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The High-Ethanol Preferring rat as a model to study the shift between alcohol abuse and dependence

Elena Terenina-Rigaldie[a], Byron C. Jones[b], Pierre Mormède[a,*]

[a]*Laboratoire de Neurogénétique et Stress, UMR 1243 INRA–Université Victor Segalen, 33076 Bordeaux, France*
[b]*Department of Biobehavioral Health, The Pennsylvania State University, University Park, PA 16802-6508, USA*

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Abstract

The High-Ethanol Preferring line of rats (HEP), recently selected by R.D. Myers, is characterised by a high voluntary consumption of alcohol (3–4 g/kg/day for males and 6–8 g/kg/day for females, when a 10% ethanol solution is available as a choice vs. water) and a high sensitivity to taste reinforcement (saccharin, quinine). Our previous data obtained with HEP rats showed no evidence of development of dependence after long-term sustained alcohol intake. In this study, we subjected these rats to several long-term administration protocols suggested to favour the development of alcohol dependence, including multiple alcohol concentrations or sweetened alcohol solutions (ethanol 10% or 20%+saccharin), and deprivation periods. The results showed no increase in alcohol consumption, no shift of preference for alcohol solutions when offered as a free choice vs. a preferred saccharin solution, and a very limited alcohol-deprivation effect when alcohol is made available after a period of deprivation, the three criteria used to demonstrate the development of dependence. Regardless of the method used, HEP rats failed to show dependence after long-term, heavy ethanol consumption. Resistance to ethanol dependence may in fact be genetically influenced and the HEP rat appears as a valuable model to search for factors involved in the transition from alcohol abuse to dependence.

Keywords: Alcohol dependence; Alcohol abuse; Saccharin; HEP, rat; Taste preference

1. Introduction

Alcohol use disorders include *alcohol dependence* and *alcohol abuse*. Substance dependence is a pattern of repeated self-administration that usually results in tolerance, withdrawal and compulsive drug-taking behaviour. Compulsive substance use is characteristic of dependence and its criteria are central to the diagnosis (DSM-IV, American Psychiatric Association, 1994). The essential feature of alcohol abuse is a maladaptive pattern of alcohol use made manifest by recurrent and significant adverse consequences caused by the repeated use of alcohol (Cloninger, 1987). These may include such events as inappropriate aggression, increased risk-taking and putting oneself or others in danger. Unlike the criteria for alcohol dependence, the criteria for alcohol abuse do not include tolerance, withdrawal symptoms or a pattern of compulsive use. It is an important objective in alcohol research to elucidate the factors involved in the transition from abuse to dependence and the biological mechanisms involved.

Methods designed to make an animal dependent on ethanol by forced administration are well established. These include inhalation (Aufrère et al., 1997; Roberts et al., 2000; Rogers et al., 1979), intubation (Marfaing-Jallat and Le Magnen, 1982) and consumption of liquid diets (Cicero, 1980; Hunter et al., 1975; Pohorecky, 1981). A more desirable approach, analogous to human self-administration is the voluntary consumption of alcohol in the presence of food and water ad libitum. There is a prevailing notion that the voluntary oral consumption of ethanol by experimental animals is insufficient to produce physical dependence

* Corresponding author. Tel.: +33 557 57 37 51; fax: +33 557 57 37 52.
E-mail address: mormede@bordeaux.inserm.fr (P. Mormède).

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(Cicero, 1979), because most animals dislike solutions containing high concentrations of ethanol (Myers and Veale, 1972). It is advisable, thus, to use animals genetically selected for high voluntary alcohol intake which can be considered as a model of abuse in humans (Crabbe et al., 1999). However, most animals do not consume quantities in excess of that which is readily metabolized (Meisch, 1984), and various techniques have been proposed to increase alcohol intake and/or the development of dependence by sweetening the alcohol solution with saccharin (Lumeng et al., 1978), by administration of escalating concentrations of alcohol (Veale and Myers, 1969) or by food deprivation (Waller et al., 1982). Repeated alcohol deprivation may also promote the development of alcohol dependence (Hölter et al., 1998, 2000; Hunter et al., 1974; Marcucella et al., 1984; Spanagel and Hölter, 1999).

Various approaches have been used to evaluate the occurrence and the degree of dependence; most are based on changes in alcohol intake and the appearance of withdrawal symptoms. One obvious index should be the increase in ethanol intake, and its resistance to interfering factors like concurrent choice of preferred flavours such as saccharin or sucrose, or adulteration with quinine (Hunter et al., 1974; Wolffgramm and Heyne, 1995). Indeed, alcohol preference is often associated with preference for sweet-tasting solutions (Colombo et al., 1997; Kampov-Polevoy et al., 1999; Lankford and Myers, 1994; Sinclair et al., 1992). Moreover, preference for both alcohol and sweet solutions may have a common genetic basis (Terenina-Rigaldie et al., 2003a,b). Nevertheless, there is little evidence to document the shift of preference from sweet solutions to alcohol with subsequent development of dependence. Spanagel and Hölter (1999) suggested that the development of dependence should also modify preference towards more concentrated ethanol solutions. In their study, a multiple choice of ethanol solutions was offered to the animals and consumption of each of the solutions was measured during 10 successive periods of 4 weeks, including 3 weeks of choice and 1 week of alcohol deprivation (water being the sole source of fluid).

The alcohol deprivation effect is defined as a temporary increase (from hours to days) in the voluntary intake of ethanol over baseline drinking conditions when alcohol is reinstated after a period of deprivation (Sinclair and Senter, 1967). The alcohol deprivation effect is a robust phenomenon that has been observed in rats (McKinzie et al., 1998; Rodd-Henricks et al., 2000a,b; Sinclair and Senter, 1967), mice (Salimov et al., 1993), monkeys (Kornet et al., 1990; Sinclair, 1971) and humans (Burish et al., 1981; Mello and Mendelson, 1972). An alcohol deprivation effect can be observed after a short (12 h or less; Sinclair and Li, 1989) or long (up to 75 days; Sinclair et al., 1973) deprivation interval, and the alcohol deprivation effect may persist long after observable withdrawal symptoms that usually dissipate within 1 week (Cicero et al., 1971; Waller et al., 1982). Furthermore, an alcohol deprivation effect may occur in animals in which the duration of exposure to ethanol is not sufficient to result in other indices of physical dependence (McKinzie et al., 1998; Sinclair and Senter, 1968). Additionally, there is evidence that the magnitude of the alcohol deprivation effect may be positively correlated with deprivation length (Heyser et al., 1997; Kornet et al., 1990; Sinclair et al., 1973) or repeated deprivation episodes (Rodd-Henricks et al., 2000a,b, 2001). An alcohol deprivation effect has been demonstrated in several rat lines selected for high alcohol intake, although its duration and intensity varies considerably among lines (Rodd-Henricks et al., 2000b), suggesting that specific genetic factors are involved in the transition between high ethanol intake and development of an alcohol deprivation effect. The alcohol deprivation effect has been hypothesized to be an animal model of alcohol craving (Heyser et al., 1997; Sinclair and Li, 1989) and has been used to examine the efficacy of pharmacological agents to prevent relapse drinking (Heyser et al., 1998; Kornet et al., 1991; Spanagel and Zieglgansberger, 1997). Other withdrawal symptoms, such as hyperreactivity in response to a mild stressor (novel environment) (Spanagel and Hölter, 1999), anxiety-related behaviour (Hölter et al., 1998) or hyperlocomotion (Hölter et al., 2000) have also been used to evaluate the degree of dependence (Waller et al., 1982).

The High-Ethanol Preferring line of rats (HEP), recently selected by Myers et al., (1998), is characterised by a high voluntary consumption of alcohol (3–4 g/kg/day for males and 6–8 g/kg/day for females, when a 10% ethanol solution is available) and a high sensitivity to taste reinforcement (saccharin, quinine) (Mormède et al., 2004; Terenina-Rigaldie et al., 2003b). We have shown previously that voluntary alcohol intake changes with continuous administration of a 10% alcohol solution, with males progressively increasing and females progressively decreasing their intake to the same level of approximately 7 g/kg/day after 6 months (Mormède et al., 2004), an amount approaching the elimination rate (7.56 and 9.10 g/kg/24 h in males and females, respectively; Terenina-Rigaldie et al., 2003b). Even after weeks of prolonged, high ethanol intake, however, these rats did not develop signs of dependence in alcohol consumption, showing instead a very brief, 30 min increase in ethanol drinking after 5 days of ethanol deprivation. Also, they decreased their intake of ethanol when adulterated by quinine and still preferred a saccharin solution to alcohol. In order to elucidate the factors involved in the transition from abuse to dependence and the biological mechanisms involved, the present experiments were designed to study whether different protocols of chronic ethanol administration could induce dependence, which could be measured by increases in alcohol intake, shifts of preference from saccharin to alcohol and the development of an alcohol deprivation effect.

2. Animals and methods

2.1. Animals

The animals used were HEP rats of both sexes born and raised in our laboratory from breeders from the S_6 and S_7 generations kindly provided by Robert D. Myers (East Carolina University at Greenville, NC, USA). These rats were genetically selected from an intercross between Sprague–Dawley and P (Li et al., 1993) rats for their high voluntary intake of alcohol (Myers et al., 1998). Housing conditions were: temperature maintained at 21 °C, 50–70% relative humidity, 12 h light/dark cycle with lights on at 07:00 and food available ad libitum. Throughout the duration of testing, all animals were weighed weekly. All procedures used in this study were in compliance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, 18 March 1986.

2.2. Procedures

2.2.1. Study 1: long-term presentation of multiple alcohol solutions

Nine male (mean weight 411 g) and nine female (243 g) HEP rats, 15 weeks old, were housed three per cage. Four bottles were continuously available during 3 weeks, and contained water, 5%, 10% and 20% (v/v) alcohol solutions. During the fourth week, the animals had access to water only (alcohol deprivation period). This sequence was repeated 10 times. Body and bottle weights were recorded once a week. Results are expressed as the mean preference (averaged over each 3-week period) for each of the four bottles as a percentage of total fluid drinking, and as the total amount of alcohol consumed (g) related to body weight. The cage was the experimental unit (n=3). The results were analysed by analysis of variance with sex as a between-animals factor and block and week within blocks as repeated measures.

2.2.2. Study 2: long-term drinking of a sweetened alcohol drink (ethanol 10%+saccharin)

A 10% ethanol solution was sweetened with saccharin (7.5 mM) as an incentive to increase the voluntary intake of ethanol, and presented as free choice vs. water. Abstinence periods were also introduced, because this procedure was suggested to develop dependence (Spanagel and Hölter, 1999). The preference for ethanol vs. saccharin was tested every 4 weeks and used as an index of the development of dependence for alcohol. The experiment lasted 40 weeks.

Eleven male (mean weight 460 g) and 11 female (260 g) HEP rats were kept in individual cages. The experiment was organised in 10 successive, 4-week series. During the first 3 weeks of each series (phase 1), rats had free access to two bottles, one with water and the other with a solution of ethanol (10% v/v) and saccharin (7.5 mM=1.34 g/l). The weights of the animals and of the bottles were measured every week. During the first 5 days of the fourth week in each series, rats were deprived of alcohol and had therefore access to water only. On the last 2 days of the week (phase 2), the animals were presented with two bottles, one containing a solution of ethanol only (10% v/v), the other containing a solution of saccharin (7.5 mM). The bottles were weighed every day. The data were expressed as the daily amount of ethanol ingested (g/kg), the total volume of fluid ingested daily (ml/kg) and preference ratios (alcohol/saccharin solution vs. total intake during phase 1; alcohol vs. saccharin solution during phase 2). The results were analyzed by analysis of variance with sex as a between-animals factor and series and week (phase 1) or day (phase 2) within series as repeated factors. Because of a technical problem, the data from the second phase of the 6th series are missing.

2.2.3. Study 3: long-term drinking of a sweetened alcohol drink, high concentration (ethanol 20%+saccharin)

An identical experiment was conducted with a 20% ethanol solution sweetened with saccharin, as an attempt to increase alcohol intake, for nine 4-week cycles. The subjects for this study were eleven male (mean weight 435 g) and 11 female (260 g) HEP rats housed in individual cages as in study 2. Because of a technical problem, the data from the second phase of the 2nd series are missing.

3. Results

3.1. Study 1: long-term presentation of multiple alcoholic drinks

For the total amount of ethanol consumed, the main effect of sex was not significant ($F_{1,4}$<1), unlike the effect of blocks (F(9,36)=5.12, P<0.001) and the sex × blocks interaction (F(9,36)=2.68, P<0.02). Fig. 1 shows that, as observed previously, males consumed less ethanol than females initially, and progressively increased their consump-

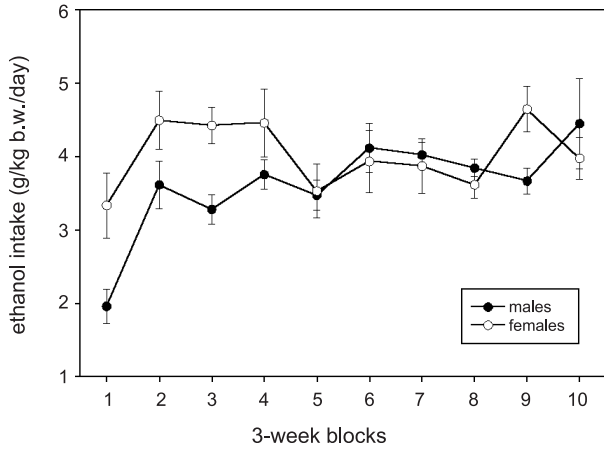

Fig. 1. Total ethanol consumption by male and female HEP rats given multiple choice among water and 5%, 10% and 20% ethanol solutions. Data are shown as the means of three cages with three animals in each cage, averaged over 3 successive weeks (blocks).

tion to reach the same levels as females (3.5−4.5 g/kg b.w.) from the 5th block on.

Fig. 2 shows the evolution of the preference for the various choices available. At the beginning of the experiment, males preferred water and low-concentration alcohol solution (5%). Preference for the 5% solution remained stable over the whole experiment; preference for the 10% solution increased, and preference for water decreased regularly, the preference for the most concentrated solution (20%) being stable. In females, the 5% solution was also preferred at the beginning of the experiment, and regularly decreased, so that water was the preferred fluid, the preference for the two most-concentrated solutions being stable over the experiment.

3.2. Study 2: long-term drinking of a sweetened alcohol solution (ethanol 10%+saccharin)

The data are shown in Fig. 3.

During the first phase of each series, when sweetened alcohol (vs. water) was presented for 30 weeks, the daily mean intake of alcohol was 4.20 g/kg for males and 8.63 g/kg for females (panel a), and the difference was highly significant ($F(1,209)=78.57$, $P<0.0001$). There was a significant effect of series ($F(9,180)=3.08$, $P<0.002$) and a significant sex×series interaction ($F(9,180)=4.19$, $P<0.001$). The latter resulted from the progressive increase in the difference between sexes over the whole experiment. For preference data, the main effects of sex ($F(1,20)=5.06$, $P<0.05$) and series ($F(9,180)=5.90$, $P<0.0001$) were significant, unlike their interaction ($F=1.00$). Both sexes preferred the ethanol/saccharin solution over water (panel c; overall mean: 66.2% for males and 79.7% for females). As for the total volume of fluid consumed, the main effects of sex ($F(1,20)=38.84$, $P<0.0001$), series ($F(9,180)=8.03$, $P<0.0001$) and their interaction ($F(9,180)=2.65$, $P<0.01$) were significant. However, the total fluid intake when the alcohol / saccharin solution was presented vs. water (phase 1; males: 82.6 ml/kg; females: 138.9 ml/kg) was much lower than when the saccharin-only solution was presented vs. alcohol (phase 2; males: 275.2 ml/kg; females: 445.2 ml/kg) (panel b).

In the second phase of each series, when the animals were offered the choice between saccharin and unsweetened alcohol, alcohol consumption was low (panel a; overall mean: 1.28 g/kg b.w./day for males and 2.04 g/kg b.w./day for females, the sex difference being almost significant, $F(1,20)=4.34$, $P<0.06$), the preference for saccharin exceeded the preference for the ethanol solution (overall preference for ethanol: 6.9% for males and 6.1% for females, the sex difference being not significant, $F(1,20)<1$). Consumption of alcohol was slightly higher on the first day of reinstatement of alcohol than on the second day (overall mean: 1.83 g/kg b.w. on day 1 and 1.48 g/kg b.w. on day 2, $F(1,20)=18.84$, $P<0.001$). The amount

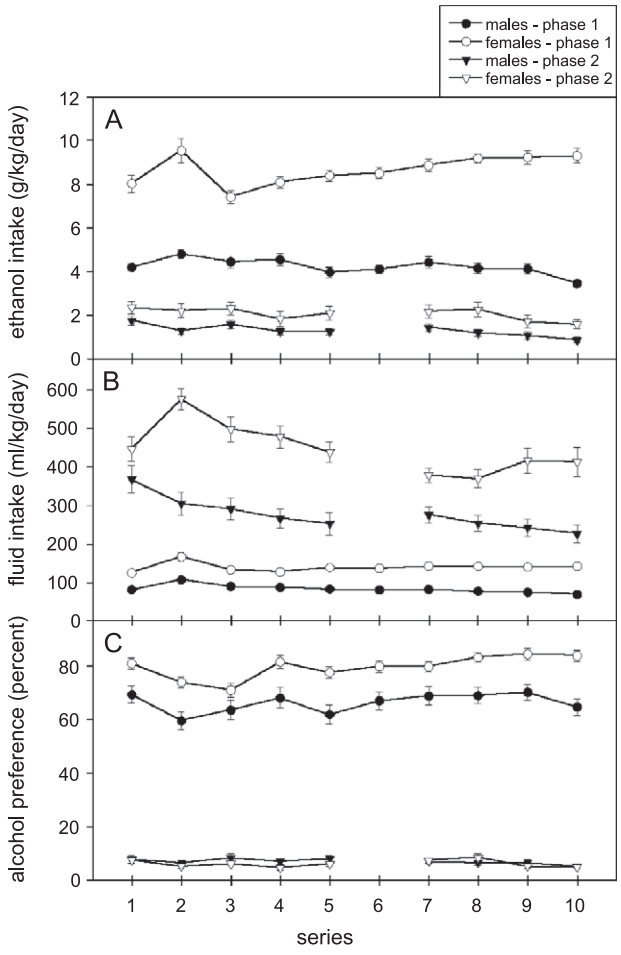

Fig. 3. Ethanol intake (panel A), total fluid intake (panel B) and preference ratio (alcohol/saccharin vs. total or alcohol vs. saccharin) (panel C) by male ($n=11$) and female ($n=11$) HEP rats offered the choice between an alcohol/saccharin solution for 3 weeks (phase 1) or, after 5 days of water-only, between ethanol and saccharin for 2 days (phase 2). This protocol was repeated for 10 series over a 40-week period.

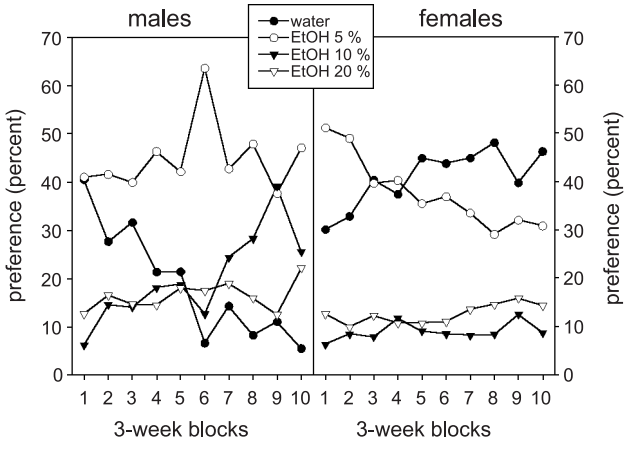

Fig. 2. Changes in preference for water and the different alcohol solutions presented as a free choice. Data are shown as the means of three cages with three animals in each cage, averaged over 3 successive weeks (blocks). Error bars are not shown for the sake of clarity.

of alcohol consumed during this phase decreased across series ($F(8,160)=3.61$, $P<0.001$) in both sexes (interaction sex×series, $F(8,160)=0.36$, $P<0.001$).

3.3. Study 3: long-term drinking of a sweetened alcohol drink, high concentration (ethanol 20%+saccharin)

The data are shown in Fig. 4.

During the first phase of each series, when alcohol was presented as a 20% solution sweetened with saccharin (vs. water), the overall mean intake of alcohol (over 27 weeks) was 4.72 g/kg for males and 6.68 g/kg for females (panel a), and the difference between sexes was almost significant ($F(1,20)=4.26$, $P<0.06$). The main effect of series was significant ($F(8,160)=5.97$, $P<0.0001$), but not the sex ×series interaction ($F(8,160)=1.80$, $P>0.05$). For preference data, the main effect of series ($F(8,160)=24.69$, $P<0.0001$) was significant, unlike the main effect of sex ($F(1,20)=2.55$, $P>0.10$) and their interaction ($F=1.59$, $P>0.10$). Both males and females preferred water over the ethanol/saccharin solution (panel c; overall preference for ethanol/saccharin: 45.6% for males and 39.2% for females, $F(1,20)=2.54$, $P>0.10$). As for the total volume of fluid consumed, the main effects of sex ($F(1,20)=18.69$, $P<0.001$), series ($F(8,160)=5.24$, $P<0.0001$) and their interaction ($F(8,160)=2.95$, $P<0.005$) were significant. However, their total fluid intake when this alcohol/saccharin solution was presented vs. water (phase 1; males: 68.4 ml/kg; females: 105.4 ml/kg) was much lower than when the saccharin-only solution was presented vs. alcohol (phase 2; males: 254.7 ml/kg; females: 473.5 ml/kg) (panel b).

In the second phase of each series, when the animals were offered the choice between saccharin and alcohol, alcohol drinking was low (panel a; overall mean: 0.84 g/kg b.w./day for males and 1.50 g/kg b.w./day for females, the sex difference between significant, $F(1,20)=4.87$, $P<0.05$), the preference for saccharin greatly exceeding the preference for the ethanol solution (overall preference for ethanol: 5.1% for males and for females). Consumption of alcohol was higher on the first day than on the second (overall mean: 1.28 g/kg b.w. on day 1 and 1.06 g/kg b.w. on day 2, $F(1,20)=10.14$, $P<0.005$). The amount of alcohol consumed during this phase did not change significantly across series.

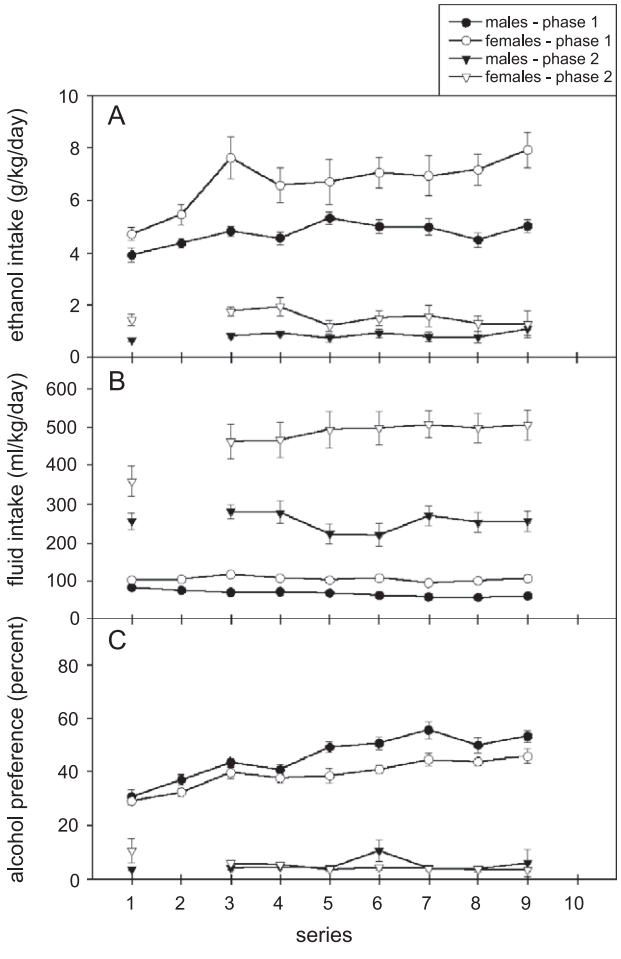

Fig. 4. Ethanol intake (panel A), total fluid intake (panel B) and preference ratio (alcohol/saccharin vs. total or alcohol vs. saccharin) (panel C) by male (n=11) and female (n=11) HEP rats offered the choice between an alcohol/saccharin solution for 3 weeks (phase 1) or, after 5 days of water-only, between ethanol and saccharin for 2 days (phase 2). This protocol was repeated for nine series over a 36-week period.

4. Discussion

Our previous work with HEP rats showed no evidence of development of dependence after long-term sustained alcohol intake (Mormède et al., 2004). In the present study, we subjected this strain to several protocols designed to favour the development of alcohol dependence.

The long-term presentation of multiple alcoholic concentrations (study 1) shows that the evolution of preference differed between sexes, with males increasing their preference for a more concentrated solution (together with an increased total intake), and females being rather stable. As shown previously, alcohol consumption reached the same level in males and females but altogether, the consumption was lower than previously shown (Mormède et al., 2004). This can be due to procedural factors like the way alcohol was distributed, or group housing. Indeed, it was shown that the consumption of alcohol is influenced by housing conditions and that isolation during development increases the consumption of alcohol (Rockman et al., 1986, 1988; Wolffgramm, 1990). Nevertheless, in the time frame studied here, there was neither evidence of any sharp increase in alcohol intake nor for the development of preference for the most concentrated alcohol solution. Spanagel and Hölter (1999) showed in Wistar rats that although preferences shifted towards more concentrated alcohol solutions during long-term intake, the total amount of ethanol progressively decreased, thus producing some uncertainty about the significance of this shift. The addition of repeated depriva-

tion periods was shown to be a more effective protocol to increase intake (Hölter et al., 1998). However, Rodd-Henricks et al. (2001) showed in the P line that the total amount of ethanol consumed and the shift of preference towards higher concentrations were only transient during the first 4–6 days following deprivation periods.

In the study of long-term drinking of sweetened alcohol solutions (study 2), the variation in alcohol consumption over the series, and the sex×series interaction resulted from the progressive increase in the difference between the sexes over the whole experiment. This sex difference is at variance with previous results where a 10% alcohol solution without saccharin was freely available for eight months. In these conditions, males and females converged towards a similar intake of approximately 7 g/kg (Mormède et al., 2004). The sustained high ethanol intake by females observed in the present study may be the result of their high sensitivity to reinforcement by saccharin (Terenina-Rigaldie et al., 2003b). Indeed, the present experiments show that the consumption of saccharin is diminished by the addition of alcohol because the volume of saccharin solution (without ethanol) consumed during the second phase of each block was much larger than the volume of saccharin with ethanol solution consumed during the first phase of each block. The reason why males did not increase their alcohol intake during the course of long-term consumption, however, is not clear at this point. Notwithstanding, this experimental protocol allows for the sustained consumption of significant amounts of alcohol, reaching, at least for females, the maximal amount that the animal can metabolise (Terenina-Rigaldie et al., 2003b). Consumption of alcohol was higher on the first day than on the second day of alcohol reinstatement, as a typical alcohol deprivation effect, that was, however, of short duration and very limited magnitude, and could be related to factors other than dependence, such as the novelty effect. Therefore, despite the sustained drinking of ethanol enhanced by the addition of saccharin, we observed no evidence for the development of alcohol dependence to alcohol; the animals always preferred saccharin to alcohol. The results of long-term drinking of a sweetened 20% alcohol solution (study 3) are very similar to those obtained in the previous experiment when alcohol was offered as a 10% solution with saccharin. It shows that, despite the presence of saccharin that is highly reinforcing to the animals, the intake of alcohol was not increased further with this higher concentration.

The major question is whether available animal models allow for the dissociation of alcohol abuse from alcohol dependence. Several procedures, based on forced administration or various free-choice protocols with abstinence periods, have been used to induce alcohol drinking in previously abstinent animals. Aufrère et al. (1997) studied changes in ethanol intake after chronic intoxication by inhalation of ethanol vapour in Wistar rats. Intoxicated animals increased their intake but the intensity of the response varied among individuals without any clear relationship to the level of intoxication. The results clearly showed in intoxicated animals two kinds of responders: alcohol-nonpreferring (27/95) and alcohol-preferring rats (68/95). In the alcohol-preferring rats, about 75% of the animals drank more than 7 g/kg per day, a result that the authors interpret as an indication of the development of dependence. Hölter et al. (1997, 1998, 2000) and Spanagel et al. (1996) studied the effects of repeated deprivation in outbred male Wistar rats that had been given free access to ethanol for several months. In these studies, the rats evinced increased alcohol intake following abstinence, and a shift of preference towards higher concentrations of ethanol solutions, i.e., a true alcohol deprivation effect, usually considered as indicative of dependence.

Among the different approaches discussed in the introduction, the development of an alcohol deprivation effect has been largely used to evaluate motivational factors and indeed large variations are observed among lines and even between replicated selection lines in the intensity and duration of the alcohol deprivation effect. Indeed, the HEP rat line shows a very short and limited alcohol deprivation effect when alcohol is reinstated after deprivation (Mormède et al., 2004). We also obtained with the same line of rats a sharp increase of saccharin solution intake when it was made available after a 5-day deprivation period (unpublished results). These data question the interpretation of the small magnitude alcohol deprivation effect as an index of dependence, and suggest that it may be due to other factors like novelty. Furthermore, the present experiments with various long-term administration protocols did not increase preference for alcohol solutions when offered as a free choice vs. the preferred saccharin solution, a shift that could have been expected in case alcohol dependence was developing. Therefore, chronic heavy alcohol drinking, as evinced by animals selected for high alcohol preference, does not necessarily induce dependence and specific genetic or environmental factors must be involved in the development of dependence in abusing individuals. The availability of a rat line resistant to the development of dependence will be useful for the search of these factors.

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References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, Fourth edition. American Psychiatric Association, Washington, DC.

Aufrère, G., Le Bourhis, B., Beaugé, F., 1997. Ethanol intake after chronic intoxication by inhalation of ethanol vapour in rats: behavioural dependence. Alcohol 14, 247–253.

Burish, T.G., Maisto, S.A., Cooper, A.M., Sobell, M.B., 1981. Effects of voluntary short-term abstinence from alcohol on subsequent drinking patterns of college students. J. Stud. Alcohol 42, 1013–1020.

Cicero, T.J., 1979. A critique of animal analogues of alcoholism. In: Majchrowicz, E., Noble, E.P. (Eds.), Biochemistry and Pharmacology of Ethanol. Plenum Press, New York, pp. 533–560.

Cicero, T.J., 1980. Animal models of alcoholism? In: Eriksson, K., Sinclair, J.D., Kiianmaa, K. (Eds.), Animal Models in Alcohol Research. Plenum Press, New York, pp. 99–117.

Cicero, T.J., Snider, S.R., Perez, V.J., Swanson, L.W., 1971. Physical dependence on and tolerance to alcohol in the rat. Physiol. Behav. 6, 191–198.

Cloninger, C.R., 1987. Neurogenetic adaptive mechanisms in alcoholism. Science 236, 410–416.

Colombo, G., Agabio, R., Diaz, G., Fa, M., Lobina, C., Reali, R., Gessa, G.L., 1997. Sardinian alcohol-preferring rats prefer chocolate and sucrose over ethanol. Alcohol 14, 611–615.

Crabbe, J.C., Phillips, T.J., Buck, K.J., Cunningham, C.L., Belknap, J.K., 1999. Identifying genes for alcohol and drug sensitivity: recent progress and future directions. Trends Neurosci. 22, 173–179.

Heyser, C.J., Schulteis, G., Koob, G.F., 1997. Increased ethanol self-administration after a period of imposed ethanol deprivation in rats trained in a limited access paradigm. Alcohol., Clin. Exp. Res. 21, 784–791.

Heyser, C.J., Schulteis, G., Durbin, P., Koob, G.F., 1998. Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats. Neuropsychopharmacology 18, 125–133.

Hölter, S.M., Landgraf, R., Zieglgansberger, W., Spanagel, R., 1997. Time course of acamprosate action on operant ethanol self-administration after ethanol deprivation. Alcohol., Clin. Exp. Res. 21, 862–868.

Hölter, S.M., Engelmann, M., Kirschke, C., Liebsch, G., Landgraf, R., Spanagel, R., 1998. Long-term ethanol self-administration with repeated ethanol deprivation episodes changes ethanol drinking pattern and increases anxiety-related behaviour during ethanol deprivation in rats. Behav. Pharmacol. 9, 41–48.

Hölter, S.M., Linthorst, A.C., Reul, J.M., Spanagel, R., 2000. Withdrawal symptoms in a long-term model of voluntary alcohol drinking in Wistar rats. Pharmacol. Biochem. Behav. 66, 143–151.

Hunter, B.E., Walker, D.W., Riley, J.N., 1974. Dissociation between physical dependence and volitional ethanol consumption: role of multiple withdrawal episodes. Pharmacol. Biochem. Behav. 2, 523–529.

Hunter, B.E., Riley, J.N., Walker, D.W., 1975. Ethanol dependence in the rat: a parametric analysis. Pharmacol. Biochem. Behav. 3, 619–629.

Kampov-Polevoy, A.B., Garbutt, J.C., Janowsky, D.S., 1999. Association between preference for sweets and excessive alcohol intake: a review of animal and human studies. Alcohol Alcohol. 34, 386–395.

Kornet, M., Goosen, C., Van Ree, J.M., 1990. The effect of interrupted alcohol supply on spontaneous alcohol consumption by rhesus monkeys. Alcohol Alcohol. 25, 407–412.

Kornet, M., Goosen, C., Van Ree, J.M., 1991. Effect of naltrexone on alcohol consumption during chronic alcohol drinking and after a period of imposed abstinence in free-choice drinking rhesus monkeys. Psychopharmacology (Berl.) 104, 367–376.

Lankford, M.F., Myers, R.D., 1994. Genetics of alcoholism: simultaneous presentation of a chocolate drink diminishes alcohol preference in high drinking HAD rats. Pharmacol. Biochem. Behav. 49, 417–425.

Li, T.K., Lumeng, L., Doolittle, D.P., 1993. Selective breeding for alcohol preference and associated responses. Behav. Genet. 23, 163–170.

Lumeng, L., Penn, P.E., Graff, T.M., Hawkins, T.D., Li, T.K., 1978. Further characterization of a new rat strain with high alcohol preference. In: Seixas, F.A. (Ed.), Currents in Alcoholism. Grune and Stratton, New York, pp. 23–35.

Marcucella, H., Munro, I., MacDonall, J.S., 1984. Patterns of ethanol consumption as a function of the schedule of ethanol access. J. Pharmacol. Exp. Ther. 230, 658–664.

Marfaing-Jallat, P., Le Magnen, J., 1982. Induction of high voluntary ethanol intake in dependent rats. Pharmacol. Biochem. Behav. 17, 609–612.

McKinzie, D.L., Nowak, K.L., Yorger, L., McBride, W.J., Murphy, J.M., Lumeng, L., Li, T.K., 1998. The alcohol deprivation effect in the alcohol-preferring P rat under free-drinking and operant access conditions. Alcohol., Clin. Exp. Res. 22, 1170–1176.

Meisch, R.A., 1984. Alcohol self-administration by experimental animals. In: Smart, R.G., Cappell, H.D., Glaser, F.B., Israel, Y., Kalant, H., Popham, R.E., Schmidt, W., Sellers, E.M. (Eds.), Research Advances in Alcohol and Drug Problems. Plenum Press, New York, pp. 23–45.

Mello, N.K., Mendelson, J.H., 1972. Drinking patterns during work-contingent and noncontingent alcohol acquisition. Psychosom. Med. 34, 139–164.

Mormède, P., Colas, A., Jones, B.C., 2004. High ethanol preferring rats fail to develop dependence following short- or long-term ethanol exposure. Alcohol Alcohol. 39, 183–189.

Myers, R.D., Veale, W.L., 1972. The determinants of alcohol preference in animals. In: Kissin, B., Begleiter, H. (Eds.), Biology of Alcoholism. Plenum Press, New York, pp. 131–168.

Myers, R.D., Robinson, D.E., West, M.W., Biggs, T.A., McMillen, B.A., 1998. Genetics of alcoholism: rapid development of a new high-ethanol preferring (HEP) strain of female and male rats. Alcohol 16, 343–357.

Pohorecky, L.A., 1981. Animal analog of alcohol dependence. Fed. Proc. 40, 2056–2064.

Roberts, A.J., Heyser, C.J., Cole, M., Griffin, P., Koob, G.F., 2000. Excessive ethanol drinking following a history of dependence: animal model of allostasis. Neuropsychopharmacology 22, 581–594.

Rockman, G.E., Borowski, T.B., Glavin, G.B., 1986. The effects of environmental enrichment on voluntary ethanol consumption and stress ulcer formation in rats. Alcohol 3, 299–302.

Rockman, G.E., Hall, A.M., Markert, L.E., Glavin, G.B., 1988. Influence of rearing conditions on voluntary ethanol intake and response to stress in rats. Behav. Neural Biol. 49, 184–191.

Rodd-Henricks, Z.A., McKinzie, D.L., Shaikh, S.R., Murphy, J.M., McBride, W.J., Lumeng, L., Li, T.K., 2000a. Alcohol deprivation effect is prolonged in the alcohol preferring (P) rat after repeated deprivations. Alcohol., Clin. Exp. Res. 24, 8–16.

Rodd-Henricks, Z.A., McKinzie, D.L., Murphy, J.M., McBride, W.J., Lumeng, L., Li, T.K., 2000b. The expression of an alcohol deprivation effect in the high-alcohol-drinking replicate rat lines is dependent on repeated deprivations. Alcohol., Clin. Exp. Res. 24, 747–753.

Rodd-Henricks, Z.A., Bell, R.L., Kuc, K.A., Murphy, J.M., McBride, W.J., Lumeng, L., Li, T.K., 2001. Effects of concurrent access to multiple ethanol concentrations and repeated deprivations on alcohol intake of alcohol-preferring rats. Alcohol., Clin. Exp. Res. 25, 1140–1150.

Rogers, J., Wiener, S.G., Bloom, F.E., 1979. Long-term ethanol administration methods for rats: advantages of inhalation over intubation or liquid diets. Behav. Neural Biol. 27, 466–486.

Salimov, R., Salimova, N., Klodt, P., Maisky, A., 1993. Interaction between alcohol deprivation and morphine withdrawal in mice. Drug Alcohol Depend. 34, 59–66.

Sinclair, J.D., 1971. The alcohol-deprivation effect in monkeys. Psychon. Sci. 25, 1–22.

Sinclair, J.D., Li, T.K., 1989. Long and short alcohol deprivation: effects on AA and P alcohol-preferring rats. Alcohol 6, 505–509.

Sinclair, J.D., Senter, R.J., 1967. Increased preference for ethanol in rats following deprivation. Psychon. Sci. 8, 11–12.

Sinclair, J.D., Senter, R.J., 1968. Development of an alcohol-deprivation effect in rats. Q. J. Stud. Alcohol 29, 863–867.

Sinclair, J.D., Adkins, J., Walker, S., 1973. Morphine-induced suppression of voluntary alcohol drinking in rats. Nature 246, 425–427.

Sinclair, J.D., Kampov-Polevoy, A., Stewart, R., Li, T.K., 1992. Taste preferences in rat lines selected for low and high alcohol consumption. Alcohol 9, 155–160.

Spanagel, R., Hölter, S.M., 1999. Long-term alcohol self-administration with repeated alcohol deprivation phases: an animal model of alcoholism? Alcohol Alcohol. 34, 231–243.

Spanagel, R., Zieglgansberger, W., 1997. Anti-craving compounds for ethanol: new pharmacological tools to study addictive processes. Trends Pharmacol. Sci. 18, 54–59.

Spanagel, R., Hölter, S.M., Allingham, K., Landgraf, R., Zieglgansberger, W., 1996. Acamprosate and alcohol: I. Effects on alcohol intake following alcohol deprivation in the rat. Eur. J. Pharmacol. 305, 39–44.

Terenina-Rigaldie, E., Jones, B.C., Mormède, P., 2003a. Pleiotropic effect of a locus on chromosome 4 influencing alcohol drinking and emotional reactivity in rats. Genes Brain Behav. 2, 125–131.

Terenina-Rigaldie, E., Moisan, M.P., Colas, A., Beaugé, F., Shah, K.V., Jones, B.C., Mormède, P., 2003b. Genetics of behavior: phenotypic and molecular study of rats derived from high- and low-alcohol consuming lines. Pharmacogenetics 13, 543–554.

Veale, W.L., Myers, R.D., 1969. Increased alcohol preference in rats following repeated exposures to alcohol. Psychopharmacologia 15, 361–372.

Waller, M.B., McBride, W.J., Lumeng, L., Li, T.K., 1982. Induction of dependence on ethanol by free-choice drinking in alcohol-preferring rats. Pharmacol. Biochem. Behav. 16, 501–507.

Wolffgramm, J., 1990. Free choice ethanol intake of laboratory rats under different social conditions. Psychopharmacology (Berl) 101, 233–239.

Wolffgramm, J., Heyne, A., 1995. From controlled drug intake to loss of control: the irreversible development of drug addiction in the rat. Behav. Brain Res. 70, 77–94.