ELSEVIER

Pharmacology, Biochemistry and Behavior 73 (2002) 225–231

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Enduring effects of environmental enrichment on novelty seeking, saccharin and ethanol intake in two rat lines (RHA/Verh and RLA/Verh) differing in incentive-seeking behavior

A. Fernández-Teruel[a,*], P. Driscoll[b], L. Gil[a], R. Aguilar[a], A. Tobeña[a], R.M. Escorihuela[a]

[a]*Medical Psychology Unit, Department of Psychiatry and Forensic Medicine, School of Medicine, Autonomous University of Barcelona, Bellaterra 08193, Barcelona, Spain*

[b]*Institut für Nutztierwissenschaften, ETH Standort Schwerzenbach, Schwerzenbach CH-8603, Switzerland*

Received 10 September 2001; received in revised form 5 February 2002; accepted 11 February 2002

Abstract

The Roman high- and low-avoidance (RHA/Verh and RLA/Verh) rat lines represent, respectively, low emotional/anxious and high novelty seeker vs. high emotional/anxious and low novelty seeker profiles. In the present study, RLA/Verh and RHA/Verh rats, either reared in pairs from weaning (untreated) or reared in groups of 8–10 in an enriched environment until the age of 7 months, were tested for exploratory and novelty-seeking behavior in the hole board (including novel objects under the holes), as well as for their preference for saccharin–water and ethanol–water in a two-bottle free-choice paradigm. Testing started when rats were 20 months old in order to study the long-lasting effects of differential rearing. RHA/Verh rats explored more and showed greater preference for (and intake of) saccharin as well as for ethanol than RLA/Verh rats, thus confirming their validity as a rat model for sensation/reward seeking. Environmental enrichment (EE) increased head-dipping behavior (i.e., novelty seeking) in both rat lines, without affecting locomotor activity. EE treatment increased the preference for, and volume intake of, saccharin (especially at the higher concentrations tested) in the relatively low saccharin-preferring RLA/Verh rats, and also enhanced ethanol consumption in both rat lines. Thus, the results demonstrate consistent and enduring effects of EE on incentive-seeking behavior and further the analysis of how individual differential predispositions for the need of novelty and contact with (or consumption of) rewarding substances arise through either biological (genetic) or early environmental factors, or both. © 2002 Published by Elsevier Science Inc.

Keywords: Novelty/sensation seeking; Reward seeking; RHA–RLA/Verh rats; Environmental enrichment

1. Introduction

The Swiss sublines of Roman high-avoidance (RHA/Verh) and low-avoidance (RLA/Verh) rats, psychogenetically selected for rapid (RHA/Verh) vs. extremely poor (RLA/Verh) two-way active avoidance acquisition in the shuttle box, differ in many other behavioral and neuroendocrine/neurochemical characteristics, which consistently indicate that the RLA/Verh line presents higher emotionality/anxiety and reactivity to a variety of stressful situations (for reviews, see Driscoll and Bättig, 1982; Driscoll et al., 1998; Escorihuela et al., 1995; Fernández-Teruel et al., 1997; Steimer et al., 1997).

At the same time, there is an important body of behavioral and neurobiological evidence indicating that RHA/Verh rats are a good model for novelty (or sensation) seeking (Driscoll et al., 1998; Escorihuela et al., 1999; Fernández-Teruel et al., 1997; Siegel, 1997). Compared to RLA/Verh rats, RHA/Verh rats show: (i) higher levels of exploratory behavior in tests of novelty seeking (as, for instance, in the hole board test in the presence of novel objects; Escorihuela et al., 1999; Fernández-Teruel et al., 1992, 1997); (ii) higher preference for alcohol (Driscoll et al., 1990; Giorgi et al., 1996; Razafimanalina et al., 1996) as well as for saccharin and quinine solutions (Martin and Bättig, 1980; Razafimanalina et al., 1996); (iii) higher impulsivity during the acquisition of a DRL-20 task (i.e., reduced inhibition of irrelevant activity; Zeier et al., 1978), as also seen with sensation-seeking cats (Siegel, 1997); (iv) less sensitivity to aversive effects of lateral hypothalamic

* Corresponding author. Tel.: +34-3-581-1225; fax: +34-3-581-1435.
E-mail address: fernandez.teruel@uab.es (A. Fernández-Teruel).

0091-3057/02/$ – see front matter © 2002 Published by Elsevier Science Inc.
PII: S0091-3057(02)00784-0

stimulation (measured as escape behavior from the rewarded compartment; Lipp, 1979); and (v) stronger mesolimbic dopaminergic responses to drugs of abuse (e.g., cocaine, morphine, Giorgi et al., 1997a; including alcohol, Giorgi et al., 1997b).

Several studies with humans have revealed such associations among exploration, impulsivity, alcohol consumption and substance abuse (e.g., Moss et al., 1992; Nagoshi et al., 1991). Furthermore, human research on sensation seeking has additionally shown that high sensation seekers show increasing amplitudes (i.e., augmenting) of the P1 and N1 components of the visual-evoked potential (VEP) to increasing intensities of light flash, whereas low sensation seekers show reducing VEP amplitudes as a function of increasing flash intensity (Zuckerman, 1996). As in humans and cats, which are high sensation seekers, RHA/Verh rats showed a very consistent pattern of VEP augmenting, while RLA/Verh rats, as well as a group of Wistar rats studied, showed a VEP-reducing pattern (Siegel, 1997; Siegel and Driscoll, 1996; Siegel et al., 1993).

It is also known that novelty-seeking behavior (e.g., enhanced specific exploration of novel situations, unknown objects or stimuli) can be permanently increased as a consequence of particular early experiences such as living under environmentally enriched conditions (see, for instance, Bardo et al., 1996; Fernández-Teruel et al., 1992, 1997; Renner and Rosenzweig, 1987). In addition to an increase in novelty seeking, the preference for ethanol solutions and the sensitivity to amphetamine-conditioned place preference have been shown to be higher in rats reared in an enriched environment compared to group-housed controls (Bowling and Bardo, 1994; Rockman et al., 1986, 1988). Moreover, relative to impoverished (i.e., isolated) rats, EE rats more readily self-administer cocaine and barbital (Bardo et al., 1996). As no group-housed controls were included, however, the interpretation of the results of those studies is difficult, as several studies have shown differences in drug-taking (as well as in exploration and novelty seeking) behavior between social rearing and isolation rearing conditions (for a review, see Bardo et al., 1996). At the same time, studies testing EE effects on drug-taking behavior (or on drug-induced, conditioned place preference) have tested the effects of enrichment shortly (or immediately) after the treatment is finished. Thus, to our knowledge, no study has thus far evaluated whether EE can permanently affect different behavioral aspects related to the novelty/sensation-seeking construct (e.g., specific exploration of novelty, preference for rewarding substances). Likewise, studies testing the ability of EE to enduringly modify divergent, and genetically based, novelty- and drug-seeking profiles are also lacking.

As described above, the psychogenetically selected Roman/Verh rat lines appear to be a valid laboratory model of divergent sensation-seeking profiles. Thus, the aims of the present work were: (1) to evaluate both rat lines in a novelty-seeking test; (2) to test for their preference for rewarding substances, i.e., saccharin and ethanol; and (3) to investigate the long-term effects of EE treatment on their novelty and substance-seeking profiles, in order to see whether their genetically based predispositions can be enduringly modified by the experience.

2. Materials and methods

2.1. Subjects

The subjects were 30 RHA/Verh (RHA) and 30 RLA/Verh (RLA) male rats. They were born at the Barcelona laboratory, from RHA/Verh and RLA/Verh females originating in Switzerland. Except for the periods of EE (see below) and testing, the rats were housed in pairs in macrolon cages. They were maintained under controlled conditions of 22 ± 2 °C, a 12-h light–dark cycle (lights on at 0900 h), with food and water freely available.

2.2. EE and experimental groups

Half of the rats from each rat line ($n = 15$ per rat line) were reared in enriched environments between 1 and 7 months of age. EE treatment consisted of placing seven to eight rats (same line) into $100 \times 43 \times 50$ cm wire mesh (including the floor) cages containing several objects and "playthings" (e.g., rubber balls of different sizes, plastic and metallic miniature cars, plastic and cardboard geometric figures, sticks, ropes with hanging objects, etc.) selected to provide a variety of shapes, colours, textures and movements when the rats contacted them. These objects were partially changed every 2 days. The internal spatial configuration of the EE cages was also changed every 2 days, creating different spaces and floors by using several types of stairs, ropes, tunnels and platforms. The EE animals had food and water freely available throughout the EE period. The EE cages were provided with sawdust (changed twice a week) in a container placed 2 cm below the wire mesh floor.

When 7 months old (i.e., after 6 months of EE treatment), the rats were housed in pairs in macrolon cages (identically to the control rats) until the beginning of testing.

Thus, each of the following experiments consisted of four experimental groups: RHA-C, RHA-EE, RLA-C and RLA-EE, where 'C' were untreated (control) rats and 'EE' were rats submitted to the EE treatment.

As we were interested in the long-lasting effects of EE treatment, testing was initiated when animals were 20 months old. Rats were individually housed the last 2 weeks before starting Experiment 1 and throughout the whole experimental period.

2.3. Experiment 1: saccharin–water choice

Rats were tested in a two-bottle free-choice procedure to determine their preference, or not, for saccharin. Animals

were first presented, for four consecutive days, with water from two bottles in their homecages. After this habituation period, they were presented with two bottles, one containing tap water and the other containing one of the six concentrations of saccharin : 0.004%, 0.008%, 0.016%, 0.032%, 0.064% and 0.128%. The rats were exposed to graduated concentrations of saccharin for each of two consecutive days, and the position of the bottles was rotated daily to prevent place preference. Fresh saccharin solutions were prepared daily, in the morning, and the consumed volumes were monitored every day at 10 h.

As the quantity of substance consumed in a two-bottle choice test depends upon the total fluid consumed, an adjusted ''preference index'' was calculated by subtracting the 'expected consumption' (under the null assumption of no preference for any solution; thus, ''expected consumption=total fluid consumed/2'') from the actual amount of saccharin consumed (i.e., preference index = actual consumption − expected consumption) (see Meliska et al., 1995).

The free-choice experiment lasted 12 days.

2.4. Experiment 2: novelty seeking in the hole board test

One month after finishing Experiment 1, the rats were evaluated in the hole board test. The hole board apparatus was a raised, white, 66 × 66 × 47-cm wooden box (divided into 16 equal squares), containing four holes (diameter: 3.7 cm) in the floor. Four identical objects (plastic balls partially hidden in metal containers) were placed under the holes because it has been reported that specific novelty seeking (i.e., seeking for novel stimuli), rather than non-specific exploratory behavior or locomotor activity, is measured with that procedure (Escorihuela et al., 1999). Care was taken to select a configuration of objects that was unknown to EE-treated rats. Ambulation, head-dipping and self-grooming were measured for 5 min.

After Experiment 1, five animals from each group were kept for neurochemical studies, and two animals (from RHA-C and RLA-C) were excluded from the hole board and ethanol (see below) experiments because of technical problems, leaving $n = 9-10$ in Experiments 2 and 3.

2.5. Experiment 3: ethanol–water choice

One month after finishing hole board testing, the rats were given a choice between tap water and ethanol (10% vol/vol) for four consecutive days. The two-bottle choice procedure was identical to that of Experiment 1. Fresh ethanol solutions were prepared every day in the morning. 'Preference index' was calculated as in Experiment 1.

The ethanol free-choice experiment lasted only 4 days in order to prevent dependency and lasting neurobiological effects of ethanol that could affect future neurochemical studies with the brains of those animals.

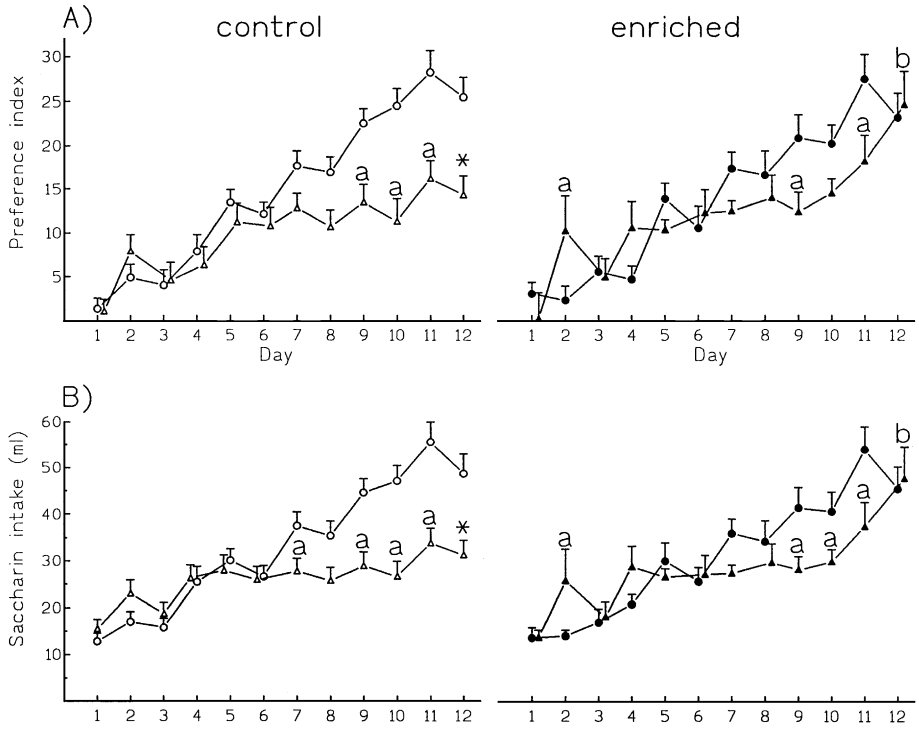

Fig. 1. (A) Preference index (see Materials and Methods) and (B) saccharin intake in control (left) and enriched (right) rats from RHA/Verh (circles) and RLA/Verh (triangles) lines. Data represent mean ± S.E.M. [a]$P < .05$ vs. the corresponding RHA group (same treatment); [b]$P < .05$ vs. the corresponding control group (same line); * $P < .05$ vs. all groups (all comparisons with Duncan's tests).

2.6. Statistical analysis

Data from Experiment 1 were analyzed by multivariate analysis of variance for repeated measures (MANOVA, '2 Lines × 2 Treatment conditions × Days'). Factorial 2 × 2 ANOVAs ('2 Lines' × '2 Treatment conditions') were applied to data from Experiments 2 and 3. Between-group comparisons after significant analyses of variance were performed by Duncan's multiple range tests. As results from previous studies permitted the formulation of hypotheses on the direction of effects (both regarding between-line differences and enrichment effects), one-tailed significances were employed.

3. Results

3.1. Experiment 1: saccharin–water choice

There was a general increase in saccharin consumption across days, as indicated by significant 'Day' effects in preference index and saccharin intake [Fig. 1A and B; $F(11,638) > 63.11$, $P < .0001$]. The MANOVA analysis also indicated that rats from the RHA line showed a higher preference index and a greater saccharin intake across days than RLA rats ['Line × Day' interaction: $F(11,638) > 9.12$, $P < .0001$]. Moreover, EE increased the preference index in RLA rats (at several days of the experiment) but not in RHA rats, as indicated by the significant 'Line × Enrichment × Day' interaction [$F(11,638) = 1.91$, $P < .05$; and the same tendency for 'saccharin intake,' $F(11,638) = 1.67$, $P < .077$]. As can be seen in Fig. 1A, this three-way interaction is explained by several findings: (1) enriched RLA (RLA-EE) rats showed higher preferences for saccharin than the corresponding RHA group on Day 2 ($P < .05$, Duncan's test); (2) the RLA-EE group also displayed higher preferences for the sweet solution than control RLA rats on the last day of testing ($P < .05$, Duncan's test); and (3) whereas control RLA rats showed significantly lower preferences for saccharin than control RHA rats along the last 4 days of testing ($P < .05$, Duncan's tests), that was not the case for RLA-EE rats, as their preference index did not differ from that of control RHA rats in Days 10 and 12, thus reflecting again the relative enhancing effects of EE treatment on preference for the sweetener in RLA rats (see Fig. 1A).

3.2. Experiment 2: novelty seeking in the hole board test

As shown in Fig. 2A and B, RHA rats ambulated more and spent more time head dipping than RLA rats on the hole board [two-way ANOVA, 'Line' effects: $F(1,37) = 44.14$, $P < .0001$ and $F(1,37) = 8.5$, $P < .01$, respectively]. EE increased exploration of the holes as indicated by a significant treatment effect on the time spent head dipping ['Enrichment' effect, $F(1,37) = 36.46$, $P < .0001$]. It is important to notice that such an effect was specific for the

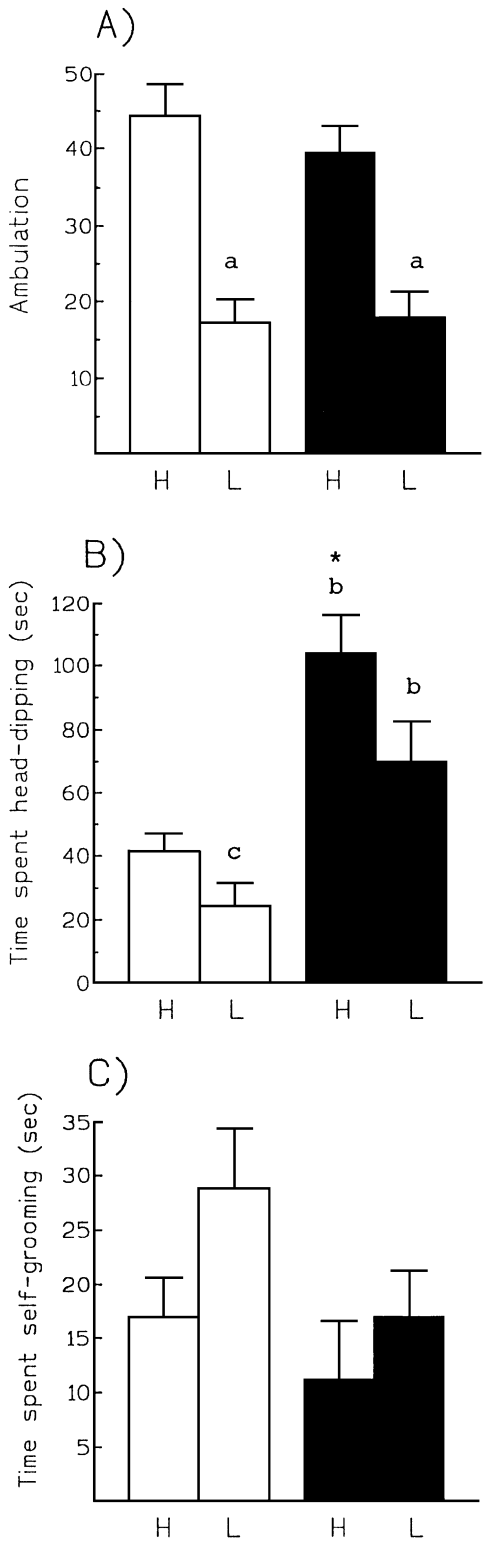

Fig. 2. (A) Ambulation (squares crossed), (B) time (in seconds) spent head dipping and (C) time (in seconds) spent self-grooming in the hole board. Mean ± S.E.M. values are represented. White bars indicate control groups and black bars enriched ones. H and L are RHA/Verh and RLA/Verh lines, respectively. [a]$P < .05$ vs. the corresponding RHA group (same treatment); [b]$P < .05$ vs. the corresponding control group (same line); [c]$P < .05$ (one-tailed) vs. RHA control group; *$P < .05$ vs. all groups (all comparisons with Duncan's tests).

exploration measure and independent of activity, as no significant treatment effects appeared on ambulation [$F(1,37)=0.29$, n.s.; Fig. 2A]. 'Line' and 'Enrichment' effects on the time spent self-grooming only approached significance [$F(1,37)=3.4$, $P=.07$ and $F(1,37)=3.3$, $P=.075$, respectively; Fig. 2C], but were in the expected direction, i.e., less time spent self-grooming in RHA/Verh than in RLA/Verh rats, and a tendency toward a reduction of self-grooming in enriched animals.

3.3. Experiment 3: ethanol–water choice

Results from this experiment are shown in Fig. 3. ANOVA analysis indicated that preference index and alcohol intake were higher in RHA/Verh rats as compared to RLA/Verh rats ['Line' effects: $F(1,37)=33.18$, $P<.0001$ and $F(1,37)=7.6$, $P<.01$, respectively]. EE significantly increased both parameters in both rat lines ['Enrichment' effect: $F(1,37)=9.58$, $P<.01$ and $F(1,37)=6.7$, $P<.05$], although that effect was more pronounced in RHA rats ($P<.05$ between both RHA groups, Duncan's test; Fig. 3A). A similar pattern of 'Line' and 'Enrichment' effects [$F(1,37)=6.5$, $P<.02$ and $F(1,37)=8.0$, $P<.01$, respectively] appeared when expressing ethanol consumption as a function of rats' body weight (see Table 1).

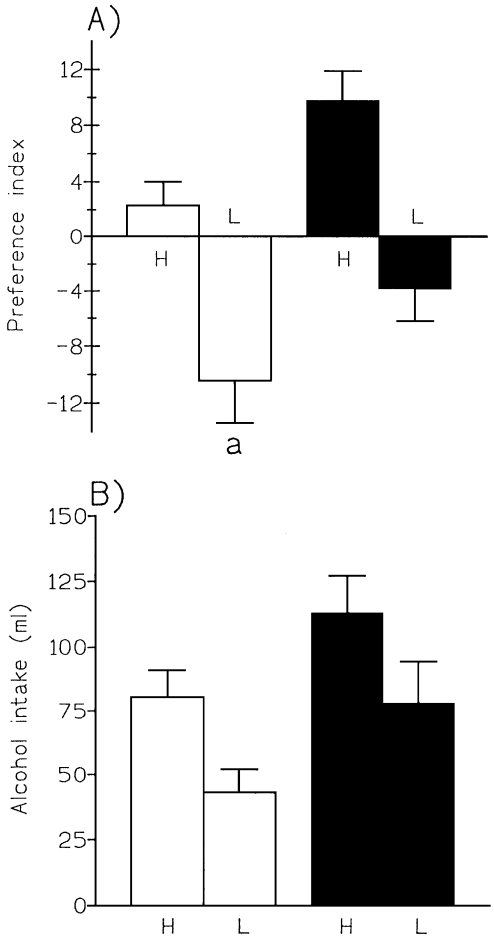

Fig. 3. (A) Preference index (see Materials and Methods) and (B) alcohol intake during the 4-day, two-bottle-choice alcohol experiment. Mean ± S.E.M. values of total ingestion measures are represented. White bars indicate control groups and black bars enriched groups. H and L are RHA/Verh and RLA/Verh lines, respectively. [a] $P<.05$ vs. the corresponding RHA group (same treatment; Duncan's test).

Table 1
Total ethanol consumption as a function of body weight

	Control RHA	Enriched RHA	Control RLA	Enriched RLA
Mean	14.3	23.4 *	8.5**	15.1***
S.E.M.	2.3	3.2	1.9	3.1

Values represented are in grams per kilogram. $n=9-10$/group.
* $P<.025$ vs. all groups (one-tailed Duncan's tests).
** $P<.05$ vs. control RHA.
*** $P<.05$ vs. control RLA.

3.4. Correlations among measures

Pearson correlation coefficients were obtained by pooling the animals tested in the three experiments ($n=38$). The only correlations found among the different dependent measures of the three experimental procedures appeared between the time spent head dipping and saccharin intake during the last 2 days (i.e., total saccharin intake at the highest concentration; $r=.27$, $P<.05$, one-tailed probability), as well as between both the time spent head dipping and number of head dips and total ethanol intake (milliliters of ethanol solution consumed during the 4 days; $r=.45$, $P<.03$ and $r=.41$, $P<.005$, one-tailed probabilities).

4. Discussion

The observations that RHA/Verh rats drank more saccharin (especially at the highest concentrations) and ethanol, while also showing higher exploratory behavior in the hole board test (including novel objects under the holes) than RLA/Verh rats, are in agreement with previously reported findings (e.g., Driscoll et al., 1998; Escorihuela et al., 1999; Fernández-Teruel et al., 1992; Giorgi et al., 1996; Razafimanalina et al., 1996). These results further support the contention that RHA/Verh rats are high sensation/novelty and substance seekers, as compared to their RLA/Verh counterparts (Fernández-Teruel et al., 1997; Siegel and Driscoll, 1996). Moreover, they also show that such between-line, divergent profiles are extremely long-lasting.

The main finding of the present study was that a 6-month exposure to EE permanently affected hole board novelty seeking (i.e., head dipping), as well as saccharin and ethanol intake, and that such EE effects were dependent upon the rat line and/or the particular test considered. Thus, whereas saccharin intake was increased by EE only in RLA/Verh rats (especially at some higher concentrations), EE treatment

enhanced head-dipping behavior and ethanol consumption in both rat lines, while not affecting motor activity in the former test.

A closer look at line and EE effects on saccharin consumption reveal several interesting aspects. Thus, the 'Line × Day' and 'Line × EE × Day' significant effects found (especially in the analysis of the 'Preference index'), in conjunction with the between-group differences observed (see Duncan's tests in Results section), indicate that: (1) RLA/Verh rats actually showed a trend for a higher preference for saccharin than RHA/Verh rats at the two lowest concentrations (especially evident in the EE-treated RLA/Verh group); (2) from the third concentration (0.016%) to the last one (0.128%), RHA/Verh rats showed higher preference for (and drank higher volumes of) the substance than their RLA/Verh counterparts; and (3) EE treatment increased saccharin preference and volume intake in RLA/Verh rats, especially at the lowest and highest concentrations. A consequence of this was that, while control RLA/Verh rats consumed significantly lower volumes of saccharin (and showed lower preference for it) than control RHA/Verh rats during the last 4 days, EE-treated RLA/Verh rats did not differ from control RHA/Verh rats by the end of the experiment. Therefore, the genetic, relatively low saccharin preference of RLA/Verh rats (observed at the three highest concentrations, in agreement with Razafimanalina et al., 1996) is partially (but long-lastingly) affected by EE.

In the ethanol preference/aversion experiment, animals were submitted to the two-bottle choice (ethanol 10% vol/vol vs. water) procedure for only 4 days in order to prevent the induction of dependency and/or lasting neurobiological effects. The experiment showed that RHA/Verh rats consumed more ethanol and displayed higher preference for it than RLA/Verh rats ('Line' effect; see Results section), whereas EE treatment increased ethanol intake in both rat lines. It is worth mentioning that only RHA/Verh rats, and especially the EE-treated ones, showed some preference for ethanol. RLA/Verh rats did not prefer ethanol, and even showed aversion for it, in agreement with previous observations from other laboratories (Beaugé et al., 1994; Driscoll et al., 1990; Giorgi et al., 1996; Razafimanalina et al., 1996). Nevertheless, it is important to note that EE treatment moderately reduced the relative aversion for ethanol in RLA/Verh rats, even though the between-line differences remained.

The association observed between head dipping (i.e., novelty seeking) in the hole board, and both saccharin intake at the 0.128% concentration and ethanol consumption, is in line with the hypothesis that there is a connection between a behavior reflecting preference for novelty (or new stimulation) and the preference for rewarding substances (i.e., positive reinforcing), as has been proposed in human personality theories of sensation/novelty seeking (e.g., Bardo et al., 1996; Zuckerman, 1996). These theories suggest a relationship between novelty/sensation seeking, disinhibited behavior and drug taking, which are hypothesized to share common neurobiological mechanisms. As reviewed by Driscoll et al. (1998), the system of most interest in this regard appears to be the mesoaccumbens dopaminergic projection, which has proven to be of particular value in assessing the effects of cocaine, morphine and alcohol (Giorgi et al., 1997a,b). All of these drugs not only induce locomotor activation in RHA/Verh rats only, but they induce increments in the output of dopamine in the shell area of the nucleus accumbens, also only in the RHA/Verh line (Giorgi et al., 1997a,b).

On the other hand, the present results also indicate that there is apparently no direct relationship between trait anxiety (which is relatively higher in RLA/Verh rats; Driscoll et al., 1998; Escorihuela et al., 1995, 1999; Fernández-Teruel et al., 1997; Steimer et al., 1997) and alcohol or saccharin consumption, thus lending further support to the contention that novelty seeking (as a trait) has probably a more important role in incentive (or substance)-seeking behavior (e.g., Zuckerman, 1996).

Two main conclusions can be drawn from the present results and the related literature. (1) The Roman/Verh rat lines appear to be a unique animal model for the study of neurobehavioral traits related to novelty/sensation seeking, as they present a number of genetically based behavioral, physiological and neurochemical differences that closely resemble the characteristics defining human novelty/sensation seekers (e.g., Driscoll et al., 1998; Zuckerman, 1996). In particular, compared to the RLA/Verh line, RHA/Verh rats show reduced HPA axis activity after stress, increased activation of the mesocorticolimbic dopaminergic pathway in response to drugs of abuse, enhanced preference for rewarding substances, increased impulsivity, and a VEP-augmenting pattern (for reviews, see Driscoll et al., 1998; Giorgi et al., 1997a; Siegel, 1997; Steimer et al., 1997). (2) The present study also shows that those genetically divergent novelty- and substance-seeking patterns can be enduringly modified (to the point of considerably reducing the between-line differences) by rearing in an enriched environment. One may hypothesize that specific early experiences, such as the aforementioned or neonatal handling (Fernández-Teruel et al., 1997), interacting with biological predispositions, can enduringly change the need for novelty and for substance/drug seeking by inducing modifications in both susceptibility to reward (as, for instance, was recently suggested by Campbell and Spear, 1999, using neonatal handling) and in corresponding neurochemical/neuroendocrine systems.

Acknowledgments

The authors gratefully acknowledge Dr. Lydia Giménez-Llort for help with the manuscript. This work was supported by FIS (99/1230), DGICYT (PM96-0068) and SGR (2000SGR-00071) grants. R.A. and L.G. were supported by DGR (1998FI 00158PG) and BFPI (AP98-36154188) fellowships, respectively.

References

Bardo MT, Donohew RL, Harrington NG. Psychobiology of novelty seeking and drug seeking behavior. Behav Brain Res 1996;77:23–43.

Beaugé F, Sébire N, Vesperini D, Aufrère G, Driscoll P. Ethanol consumption in a free choice situation after chronic inhalation in Roman high- and low-avoidance rats. Alcohol: Clin Exp Res 1994;18:49A.

Bowling SL, Bardo MT. Locomotor and rewarding effects of amphetamine in enriched, social and isolate reared rats. Pharmacol, Biochem Behav 1994;48:459–64.

Campbell J, Spear LP. Effects of early handling on amphetamine-induced locomotor activation and conditioned place preference in the adult rat. Psychopharmacology 1999;143:183–9.

Driscoll P, Bättig K. Behavioral, emotional and neurochemical profiles of rats selected for extreme differences in active, two-way active performance. In: Lieblich I, editor. Genetics of the brain. Amsterdam: Elsevier, 1982. p. 95–123.

Driscoll P, Cohen C, Fackelman P, Bättig K. Differential ethanol consumption in Roman High- and Low-avoidance (RHA and RLA) rats, body weight, food intake and the influence of pre- and post-natal exposure to nicotine and/or injection stress. Experientia 1990;46(Supplement):A60.

Driscoll P, Escorihuela RM, Fernández-Teruel A, Giorgi O, Schwegler H, Steimer Th, Wiersma A, Corda MG, Flint J, Koolhaas JM, Langhans W, Schulz PE, Siegel J, Tobeña A. Genetic selection and differential stress responses. The Roman lines/strains of rats. Ann NY Acad Sci 1998;851:501–10.

Escorihuela RM, Tobeña A, Driscoll P, Fernández-Teruel A. Effects of training, early handling and perinatal flumazenil on shuttle box acquisition in Roman low-avoidance rats: toward overcoming a genetic deficit. Neurosci Biobehav Rev 1995;19:353–67.

Escorihuela RM, Fernandez-Teruel A, Gil L, Aguilar R, Tobeña A, Driscoll P. Inbred Roman high- and low-avoidance rats: differences in anxiety, novelty-seeking, and shuttlebox behaviors. Physiol Behav 1999;67:19–26.

Fernández-Teruel A, Escorihuela RM, Nuñez JF, Gomà M, Driscoll P, Tobeña A. Early stimulation effects on novelty-induced behavior in two psychogenetically-selected rat lines with divergent emotionality profiles. Neurosci Lett 1992;137:185–8.

Fernández-Teruel A, Escorihuela RM, Castellano B, González B, Tobeña A. Neonatal handling and environmental enrichment effects on emotionality, novelty/reward seeking, and age-related cognitive and hippocampal impairments: focus on the Roman rat lines. Behav Genet 1997;27:513–26.

Giorgi O, Corda MG, Orlandi M, Valentini V, Carboni G, Frau V, Di Chiara G. Differential ethanol (ETH) consumption in Roman High-avoidance (RHA) and Low-avoidance (RLA) rats. Soc Neurosci Abstr 1996; 22:700.

Giorgi O, Corda MG, Carboni G, Frau V, Valentín V, Di Chiara G. Effects of cocaine and morphine in rats from two psychogenetically selected lines: a behavioral and brain dialysis study. Behav Genet 1997a;27: 537–46.

Giorgi O, Corda MG, Driscoll P, Orlandi M, Valentini V, Carboni G, Frau V, DiChiara G. Ethanol intake and preference in RHA/Verh and RLA/Verh rats: behavioral and brain microdialysis studies. Behav Genet 1997b;27:590–1.

Lipp HP. Differential hypothalamic self-stimulation behavior in Roman high-avoidance and low-avoidance rats. Brain Res Bull 1979;4:553–9.

Martin JR, Bättig K. Acquisition and extinction of gustatory aversion in two lines of rats selectively bred for differential shuttlebox avoidance performance. Behav Processes 1980;5:303–10.

Meliska CJ, Bartke A, McGlacken G, Jensen RA. Ethanol, nicotine, amphetamine, and aspartame consumption and preferences in C57BL/6 and DBA/2 mice. Pharmacol, Biochem Behav 1995;50:619–26.

Moss HB, Blackson TC, Martin CS, Tartar RE. Heightened motor activity level in male offspring of substance abusing fathers. Biol Psychiatry 1992;32:1135–47.

Nagoshi CT, Wilson JR, Rodríguez LA. Impulsivity, sensation seeking, and behavioral and emotional responses to alcohol. Alcohol: Clin Exp Res 1991;15:661–7.

Razafimanalina R, Mormède P, Velley L. Gustatory preference–aversion profiles for saccharin, quinine and alcohol in Roman high- and low-avoidance lines. Behav Pharmacol 1996;7:78–84.

Renner MJ, Rosenzweig MR. Enriched and impoverished environments. New York: Springer-Verlag, 1987.

Rockman GE, Borowski T, Glavin GB. The effects of environmental enrichment on voluntary ethanol consumption and stress ulcer formation in rats. Alcohol 1986;3:299–302.

Rockman GE, Hall AM, Market LE, Glavin GB. Influence of rearing conditions on voluntary ethanol intake and response to stress in rats. Behav Neural Biol 1988;49:184–91.

Siegel J. Augmenting and reducing of visual evoked potentials in High- and Low-Sensation seeking humans, cats and rats. Behav Genet 1997;27: 557–64.

Siegel J, Driscoll P. Recent developments in an animal model of visual evoked potential augmenting/reducing and sensation seeking behavior. Neuropsychobiology 1996;34:130–5.

Siegel J, Sisson DF, Driscoll P. Augmenting and reducing of visual evoked potentials in Roman high- and low-avoidance rats. Physiol Behav 1993;54:707–11.

Steimer Th, la Fleur S, Schulz PE. Neuroendocrine correlates of emotional reactivity and coping in male rats from the Roman high (RHA/Verh)- and low(RLA/Verh)-avoidance lines. Behav Genet 1997;27:503–12.

Zeier H, Bättig K, Driscoll P. Acquisition of DRL-20 behavior in male and female Roman high- and low-avoidance rats. Physiol Behav 1978; 20:791–3.

Zuckerman M. The psychobiological model for impulsive unsocialized sensation seeking: a comparative approach. Neuropsychobiology 1996; 34:125–9.