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Research report

Pharmacological modulation of anxiety-related behaviors in the murine Suok test

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Abstract

We have recently introduced a new model of anxiety – the Suok test and its light–dark modification – for behavioral characterization in mice and rats, including simultaneous assessment of their anxiety, activity, and neurological phenotypes. In the present study, testing different inbred (129S1, BALB/c) and hybrid (C57–129S1) mouse strains in both Suok test modifications, we examined the effects on anxiety-related behaviours produced by traditional anxiogenic and anxiolytic drugs. Here we show dose-dependent increases in anxiety-related behaviors produced by anxiogenic drug pentylenetetrazole (10 and 20 mg/kg). In contrast, anxiolytic drugs ethanol (0.75 and 1.5 g/kg) and diazepam (0.5 mg/kg) reduced anxiety and increased mouse exploration in this test. Hyperemotional anxious BALB/c mice were particularly sensitive to pharmacogenic anxiety in Suok test, also showing robust light–dark shifts in the light–dark version of this test. Overall, the results of this study confirm the potential utility of both murine Suok tests, especially when used in selected "sensitive" mouse strains, for high-throughput screening of potential anxiotropic drugs.
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Keywords: Anxiety; Mice; Drug-evoked alterations; Suok test; Light–dark modification

1. Introduction

Anxiety is induced by novelty, and can be studied by assessing rodent behavior in an unknown environment [2,3,5,21,40]. Numerous experimental tests measuring reduced exploration and increased risk assessment [20,44,45] are widely used to assess rodent anxiety [8,19,55,56], including its characterization in different mouse strains [13,20,22,23,53] and mutant or transgenic mice [15–17,39,44]. In addition to genetically determined anxiety, animal responses in these tests are also sensitive to various exogenous factors, such as neurotropic drugs that affect anxiety [4,28,29,46,49].

We have recently introduced the Suok test (ST) of anxiety, based on rodent exposure to elevated horizontal rod (mice) [33] or alley (rats) [31]. This test evokes the fear of novelty, height and instability, and allows simultaneous profiling of anxiety, motor functions and balancing (vestibulation) [33,31]. In addition, this test targets anxiety-evoked sensorymotor deficits [33], a phenomenon relatively well-known in clinical literature [1,6,54,57], but only recently noted in animal behavioral studies [34,52]. In addition, using several mouse strains with different emotional reactivity, we introduced and psychogenetically validated the light–dark version (LDST) of this test [33], combining principles of several well-validated mouse anxiety tests, including the light–dark box [7,27], the open field [11,30] and the elevated mazes [9,10,29,49]. As these tests seem to assess different subtypes of anxiety [16,27,44,45], the ST and especially LDST emerge as interesting multi-domain models for neurobehavioral research in mice [33,34].

Although rat studies from different groups showed the ST sensitivity to pharmacologically induced anxiety [31] and anxiolysis [51], the sensitivity of the mouse ST and LDST behavior to anxiolytic and anxiogenic drugs has not been examined previously in detail. The present study aims to assess the utility of mouse ST and LDST for detection of pharmacogenic anxiety and anxiolysis.

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2. Methods

2.1. Animals

Subjects were adult mice of different strains, including 129S1 (24 males; Experiment 1), BALB/c (24 males, Experiment 2; 24 females; Experiment 3), and F1 C57Bl/6 × 129S1 (24 males, Experiment 4). The animals were maintained under controlled temperature (22 ± 2 °C), humidity (60%) and a 12-h light:12-h dark cycle (lights on at 07:00 h), in a virus/parasite-free facility of the University of Tampere (Tampere, Finland). All animals used here were experimentally naïve and housed in groups of three to four animals per cage, with food and water freely available. The procedures used in this study were in strict accordance with European legislation and the guidelines of the National Institutes of Health. All animal experiments reported here were approved by the Ethical Committee of the University of Tampere.

2.2. Apparatus and procedures

Testing was always conducted between 14:00 and 18:00 h. The ST was a 2.6 m aluminum tube (2 cm in diameter) elevated to a height of 20 cm from the cushioned floor, separated into 10 cm sectors by line drawings and fixed to two Plexiglas side walls (50 × 50 cm) [33]. The experimental room was dimly lit during this test. The LDST consisted of the same aluminum rod, with four 60 W bulbs 40 cm above the rod (directed light) to illuminate the light part of the test, as described previously [33].

On the day of experiments, the animals were transported to the experimental room and left undisturbed for 1 h prior to testing. Mice were placed individually in the middle part of the rod, and observed for 5 min by an experienced investigator unaware of treatments. The rod was thoroughly cleaned (20% ethanol) between the animals. The following measures were collected in both tests: horizontal activity (number of sectors visited with four paws), latency(s) to leave the center (in the LDST, counted as the latency to enter the light or dark part), the number of looks down (directed exploration), time spent in the light and dark parts of the LDST, as well as the number of falls from the rod [33].

2.3. Drugs

To induce anxiety, we used pentylenetetrazole (PTZ), traditionally known to increase anxiety by inhibiting central gamma amino butyric acid (GABA) neurotransmission [18,49] without inducing non-specific motor defects at mild doses. PTZ (Sigma, Finland) was dissolved in saline 1 h prior to i.p. injection at 10 and 20 mg/kg (control animals in this and other experiments were injected with saline). These doses were chosen based on PTZ anxiogenic profile at doses >5 mg/kg (e.g., [49]).

To reduce anxiety in mice, we used diazepam and ethanol as reference drugs with known anti-anxiety effects (via positive modulation of GABA-ergic system) at low non-sedating doses [14,28,32]. Diazepam (Sigma, UK) was dissolved in saline (with 2–3 drops of Tween-20) 1 h prior to i.p. injection at 0.5 mg/kg (control mice were injected with vehicle; Experiment 2). Ethanol (Sigma, Finland) was dissolved in saline 1 h prior to i.p. injection. The following doses of ethanol were used in the present study: 0.75 and 1.5 g/kg (Experiment 4), based on their known non-sedating effects in this range [42]. Pre-treatment time was 30 min in all these experiments.

2.4. Experiments

In the regular ST, we used anxiogenic drug PTZ in two mouse strains (129S1 mice; Experiment 1 and BALB/c mice; Experiment 2), and anxiolytic drug diazepam in BALB/c mice (Experiment 2). In the LDST, we examined anxiogenic effects of PTZ in BALB/c mice (Experiment 3), and anxiolytic effects of ethanol in F1 C57–129S1 mice (Experiment 4).

2.5. Statistics

All results are expressed as mean + S.E.M. Data of experiments 1, 3 and 4 were analyzed by one-way ANOVA (factor: dose; Experiments 1, 3 and 4; drug; Experiment 2) followed by Tukey's post hoc test. A probability of less than 0.05 was considered statistically significant in all tests.

3. Results

Experiment 1 shows clear dose-dependent anxiogenic responses in 129S1 mice produced in the regular ST by PTZ (Fig. 1A and B), as assessed by reduced horizontal activity ($F(2,23) = 6.2$, $P = 0.008$) and longer latency to leave center ($F(2,23) = 4.2$, $P = 0.03$). In addition, PTZ dose-dependently impaired balance control in these mice, manifest in significantly more falls from the rod ($F(2,23) = 3.72$, $P = 0.04$; Fig. 1C).

Fig. 2 summarizes behavioral responses of BALB/c male mice in the regular ST following treatment with reference anxiogenic (PTZ) or anxiolytic (diazepam) drugs (Experiment 2). Overall, there was a significant drug effect on horizontal exploration ($F(2,23) = 17.7$, $P = 0.00001$), with PTZ reducing, and diazepam predictably increasing, the number of sectors visited. In addition, PTZ significantly reduced directed exploration (looks down; $F(2,23) = 14.2$, $P = 0.0001$), also increasing the latency to leave center ($F(2,23) = 9.1$, $P = 0.0014$), but not affecting the number of falls from the rod ($F(2,23) = 1.5$, NS).

In Experiment 3, BALB/c mice demonstrated clear-cut anxiety in the LDST after PTZ treatment, including markedly reduced horizontal activity ($F(2,23) = 5.6$, $P = 0.01$ light, $F(2,23) = 8.3$, $P = 0.002$ dark, $F(2,23) = 8.9$, $P = 0.002$ total), longer latency to enter the aversive light part ($F(2,23) = 5.4$, $P = 0.01$) and significantly less time spent in the light part ($F(2,23) = 3.7$, $P = 0.04$), with unaltered number of looks down

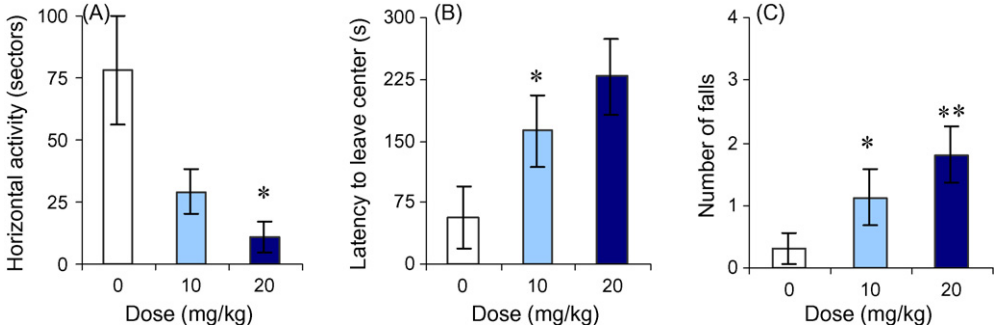

Fig. 1. Behavioral responses in the Suok test (129S1 mice, $n = 8$ in each group) evoked by anxiogenic drug pentylenetetrazole (*$P < 0.05$, **$P < 0.01$ vs. saline-treated group; Experiment 1).

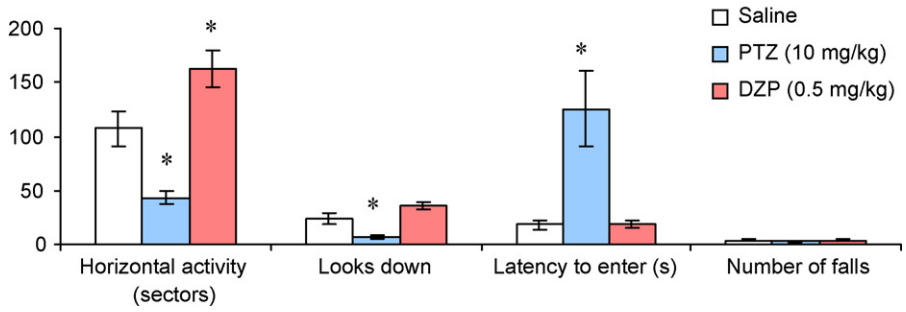

Fig. 2. Behavioral responses in the Suok test in BALB/c mice ($n = 8$ in each group) treated with anxiogenic (pentylenetetrazole, PTZ) and anxiolytic (diazepam, DZP) drugs (*$P < 0.05$ vs. saline-treated group; Experiment 2).

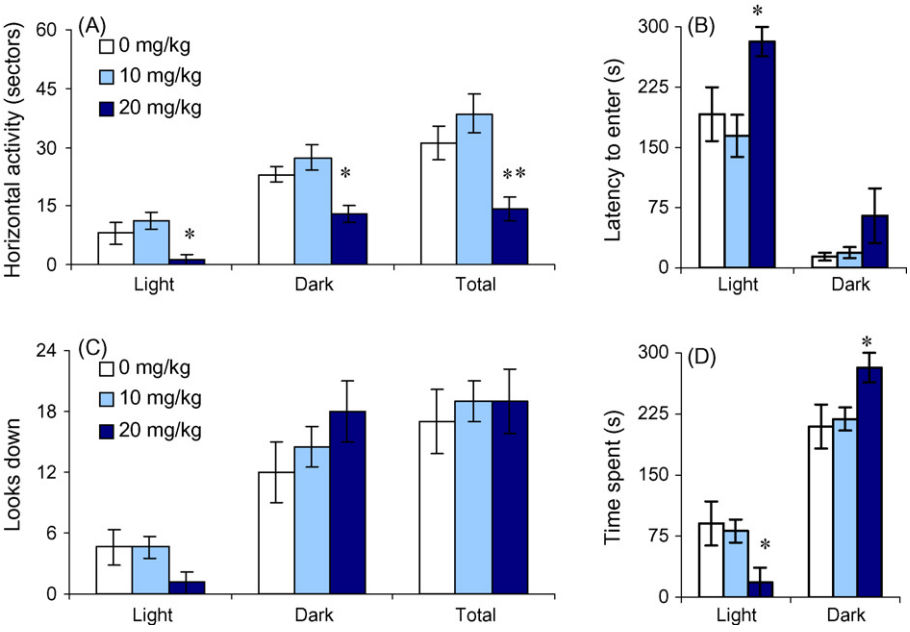

Fig. 3. Behavioral responses in the light–dark Suok test (BALB/c mice, $n = 8$ in each group) evoked by anxiogenic drug pentylenetetrazole (*$P < 0.05$, **$P < 0.01$ vs. saline-treated group; Experiment 3).

(NS) in either part of the test (Fig. 3A–D). Notably, control BALB/c mice showed a clear preference to protective dark part of the rod, visiting less sectors (light:total ratio 0.26 ± 0.09) and spending less time (light:total ratio 0.30 ± 0.09) in the light part of the apparatus. Although intermediate dose of PTZ (10 mg/kg) was unable to alter these ratios, PTZ at 20 mg/kg markedly shifted horizontal activity and time spent (light:total ratios 0.09 ± 0.09 and 0.06 ± 0.06, respectively; $P < 0.05$), consistent with increased anxiety in these mice. The number of falls from the rod, however, was unaltered in this experiment (data not shown).

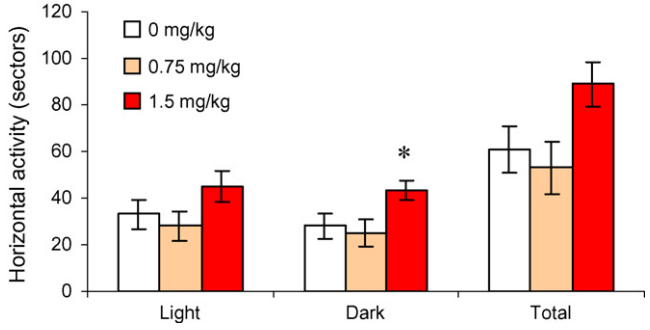

Fig. 4. Dose-dependent anxiolysis in the light–dark Suok test (F1 hybrid C57–129S1 mice, $n = 8$ in each group) evoked by anxiolytic drug ethanol (*$P < 0.05$ vs. saline-treated group; Experiment 4).

In Experiment 4, relatively anxious C57 × 129S1 F1 hybrid mice treated with anxiolytic drug ethanol (Fig. 4), showed lower LDST anxiety and no sedation, as assessed by increased horizontal activity ($F(2,23) = 3.8$, $P = 0.04$ dark, $F(2,23) = 3.2$, $P = 0.06$ total, trend). In contrast, the light horizontal activity (Fig. 4), latency to enter, the number of looks down and falls from the rod, as well as light:total ratios were unaltered in this test (data not shown).

4. Discussion

In general, ST and LDST appear to be useful tools to assess anxiety, as they are based on the innate aversion of mice to novelty, open spaces, height and brightly lit environments [33,31] –

the main factors that evoke anxiety in most of the other novelty-based anxiety models [34]. Our present findings made another step in further validation of these models, showing that they can also be used to detect pharmacogenic shifts in mouse anxiety evoked by anxiogenic (e.g., PTZ) or anxiolytic (e.g., diazepam, ethanol) drugs.

Overall, these data (Experiments 1 and 2) are in line with recent ST findings in rats [31], collectively showing that rodent ST is sensitive to pharmacogenic anxiety produced by PTZ. Consistent with the original interpretation of the model [33] and several other recent studies [37,52], the results of Experiment 1 also confirm that anxious PTZ-treated mice display balancing problems (Fig. 1C), most likely reflecting anxiety-evoked sensorymotor disintegration [38,50], the experimental modeling of which may represent an interesting task *per se* [34].

Consistent with earlier data using LDST in undrugged mice of different strains [33], our present data (Experiment 3) confirmed that anxious BALB/c mice tend to avoid aversive light part of the test, traveling less distance and spending less time there. Although intermediate dose of PTZ (10 mg/kg) did not alter this preference, anxiogenic dose of 20 mg/kg resulted in further marked shifts in light/dark behaviors, consistent with increased anxiety in these mice. The lack of balancing deficits in this experiment can be explained by generally low number of falls in BALB/c mice in this test and their freezing-like responses to novelty [33,46], resulting in a marked reduction of all behaviors, including horizontal locomotion (thus, non-specifically reducing the risks of falling from the rod).

Nevertheless, marked shifts in light–dark behaviors and clear avoidance of aversive light part of the test strongly support sensitivity of the LDST to pharmacogenic anxiety, also implying its potential utility for screening of anxiotropic drugs. Notably, these results are also consistent with several other studies noting particular sensitivity of BALB/c mice to anxiogenic/anxiolytic stimuli [27,36,42], collectively suggesting a wider utility of these mice in neurobehavioral stress research, including their extensive testing in the ST situations.

Furthermore, using anxiolytic non-sedating doses of ethanol in another relatively anxious (C57 × 129S1 hybrid) strain, we showed predictably lower LDST anxiety in these mice, as assessed by their higher total and dark horizontal activity (Experiment 4, Fig. 4). Interestingly, while showing a non-significant trend to an anxiolytic-like increase of activity in the aversive light part, ethanol markedly increased dark horizontal activity, generally consistent with reduction of anxiety according to the original interpretation of this test [33].

However, several aspects still require further elucidation using these experimental mouse models in the future studies. For example, although strain comparisons were not the main focus of the present study, it is interesting to assess the individual strain differences in drug responsivity in both ST modifications. Moreover, while both ST and LDST appear to be sensitive to effects on anxiety produced in rats [31,51] and mice (Figs. 1–4) by drugs influencing central GABA receptors [18,32,43], it may also be necessary to examine behavioral effects in this model of other, non-GABAergic drugs. Although this problem is common in experimental models of anxiety [12,27], a better knowledge of animal sensitivity to different classes of anxiolytic drugs may help define neural mechanisms underlying rodent ST behaviors, representing an important direction for targeted screening of novel neuroactive drugs.

Another interesting observation in this study is that not always drug-evoked alterations in anxiety behaviors were accompanied by altered balancing performance. Given the role of central GABA in vestibulation [25,26], and the link between balancing problems and human [24,41,47,48,57] and animal [33,37,38,34] anxiety, one would expect a better correlation between anxiety and balancing problems in this study, especially using GABAergic anxiogenic drugs. Likewise, given recent data on pharmacological correction of balancing by anxiolytic and antidepressants [35,52], one would expect better ST or LDST balancing in mice treated with anxiolytic drugs in this study.

Although this phenomenon was indeed clearly seen in 129S1 mice (Experiment 1, Fig. 1C), further studies are needed to examine the link between drug-evoked shifts in anxiety and vestibulation. A combination of several factors may contribute to this phenomenon (including floor and ceiling effects, strain-specific effects of drugs and/or anxiety on overall activity, e.g., Experiment 2, 3, as well as strain or drug-specific effects on balancing with or without affecting anxiety domain, e.g. [14]). This adds further complexity to mouse performance in this test, and certainly requires an in-depth dissection in future studies. Finally, given well-known similarity between mouse and rat anxiety-related behaviors [2,30,39], and sensitivity of rat ST to experimental anxiety [31,51], it will be interesting to assess the LDST behaviors in rats following administration of anxiolytic and anxiogenic drugs.

5. Conclusion

In general, our present study provided some evidence that ST and LDST performance in mice may be used to assess alterations in anxiety (evoked by anxiogenic and anxiolytic drugs) as well as anxiety-evoked motorisensory disintegration (Fig. 1A–C), implying the utility of these tests in modeling both anxiety and anxiety-evoked balancing deficits. Some strains (such as anxious emotional BALB/c mice [42]) may be particularly sensitive to such stimuli, and therefore suggested as reference strains for screening of anxiotropic drugs in these tests. Taken together, the results of this study show sensitivity of ST and LDST to pharmacologically induced alterations in mouse anxiety, confirming their potential utility in the search for novel anxiolytic agents.

Conflict of interest

None declared.

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