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The AA and ANA rat lines, selected for differences in voluntary alcohol consumption

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Summary. The offspring of rats that voluntarily select larger quantities of alcohol are heavier consumers of alcohol than the offspring of rats that tend to avoid it. Such selective breeding, repeated over many generations, was used to develop the AA (Alko, Alcohol) line of rats which prefer 10% alcohol to water, and the ANA (Alko, Non-Alcohol) line of rats which choose water to the virtual exclusion of alcohol. In addition to demonstrating the likely role of genetic factors in alcohol consumption, these lines have been used to find behavioral, metabolic, and neurochemical correlates of differential alcohol intake. Some of the line differences that have been found involve the reinforcing effects of ethanol, the changes in consumption produced by alcohol deprivation and nutritional factors, the behavioral and adrenal monoamine reactions to mild stress, the development of tolerance, the accumulation of acetaldehyde during ethanol metabolism, and the brain levels of serotonin. It is hoped that these studies will lead to a better understanding of the genetically-determined mechanisms that influence the selection of alcohol.
Key words. AA and ANA rats; alcohol consumption; genetic selection; neurochemistry; stress; alcohol withdrawal; behavior; ethanol metabolism.

Introduction

A rapidly developing area in alcohol research is the study of genetic factors underlying alcoholism. It is now generally accepted that genetic factors are responsible for a predisposition in some people for becoming alcoholics. Genetics alone does not, of course, cause alcoholism. Environmental factors are necessary for the manifestation of the disease: at the very least, the individual must first have experience with alcohol drinking, probably for many years, before any symptoms of alcoholism are shown. Genetic factors are important, however, in help-

ing to determine why some people who drink alcohol eventually become alcoholics.

The demonstration of the importance of genetic factors in human alcoholism has come primarily from studies involving adoption and twins[8,40]. Another important early contribution to this research, and probably an impetus for deciding to conduct the difficult human studies, has been the demonstration that genetic factors are important for determining the alcohol consumption of laboratory animals.

Early studies showed that existing inbred strains of mice and rats differed in their voluntary ethanol selection. A better method, however, for determining whether genetic factors are important is to breed the heavier drinkers within a normal heterogenous population together and to breed the lower drinkers together and then see if the offspring display differential drinking behaviors similar to their parents. This was done with rats over 20 years by Kalervo Eriksson[11,12] in the Alko Research Laboratories in Helsinki, and the results clearly indicated that genetic factors do influence the animals' alcohol consumption.

A natural extension of this method is to continue the selective breeding after the first generation, and thus develop selected lines of high and low alcohol drinkers. Two such programs were started many years ago, leading to the AA/ANA rat lines[11] at Alko and the UCHA/UCHB rat line[42] at the University of Chile. A similar program under the direction of T.-K. Li at the University of Indiana has resulted in the P/NP lines and the HAD/LAD lines[39]. Each of the selective breeding programs has succeeded in producing a line of rats that prefers moderate alcohol solutions to water. After extensive research, it has been concluded that such high drinking lines fulfill most of the requirements for being an animal model of human alcoholism[28,38].

The existence of these selected lines of high and low alcohol drinking rats has also been instrumental in generating a new branch of alcohol research with laboratory animals: the search for correlates of the differential alcohol drinking and, with them, the attempt to determine what genetically-controlled physiological mechanisms are responsible for making some rats drink large amounts of alcohol, and what mechanisms cause others to reject practically all alcohol.

As a follow-up to earlier reviews on the AA and ANA rats[10,17,18,22], the present review covers more recent developments, primarily since the revitalization of these lines in 1983. The procedures employed in the development and the revitalization of the AA and ANA lines will first be described. Then we will present briefly all of the more recently discovered differences between these lines: the behavioral differences seen in sober animals, the physiological differences without alcohol, the behavioral differences in the reactions to alcohol, the physiological differences in the effects of ethanol, and the differential effects of various procedures on alcohol drinking. These are presented without speculation about the possible relevance to alcohol selection, but the following section discusses some of the hypotheses that might account for differential alcohol preference. Finally, some of the ways these lines might be used in the future are presented.

Procedures used in the development of the AA/ANA lines

The animals from which the AA/ANA lines were developed were albino rats of Wistar origin that had been systematically bred using as distant relatives as possible for more than 20 generations[11,12]. Large individual variations were found when they were first tested for voluntary alcohol intake.

The methods used for selection of AA and ANA breeders have been described in detail earlier[12]. The alcohol drinking behavior is tested in every generation, beginning when the animals are 3 months old. Food is available at all times. Ethanol solution (10% v/v) is provided as the sole drinking fluid for 10 days, and then the animals are given a free choice between it and tap water for 3 weeks, with the consumption during the third week being used in the selection of breeders. The highest drinking female and male from each AA litter are selected as the 40 AA breeders and mated across litters, following the procedure of within-family selection. The same procedure is used with the ANAs except the 40 lowest drinkers are chosen. The population size in both lines has varied between 80 and 140. Alcohol consumption has been measured both as the ratio of ethanol solution to total fluid intake (E/T = preference) and as the ethanol intake per body weight (g/kg); the percentage of energy obtained as ethanol was later added as a third measure[18].

Despite the use of outbreeding and the relatively large breeding populations, some problems emerged that were apparently related to the loss of heterozygosity, such as poor fertility and increased susceptibility to infection[16]. Consequently, a program of revitalization was started: the F_{37} AA and ANA breeders were crossed with F_1 hybrids from Brown Norwegian and Lewis rats[22,24], and the selection for differential alcohol consumption resumed with the F_{39} generation. This resulted in an increase in litter size and fertility in the lines. The alcohol consumption of the AAs was slightly reduced immediately after revitalization but since has increased: in the most recent generation, F_{55}, the males averaged 7.6 ± 2.1 (SD) and the females 8.0 ± 2.3 g/kg/d. The revitalization allowed the alcohol intake of the ANAs to be reduced significantly lower than it had been just before, and now in the F_{55} generations the ANA males averaged 0.4 ± 0.5 and the females 0.3 ± 0.2 g/kg/d.

Behavioral differences in the absence of alcohol

Open-field test

Emotional factors are frequently suggested to play a role in alcohol consumption. Consequently, the open-field

test, which supposedly measures emotionality, has been given to the AA and ANA several times: in the F_{17} and F_{20} before revitalization[15,47] and in the F_{40} after it[22]. Emotionality, as measured by defecation, has not been found to differ in the lines. Each of these studies, however, found a tendency for the AAs to be more active than the ANAs, although it no longer was significant in the test with F_{40} generation.

Swim test and escapable shock test

More recently, other tests measuring activity in more stressful environments have been conducted[33,34]. Instead of being more active, F_{48} AA males were significantly less active than ANA males in a low-stress swim test (i.e., forced swimming in a 45-l tub of 33 °C water). A still larger difference in the same direction was found repeatedly with the escapable electric shock test (EEST) involving a mild, unscrambled shock, which could be avoided by touching only alternated floor bars. The AAs tended to stand still and avoid the shock, but the ANAs continued jumping about the cage much of the time.

Spontaneous alternation

If rats are put into a T-maze when they are neither hungry nor thirsty and given a second trial immediately after the first, about 80% normally turn in the opposite direction on the second trial than the first. Similarly, among Alko-Mixed rats, 81% showed such spontaneous alteration[49]. In the F_{38} males of our selected lines, only 67% of the AAs alternated, but 88% of the ANAs did so; this line difference was highly significant statistically.

Sleep and circadian rhythms

The alcohol consumption of Long Evans rats has been found to be increased during deprivation of rapid-eye-movement (REM) sleep and decreased afterward[3]. Because of this relationship, the amount of REM sleep was measured in AA and ANA rats[2]: the AAs had significantly less REM sleep and more slow-wave sleep than the ANAs. This was found both in adult (4-month-old) F_{45} animals and in very young (10-day-old) F_{46} ones.

The circadian rhythm of the F_{46} AA rats while having access to alcohol showed three peaks in both alcohol and water intake during the dark phase[1], in agreement with earlier F_{15} results before revitalization[14]. (Recently, this has also been confirmed with F_{45} AA males lever pressing for alcohol [Hyytiä, unpublished results].) The F_{46} ANAs had only two peaks in their water intake[1].

Physiological differences in the absence of alcohol

Central nervous system

The serotonin (5-hydroxytryptamine) concentration in the brain had been found to be higher in AA rats than in ANAs, both before[5,6] and shortly after revitalization[29]. This has recently been confirmed in F_{48} males[35]. The difference was found in all brain regions studied (hypothalamus, midbrain-brainstem, frontal cortex, hippocampus, and striatum). It was also seen in rats given the escapable shock test immediately before being sacrificed. (The test itself produced various changes related to other monoamines, but no significant changes in serotonin levels). There tended to be little difference in the levels of the precursor, tryptophan, and no significant differences in the level of the metabolite, 5-hydroxyindoleacetic acid. (The shock test tended to increase the levels of both tryptophan and 5-hydroxyindoleacetic acid in all areas, but did so similarly in both lines.) Previously it had been found that the AAs had a higher level of dopamine in the striatum, limbic forebrain, and whole brain than the ANAs[4,7]. This line difference was again found in the F_{42} in the striatum[30] and in the F_{48} generation in the frontal cortex and striatum[35]. (The shock test significiantly increased dopamine levels in the other brain regions, similarly in both lines, but did not increase the levels in the frontal cortex and striatum.) An in vivo study with F_{42} animals found no differences between the lines in the synthesis rates and metabolism of dopamine, norepinephrine, and serotonin[30].

The activities of the enzymes synthesizing and inactivating catecholamines were determined in vitro in the whole brains of AA and ANA rats[45]. The activity of tyrosine hydroxylase was markedly higher (42%) in the AAs than in the ANAs. Dopa decarboxylase activity was also higher (24%) in the AAs, but there were no differences in the activities of the other enzymes studied (dopamine beta-hydroxylase, monamine oxidase, and catechol-O-methyltransferase). Similarly, a lack of line difference in monoamine oxidase-A and -B in brain homogenates has also been found[44].

The dopamine D_2 binding in striatal membranes was checked in F_{47} males[34]. The estimate of the B_{max} was significantly lower in the AAs, but the magnitude of the difference was small, and there were no significant differences in the estimates of K_d values. The lines in the F_{49} generation were also found not to differ in their cerebrocortical synaptosomal binding of [^{3}H]batrachotoxinin A 20-α-benzoate and the uptake of [^{14}C]guanidine, which measure properties of the voltage-sensitive sodium channels[32].

Adrenal monoamines

F_{48} AA males tended to have higher levels of dopamine, norepinephrine, and epinephrine in their adrenal glands than the ANAs[35]. The realtionship was reversed, however, in animals immediately after EEST; the interactions indicating differential adrenal reactions of the two lines to the EEST were significant in the case of dopamine and epinephrine, but whether the adrenal differences caused or were caused by the behavioral differences in the EEST could not be determined.

Body weight

Size is apparently very sensitive to genetic selection and thus has varied with the selection criterion used for the

AA and ANA lines. Initially, the selection was based primarily upon the g ethanol/kg body weight measure: as might be expected, the AAs were lighter than the ANAs, as reported for the F_8 generation[11,12] and F_{16} generation[13,15]. Subsequently, more emphasis was placed on the ratio of ethanol intake to total fluid intake and to total caloric intake, and the line difference first disappeared and eventually was reversed, with the AAs being significantly heavier in the F_{29} generation[18]. After revitalization the weights initially were about the same until the F_{48} generation, but recently the original tendency for the AAs to be lighter has again emerged. In the most recent generation, F_{55}, the weights ($\pm$SD) at the beginning of testing for alcohol preference were: AA females, 199 $\pm$ 17; ANA females, 232 $\pm$ 27; AA males, 307 $\pm$ 21; ANA males, 368 $\pm$ 33 g.

Color pattern

Originally all AA and ANA rats were albinos. The revitalization introduced a variety of coat patterns into both lines. Among the F_{55} females currently being bred, the frequencies in AAs are: hooded or almost solid black, 16; hooded or almost solid brown, 3; albino, 1; in ANAs: black hooded, 19; albino, 1. Thus the red-eyed, albino coloration of the original AA and ANA rats has almost been eliminated in both lines today; even with only accidental genetic drift[55], it will probably be lost completely in the near future. The distinction between the brown and black pigmentation is difficult to make, especially in younger animals, so it cannot yet be determined whether the brown allele has been lost in the ANAs. The brown pigmentation still seen in the AAs is a dark, soft, even coloring, different from the agouti pigmentation that was lost in the AT line developed for low sensitivity to alcohol[55]. There also appears to be a line difference in the form of the hooded pattern: the ANAs have a hood covering only the head and upper portion of the back, but many of the AAs (5 of the 20 breeding females) have the darker pigmentation covering almost all of the body, with only a stomach patch and sometimes the paws remaining white.

Behavioral differences with alcohol

Depressant effects

One possible reason for why the AAs drink more alcohol than the ANAs is that the lines may differ in their sensitivity to ethanol. Consequently, a variety of acute effects of ethanol have been examined in these animals.

In earlier studies, AA rats were found to be more resistant to the hypnotic[47] and motor impairment[41,43] effects of alcohol than the ANA rats. The AAs were also found to be less sensitive to the motor impairment induced by other alcohols, such as propanol and tert-butanol, and by barbital, than the ANAs[41]. After revitalization, the lines did not differ significantly in ethanol-induced motor impairment in the F_{40}, F_{43}, and F_{49} generations[22,36,37], in the hypothermic effects of ethanol in the F_{49} generation[36,37], and in the hypnotic effect in native animals of the F_{43} generation[22] and F_{49} generation[36].

Stimulatory effects

The stimulatory effect of 1 g/kg of ethanol (an increase of locomotor activity in the open field) was found to be significant in F_{40} AAs but not in ANAs[22,53]. A significant line difference was found in the effect of alcohol on defecation in the open field, increasing it in AAs and slightly decreasing it in ANAs.

Tolerance development

The acquisition of tolerance to ethanol by AA and ANA rats was examined recently[36,37]. Following an i.p. administration of 2.5 g/kg of ethanol, maximal motor impairment was observed for both the AA and ANA rats at 30 min. Although there was no difference in the maximal degree of impairment, the AAs recovered from the impairment at a faster rate than the ANAs despite having similar blood alcohol concentrations.

In the rapid tolerance paradigm, the AA rats also showed a better capacity to develop tolerance than did the ANAs. In this paradigm, the differences in the degree of intoxication induced by the same test doses of ethanol administered 24 h apart were examined. On both the hypothermic and hypnotic measures, tolerance was observed in the AA but not the ANA rats[36].

The development of chronic tolerance was also examined. It had been reported[43] that AAs develop more tolerance to the motor-impairment effect as a result of chronic ethanol treatment. The F_{49} study similarly showed that following treatment with 5 g/kg p.o. per day for 16 days the AA rats acquired tolerance to the motor impairment, hypothermic, and hypnotic effects of ethanol at a faster rate and to a greater extent than did the ANAs[36].

Kalant[28] showed that when the rats worked for alcohol the AAs developed tolerance to the motor-impairment and hypothermic effects of ethanol, which was lost after 25 days of abstinence. The ANAs, which obtained much less alcohol, did not develop such tolerance.

Physiological differences with alcohol

Central nervous system

There has been relatively little work published recently on the neuronal effects of alcohol in the AA and ANA rats, although projects covering this are currently underway. It has been found that ethanol has rather similar effects in the two lines on the synthesis and metabolism of norepinephrine, dopamine, and serotonin[39,30]. Thus it was concluded that there appears to be no difference in the sensitivity to ethanol of the catecholamine enzyme systems of the two lines.

Ethanol metabolism

The rate of ethanol metabolism had been found to be higher in naive F_{17} AAs than in ANAs[9]. This was again found in F_{48} females[20]. The elimination rate in AAs was also found to be monotonically related to the protein/carbohydrate content to the diet, with a 5% protein/85% carbohydrate diet reducing it almost to the level found in ANAs. The ethanol elimination rate in ANAs was not significantly affected by the diets, with only a tendency for the highest (40%) protein diet to increase it. The blood alcohol levels 30 min after administration of a fixed dose of ethanol had been found to be lower in AAs than ANAs in the F_{40} and F_{43} generations[22].

Acetaldehyde levels

ANA rats accumulate much higher blood levels of acetaldehyde during ethanol metabolism than do AAs. This was first noted in the F_{17} generation[9] and confirmed in the F_{29} one (K. Lindros, pers. comm.). After revitalization, this line difference was still clear, as measured in the F_{40} and F_{43} generations[22]. The reason for the elevated acetaldehyde concentrations seems to be both greater production because of faster ethanol metabolism and less hepatic aldehyde dehydrogenase activity in the ANAs[31]. The whole brain aldehyde dehydrogenase activities in native animals do not, however, differ significantly in the two lines, and after voluntary consumption of alcohol (during which the AAs drank much more) the ANAs had a higher rate of brain aldehyde dehydrogenase activity[27]. A recent, more detailed, study with naive F_{51} rats found that the AAs had lower aldehyde dehydrogenase activity (substrate = acetaldehyde) in the neuropil of the olfactory tubercle than the ANAs, but the AAs had higher aldehyde dehydrogenase activity (substrate = benzaldehyde) than the ANAs in their spinal cord motoneurons, Purkinje cells, and capillary endothelium of the cerebellum (Zimatkin and Lindros, pers. comm.).

Influences on alcohol drinking

Alcohol-deprivation effect

One of the more robust phenomena related to alcohol consumption is the temporary increase observed when access to alcohol is first returned after a period without it, i.e., the alcohol-deprivation effect (ADE). When tested before revitalization, with the F_{30} males, the AAs showed a smaller but more persistent increase than normal rats after 7 days of alcohol deprivation; the ANAs showed the normal time course, but the initial magnitude was smaller[49].

After revitalization, a study with F_{46} animals[23] suggested that the ADE might have subsequently disappeared completely in AA rats. This possibility was confirmed in a study with F_{51} males[54] using the same conditions as the F_{30} study. A week of alcohol deprivation produced essentially no change in the daily intake of the AA rats, but the usual ADE was seen in Long Evans controls[54]. During the first 30 min of renewed access, the AAs actually drank significantly less alcohol than the controls. The lack of ADE in AAs was again found with F_{52} males, using Wistar controls[56]. The same AAs did, however, show an increase in saccharin consumption after a week of being deprived of it.

The alcohol consumption during the first hour, after short periods of alcohol deprivation, was also tested in F_{52} AA males[56]. Deprivation periods of 24 h or less had little effect on the alcohol consumption of Wistar rats, but the intake by AAs increased progressively with 3, 6, 12, and 24 h of deprivation. New unpublished results show, however, that still longer periods of deprivation (2, 3, 5, 7 days) cause the AAs' first-hour alcohol intake to decrease again, progressively; in contrast, the alcohol intake by the Wistar rats increased slowly, but monotonically, with the longer durations of deprivation.

Nutritional factors

Increasing the protein content of the diet, while decreasing the carbohydrate content, has frequently been reported to increase alcohol consumption. This nutritional effect has now been observed also in F_{49} AA females[20]. A nearly linear relationship between protein/carbohydrate content and ethanol consumption was seen: on the lowest protein diet (5% protein, 85% carbohydrate by energy), the AAs averaged less than 1 g/kg/d of ethanol, i.e., less alcohol than most Wistar or Long Evans rats drink. These nutritional changes were unable, however, to increase the low alcohol intake of the ANAs.

Diabetes and insulin

The effects of streptozotocin-induced diabetes were tested in F_{42} females[19]. The treatment produced significant increases in blood glucose levels, water intake, and food consumption in both lines which were reversed by insulin. The ANAs showed greater susceptibility to the streptozotocin treatment. There were, however, no significant changes in alcohol consumption in either line during either the treatment period or subsequently during normalization with insulin.

Working for alcohol

AA rats rapidly learn to lever-press in order to obtain drops of alcohol solution, despite continual free access to food and water, but ANAs normally do not acquire the ethanol-reinforced operant response[21,25,28,46,48]. Furthermore, it has been shown that AAs learn to work for alcohol, although somewhat more slowly, even if they have never had experience drinking it prior to being put into the operant chamber[26].

Hypotheses for differential alcohol preference

Although ethanol clearly can provide positive reinforcement, it also can be aversive, e.g., producing conditioned taste aversions[50]. The distinction is probably dose-

dependent and related to the biphasic nature of ethanol, with the lower doses that produce stimulatory effects being reinforcing[57], and higher doses being aversive.

Most of the possible explanations for why the AAs select large amounts of alcohol can be subsumed under a hypothesis of differential reinforcement: that the cross-over point between reinforcing and aversive properties of ethanol is higher in AAs than in normal or ANA rats. The AAs' greater development of tolerance to the depressive effects and their faster ethanol metabolism would allow them to drink more before reaching a blood alcohol level that was no longer reinforcing. The greater stimulatory effect in AAs, their lower rate of acetaldehyde accumulation, and perhaps their reduced reactivity to aversive stimulation (as indicated by the swim test and EEST results) could contribute to having a higher cross-over point. The ability of high protein/low carbohydrate diets to increase alcohol consumption in AA but not ANA rats may also be operating by increasing the cross-over point in the AAs. A greater energy need could perhaps have contributed to greater reinforcement from alcohol in the AAs during the early generations, as previously suggested[10], and again today when the AAs grow more slowly than the ANAs, but not during the many generations when this relationship was absent or reversed.

The rapid increase in alcohol drinking produced by only a few hours of alcohol deprivation could also contribute to more reinforcement in AAs. If the consumption when ethanol is first returned is seen as an indication of the craving or hunger for alcohol, then the AAs can receive reinforcement by satisfying this craving after only a few hours of abstinence, e.g., after sleeping during the day. Of course, this factor could by itself, independent of reinforcement, help to increase the alcohol intake of the AAs.

The relevance of many of the line differences remains to be determined. Some may be only linked to other differences that more directly affect alcohol drinking. For instance, there is evidence from hamsters suggesting that a low rate of spontaneous alternation may be related to the lack of an alcohol-deprivation effect[52]. The fact that manipulations of REM sleep alter alcohol drinking suggests that the line difference in REM sleep is relevant; it may also be linked to the neurochemical differences and perhaps to those in diurnal rhythms, but the mechanisms through which this cluster of factors alters alcohol drinking is still unknown. It is also possible that some of the line differences, such as those involving coat color, are not related in any way to alcohol preference, but are spurious differences produced by genetic drift, as discussed in the next section.

Future directions

One problem in using long-established, selected lines is the progressive accidental loss of alleles or genetic drift unrelated to the selected characteristic[55]. Although the problem has been lessened by the relatively large number of breeders used with AAs and ANAs, it nevertheless grows with each succeeding generation, and even now there is a substantial probability that any line difference observed may be completely unrelated to alcohol drinking. Although a related difficulty, the development of poor breeding success and viability, was temporarily corrected by the revitalization[22,24], this procedure is of limited usefulness in the prevention of spurious line differences[55].

One solution currently being used for this problem is to test whether observed AA/ANA line differences also occur in other line pairs developed for differential ethanol selection, such as the P/NP lines. This solution is, however, limited. Although finding the same difference in other lines helps to confirm the relevance to alcohol drinking, failure to find the same difference does not prove that the AA/ANA line difference is spurious. For instance, the P and NP lines differ in brain serotonin in the opposite way than the AA and ANA lines, with the alcohol-preferring P rats having the lower serotonin levels. This could mean that the serotonin differences are spurious (i.e., caused only by random genetic drift and not functionally related to alcohol preference) or it could mean that we have two differing animal models for different forms of high alcohol consumption. The finding of two different forms of human alcoholism[8] gives additional impetus for believing in the latter possibility. On the other hand, it is possible that there are some critical factors controlling alcohol consumption in all subtypes of drinkers. Thus, it obviously is important to search for any commonalities among AA, P, and other high drinking lines, that differentiate them from ANA, NP, and all other low drinking lines.

The eventual purpose for alcohol research with animals is not merely to develop an understanding of the basis for heavy alcohol consumption but rather to develop the ability to do something about, i.e., to find better methods for preventing and/or treating alcoholism. As reviewed elsewhere[51], the study of voluntary alcohol consumption by rats has good predictive validity for screening procedures that will suppress alcohol drinking in humans. It is expected that rat lines, such as the AAs, will provide a useful tool in the search for methods to combat alcoholism. In particular, they may be useful in looking for ways of treating those forms of alcoholism that are especially dependent upon genetic factors.

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Selected mouse lines, alcohol and behavior

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Summary. The technique of selective breeding has been employed to develop a number of mouse lines differing in genetic sensitivity to specific effects of ethanol. Genetic animal models for sensitivity to the hypnotic, thermoregulatory, excitatory, and dependence-producing effects of alcohol have been developed. These genetic animal models have been utilized in numerous studies to assess the bases for those genetic differences, and to determine the specific neurochemical and neurophysiological bases for ethanol's actions. Work with these lines has challenged some long-held beliefs about ethanol's mechanisms of action. For example, lines genetically sensitive to one effect of ethanol are not necessarily sensitive to others, which demonstrates that no single set of genes modulates all ethanol effects. LS mice, selected for sensitivity to ethanol anesthesia, are not similarly sensitive to all anesthetic drugs, which demonstrates that all such drugs cannot have a common mechanism of action. On the other hand, WSP mice, genetically susceptible to the development of severe ethanol withdrawal, show a similar predisposition to diazepam and phenobarbital withdrawal, which suggests that there may be a common set of genes underlying drug dependencies. Studies with these models have also revealed important new directions for future mechanism-oriented research. Several studies implicate brain gamma-aminobutyric acid and dopamine systems as potentially important mediators of susceptibility to alcohol intoxication. The stability of the genetic animal models across laboratories and generations will continue to increase their power as analytic tools.
Key words. Mouse lines; selective breeding; ethanol effects; pharmacogenetics; long-sleep mouse; short-sleep mouse.

General introduction

Selective breeding takes advantage of genetic variability and has been utilized for many years in the fields of agriculture and animal husbandry to produce plants and animals with desired characteristics. However, it is only within the last 25 years that this technique has been widely recognized as a particularly powerful one in the field of pharmacogenetics, principally for studying the drug, ethanol (EtOH). A number of rat and mouse lines are now available which are highly sensitive or insensitive to various effects of alcohol (EtOH). Most originated from genetically heterogeneous foundation populations whose individuals were screened for sensitivity to the relevant EtOH effects. Breeding pairs, chosen for extreme sensitivity or insensitivity, produced offspring who were themselves screened and selectively bred according to their relative sensitivities. This process continued for a number of generations until highly sensitive and insensitive lines were produced. The success of a selective breeding program attests to the presence of genetic factors influencing the response in question. The speed and pattern of divergence between the sensitive and insensitive lines provide some indication of the genetic complexity underlying the response.

This paper reviews work which has been performed using selected mouse lines. A large portion is devoted to Long-Sleep (LS) and Short-Sleep (SS) mice because they have been the most extensively investigated. To avoid redundancy in the literature, we provide a short summary of two recent reviews which included data from LS and SS mice, and more thoroughly address more recent work and research that has not been exhaustively reviewed elsewhere. Other research reviewed pertains to the select-