Integrating Genetic and Behavioral Models in the Study of Substance Abuse Mechanisms

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INTRODUCTION

Over the past several years it has become broadly accepted that genetic factors play an important role in determining the robustness of certain drug-seeking behaviors. However, relatively little effort has been made to integrate the elegant methods established in behavioral genetics and the sophisticated techniques that form the basis for studying operant behavior. This chapter will hopefully serve to aid in this effort by reviewing some of the findings obtained in studies that have combined these approaches, and by illustrating how genetic methods can be used as a tool for achieving a greater understanding of the behavioral mechanisms of substance abuse.

A number of years ago the author and his colleagues began a series of studies that demonstrated genetic differences in the reinforcing effects of ethanol (EtOH) and other drugs. In the initial study, EtOH-reinforced behavior was examined in ALKO Alcohol-Accepting (AA) and Alcohol Non-Accepting (ANA) rats, animals that had been selectively bred for high versus low EtOH preference using a home cage, free access, two-bottle choice procedure, respectively (Ritz et al. 1986). It was found that, under a fixed ratio (FR) 1 schedule of reinforcement, AA rats would press a lever for 5.7 percent (w/v) EtOH more frequently than they would for water. Indeed, when water was substituted for the EtOH their operant behavior extinguished over a period of a few days, but was quickly reestablished when EtOH was reintroduced. This demonstrated that EtOH was functioning as a positive reinforcer in these animals. Conversely, the ANA rats showed no differences between responding for EtOH and water. While this was consistent with their low preference, this was the first demonstration that these two lines actually differed in positive reinforcement from EtOH.

That study and those which followed (Elmer et al. 1986, 1987*a*, 1987*b*, 1988, 1990; George 1987, 1990; Ritz et al. 1989*a*, 1989*b*; Suzuki et al. 1988) illustrate a number of important points. One is

the importance of control for genetic variability in experimental research. For example, it is rare to find an experiment in which the subjects consisted of one rhesus monkey, one beagle dog, and one rat. Control for species differences has been standard practice for many years, and represents a partial control of genetic variability. However, within a species, less attention has been given to further genetic definition and control. An important perspective on this is that using genetically undefined animals is akin to using an undefined "stimulant" drug. Scientists do not say subjects self-administered a stimulant; instead, they are very precise in defining the actual chemical used, such as cocaine-HCl. Similarly, researchers can exercise the same amount of experimental control over the tissue with which the drug is interacting by precisely controlling genotype, and using "reagent grade" subjects. To the extent that scientists are able to control for such variability, they should do so.

Second, a major advantage of genetic control and the use of genetically defined subject populations is that findings contribute to and become a part of an ever-growing database for use in correlational analyses. For example, the data that are obtained when using readily available inbred rodent strains add to the existing database for that genotype, and may be repeatedly used by the original investigator as well as by other investigators.

There are additional advantages to using genetic methods, but the two described above form a significant portion of the basis for incorporation of this genetic approach into behavioral research. The remainder of this chapter is devoted to describing some of the ways in which these genetic factors may be used to aid in understanding the behavioral as well as biochemical mechanisms of substance abuse.

REINFORCEMENT: A UNIQUE EFFECT OF CERTAIN DRUGS

One question that researchers have been interested in exploring is the relationship among different responses to drugs, such as reinforcing effects, depressant effects, stimulant effects, etc. This question can be approached in a systematic manner using a number of genetic methods. Through the use of genetic correlational analyses, genotypes that differ for a given trait can be used to test associations between that trait and any other traits hypothesized to be causally related. A lack of correlation indicates that the measures studied are not mechanistically related. A strong positive correlation, while not conclusive, provides supportive evidence that the measures are

causally related and mediated at least in part by common genetic mechanisms.

For example, in developing an effective animal model of drug taking, it is important to understand the degree of relationship among various methods of measuring alcohol or other drug intake. In the area of alcohol consumption, it is important to determine the degree to which homecage preference paradigms and operant drug reinforcement studies measure the same or similar phenomena, both behaviorally and biochemically. Animals that prefer EtOH when given a choice between a drug solution or water in a 24-hour access homecage testing situation may or may not work to a significant extent to obtain the drug under more rigorous and constrained operant chamber conditions. Similarly, lack of drinking in a preference paradigm may or may not suggest lack of reinforcement under other operant conditions.

Reinforcement Versus Preference

The relationship between reinforcement from EtOH and EtOH preference has been estimated by comparing EtOH-reinforced responding using operant procedures and EtOH preference scores from a number of rodent genotypes (George 1990; George and Ritz 1993). The results suggest a moderate but not significant positive relationship between these two measures of EtOH drinking (figure 1A). The most notable exceptions to a general positive relationship are Long Sleep (LS) mice, which show a high degree of reinforcement from EtOH but very low EtOH preference, and Non-Preferring (NP) rats, which are reinforced by EtOH even though they have been genetically selectively bred for having low EtOH preference.

Thus, while preference paradigms may provide a rapid method useful in initial screening of subjects, this model does not appear to be a good predictor of positive reinforcement from EtOH. There are a number of possible reasons for this lack of association. One is that preference studies typically are confounded by taste and prandial influences, since the measure of drinking is based upon consumption over time with food concurrently available. A second is that preference paradigms may not be sufficiently sensitive to detect intake of significant amounts of EtOH in animals whose absolute levels of intake are limited by neurosensitivity factors, such as the LS mice, but for which EtOH is reinforcing (Elmer et al. 1990). A third possible reason is that in preference studies that do not

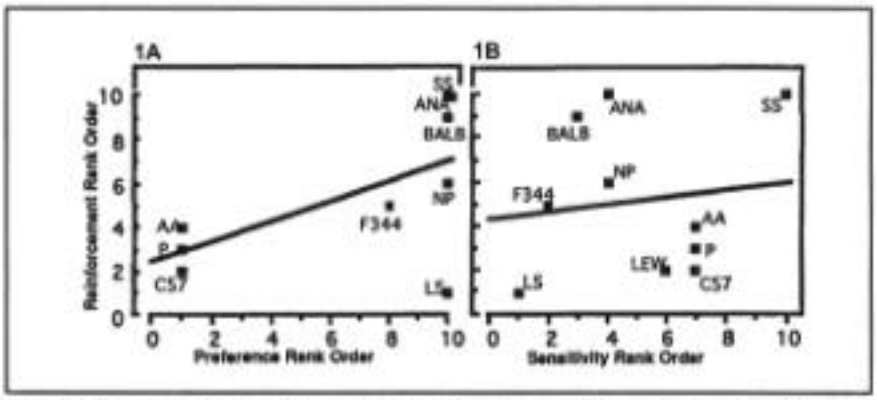

FIGURE 1. *Comparison of rank order for EtOH reinforcement versus EtOH preference (T=0.39) (1A) and EtOH reinforcement versus neurosensitivity to EtOH defined by duration of loss of the righting reflex (T = 0.12) (1B) for several rat and mouse genotypes. Linear regression lines are included for illustrative purposes. Concordance between measures is based upon Kendall's Tau coefficient (T) for rank-order correlations.*

SOURCE: George (1990).

incorporate exposure to significant amounts of the drug through some form of initial training, low preference may be due to avoidance of the drug solution for reasons related to taste or smell, resulting in a situation where consumption is too low for the animals ever to experience the postabsorptive interoceptive cues related to initiation of reinforcement. Thus, preference may be a permissive factor, particularly important for drug taking via the oral route, which allows the organism to consume significant amounts of a drug. Consumption of large doses over a sustained period of time may then result in association of the drug-taking behavior with its postabsorptive, presumably central effects, and the drug may then come to serve as a positive reinforcer. However, preference per se does not appear to be equatable with reinforcement.

Reinforcement Versus Neurosensitivity

The relationship between reinforcement from EtOH and neurosensitivity to EtOH has also been studied. In this context, neurosensitivity to EtOH is more specific than sensitivity to EtOH in a broad sense, in that differences in neurosensitivity implies a difference in some aspect of central nervous system (CNS) function, in the absence of any detectable pharmacokinetic or metabolic differences. For example, the highly neurosensitive LS and the

highly neuroinsensitive Short Sleep (SS) mice show extreme differences in response to the depressant effects of EtOH as measured by duration of loss of the righting reflex; yet, Elmer and colleagues (1990) showed that EtOH could readily function as a positive reinforcer in LS mice but not in SS mice. This outcome is the opposite of what would be expected if reduced neurosensitivity to EtOH was a primary factor in establishing EtOH as a reinforcer, and when combined with other findings (figure 1B) indicates that there appears to be virtually no relationship between propensity to self-administer EtOH and this measure of neurosensitivity to EtOH (George 1990). Thus, while neurosensitivity may be a limiting factor in terms of absolute intake of EtOH, neurosensitivity, at least as defined by the depressant effect of duration of loss of the righting reflex, does not appear to influence the ability of EtOH to function as a positive reinforcer.

Other recent findings suggest that reinforcement from EtOH also is not related to the severity of withdrawal from EtOH nor to the locomotor stimulant effects of EtOH. EtOH has a broad dose-response curve and produces many effects, any of which could be related to or predictive of drinking and/or reinforcement from EtOH. For example, neurosensi-tivity is important in determining the severity of EtOH withdrawal. A common measure of EtOH withdrawal is the occurrence of seizures, since many animals, including humans, exhibit seizures during EtOH withdrawal (McSwigan et al. 1984). These EtOH withdrawal convulsions are quantifiable and positively correlated with dose and duration of EtOH exposure (McSwigan et al. 1984). Interestingly, when LS and SS mice were tested for EtOH withdrawal severity, SS mice showed the most severe withdrawal seizures (Goldstein and Kakihana 1975). Since SS mice do not appear to prefer or be reinforced by EtOH, while LS mice are readily reinforced by this drug (Elmer et al. 1990), it is possible that genes related to severity of EtOH dependence or withdrawal reactions may be involved in mediating at least a portion of EtOH's rewarding effects.

Recently, mice have been selectively bred to be either Withdrawal Seizure Prone (WSP) or Withdrawal Seizure Resistant (WSR) to EtOH withdrawal as assessed by the extent of handling-induced convulsions following establishment of physical dependence on EtOH and subse-quent withdrawal of this drug (Crabbe et al. 1983). Currently, these WSP and WSR mice differ by some tenfold in severity of withdrawal seizures, and by implication, in their degree of physical dependence on EtOH (Kosobud and Crabbe 1986). It has also been shown that

differences between these lines with regard to CNS excitability are specific to EtOH (McSwigan et al. 1984).

The relationship between EtOH-reinforced behavior and physical dependence on EtOH as measured by withdrawal severity has been examined by using operant methodology to test for reinforcement within the WSP and WSR mice (Barbera et al. 1994). EtOH did not serve as a reinforcer for any of the groups. However, further analysis revealed individual differences in responding within each of the four groups (WSP1, WSP2, WSR1, WSR2), as at least one animal from each group did show EtOH-reinforced behavior. These individual differences did not show any systematic pattern within or between groups, suggesting that genes regulating the rewarding effects of EtOH are independent of genes mediating withdrawal severity and appear to be segregating randomly within and between groups. These findings indicate a lack of relationship between the traits of withdrawal severity and the reinforcing effects of EtOH and are consistent with a lack of association between propensity to develop physical dependence on EtOH and propensity to find this drug reinforcing. There are several possible reasons for the absence of group effects in this study. It is possible that there was a problem with the procedure or that animals were inappropriately trained. This seems unlikely since the procedure used is similar to that used successfully in several previous studies with mice (Elmer et al. 1986, 1987*a*, 1987*b*, 1988, 1990); similar studies were simultaneously being conducted in the author's laboratory in which robust reinforcement effects were found; and all animals showed elevated blood EtOH concentrations (BECs) during the training phase. A second possibility for the absence of robust reinforcing effects of EtOH is simply that none of the animals were in fact reinforced by EtOH. This also seems unlikely since some animals did achieve BECs above 100 mg/dL within a brief 30-minute session. These levels are typically associated with overt behavioral effects of EtOH, and were achieved in the absence of any prandial or postprandial confounds since food was not available prior to or during the test sessions. A third possible explanation appears correct based upon the findings obtained. The data indicate that some individual animals within each selection line were indeed positively reinforced by EtOH, but these individual animal data were masked by those of other animals within each selection line group, which were not reinforced. When combined as group averages, data from the reinforced and nonreinforced animals effectively canceled out one another, such that the group averages indicated an overall lack of positive reinforcement.

With the exception of those genes mediating EtOH withdrawal severity, the genotypes of the mice used in this study should represent a sample from a randomly segregating population with substantial heterogeneity. Since mice are capable of showing reinforcement from EtOH (Elmer et al. 1986, 1987*a*, 1987*b*, 1988, 1990), and since the WSP and WSR populations are derived from several inbred strains, which include EtOH drinkers and EtOH avoiders (Crabbe et al. 1983), some individual animals would likely show reinforcement, some might show avoidance, and some might show no effect, consistent with the third explanation for the lack of robust group effects in this study. If withdrawal severity is not indicated in EtOH reinforcement, then EtOH reinforcement becomes an independently segregating phenomenon and should be represented, in a random pattern, across all genotypes. While there are several factors that could contribute to this type of response distribution, the data are consistent with the conclusion that the genes mediating the reinforcing effects of EtOH are segregating independently of genes mediating the withdrawal effects of EtOH.

One further issue is whether animals selected for withdrawal seizure proneness or resistance must experience their selected phenotype to allow the genes mediating the phenotype to exert pleiotropic effects on other phenotypes, such as EtOH-reinforced behavior. However, if genes mediating withdrawal seizure severity are exerting pleiotropic effects on EtOH drinking or reinforcement, they should do so regardless of the experience or naivete of the subject with regard to the selection phenotype. Thus, the present findings suggest that there is little influence of withdrawal seizure genes, as opposed to withdrawal seizure experience, on drinking and reinforcement.

In another study (Sanchez et al. 1994), operant self-administration of EtOH was examined in mice selectively bred for high locomotor stimulation in response to EtOH injection (FAST mice) and mice selectively bred to produce little locomotor stimulation response to EtOH (SLOW mice). This study examined EtOH consumption and rein-forcement in replicate lines of mice that have been selectively bred for differential locomotor stimulation in response to EtOH. This particular genetic trait of the animals allows for a test of the relationship between locomotor stimulation and EtOH reward.

There were no differences between the selected lines in the extent to which the animals would self-administer EtOH. None of the groups of mice showed EtOH-reinforced behavior, although within each group there were both responders and nonresponders. These findings

provide initial evidence that the genes mediating locomotor stimulant effects of EtOH are distinct from those associated with the rewarding effects of this drug.

When combined with similar data from other drugs, evidence suggests that the reinforcing effects of drugs comprise a unique dimension of effect that is not the result of, nor due to, causal genetic relationships with other drug effects. Reinforcement appears to be a unique effect associated with a subset of psychoactive compounds, and determination of the causes of and controls for this effect requires direct study of drugs as reinforcers and not indirect implications of reinforcement based upon other possibly correlated measures.

REINFORCEMENT: COMPRISED OF MULTIPLE COMPONENTS

Research findings from several areas of research suggest that there exist several related but distinct dimensions of drug-seeking behavior, and that these dimensions can be separated for detailed analysis of their contributions to substance abuse. For example, studies of EtOH-reinforced behavior in animals genetically selected for high or low EtOH preference indicate that EtOH-reinforced behavior may be influenced by not only the intrinsic rewarding effects of the drug, but also factors that determine motivation to work for the drug (i.e., incentive value). AA rats, genetically selected for maximal EtOH consumption in a two-bottle choice paradigm, while reinforced by EtOH, will not exhibit prolonged responding in operant paradigms requiring learned sequences of behavior to gain access to EtOH solutions (Ritz et al. 1986, 1989*a*, 1989*b*). For these rats, as FR size increases above FR1, response rates decrease substantially, especially when compared to response rates of other "alcohol preferring" rats, such as the EtOH-Preferring (P) rat line. In similar recent experiments, EtOH-reinforced behavior was studied in EtOH P and High Alcohol Drinking (HAD) rats and NP and Low Alcohol Drinking (LAD) rats. Genetic differences in EtOH-reinforced behavior were observed. EtOH served as a strong positive reinforcer for P rats, a slightly less efficacious reinforcer for NP and HAD rats, and was not shown to be reinforcing for LAD rats (Ritz et al. 1994*a*, 1994*b*; Samson et al. 1988; Waller et al. 1984). These findings are consistent with results discussed earlier, indicating that EtOH drinking in a preference paradigm is not highly predictive of the reinforcing effects of EtOH. NP rats, like P rats, will exhibit EtOH-reinforced responding under operant conditions. Further, preferring HAD rats exhibit significantly fewer responses for EtOH under a range of

concentrations and FR sizes relative to their P rat counterparts, even though both lines have been genetically selected for EtOH preference using a home-cage, two-bottle choice paradigm, and rats from both lines consume similarly high quantities of EtOH on a gram/kilogram/day basis in a preference test.

In addition, these results illustrate genetic differences with regard to the propensity of animals to maintain EtOH-reinforced behaviors as work requirements were increased. As shown in table 1, P rats are high preferring, reinforced by EtOH, and show persistent responding under increasing workloads, while high preferring HAD rats are more modestly reinforced and show little persistence in responding for EtOH under conditions of high workloads. It is interesting to note that while the parental stocks for these two lines differed, the similar selection processes used produced rats that consume similar amounts of EtOH when tested in a two-bottle preference task. NP rats, on the other hand, are very low preferring, but show EtOH-reinforced responding for EtOH equivalent to that of the HAD rats when only one lever press was required. Interestingly, NP rats also show a moderate level of persistence in responding, and this persistence is much greater than that seen in HAD rats. Finally, the low preferring LAD rats are not reinforced by EtOH and show no significant persistence in responding for EtOH (Ritz et al. 1994*a*, 1994*b*).

Thus, although EtOH can be readily established as a reinforcer for AA, NP, and HAD rats, rats from these lines appear to lack specific motivational factors that would facilitate continued responding under conditions requiring higher workloads. These data suggest that continued chronic abuse of a drug requires not only specific reinforcing effects of a drug, but also motivational factors, which appear to vary independent of response to reinforcing effects. Taken together, the results suggest that reinforcing effects of EtOH may be due to the influence of multiple components, including: (1) an intrinsic permissive factor contributing to EtOH preference, (2) direct rewarding effects, and (3) motivational factors.

TABLE 1. *Qualitative expression of preference, reinforcement, and persistence for EtOH-seeking in rats selectively bred for high or low EtOH preference.*

Genotype	Preference		Reinforcement		Persistence
P	+++		+++		+++
NP	---		++		++
HAD	+++		++		-
LAD	---		---		---

KEY: + = relative degree of positive performance (e.g., P and HAD rats each have three plus symbols under the preference column to indicate highly similar preference tests results and to indicate higher preference than the other listed genotypes). å = relative degree of nondrinking or avoidance. These symbols indicate a qualitative relationship rather than an absolute quantitative one.

SOURCE: George and Ritz (1993).

REINFORCEMENT: A GENERALIZABLE EFFECT

Another important question in substance abuse that can be effectively addressed using genetic correlation methods is whether propensity to self-administer one drug, such as EtOH, shares common genetic control with the propensity to self-administer other drugs, such as cocaine or opiates. This "commonality" question can be addressed by measuring the extent to which animals from various inbred strains self-administer a variety of drugs. Researchers in the author's laboratory have begun to address this commonality question by examining operant self-administration of alcohol, cocaine, and opiates in several mouse and rat strains (George and Goldberg 1989). The potent opioid agonist etonitazene (ETZ) has been established as a reinforcer in Lewis rats and C57BL/6J mice, but not for F344 rats or DBA/2J mice. F344 rats and DBA mice in fact tend to avoid ETZ solutions. Similar results have been obtained with cocaine. Lever-press responding by Lewis rats and C57BL/6J mice was high for cocaine but low when only water was present as the reinforcer, whereas responding by F344 rats was minimal and occurred sporadically. Overall, the results suggest that a high degree of qualitative commonality exists across these genotypes and drugs, as summarized in table 2 (George 1991).

TABLE 2. *Summary of qualitative commonality.*

Genotype	Alcohol	Opiates	Cocaine
Rats			
LEW	+++	+++	++
F344	+å	åå	å
Mice			
C57BL/6J	+++	+++	+++
DBA/2J	åå	åå	NA

KEY: + = relative degree of positive reinforcement; å = relative degree of nonreinforcement or avoidance. Three symbols is maximum response relative to all genotypes tested. NA = Data not available.

SOURCE: George (1991).

These initial results from studies of drug self-administration across different drugs and genotypes suggest that genotypic patterns of reinforcement from EtOH may correlate highly with patterns of reinforcement from cocaine and opiates. Thus, drug-seeking behaviors maintained by EtOH, cocaine, and opiates may have at least some common biological determinants. The fact that this significant level of commonality or generalizability exists would suggest that reinforcement, while a unique drug effect, is a broad-based phenomenon defined by the responsivity of the individual organism to this effect, and may be generalizable across substances.

Thus, the integration of behavioral genetic and operant methodologies has potential for increasing researchers' understanding of the contributions and interactions of genetic and environmental factors in determining drug-seeking behavior, and in distinguishing between various aspects of reward and motivation as they contribute to substance abuse. Further, the demonstration of genetic differences in animal models of drug-seeking behavior suggests that there may exist human populations with differing degrees of biological risk for drug abuse.

Thus, reinforcement is a unique dimension of effect that occurs following administration of certain psychoactive drugs; it appears to be composed of multiple, distinct components; and there appears to

be a substantial degree of generalizability of reinforcement within a given genotype across drugs.

USING GENETIC METHODS TO DETERMINE ASSOCIATED BIOCHEMICAL CORRELATES OF DRUG-SEEKING BEHAVIOR

The density of serotonin (5HT) receptors and the influence of 5HT systems have been implicated in alcohol preference and reinforcement. The author has recently begun a systematic investigation into the role of 5HT systems in the operant reinforcing actions of EtOH. Through the use of mice from two genetically similar strains, which differ in their densities of 5HT receptors, genetic influences on alcohol-reinforced behavior that may be mediated by $5HT_2$ receptors have been shown. C57BL/6J mice have significantly lower $5HT_2$ receptor densities than do C57BL/6ByJ mice (figure 2). In order to explore differences in EtOH consumption between these two strains, operant conditioning studies were used to examine the self-administration of EtOH.

The purpose of experiment one was to determine if alcohol would serve as a reinforcer, and to what extent, for these genetically different but similar mouse strains. Subsequently, by increasing the number of lever presses needed to receive EtOH reinforcement, experiment two attempted to establish how much work the mice would be willing to perform in order to obtain access to a solution of 8 percent EtOH. The responses of the two strains at different EtOH concentrations were then examined.

Using standard food-induced training procedures, mice were exposed to a series of increasing EtOH concentrations (0, 2, 4, 5.7, and 8 percent w/v) in response to a lever press during repeated daily 30-minute test sessions. Subsequently, the amount of food received before each session was gradually reduced to zero. To determine if EtOH served as a reinforcer, the liquid consumed was alternated between 8 percent EtOH and vehicle (0 percent). To test if EtOH served as a reinforcer under

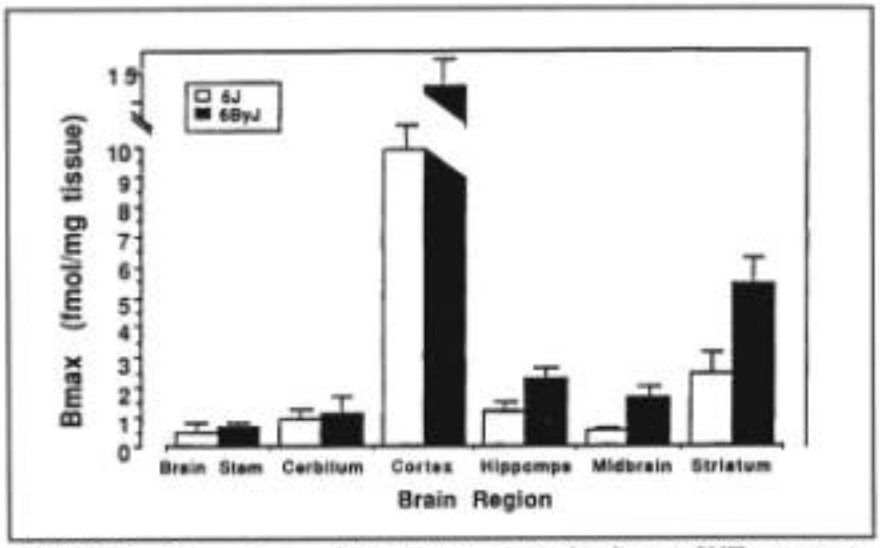

FIGURE 2. *Comparison of tritiated ketanserin binding at $5HT_2$ receptors across several brain regions in C57BL/6J and C57BL/6ByJ male mice. Cerbllum = cerebellum. Hippcmps = hippocampus. Differences significant ($p < 0.05$) in hippocampus, midbrain, and striatum.*

varying FR conditions, the number of lever presses required to obtain a reinforcement was increased in order from 1 to 2, 4, 8, 16, 32, 64, and 128. The concentration of EtOH was also manipulated in a subsequent experiment.

The differences in BECs and trials completed between the two strains were significant during training. The highest group BEC observed was 264 mg/dL in the C57BL/6J mice, and the highest group BEC observed for the C57BL/6ByJ mice was 150 mg/dL. None of the groups showed a pattern of responding consistent with extinction or the development of taste aversion. At FR1, the C57BL/6J (low $5HT_2$ receptor density) mice completed more trials (figure 3) and had higher BECs than the C57BL/6ByJ mice. Trials completed, BECs, and lever presses were all higher for the C57BL/6J (low $5HT_2$ receptor density) mice than for the C57BL/6ByJ mice in the FR conditions (figure 4). No differences were found between the groups when the EtOH concentration was varied.

The results of these experiments provide evidence that the density of 5HT receptors may influence the extent to which EtOH serves as a

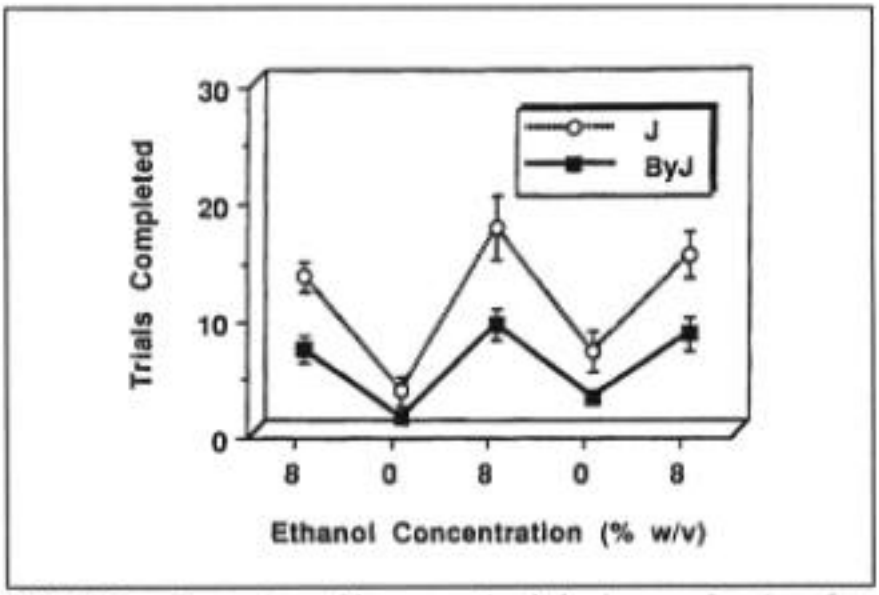

FIGURE 3. *Comparison of lever-pressing behavior as a function of EtOH or vehicle availability in C57BL/6J and C57BL/6ByJ male mice.*

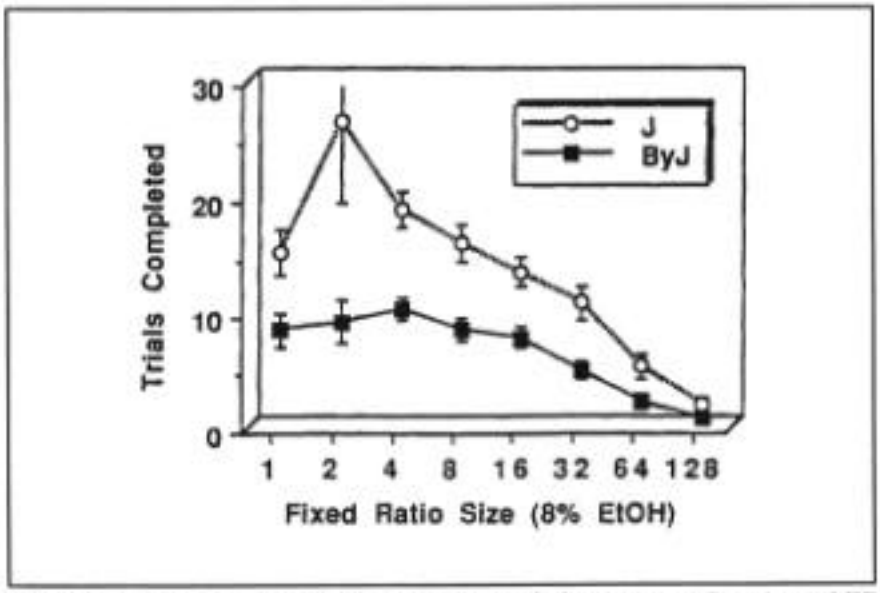

FIGURE 4. *Comparison of lever-pressing behavior as a function of FR size in C57BL/6J and C57BL/6ByJ male mice.*

reinforcer. The results of experiment one indicate that alcohol served as a reinforcer for both the C57BL/6J (low $5HT_2$ receptor density) and the C57BL/6ByJ mouse strains. The consumption of EtOH by the C57BL/6J mice, however, was in all instances significantly greater than alcohol consumption by the C57BL/6ByJ mice. The C57BL/6J mice appear to work harder in general than the C57BL/6ByJ mice for EtOH reinforcement.

Because these two strains of mice are so similar genetically and differ at only a few loci, the results suggest that the density of $5HT_2$ receptors present may influence motivational factors associated with the reinforcing properties of alcohol. Animals with greater densities of $5HT_2$ receptors showed less persistence in responding for EtOH, even though all animals were reinforced by EtOH to some extent. This conclusion supports the hypothesis that predisposition to alcohol abuse involves multiple genetic factors, and that some of those genetic factors may be related to $5HT_2$ receptor function.

CONCLUSIONS

For too long, geneticists have been studying the role of genetic factors in conveying susceptibility to drug abuse, while behavioral scientists have been dissecting the roles of learning and behavioral patterns in initiating and maintaining drug use, both with little recognition of the other's contributions to science. Much could be gained, however, by combining these fields into a more integrated view of the problem of addiction. Behavioral scientists could achieve improved control over variation and subsequent error in their studies by incorporating the use of better-defined subjects in terms of genetic heritage. For example, the use of Sprague-Dawley rats conveys little genetic control relative to the precise behavioral measurements used in most behavioral pharmacology experiments. Much better experimental control over subject variance could be easily obtained by choosing a more precisely defined experimental subject, such as a rat from a truly genetically inbred strain, such as the Lewis strain. By using genetically identical subjects, it should be readily apparent to the reader that any resulting variation in response to a drug or other experimental challenge would be the result of "environmental" variance and that it could be explored parametrically without the confounds of undefined "genetic" variance acting to increase the overall variation and "noise" in one's studies. Years ago, in the absence of evidence to the contrary, it was simple for behaviorists to state that any subject will respond to a positive reinforcer under the appropriate learning conditions. But it is now clear that this is not

the case, and that while the environmental conditions are important for the expression of a trait, there are also biological, i.e., genetic constraints that greatly affect the ability of subjects to perform even the most species-appropriate learned tasks.

Thus, genetic methods have great potential for increasing scientists' understanding of addictions, especially if these methods are integrated into other established approaches. The objectives of this integrative approach are to identify, at the molecular, cellular, and behavioral levels, those factors that maintain drug-taking behaviors. Issues such as the biochemical sites of drug reinforcement, the relationship between drug preference and drug reinforcement, and the commonality of self-administration behavior across drugs can be effectively addressed using behavioral genetic approaches. The use of genetic models in this area is not only improving researchers' understanding of genetic contributions to addiction, but can also aid in understanding the environmental factors involved in vulnerability to drug abuse.

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