinking. Data shown are averages for consecutive 2-day periods. The increase in alcohol intake over successive days in these rats is consistent with the development of tolerance.

on neuropharmacological studies and on studies in which rats learn an operant response to electrically self-stimulate their brain "reward" areas, the neurotransmitters 5-HT, dopamine, GABA, and the endogenous opioids all have been implicated in the circuitries of the brain reward pathway (Wise 1980; Koob and Bloom 1988).

One of the most consistent neurochemical and neuroanatomical findings observed in P/NP and HAD/LAD rats is a deficiency of 5-HT in the alcohol-preferring lines (McBride et al. 1991; Li and McBride 1995). Compared with rats that drink little alcohol, the levels of 5-HT in rats that drink large amounts of alcohol are significantly reduced in several brain regions, including the frontal cortex, hippocampus, corpus striatum, thalamus, hypothalamus, pons-medulla, and nucleus accumbens. These regions are involved either in the brain reward pathway or in neural processes that are relevant to alcohol-seeking behavior (e.g., learning, memory, and tolerance development processes). Closer examination of the neurons in some of these brain regions (such as the frontal cortex, nucleus accumbens, and hippocampus) suggests that these differences may be caused by a relative scarcity of 5-HT–containing axons. Interestingly, research has shown that the decrease in 5-HT–containing axons in P rats results in compensatory up-regulation of 5-HT receptor activity (McBride et al. 1991; Li and McBride 1995). That is, the number or sensitivity of the target 5-HT receptors apparently increases to make up for the reduction in the availability of 5-HT.

An abnormality in one of the major components of the brain reward circuitry—the ventral tegmental area-nucleus accumbens dopamine system—also has been associated with high alcohol preference. Specifically, scientists have observed low levels of dopamine and chemicals associated with its breakdown in the nucleus accumbens and anterior striatum of P and HAD rats in the absence of alcohol. This finding is of interest, because abused drugs from many pharmacological classes (including stimulants, opiates, and sedatives), as well as low doses of alcohol, stimulate the release of dopamine in the nucleus accumbens. The P rats may be particularly sensitive to this alcohol-induced dopamine release in the nucleus accumbens. That is, alcohol consumption by P rats may be, in a sense, a regulatory action aimed at increasing the rats' abnormally low levels of dopamine in the accumbens. Because the 5-HT system plays a role in regulating the dopamine system in the brain reward pathway, the decreased 5-HT innervation noted in alcohol-preferring rat lines also may affect the function of the dopamine system in these rats.

In addition to stimulating dopamine release in the nucleus accumbens, alcohol's actions on neuronal activity also stimulate GABA receptors. Noting that anxiety-reducing drugs such as the benzodiazepines (e.g., Valium®) produce their effects by facilitating nerve signal transmission at synapses using the neurotransmitter GABA, researchers theorize that alcohol may produce its rewarding and anxiety-reducing effects via GABA neurons as well. Interestingly, studies in the P/NP and HAD/LAD rat lines have demonstrated a higher density of axon terminals containing GABA in the accumbens of the rats with high alcohol preference. This suggests a potential for increased GABA activity in P and HAD rats in an area of the brain involved in alcohol reinforcement.

The endogenous opioid systems also are involved in the regulation of alcohol drinking, as evidenced by the ability of opiate drugs to alter alcohol consumption. The endogenous opioid systems have been studied in P/NP rats (Froehlich and Li 1993) and in the Finnish AA/ANA lines (Nylander et al. 1994). The high- and low-alcohol-drinking rat lines differ in opioid activity in the absence of alcohol as well as in alcohol-stimulated opioid activity in the nucleus accumbens and pituitary gland (Froehlich and Li 1993; Nylander et al. 1994). However, the brain reward pathway of the Finnish AA rats does not appear to have low levels of dopamine or 5-HT (Korpi et al. 1988) as is the case with the selectively bred P and HAD rats and other rodent strains that consume large amounts of alcohol (see Li and McBride 1995 for a review).

The apparently discordant findings from the comparison of P/NP and AA/ANA rat pairs may result from variances in the foundation stocks from which the two pairs of genetically selected lines were derived. If so, selective-breeding experiments may achieve the same endpoints (e.g., high and low alcohol preference) by altering different brain mechanisms. Such findings may reflect the multiplicity of

mechanisms that may contribute to high alcohol intake. Indeed, the challenge to alcohol researchers and clinicians is that alcoholism results from the interaction of many biological factors (inherited and environmental) and is not a unitary phenomenon.

SIGNIFICANCE

Studies with rats selectively bred for alcohol preference or nonpreference support several hypotheses on factors that may be associated with alcoholism in humans. For example, the demonstrated sensitivity of alcohol-preferring rats to the stimulatory effects of low to moderate alcohol doses is in agreement with the contention that these effects are important in the initiation and maintenance of alcohol drinking. The alcohol-preferring rats also show an innate insensitivity to the aversive effects of alcohol at high doses, which may tend to limit the amount of alcohol consumed by rats that are normal or genetically selected for low alcohol preference. Tolerance development to these aversive effects, which occurs to a greater extent in the alcohol-preferring rats, also may encourage increased alcohol intake. Furthermore, behavioral research with selectively bred rat lines indicates that individual differences in responsiveness to alcohol can be heritable traits and that these animal models are valuable tools for investigating neural mechanisms relevant to alcohol-seeking behavior.

These animal models also have provided the underpinning for a new direction in the treatment of alcoholism and alcohol abuse: testing pharmacotherapies related to the postulated neural reward mechanisms. The 5-HT and opioid systems have long been implicated as having a role in alcohol drinking (Myers and Melchior 1977; Altshuler et al. 1980), and basic research findings, such as the line differences in the brain reward systems of selectively bred rats, have provided a theoretical basis for clinical studies on the effects of drugs that may influence activity in these systems. Various agents that alter 5-HT, dopamine, GABA, and opioid functioning decrease alcohol consumption in animal models, including selectively bred alcohol-preferring rats (see Lumeng et al. 1995 for a review). For example, fluoxetine (Prozac®) is an antidepressant drug that inhibits the reuptake of 5-HT by the neurons that secrete it and thereby facilitates 5-HT activity. Fluoxetine has been found to significantly reduce alcohol intake in populations of heavy drinkers (Naranjo et al. 1986), but clinical trials to date have not shown fluoxetine to be effective in treating alcoholism (Litten et al. 1996). Nevertheless, some alcoholic subtypes, such as those with comorbid depression, may respond favorably to fluoxetine. The opioid blocker naltrexone (ReVia™ or Trexan®) also has been tested in clinical trials with alcoholics (O'Malley et al. 1992; Volpicelli et al. 1992). Subjects receiving naltrexone showed decreases in the mean number of drinking days per week, frequency of relapse, desire to drink (i.e., craving), and the alcohol-induced subjective "high." Such results suggest that these pharmacological manipulations decrease alcohol's reinforcing effects. The fact that drugs such as fluoxetine and naltrexone reduce alcohol intake in both rodents and humans supports the predictive validity of the use of genetic animal models for evaluating therapies that can potentially reduce or prevent excessive alcohol consumption. ■

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