*Pharmacology Biochemistry & Behavior*, Vol 29, pp 601–607 Pergamon Press plc, 1988 Printed in the U S A 0091-3057/88 $3 00 + 00

# Voluntary Consumption of Ethanol in WSP, WSC and WSR Selectively Bred Mouse Lines

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Received 20 May 1987

KOSOBUD, A , A S BODOR AND J C CRABBE *Voluntary consumption of ethanol in WSP, WSC and WSR selectively bred mouse lines* PHARMACOL BIOCHEM BEHAV **29**(3) 601–607, 1988 —The genetic correlation between voluntary consumption of ethanol solutions and severity of withdrawal seizures after chronic ethanol exposure was assessed using the selectively bred Withdrawal Seizure Prone (WSP) and Resistant (WSR) mouse lines WSP mice have at least ten-fold more severe withdrawal than WSR mice after equal chronic ethanol exposure, and withdrawal in a non-selected control line (WSC) is intermediate to withdrawal in the WSP and WSR lines [4] In the first experiment, mice from the WSP, WSC and WSR lines were offered a choice between 2 2, 4 6 and 10 0% ethanol solutions and water in three consecutive eight-day sessions WSR mice consumed more ethanol than WSP mice, and WSC mice were intermediate In a second experiment, WSP and WSR mice were offered ethanol solutions in concentrations that were adjusted up or down every two days depending upon the amount of ethanol consumed WSP and WSR mice displayed very different patterns of drinking, with WSP mice drinking more ethanol in early stages of the experiment, and WSR mice drinking more ethanol later Results of these experiments suggest that some genes influencing severity of withdrawal from ethanol also influence voluntary ethanol drinking

Pharmacogenetics Ethanol withdrawal Ethanol preference Selective breeding WSP and WSR selected lines

MOST people consume alcohol with no serious consequences, but for a subset of the population, ethanol (EtOH) use is excessive and disruptive The variation in the response of individuals to EtOH is a result of both environmental and genetic factors (for review see [5]). The existence of a significant genetic contribution to human susceptibility to alcoholism implies that there are physiologic traits which distinguish individuals predisposed to developing alcoholism A major effort has been directed at identifying these biologic factors, better to understand the biological basis of alcoholism, and to find markers that could identify the potential alcoholic prior to his or her development of the disorder

Administration of EtOH to animals and humans results in a wide range of physiological and behavioral changes By applying genetic tools, the actions of EtOH which have similar genetic bases can be identified Specifically, certain responses to EtOH can be shown to be genetically correlated, or, in other words, to covary consistently when the genotype of the animals is manipulated Such a genetic correlation can be interpreted as the result of proximity and cosegregation of the genes underlying each trait, pleiotropic (multiple) actions of a single gene, or multiple effects of EtOH on a single physiological system

We have developed lines of mice genetically selected for severe and mild withdrawal seizures following three days of inhalation of ethanol vapor in concentrations sufficient to induce constant high levels of intoxication The Withdrawal Seizure Prone (WSP) lines display at least 10-fold more severe handling-induced convulsions than the Withdrawal Seizure Resistant (WSR) lines following equivalent EtOH treatment, while the nonselected Withdrawal Seizure Control (WSC) lines are intermediate [4] These animals constitute an excellent population for the identification of genetic correlations between withdrawal and other effects of EtOH and for the study of the physiological mechanisms underlying EtOH withdrawal In the experiments reported here, we

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sought to determine whether the genes which influence EtOH withdrawal also influence voluntary EtOH consumption In the course of the selection these animals have been made dependent using forced intoxication, while no direct selection pressure has been exerted on voluntary consumption of EtOH Therefore, any difference in voluntary consumption between WSP and WSR lines should be due to the genes responsible for the difference in withdrawal, or to closely linked genes

Rodgers [23] measured voluntary consumption of ethanol in a number of inbred strains of mice Some of these inbred strains (though not necessarily of the same subline) have also been tested for susceptibility to withdrawal following forced EtOH inhalation [6] Three inbred strains showed high levels of EtOH consumption and low withdrawal (C57BL, C58 and C57BR), while 3 showed low consumption and severe withdrawal (DBA, C3H and A) This suggests a negative genetic correlation between susceptibility to withdrawal and voluntary consumption Animals genetically resistant to EtOH withdrawal are more willing to consume ethanol, while animals susceptible to severe withdrawal are less willing to consume EtOH However, one strain (BALB) displayed mild withdrawal but drank little EtOH

Allen *et al* [1] assessed the phenotypic correlation between withdrawal from chronic EtOH and voluntary consumption of EtOH HS/Ibg mice, the outbred stock from which our selected lines were derived, were given a choice between a 7% EtOH/water solution and water before and after induction of physical dependence on EtOH Physical dependence was induced using an EtOH-adulterated liquid diet as the sole food source Preference for the 7% EtOH solution before and after induction of dependence did not correlate with either consumption of liquid diet or severity of withdrawal Therefore, these investigators concluded that there was no evidence of a correlation between severity of withdrawal and voluntary consumption of ethanol However, the use of phenotypic correlations within outbred mice confounds genetic and environmental influences A genotypic correlation might be hidden by an environmental correlation of opposite sign (for discussion see [5]) For example, in the Allen experiment, consumption of the liquid diet correlated positively with severity of withdrawal. Thus, the animals' drinking behavior was largely responsible for the severity of withdrawal, and the genetic susceptibility to withdrawal was not measured in these animals A better assessment might have been made with a forced intoxication procedure, so that all animals received the same dose of EtOH

In the experiments reported below, we studied the EtOH drinking behavior of WSR, WSP and WSC mice, never exposed to EtOH, in a two bottle preference test In the first experiment, three concentrations of EtOH were offered for eight days each In the second experiment, EtOH concentration was varied every two days depending upon the animal's behavior. If an animal drank large amounts of EtOH, the concentration of EtOH was increased, if an animal drank small amounts of EtOH, the concentration was decreased

## GENERAL METHOD

### SELECTED LINES

WSC, WSR and WSP mice used in these experiments were bred at the Veterans Administration Medical Center (Portland, OR) The genetic selection procedure used in developing these mice has been described [4] Two reproductively isolated sets of WSP, WSR and WSC mice are maintained, referred to hereafter as WSP1, WSR1, WSC1, WSP2, WSR2, and WSC2 Mice used in the experiments reported below were from litters bred specifically for these experiments They had not, therefore, experienced chronic EtOH intoxication and withdrawal

## EXPERIMENT 1

### METHOD

*Subjects*

Sixty female mice from the 17th selected generation of the WSP1, WSP2, WSR1, WSR2, WSC1 and WSC2 lines were used Ten mice from each line were included in each group Seven days prior to the experiments reported here, these mice had been used in a pilot experiment in which they experienced 1 day of fluid deprivation, followed by 1 day of consumption of a 10% EtOH solution (data not reported) The mice were 41–61 days old at the beginning of the test, and weighed 21 2±0 2 grams (mean±SE) The mice were housed individually in polycarbonate cages (28×17×11 5 cm) containing wood chips as bedding Food and water were available ad lib.

*Procedure*

Each mouse was provided with 2 inverted 25 ml graduated cylinders fitted with rubber corks and stainless steel drinking spouts, one containing tap water and one containing a solution of EtOH and tap water Each day, volume of fluid remaining was recorded, and the position of the bottles was reversed Because some animals show strong position preferences, all data were averaged over two day blocks To correct for loss of fluid due to leaks or spills, bottles of tap water and EtOH solution were placed on empty cages and volumes recorded. The average fluid loss from these bottles was subtracted from the experimental data Fresh EtOH solution was provided every two days, and fresh water was provided as needed. EtOH was measured in three 8-day sessions In Session 1, the concentration of EtOH solution offered was 2 2% (all concentrations v/v), in Session 2, the concentration was 4 6%, and in Session 3, 10.0% Following Session 3, the bottle containing EtOH solution was removed, and water consumption was measured for two 2-day blocks, constituting Session 4

We calculated for each animal (a) the average daily total fluid intake for each session, (b) the average daily EtOH preference score (ml of EtOH consumed/ml total fluid consumed) for Sessions 1–3, and (c) the average daily consumption of EtOH expressed as g EtOH/kg body weight for Sessions 1–3

### RESULTS

Figure 1 shows preference ratios at 2 2, 4 6 and 10.0% EtOH concentration The data were analyzed for each concentration independently using a two-way ANOVA (Line × Replicate), and significant main effects were further assessed using a Newman-Keuls test [27]. WSR mice had significantly higher preference ratios at 2 2% and 10% ($p<0.002$, $p<0$ 02 respectively) than both WSC and WSP mice ($p<0$ 05) When the lines were offered 4 6% EtOH solutions, a trend towards higher preference ratios in the WSR mice was seen ($p<0$ 07) At 10 0%, a significant Line × Replication interaction was

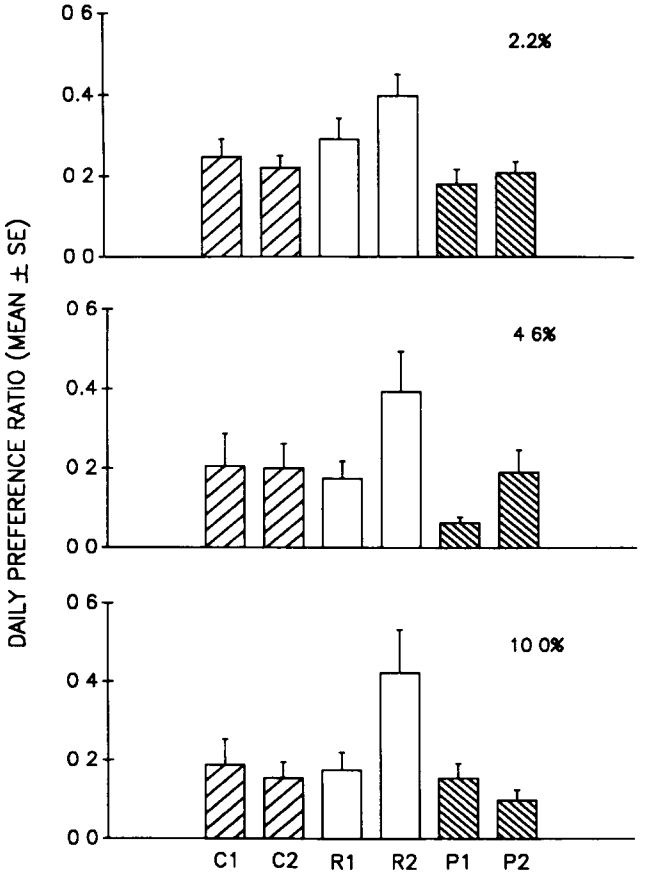


FIG 1 Average daily preference ratio (ml EtOH solution/ml total fluid) during three consecutive sessions of an EtOH solution/water choice test Concentrations of ethanol were 2 2, 4 6 and 10 0% WSR mice of both replications showed higher preference ratios at 2 2 and 10 0% EtOH solutions ($p<0$ 05) For analysis, see text

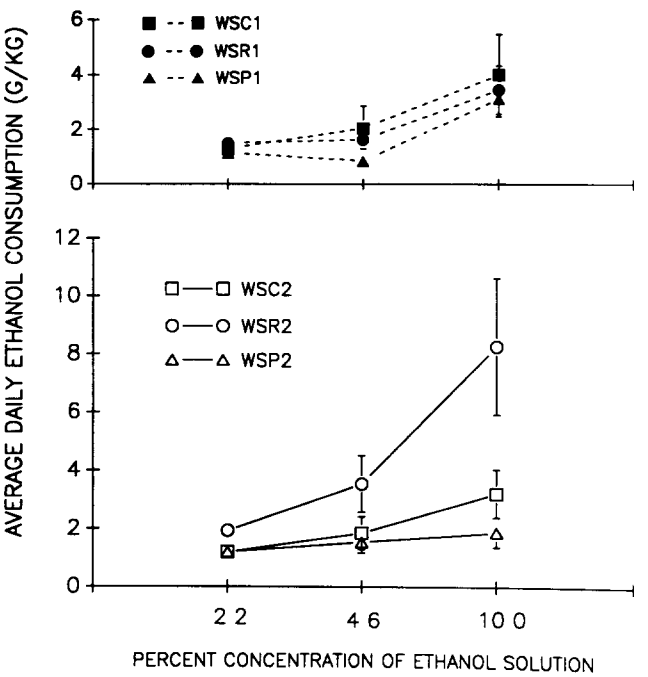


FIG 2 Mean±SE for ethanol consumption (g/kg) during three consecutive sessions of an ethanol solution/water choice test Data points with no error indicate that error was within symbol boundaries WSR mice of both replications consumed greater amounts of ethanol than WSP and WSC mice at 2 2 and 10 0% EtOH solutions ($p<0$ 03) For analysis, see text

observed ($p<0$ 03), occurring because the line effect (WSR > WSC = WSP) was present only in Replicate 2

EtOH consumption (g/kg) is illustrated in Fig 2 The analysis (two-way ANOVAs done independently for each block) revealed a pattern very similar to that seen for preference ratios. WSR mice consumed significantly greater amounts of EtOH than WSC and WSP mice at 2 2 and 10 0% ($p<0.03$), and tended to consume more at 4 6% ($p<0$ 08) Again, the Line × Replication interaction was significant at 10% because the WSR2 drank much more, and the WSP2 less, while all other groups drank comparable amounts

Total fluid consumption was also analyzed (Table 1) using a 3-way ANOVA (Line × Replication × Session) Average amount of fluid consumed daily is presented for each EtOH concentration, and for the four day water-only session which succeeded the EtOH choice session Fluid intake was reduced during the 4 6% and 10% EtOH choice sessions, $F(3,162)=33$ 7, $p<0.0001$, relative to the 2.2% session and the water-only session ($p$'s$<0$ 01, Newman-Keuls) A significant difference was seen in the amount of fluid the different lines drank, $F(2,54)=7.26$, $p<0.002$, specifically, WSR mice of both replications drank less fluid than WSP and WSC lines ($p<0$ 01, Newman-Keuls) As age of mice, and bodyweight, could influence fluid consumption and ethanol consumption, these factors were assessed for correlation with average amount of fluid consumed, and average amount of EtOH consumed Specifically, correlation coefficients between bodyweight and age at the beginning of each session, and average fluid intake and average EtOH intake during the session were calculated for all mice Total fluid and EtOH intake did not correlate significantly with age, bodyweight, or each other ($r\leq 0$ 2)

## EXPERIMENT 2

### METHOD

*Subjects*

The subjects were 32 naive female mice from the 19th selected generation of the WSP1, WSP2, WSR1, and WSR2 lines. Eight mice from each line were included in each group Since we were primarily interested in the difference between WSP and WSR mice, WSC mice were not tested. The mice were 80–93 days old, and weighed 22 4±0 4 grams (mean±SE) at the beginning of the experiment. The mice were housed individually in polycarbonate cages containing wood chips as bedding Food and water were available ad lib

*Procedure*

Each mouse was provided with 2 inverted 25 ml graduated cylinders fitted with rubber corks and stainless steel drinking spouts Initially, both bottles were filled with tap water, and water consumption measured daily for four

TABLE 1

TOTAL FLUID (WATER AND EtOH+WATER SOLUTIONS) CONSUMED DAILY (MEAN ± SE)

| | | Ethanol Concentration | | | |
|---|---|---|---|---|---|
| Line | N | 2 2% | 4 6% | 10 0% | Water Only |
| WSC1 | 10 | 7 2 ± 0 3 | 6 5 ± 0 1 | 6 2 ± 0 4 | 6 7 ± 0 4 |
| WSC2 | 10 | 6 9 ± 0 3 | 5 9 ± 0 2 | 6 2 ± 0 2 | 7 4 ± 0 4 |
| WSR1 | 10 | 6 4 ± 0 3 | 5 5 ± 0 3 | 5 5 ± 0 3 | 5 9 ± 0 3 |
| WSR2 | 10 | 6 3 ± 0 1 | 5 6 ± 0 2 | 5 5 ± 0 2 | 6 0 ± 0 2 |
| WSP1 | 10 | 7 9 ± 0 4 | 6 9 ± 0 4 | 6 5 ± 0 3 | 7 7 ± 0 3 |
| WSP2 | 10 | 6 9 ± 0 4 | 5 5 ± 0 3 | 5 8 ± 0 3 | 6 3 ± 0 4 |

Fluid consumption was greatest during Session 1 of the ethanol/water choice tests ($p<0$ 01) Fluid consumption during the water only session also exceeded that during the 4 6 and 10% choice tests WSR mice consistently drank less fluid than WSP and WSC mice ($p<0$ 01) For a description of the analysis, see text

TABLE 2

MAXIMUM EtOH CONCENTRATION ACCEPTED

| Line | N | Mean ± SE |
|---|---|---|
| WSR1 | 8 | 6 0 ± 1 6 |
| WSR2 | 8 | 7 4 ± 0 9 |
| WSP1 | 8 | 5 7 ± 0 6 |
| WSP2 | 8 | 5 2 ± 0 8 |

2-day blocks Beginning on the ninth day, the animals were offered a choice between tap water and a solution of EtOH and tap water A given EtOH concentration was presented for one 2-day block Procedures for administering fluids and recording data were the same as for Experiment 1 Preference ratios were calculated as the sum of EtOH solution consumed in 2 days divided by the total fluid consumption for those days If this ratio was 0 2 or greater, the EtOH concentration was increased for the next 2-day block If the ratio was less than 0 2, the EtOH concentration was decreased All animals were offered 1% EtOH solutions initially, and concentrations were increased or decreased on an accelerating scale (1, 2 1, 3 3, 4 6, 6 0, 7 5, 9 1, 10 8, 12 6 and 14 5%) Mice with preference ratios of less than 0 2 when offered 1% EtOH remained at 1% This procedure was continued for ten 2-day blocks At this time, all animals but one had refused at least one concentration of EtOH Following the EtOH test, water consumption was measured for two more 2-day blocks

## RESULTS

Examination of the pattern of drinking behavior for each mouse revealed that most mice accepted increasing concentrations of EtOH for a few blocks, and then refused a higher concentration Once they refused a given concentration of EtOH, they subsequently refused all lower concentrations as well, even 1%. This pattern of consumption was present in 15 out of 16 WSP mice, but only 10 of 16 WSR mice Only one mouse (a WSR1) had not refused at least one concentration

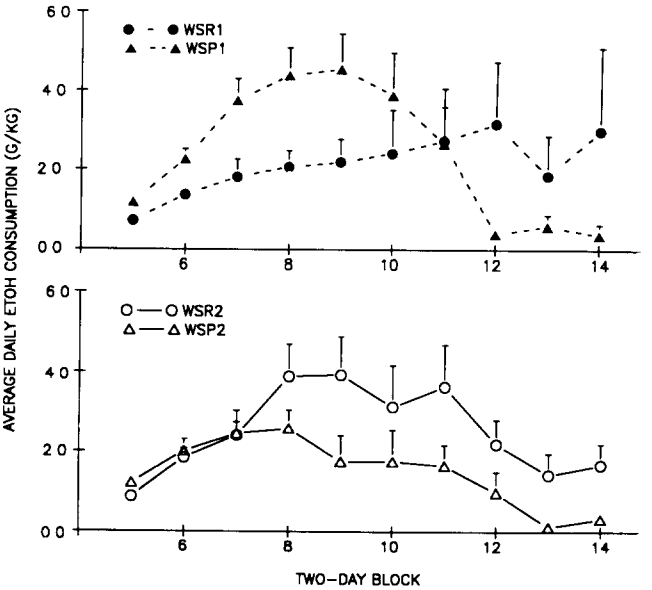


FIG 3 Average daily ethanol consumption (g/kg) during twenty days (blocks 5–14) of free choice between water and EtOH solutions in a variety of concentrations Data points with no error indicate that error was within symbol boundaries For analysis, see text

of EtOH by Block 14 Table 2 shows the highest concentration accepted by each line (mean±SE) A 2-way ANOVA (Line × Replicate) revealed no significant differences

Figure 3 illustrates EtOH consumption (g/kg) during blocks 5–14 (during blocks 1–4, 15 and 16 the animals were offered water only) To simplify the analysis, data were analyzed independently for each replicate using a 2-way ANOVA (Line by Block) with one factor repeated WSR2 mice tended to consume more ethanol than WSP2 mice throughout the experiment, $F(1,14)=3$ 82, $p<0$ 07 WSP1 and WSR1 mice displayed very different patterns of consumption WSP1 mice drank more ethanol in the early stages of the experiment, but by the end, 7 of the 8 mice were refusing all ethanol WSR1 mice, however, continued to drink moderate amounts of ethanol throughout the experiment Consistent with this pattern of behavior, the 2-way ANOVA revealed an interaction of Line and Block, which was further analyzed using a test of simple effects [14] WSP1 mice drank significantly more ethanol than WSR1 mice during blocks 6, 7 and 8, $F(1,14)>7$ 38, $p<0$ 025, and tended to drink more during blocks 5 and 9, $F(1,14)>4$ 02, $p<0$ 10 WSR1 mice tended to drink more EtOH than WSP1 mice during block 12, $F(1,14)=3$ 11, $p<0$ 10

Figure 4 shows total fluid consumption Similar to the result seen in Experiment 1, WSR mice consistently drank less fluid than WSP mice, $F(1,28)=31$ 63, $p<0$ 0001, three-way ANOVA with one factor repeated, Line × Replicate × Block

## GENERAL DISCUSSION

These experiments demonstrate a small but consistent difference in EtOH consumption in mice selectively bred for differences in EtOH withdrawal WSR mice, genetically resistant to withdrawal seizures after ethanol treatment, voluntarily consume more ethanol than WSP mice, genetically prone to withdrawal This suggests that there is a negative

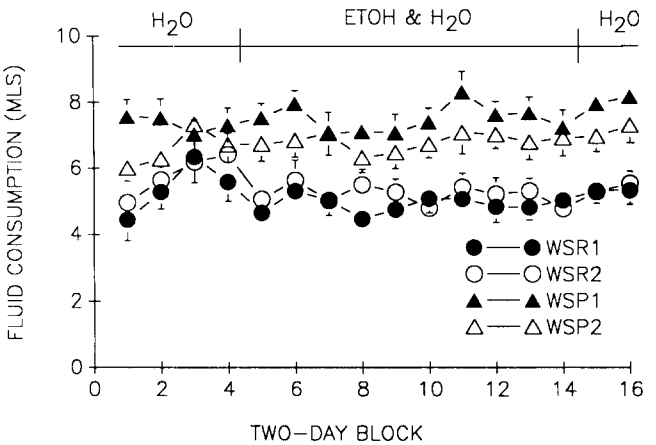


FIG 4 Average daily fluid consumption (ml) Subjects were offered a choice between water and an EtOH solution on 2-day blocks 5–14 Water consumption alone was monitored on 2-day blocks 1–4, 15 and 16 WSR mice drank less fluid than WSP mice consistently throughout the experiment, and this effect appears to have been enhanced by presentation of ethanol solution Data points with no error indicate that error was within symbol boundaries For analysis, see text

genetic correlation between ethanol withdrawal susceptibility and voluntary ethanol consumption This could be the result of single, pleiotropic gene, which modulates a particular physiological system in such a way that both EtOH drinking and withdrawal are affected, or which has multiple, independent actions Alternatively, two or more closely linked, cosegregating alleles might be involved In this case, the correlation between EtOH drinking and withdrawal would be the result of the independent actions of different genes

In Experiment 1, the WSC2 mice drank similar amounts of ethanol as the WSP2 mice, while WSR2 mice drank more, suggesting that the primary genetic effect in Replicate 2 was an increase in EtOH consumption in the WSR2 line, while the EtOH consumption in WSP mice was not affected by selection Mice in Replicate 1, however, displayed a somewhat different pattern of drinking In Experiment 1, WSR1 mice drank amounts of ethanol similar to WSC1 mice, while WSP1 mice drank less The second experiment revealed a more complicated pattern of consumption, with WSP1 mice drinking more EtOH than WSR1 mice in the first part of the experiment, but drinking less EtOH in the later stages Thus, in Replicate 1, the difference between EtOH consumption in the WSR1 and WSP1 lines appears to be primarily in a reduction in EtOH consumption in the WSP line, that appears only after many days of exposure, and/or after exposure to high ethanol concentrations In fact, the behavior of the WSP1 line is consistent with the development of a taste aversion to EtOH in these mice.

Because the WSP vs. WSR lines from the two replicates display different patterns of ethanol consumption, it is possible that different genes are responsible for the drinking differences within each replicate Withdrawal is presumably affected by multiple genes, and the selected genes relevant to withdrawal in the two lines may also differ between replicates. Although the genetic data from these experiments raise the possibility that different genes control drinking in the two replicates, to the extent that the direction of the line differences are consistent, a common physiological endpoint is suggested

What physiological processes might be common to both EtOH drinking and EtOH withdrawal? Although the data presented in this paper allow only the most general consideration of this question, some speculations can be made The factors thought to be primarily responsible for variations in EtOH consumption can be divided into three categories nutritive or caloric factors, differences in neurosensitivity to ethanol and acetaldehyde, and metabolic factors. Within each of these categories there is the potential for genetic variation

The value of EtOH as a source of calories can have a significant impact on its consumption AA rats, genetically selected for high EtOH consumption, have as a correlated response to selection an increased caloric need relative to ANA (low EtOH consuming) rats [9] Food deprived rats consume more EtOH than free-feeding ones [20] and will choose a calorie-dense ethanol solution over a more palatable saccharin solution [21] Similarly, increasing the fat and/or sugar content of the diet decreased EtOH consumption in C57BL mice [8] When the selectively bred P (Preferring) and NP (Non-Preferring) rats were reduced to 80% free-feeding weight, NP rats increased their daily consumption of EtOH to levels nearly identical to P rats [26] Finally, ANA rats increased their ethanol consumption to match that of AA rats when the ethanol was given in the form of wine or an ethanol/fruit punch solution [28] Although no obvious differences exist between WSP and WSR mice in body weight, they may differ in their need of EtOH as an energy source WSP and WSR mice have been offered ethanol in a palatable solution (EtOH mixed with fruit punch), unlike the rat lines, the difference in ethanol consumption was maintained (unpublished observations)

EtOH consumption may also be affected by differences in neurosensitivity to the pharmacologic actions of EtOH P rats were shown to be less sensitive to the ataxic effects of EtOH than NP rats [18]. AA rats were less sensitive than ANA rats to the ataxic effect of EtOH as assessed with a tilting plane [19,21], and recovered from loss of righting reflex more rapidly than ANA rats following an acute injection of ethanol [24]. WSP and WSR mice, however, showed no difference in sensitivity to ethanol using acute hypothermic response or loss of righting reflex as indices [2] WSP mice show more severe withdrawal after a single IP injection of EtOH than WSR mice [16] If the acute withdrawal syndrome constitutes an aversive event for animals, WSP and WSC mice may develop a stronger aversion to EtOH than WSR mice Although the levels of consumption recorded in the present drinking studies were unlikely to result in blood ethanol concentrations as high as those which preceded acute withdrawal, studies of the pattern of EtOH drinking in rats and mice revealed blood EtOH levels following discrete bouts ranging from 75 to greater than 200 mg/dl [10,11]

A third mechanism by which ethanol consumption might be altered genetically is in metabolism of EtOH and its breakdown product, acetaldehyde, which is known to cause a number of dysphoric reactions in man, including nausea, flushing and tachycardia [25]. ANA rats show a high rate of EtOH metabolism relative to acetaldehyde, and may therefore accumulate higher acetaldehyde levels than AA rats The dysphoric actions of acetaldehyde may be partly responsible for the decreased EtOH drinking in ANA rats [15] EtOH elimination rates were similar in early generations of WSP and WSR mice [16] By generation S10, WSP mice accumulated slightly higher blood EtOH levels during chronic EtOH intoxication, but blood and brain concentra-

tions following acute administration of EtOH were similar in WSR and WSP mice when measured in generation 21 (Kosobud *et al*, manuscript in preparation) Acetaldehyde metabolism has not been measured in WSP and WSR mice, so the relative rates of metabolism of EtOH and acetaldehyde are not known

Recently, a single genetic locus has been identified which appears to be a major determinant of ethanol intake in the mouse (Goldman *et al* [13]) This locus maps to chromosome 1, and its expressed product is a protein, LTW-4, found in brain, liver and kidney This protein has two genetic variant forms which differ in isoelectric point Goldman and Crabbe [13] typed 15 B×D recombinant inbred mouse strains and the two parental strains (C57BL/6J and DBA/2J) for this locus and compared their genotype with previously-determined levels of ethanol acceptance [3] Five of 7 low ethanol accepting strains (including DBA/2J) had the acidic form of LTW-4, while 9 of 10 high ethanol accepting strains (including C57BL/6J) had the basic form Subsequently, 19 distantly related inbred strains were tested for ethanol consumption and typed for expression of LTW-4 Nine of 13 low accepting inbred strains had the acidic form of LTW-4, while 4 of 6 high accepting strains had the basic form (Goldman *et al* [13]) No correlation between the expression of the LTW-gene and withdrawal severity was seen in either the RI or inbred strains, but a significant negative correlation between ethanol intake and severity of withdrawal was found in the inbred strains (unpublished observations). Thus, it appears that decreased withdrawal severity is genetically correlated with increased ethanol intake, and ethanol intake is genetically correlated with locus A12, but no direct correlation between withdrawal severity and allelic state at locus A12 exists WSP, WSC and WSR mice have also been typed for this locus WSR mice showed a greater expression of the basic form of LTW-4, consistent with their increased ethanol consumption, while WSC and WSP mice showed relatively more of the acidic form [12] We tentatively conclude that genetic selection for withdrawal severity has directly resulted in changes in ethanol intake in the selected lines, and this has indirectly led to a shift in the distribution of locus A12 in the lines

WSR mice from both replications consistently drank less total fluid than WSP and WSC mice. This phenomenon appeared to reflect a condition independent of ethanol experience, but may have been intensified by the presence of ethanol solution as a fluid choice (see Fig 4) Because this difference is robust, and present in both replicates, it appears to represent a true genetic correlation. However, the possible relationship between fluid consumption and withdrawal is not obvious This correlation may be the result of proximate genes, rather than representing a common physiological basis AA rats drink more fluid than ANA rats [17], but they also eat more, and are heavier When these factors are considered, fluid consumption in the two rat lines appears to be equivalent

In summary, WSR mice, selectively bred for decreased severity of withdrawal following chronic EtOH intoxication, were found to consume more ethanol solution in a two-bottle choice test than WSP mice (genetically selected for increased severity of withdrawal) or WSC mice (a nonselected control line) Thus, it appears that some of the genes responsible for the withdrawal seizure resistance of the WSR line also increase their ethanol consumption A variety of mechanisms could underlie this relationship. For instance, this difference could reflect differences in the relative rewarding or aversive properties of ethanol in these lines Alternatively, this difference may be the result of differing nutritional needs, metabolic capacity, or fluid balance in these lines

ACKNOWLEDGEMENTS

Supported by a grant from the Veterans Administration and PHS-ADAMHA-NIAAA grants AA05828, AA06243, and AA06498

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