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ORIGINAL INVESTIGATION

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Differences in anxiety-related behaviours and in sensitivity to diazepam in inbred and outbred strains of mice

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Abstract *Rationale:* Natural strain differences exist in mice for behavioural traits such as emotional reactivity. *Objective:* The present experiments compared the behavioural profiles of nine strains of mice (BALB/c, C57BL/6, C3H, CBA, DBA/2, NMRI, NZB, SJL, Swiss) in two models of anxiety after the administration of the benzodiazepine diazepam. *Methods*: The tests used were the light/dark choice task and the elevated plus-maze, two well-validated anxiolytic screening tests. *Results:* In vehicle-treated animals, differences on variables designed to measure anxiety-related behaviours were observed in both tests. In the light/dark test, the strains could be divided into three distinct groups: two non-reactive strains (NZB and SJL), an intermediate-reactive group (C3H, CBA, DBA/2, NMRI, C57BL/6 and Swiss), and one highly reactive strain (BALB/c). In the elevated plus-maze, SJL, NMRI, CBA and, to a lesser extent, C3H strains of mice, consistently showed low levels of anxiety-related behaviours. Intermediate levels were seen in the Swiss and BALB/c strains, and high levels of emotional reactivity were seen in C57BL/6, DBA/2 and NZB. The strain distribution between the light/dark and the elevated plus-maze tests shows similarities and differences, suggesting that each of these experimental procedures represents a different set of behaviours. Marked differences between a number of strains of mice in their sensitivity to the anxiolytic-like action of diazepam were observed in both the light/dark and the elevated plus-maze tests. Mice of the BALB/c, Swiss and, to a lesser extent, CBA and C3H strains were responsive to diazepam in both tests, although in the case of CBA mice, effects may have been contaminated by behavioural suppression. SJL mice were largely unresponsive to the action of the benzodiazepine in both tests, whereas in C57, DBA/2, NMRI and NZB mice, diazepam produced positive effects only in the elevated plus-maze. *Conclusion:* The finding of differential strain distributions both with and without diazepam treatment in the light/dark and the elevated plus-maze tests, indicates that not all strains of mice are suitable for investigating the effects of GABA/BZ receptor ligands. This study may thus provide a useful guide for choosing the best strain of mice for studying the pharmacology of fear-related behaviours.

Key words Anxiety · Benzodiazepine · Diazepam · Elevated plus-maze · Inbred and outbred mouse strains · Light/dark test

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Introduction

It is widely acknowledged that natural strain differences exist in mice for behavioural traits such as learning, aggression, locomotion or emotional reactivity (for review, see Crawley et al. 1997). For example, strain distribution analyses of inbred strains of mice on the elevated plus-maze, the light/dark and the free-exploration tests showed pronounced differences in fear-related behaviours (Trullas and Skolnick 1993; Beuzen and Belzung 1995). The reasons for these differences remain largely unknown, but certainly include many factors such as life history, test situation or housing conditions. It was also postulated that these differences might be due to neuroanatomical, neurochemical or genetic factors. For example, it was reported that BALB/c and C57BL/6 mice differ in the density and/or the affinity of benzodiazepine (BZ) receptors (Robertson 1979; Chapouthier et al. 1991). These authors showed that the affinity for these receptors is higher in BALB/c than in C57BL/6, whereas the latter strain displays a greater density in BZ receptor sites than the former. In line with these data are results of a number of studies which indicated that there are genet-

ically determined differences in behavioural responses to BZ (for example, Crawley and Davis 1982; Schweri et al. 1983; Nutt and Lister 1988; Desforges et al. 1989; Kosobud and Crabbe 1990; Mathis et al. 1994; Garrett et al. 1998). Several of these have focused on strain susceptibility to BZ receptor inverse agonists. For example, Nutt and Lister (1988) investigated the sensitivity of a number of different inbred strains of mice to the BZ receptor partial inverse agonist, FG7142 and reported clear differences. In some strains (DBA/2J, C58/J and CBA/J), the drug produced full seizures, whereas in others (C57BL/6J, C57BL/10J, LP/J, C3H/HeJ, A/J, MA/MyJ), FG7142 failed to provoke convulsions.

Other studies have quantitated strain-specific responsiveness to BZ using models of anxiety. In mice, diazepam produced strain-dependent differences in several models, including the light/dark transition, the elevated plus-maze and the mirrored chamber tests (Crawley and Davis 1982; Mathis et al. 1994; Garrett et al. 1998). The C57BL/6J and A/J strains have been the most thoroughly investigated and in every study, the C57BL/6J was found to be more sensitive to the anxiolytic effects of diazepam than the A/J strain.

A majority of strain-difference studies have focused on assessing behavioural effects of drug administration in a limited number of strains, usually in only two or three strains per study. In addition, most studies have examined only a restricted number of behaviours in a limited number of models following drug administration. This approach limits the potential scope of the behavioural findings. The inclusion of a number of different behavioural measures and/or tests could expand the relevance of strain-difference studies to include tests thought to model a variety of aspects of anxiety. There is now growing evidence that the measures of anxiety from different tests may reflect different states of anxiety (File 1992; Belzung and Le Pape 1994; Beuzen and Belzung 1995; Rodgers 1997). This was shown by the application of factor analysis of the various behavioural parameters obtained in different anxiety models. For example, File (1992) and Lister (1987) revealed that parameters recorded in several anxiety models (e.g. elevated plus-maze, social interaction, holeboard, Vogel conflict) produced distinct anxiety factors, thereby indicating that they reflect different emotional states. More recently, Belzung and Le Pape (1994) subjected the scores from several anxiety models, including the mouse light/dark and the elevated plus-maze tests, to a factor analysis. They showed that the elevated plus-maze loaded on a factor related to exploration criteria, whereas the light/dark test loaded on a factor related to neophobia and locomotion.

The purpose of the present experiments was to compare the anxiolytic-like effects of diazepam in the light/dark and the elevated plus-maze tests across nine strains of mice (BALB/c, C57BL/6, C3H, CBA, DBA/2, NMRI, NZB, SJL, Swiss). These mice were chosen on the basis of differences in behavioural profile as revealed in several models of anxiety (Roullet and Lassalle 1990; Makino et al. 1991; Trullas and Skolnick 1993; Beuzen and Belzung 1995; Griebel et al. 1997).

Materials and methods

Animals

Subjects were naive male mice from seven inbred strains (BALB/cByJIco, C57BL/6JIco, C3H/HeOuJIco, CBA/JIco, DBA/2JIco, NZB/Ola/Hsd, SJL/J) and from two outbred lines (NMRI, Swiss) aged 7–8 weeks at the time of testing. They were obtained from Iffa-Credo (L'Arbresle, France). Prior to experimental testing, they were housed in groups of six in standard sized cages (30×20×14 cm) containing a constant supply of food pellets and water. All animals were maintained under standard laboratory conditions (21–23°C) and kept on a 12-h light/dark cycle with light onset at 6 a.m.

Drug

Diazepam (synthesized by the Medicinal Chemistry Department, Synthélabo Recherche) was prepared as a suspension in physiological saline containing Tween 80 (0.1%). It was injected in a volume of 20 ml/kg. All doses are expressed as the bases.

Light/dark test

This model of anxiety was based on that described by Misslin et al. (1989) and consists of two polyvinyl chloride boxes (20×20×14 cm) covered with Plexiglas. One of these boxes was darkened. A neon tube fixed on the ceiling provided the room illumination so that the light intensity in the centre of the illuminated box was 150 lux. An opaque plastic tunnel (5×7×10 cm) separated the dark box from the illuminated one. At the beginning of the experiment, a mouse was placed in the illuminated box, facing the tunnel. Recording started when the animal entered the dark box for the first time. The apparatus was equipped with infrared beams and sensors capable of recording the following two parameters during a 4-min period: (a) time spent by mice in the lit box; (b) total number of tunnel crossings. Although this parameter may be contaminated by anxiety, it was recorded in order to evaluate general motor activity in the same context as the anxiety measures. The results were expressed as mean time spent in the lit box(es) and mean total number of tunnel crossings. Testing was performed between 8.30 a.m. and 2 p.m.

Elevated plus-maze

The test apparatus was based on that described by Pellow et al. (1985) and Handley and Mithany (1984). All parts of the apparatus were made of dark polyvinyl plastic with a black rubber floor. The maze was elevated to a height of 50 cm with two open (50×10 cm) and two enclosed arms (50×10×50 cm), arranged so that the arms of the same type were opposite each other, connected by an open central area (10×10 cm). To prevent mice falling off, a rim of Plexiglas (1 cm high) surrounded the perimeter of the open arms. The illumination in the experimental room consisted of one neon tube fixed on the ceiling. The light intensity on the central platform was 50 lux. At the beginning of the experiment, a mouse was placed in the centre of the maze, facing one of the enclosed arms, and observed for 4 min. The apparatus was equipped with infrared beams and sensors capable of measuring time spent in open arms, number of open-arm entries and number of closed-arm entries (defined as entry of all four limbs into an arm of the maze). In addition, mice were observed via video-link by an observer located in an adjacent room. The results were expressed as mean ratio of time spent in open arms to total time spent in both open and closed arms, mean ratio of entries into open arms to total entries into both open and closed arms, mean total number of both closed and open arm entries.

Statistical analysis

Data were analysed by a single factor ANOVA or, for some infrequently occurring or highly variable behaviours, with the non-parametric Kruskal-Wallis (KW) test. Subsequent comparisons between treatment groups and control were carried out using Dunnett's *t*-test or the non-parametric Siegal and Castellan test (Siegal and Castellan 1988).

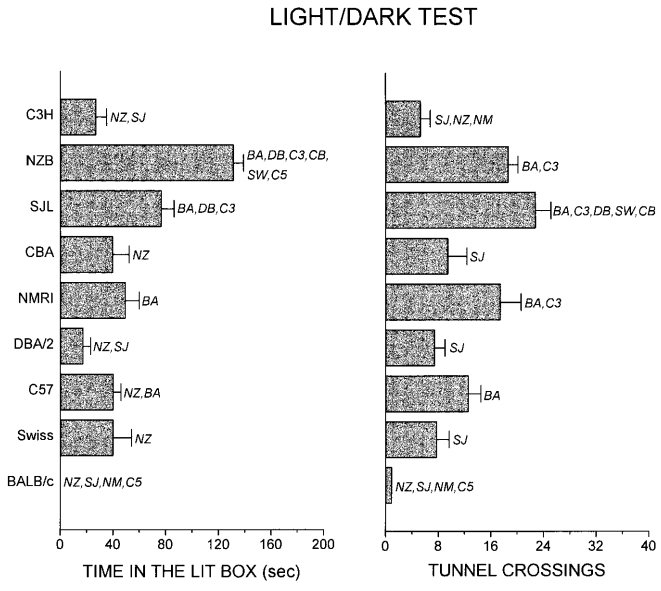

Fig. 1 Behaviours exhibited by saline-treated mice from several strains in the light/dark test. Saline was administered IP 30 min before testing. *BA*, *C3*, *C5*, *CB*, *DB*, *NM*, *NZ*, *SJ* and *SW* indicate significantly different from BALB/c, C3H, C57BL/6, CBA, DBA/2, NMRI, NZB, SJL and Swiss mice, respectively ($P<0.05$). Data represent mean±SEM. n=10–15

Results

Inter-strain comparisons

Light/dark

Significant between-strain effects were observed for the time spent in the lit box (KW=58.96, $P<0.001$) and for the number of tunnel crossings (KW=58.76, $P<0.001$). Siegal and Castellan analysis revealed that these mouse strains could be divided into three distinct groups with respect to the time spent in the lit box and the number of tunnel crossings. As shown in Fig. 1, NZB and SJL spent significantly more time in the illuminated box than the other strains. These can be divided further into intermediate (CBA, NMRI, C57BL/6 and Swiss) and low (C3H, DBA/2 and BALB/c) time groups. SJL, NZB and NMRI mice displayed the highest number of tunnel crossings, while BALB/c showed the lowest. For the other strains, activity was distributed in a continuum between the intermediate-low activity of C3H mice and the intermediate-high activity of C57BL/6 mice.

Elevated plus-maze

Data are presented in Fig. 2. A significant effect of strain was observed for all measures: percentage of time spent in open arms: KW=33.74, $P<0.001$; percentage of entries into open arms: KW=27.14, $P<0.001$; number of total arm entries: $F(8,61)=15.75$, $P<0.001$. Thus, SJL, CBA and NMRI mice displayed the highest time in open

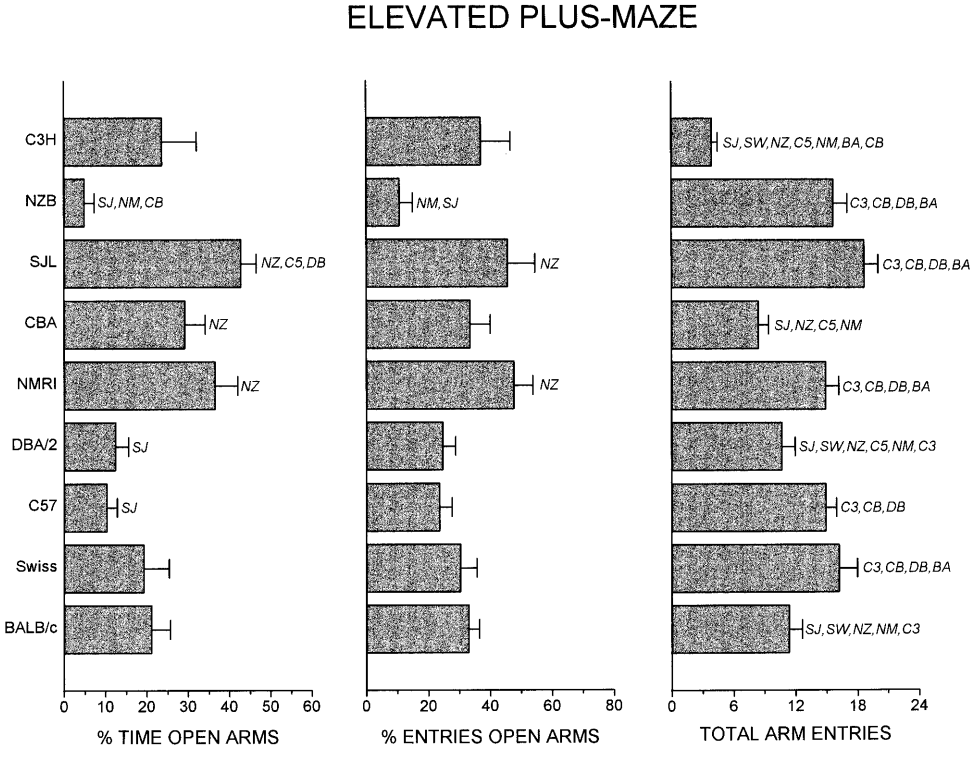

Fig. 2 Behaviours exhibited by saline-treated mice from several strains in the elevated plus-maze test. Saline was administered IP 30 min before testing. *BA*, *C3*, *C5*, *CB*, *DB*, *NM*, *NZ*, *SJ* and *SW* indicate significantly different from BALB/c, C3H, C57BL/6, CBA, DBA/2, NMRI, NZB, SJL and Swiss mice, respectively ($P<0.05$). Data represent mean±SEM. n=7–8

arms, C3H, Swiss and BALB/c mice intermediate activities, and NZB, DBA/2 and C57BL/6 mice the lowest score for this parameter. With respect to the open arm entries, the rank order of the strains was not different from that obtained for the time in open arms, except that C3H mice showed higher scores than CBA mice. With respect to total arm entries, C3H displayed the lowest activity responses while the other strains clustered in a high activity range in which several strains (SJL, NZB, NMRI, Swiss and C57BL/6) showed the highest activity scores.

Effects of diazepam

Light/dark

Figure 3 shows that diazepam significantly increased the time spent in the lit box in BALB/c (KW=35.02, $P<0.001$), Swiss (KW=18.9, $P<0.01$), CBA (KW=27.82, $P<0.001$) and C3H (KW=15.19, $P<0.01$) mice, but not in the other strains. The number of tunnel crossings was significantly increased by diazepam in BALB/c (KW=30.41, $P<0.001$), Swiss (KW=16.02, $P<0.01$) and SJL (KW=19.94, $P<0.01$) mice. In NZB mice (KW=37.5, $P<0.001$), the drug produced a biphasic effect, significantly increasing the measure at 1 mg/kg and decreasing it at 8 mg/kg. No significant differences between control and diazepam-treated animals were shown in all other strains with respect to this measure.

Elevated plus-maze

Figure 4 shows that with the exception of CBA and SJL mice, diazepam significantly increased the percentage of time spent in open arms: BALB/c: $F(4,30)=13.3$, $P<0.001$; Swiss: $F(4,30)=2.9$, $P<0.05$; C57BL/6:

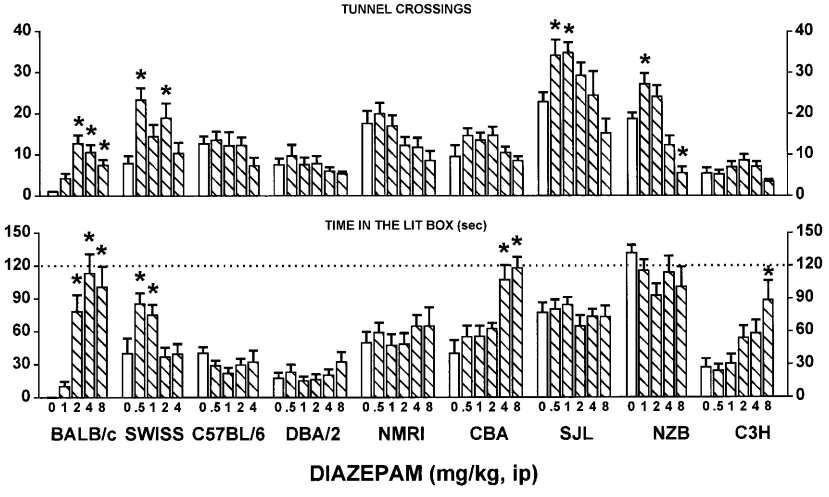

Fig. 3 Behaviours exhibited by mice from several strains in the light/dark test after the injection of diazepam. The drug was administered IP 30 min before testing. Data represent mean±SEM. n=10–15. *$P<0.05$

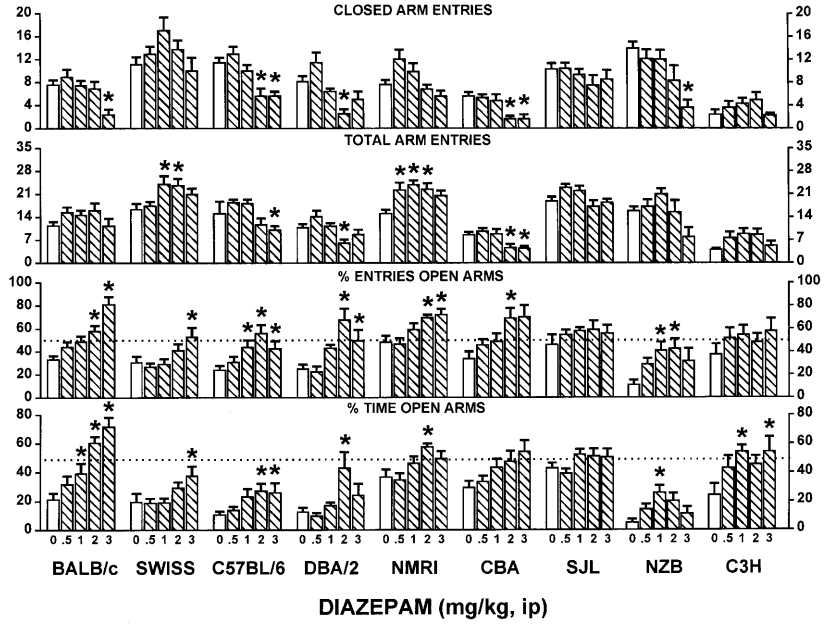

Fig. 4 Behaviours exhibited by mice from several strains in the elevated plus-maze test after the injection of diazepam. The drug was administered IP 30 min before testing. Data represent mean±SEM. n=7–8. *$P<0.05$

KW=10, $P<0.05$; DBA/2: KW=14.59, $P<0.01$; NMRI: KW=13.97, $P<0.01$; NZB: KW=10.89, $P<0.05$; C3H: $F(4,35)=2.6$, $P<0.05$. Percentage of entries made into open arms was significantly increased by diazepam in BALB/c (KW=21.69, $P<0.001$), Swiss [$F(4,30)=3.7$, $P<0.05$], C57BL/6 [$F(4,35)=4.4$, $P<0.01$], DBA/2 (KW=19.9, $P<0.001$), NMRI [$F(4,35)=5.6$, $P<0.001$], CBA [$F(4,34)=2.6$, $P<0.05$], NZB (KW=8.5, $P<0.05$), but not in SJL and C3H mice. The number of total arm entries was significantly increased by diazepam in Swiss [$F(4,30)=3.4$, $P<0.05$] and NMRI [$F(4,35)=4.2$, $P<0.01$] mice, and decreased in C57BL/6 [$F(4,35)=8.1$, $P<0.001$], DBA/2 [$F(4,35)=5$, $P<0.01$] and CBA [$F(4,34)=5.7$, $P<0.01$] mice. The drug did not modify this measure in all other strains. In BALB/c [$F(4,30)=5.2$, $P<0.01$], C57BL/6 [$F(4,35)=9.6$, $P<0.001$], DBA/2 (KW=18.97, $P<0.001$), CBA [$F(4,34)=6.3$, $P<0.001$] and NZB (KW=15.28, P<0.01) mice, diazepam decreased the number of entries into closed arms. No significant drug effect on this measure was observed in the other strains of mice.

Discussion

The results of the present study suggest that each of the nine strains of mice, BALB/c, C57BL/6, C3H, CBA, DBA/2, NMRI, NZB, SJL and Swiss, can be differentiated phenotypically according to the behavioural effects observed in the light/dark and elevated plus-maze tests, following saline administration or various doses of diazepam.

The results obtained in the present experiments are consistent with previous studies that have reported differences on variables designed to measure fear-related behaviours in the light/dark and the elevated plus-maze tests (Trullas and Skolnick 1993; Beuzen and Belzung 1995). In the light/dark test, the strains could be divided into three distinct groups based on the time spent in the lit box, the main index of anxiety: two non-reactive strains (NZB and SJL), an intermediate-reactive group (C3H, CBA, DBA/2, NMRI, C57BL/6 and Swiss), and one high reactive strain (BALB/c). With the exception of the CBA and DBA/2 strains, these results confirm those from a previous study with the light/dark test showing that NZB and SJL mice spent significantly more time in the illuminated box than C3H and BALB/c mice (Beuzen and Belzung 1995). Unlike the present experiments, this latter study revealed that CBA and DBA/2 displayed high activity in the bright area. The reasons for these differences remain to be determined, but may be explained by the use of both females and males in the study of Beuzen and Belzung, since there is some evidence of gender differences in anxiety in strains of mice (Rodgers and Cole 1993; Beuzen and Belzung 1995). In contrast, the strain distribution analysis on tunnel crossing, an index related to anxiety and locomotor activity, agrees with that observed in the latter study. Thus, rank order of number of tunnel crossings was SJL=NZB=NMRI>C57BL/6>C3H=DBA/2=CBA=Swiss>BALB/c.

Whether the high level of time in the bright box of NZB and SJL is indicative or their low emotionality or is due to processes unrelated to anxiety is unclear. SJL mice are known to have retinal degeneration. It might be argued that their performance in the light/dark test could be affected by impaired vision. However, CBA and C3H mice, which displayed clear preference for the dark box, also carry the retinal degeneration gene (Lolley 1973; Cagianut et al. 1985). Alternatively, cognitive deficits may account for the performance of NZB and SJL in the light/dark test. However, although NZB are described as poor learners, other strains (i.e. BALB/c, C3H, CBA) which displayed a high level of reactivity in this study also show impaired learning performance (for review, see Crawley et al. 1997). Since SJL, but not NZB mice displayed low levels of anxiety-related behaviours in both tests and did not respond to the anxiolytic effects of diazepam, one can assume that the SJL strain has low emotionality.

In the elevated plus-maze, SJL, NMRI, CBA and, to a lesser extent, C3H strains of mice consistently show low levels of anxiety-related measures. Intermediate strains include the Swiss and BALB/c strains, and high levels of emotional reactivity include C57BL/6, DBA/2 and NZB. Although the strain distribution pattern was somewhat different from that of a previous study (Trullas and Skolnick 1993), both experiments agree that CBA, C3H and BALB/c display higher levels of open arm activity than C57BL/6, DBA/2 and NZB mice. While marked differences were also manifested among strains in the measures of general motor activity (total and closed arm entries), they were not related to fear-motivated behaviours. Thus, NZB and SJL mice that showed low and high levels of open arm activity, respectively, displayed the highest number of arm entries among all strains. This observation would be in agreement with results from factor analyses performed on the behaviours in the mouse elevated plus-maze which showed that open arm activity (viewed as an index of anxiety) loaded on a different factor than total and closed arm entries (assumed to be measures of general activity) (Lister 1987; Rodgers and Johnson 1995).

Interestingly, the strain distribution between the light/dark and the elevated plus-maze tests shows both similarities and differences. The DBA/2 and SJL strains were among the most and least fearful in both tests. While NZB exhibited low fearfulness in the light/dark test, it was the most fearful in the elevated plus-maze test. The NMRI strain was moderate in the light/dark test, while showing low levels of avoidance responses of the open arms in the plus-maze. The BALB/c strain was the most fearful in the light/dark test and exhibited moderate fearfulness in the plus-maze. The C3H, CBA, C57BL/6 and Swiss strains were moderate on anxiety-related measures from both models. These differences in strain distribution between two animal models of anxiety further indicate that measures from different tests which claim to model anxiety may reflect different aspects of behaviour, which are related to anxiety responses, loco-

motor activity and/or processes unrelated to anxiety and locomotion (File 1992; Belzung and Le Pape 1994; Beuzen and Belzung 1995; Rodgers 1997). Although the light/dark test and the elevated plus-maze model are both based on a similar conflict between the tendency of mice to explore a novel environment and its aversive properties, the main stressful stimulus of each test is clearly different (bright light versus open, elevated spaces, respectively). It is therefore possible that each of these experimental situations represents a different set of behaviours. This assumption is substantiated by a factor analysis study which showed that the elevated plus-maze loaded on a factor related to exploration criteria, whereas the light/dark test loaded on a factor related to neophobia and locomotion (Belzung and Le Pape 1994).

The present data clearly show marked differences between a number of strains of mice in their sensitivity to the anxiolytic-like action of the BZ diazepam in both the light/dark and the elevated plus-maze tests. Mice of the BALB/c, Swiss and, to a lesser extent, CBA and C3H strains were responsive to diazepam in both tests. However, in the case of CBA mice, doses of diazepam that produced anxiolytic-like activity also decreased total and closed arm entries in the elevated plus-maze, suggesting a behaviourally non-specific action. SJL mice were hyporesponsive to the action of the BZ in either test, whereas in C57, DBA/2, NMRI and NZB mice, diazepam produced positive effects only in the elevated plus-maze. The present results with the C57BL/6 and BALB/c mice in the light/dark test contrast with those obtained in an earlier study by Crawley and Davis (1982) showing that C57BL/6, but not BALB/c mice were sensitive to the anxiolytic action of diazepam. However, methodological differences may account for this discrepancy. For example, the light/dark apparatus and the experimental protocol used by Crawley and Davis are substantially different from those employed in the present experiments. These authors measured anxiety-related behaviours by recording only the number of transitions between a brightly lit open field and a dark enclosed compartment during 10 min. This suggests that the light/dark test used by Crawley and Davis does not measure the same behavioural processes than that employed in this study.

Interestingly, strains of mice which showed high levels of anxiety-related behaviours in the light/dark test were not necessarily sensitive to diazepam. This is best exemplified by C57BL/6 and DBA/2 mice which displayed marked avoidance of the bright area but their behaviour remained unaffected by diazepam. A few attempts have been made to relate the inherent susceptibility of some strains of mice to BZ receptor ligands and pharmacokinetic or pharmacodynamic factors. For example, Chapouthier et al. (1991) and Robertson (1979) demonstrated that BALB/c and C57BL/6 differ in the density and/or the affinity of BZ receptors. These authors showed that the affinity for these receptors is higher in BALB/c than in C57BL/6, whereas the latter strain displays a greater density in BZ receptor sites than the former. It was also suggested that pharmacokinetic differences in metabolism or transport of BZ receptor ligands into the central nervous system of these mice could produce differential responses to the drugs (Schweri et al. 1983; Mathis et al. 1994). Whether these findings may explain the strain differences in the behavioural profiles remains to be determined. Continuing research in this area will provide a wealth of understanding about the mechanisms underlying the differential sensitivity to BZ receptor ligands.

In summary, the results of the present experiments with the light/dark and the elevated plus-maze tests are in agreement with previous studies which reported strain differences on variables designed to measure fear-related behaviours. After the administration of the BZ diazepam, differences between a number of strains in their sensitivity to the anxiolytic-like action of the drug were observed in both tests. It is important to note that the strain distribution between the light/dark and the elevated plus-maze tests shows similarities and differences suggesting that they measure different aspects of the behaviour.

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