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Effects of taurine on rat behaviors in three anxiety models

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Abstract

In our previous studies using an elevated plus-maze test in mice, taurine was shown to present an anxiolytic-like effect after single and repeated administration [Chen SW, Kong WX, Zhang YJ, Li YL, Mi XJ, Mu XS. Possible anxiolytic effects of taurine in the mouse elevated plus-maze. Life Sci 2004;75: 1503–11]. The aim of the present study was to investigate the anxiolytic and behavioral effects of taurine on rats in the open field, hole-board, and social interaction test compared to the positive control diazepam. Taurine (14, 42, and 126 mg/kg, i.p.) was administered 30 min before the tests. In the social interaction and hole-board tests, taurine (42 mg/kg) significantly increased social interaction time and the number and duration of head-dipping. In the open field test, taurine (126 mg/kg, i.p.) presented anxiolytic-like effects by increasing the number of center entries, time spent in the central area and the anti-thigmotactic score while having no effect on the locomotor activity. Results from these experiments suggest that taurine produces an anxiolytic-like effect in these animal models and may act as a modulator or anti-anxiety agent in the central nervous system.

Keywords: Taurine; Anxiolytic; Diazepam; Social interaction; Hole-board; Open field; Rat

1. Introduction

Taurine is one of the most abundant amino acids in the brain (Jacobsen and Smith, 1968). The high levels of taurine in this organ have stimulated much research to establish the possible function for it. The role of taurine as a putative neurotransmitter was reviewed by Kuriyama (1980). McBride and Frederickson (1979) proposed taurine as a possible inhibitory transmitter in the cerebellum. Taurine levels are increased during stress, hypoxia, energy deprivation (Milakofsky et al., 1984; Bockelmann et al., 1998; Colivicchi et al., 1998) and regions that have extremely high taurine levels or are very sensitive to taurine manipulation include hippocampus (Galarreta et al., 1996), striatum (Lombardini, 1977), and corticostriatal projection (Sergeeva and Haas, 2001). Following systemic administration taurine enters the brain via a sodium and chloride dependent carrier from blood to the endothelial cell (Benrabh et al., 1995; Molchanova et al., 2004). Endogenous taurine is released from nervous tissue in response to depolarizing agents such as *N*-methyl-D-aspartate (NMDA) and high concentration of K^+ (Saransaari and Oja, 2003) and sequestered by an active high-affinity uptake system (Oja and Kontro, 1984). Extracellular taurine modifies the release of amino acid transmitters and modulates intracellular Ca^{2+} homeostasis (Foos and Wu, 2002). Although the mode of action of taurine still remains to be elucidated, it has been shown that taurine affects the metabolism of transmitters such as γ-aminobutyric acid (GABA) (Medina and De Robertis, 1984; Kontro and Oja, 1990; Michel and Richard, 1991; Liljequist, 1992) and 5-hydroxytryptamine (5-HT) (Sgaragli et al., 1981; Becquet et al., 1993). Taurine inhibits the Ca^{2+}-dependent release of GABA and reduces 5-HT concentration in the hypothalamus. In the rat striatum, strychnine-sensitive glycine receptors are present on cholinergic interneurons (Darstein et al., 2000) and taurine, together with glycine, is their highly potent agonist (Sergeeva and Haas, 2001).

Behaviorally, i.p. injections of taurine (0.3–3.0 mg/kg) have produced a dose-dependent depression of habituated psychomotor

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activity in rats (Baskin et al., 1974). Sanberg and Ossenkopp (1977) reported that increasing dose (25–200 mg/kg) of taurine significantly decreased ambulation levels, increased latency scores and increased thigmotaxis in the rat open field test. In mice, i.p. injections of large amounts (9–21.3 mmol/kg) of this amino acid resulted in decreased locomotor activity and decreased instrumental responding for food or water (Hruska et al., 1975). In our previous studies using an elevated plus-maze test in mice, taurine could significantly increase the percentage of time in the open arms after acute oral administration (60 mg/kg) and repeated oral administration (2.5 mg/kg) for 7 days (Chen et al., 2004). The results suggested that taurine might play a role in the modulation of anxiety. In the present study, we were interested to see whether it will exhibit similar effect in the same kind of models in rats. We selected three anxiety tests of rats: social interaction, hole-board and open field test. The social interaction test provided a good model of generalized anxiety disorder (GAD) (Cheeta et al., 2000). The test conditions were manipulated to generate different levels of anxiety and both anxiolytic and anxiogenic drug effects could be detected. The hole-board test and open-field test provide simple methods for measuring the response of an animal to an unfamiliar environment. They can be used to assess emotionality, anxiety and/or responses to stress in animals. Diazepam is still the most widely used and an effective anxiolytic drug, and it has been found to be effective in many anxiety models including society interaction, hole-board and open field test (Kamei et al., 2001; Min et al., 2005). So, diazepam was chosen as the positive control in our present study. The doses of mice in our previous studies were converted to the equivalent rat dose based on body surface area.

2. Material and methods

2.1. Animals

Male Wistar rats (Experimental Animal Center of Shenyang Pharmaceutical University) weighing 180–200 g were kept under a 12 h reversed light cycle (light off 07:00) at 22±2 °C with free access to food and water for at least 7 days before experimentation. During this period they were handled daily and the position of the cages in the rack was changed so that all rats received equal experience of the different levels of illumination. In the social interaction test rats were individually housed (cage size: 25×14×12 cm) and in the hole-board and open field test rats were housed in group of five. Independent animals were tested in each of these paradigms and in all tests of anxiety, rats were injected in their holding rooms before testing in an adjacent laboratory.

All animal treatments were strictly in accordance with the National Institutes of Health Guide of the Care and Use of Laboratory Animals. The experiments were carried out under the approval of the Committee of Experimental Animal Administration of the University.

2.2. Drugs and treatments

Taurine, 2-aminoethane-sulphonic acid, was purchased from Shanghai Reagent Co. (Shanghai, China), diazepam from Hubei Pharmaceutical Factory (Hubei, China), and Tween 80 from Shenyang Dongxing Reagent Factory (Shenyang, China). Diazepam (2 mg/kg for social interaction and open-field test and 0.3, 0.6 mg/kg for hole-board test) and taurine (14, 42, 126 mg/kg) were suspended by ultrasound in 0.9% saline to which Tween 80 (2 drops/10 ml) had been added. All drugs were prepared freshly on test days and administered i.p. in a volume of 2 ml/kg 30 min before testing. Control animals were administered with the vehicle.

3. Behavioral tests

3.1. Social interaction test

The general design was essential as reported by File and Hyde (1978). The test was conducted in a Perspex box with opaque walls on four sides (60×60×35 cm), the floor of which was divided into nine (20×20 cm) squares. The test conditions were manipulated by altering the familiarity of rats to the test arena. Two test conditions were performed: high light level in unfamiliar conditions (HU) and in familiar conditions (HF). The light intensity of the arena was 380 lux.

A total of 60 male rats were divided into five treatment groups: vehicle control, diazepam (2.0 mg/kg), TA (14, 42 and 126 mg/kg). At the first day of the test, rats were tested in the HU condition. Each rat was tested for social interaction with an unknown test partner that did not differ by more than 15 g in weight. Both members of a pair had the same prior familiarization experience and the same drug treatment. Pairs of rats were placed in opposite corners of the arena and then left for 10 min. Their behaviors were recorded with a video camera and observed on a monitor in an adjacent room. The total time of non-aggressive, active social interactions including sniffing, nipping, allogrooming, following, jumping on, crawling under and over the partner and locomotor activity (the number of squares crossed) behaviors were recorded for each pair by two blind observers and the average scores used for subsequent analysis. Passive body contact was not regarded as a social interaction. After the first day of test, rats were returned to their home-cages. In the following two consecutive days, these rats were placed singly, undrugged, in the same test box for 10 min to familiarize them with the environment. On the fourth day, the same pairs of rats were once again tested in the HF condition and the same test procedure was carried out.

3.2. Hole-board test

The hole-board apparatus consisted of Perspex box (60×60×35 cm) with four equidistant holes 4 cm in diameter in the floor. The floor of the box was positioned 12 cm above the ground and divided into nine (20×20 cm) squares. For the hole-board experiments, each animal was placed in the center of the hole-board and allowed to freely explore the apparatus for 5 min. Total number of squares crossed, number and duration of rearing and head-dipping, and latency to the first head-dipping were recorded by a video camera. Videotapes were later scored by a trained observer blind to the treatment conditions.

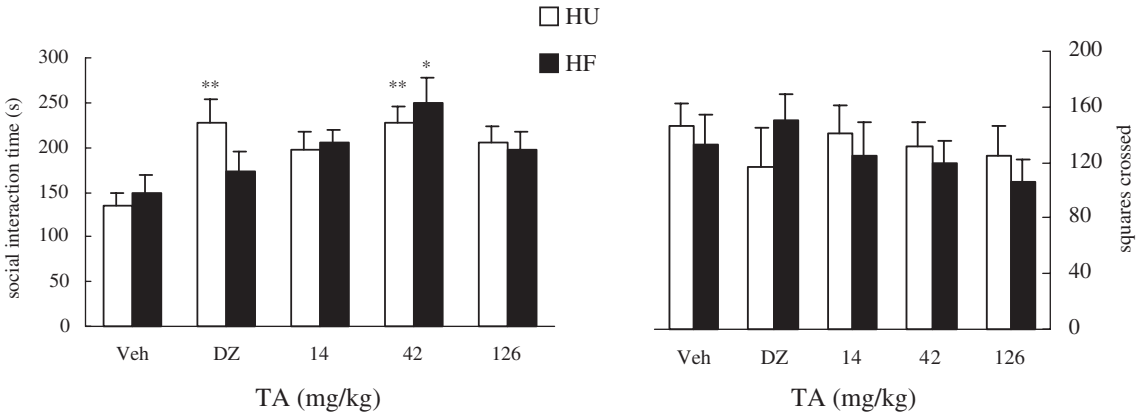

Fig. 1. Effects of taurine and diazepam on total interaction time and locomotion (number of squares crossed) in a 10-min social interaction test. Results given as mean± SEM (n=5∼6 pairs). Pair of rats was treated as a unit and tested 30 min after i.p. of vehicle, taurine (14, 42, 126 mg/kg) and diazepam (2 mg/kg). Only one score for the pair was used. *P<0.05, **P<0.01 compared with vehicle group. HU: high light, unfamiliar condition; HF: high light, familiar condition.

3.3. Open-field test

A round (80-cm diameter) open field with an opaque black floor surrounded by 30-cm high walls was used for the behavioral test. The floor was marked off in two concentric circles (the inner circle's diameter is 50 cm) and divided into 10×10 cm squares. Four 25-W red bulbs 100 cm above the field provided illumination and the test was performed in a quiet room without previous habituation. The experimental sessions were recorded by a video camera interfaced with a monitor and a videocassette recorder in an adjacent room. Each animal was placed in the periphery of the arena and three behavioral measures were recorded in the 5-min test duration: locomotor activity (the number of squares entered by the four paws of the rat), the number and duration of center entries (defined as a movement of an animal from the wall to the central area crossed the inner circle line). The anti-thigmotactic effect was calculated as a ratio of the number of entries into the central part to the locomotor activity and multiplied by 1000 (Siemi1tkowski et al., 2000). A higher value in score indicates a more pronounced anxiolytic-like effect. This parameter was calculated for each rat separately, and then the mean value for each experimental group was obtained.

3.4. Statistics

Results are reported as means±SEM. Data were analyzed by means of analysis of variance (ANOVA). Whenever ANOVA was significant, further multiple comparisons were made using the Dunnett's t-test. All analyses were performed using the software SPSS V11.5 for windows. The level of statistical significance adopted was P<0.05.

4. Results

4.1. Social interaction test

The results for the social interaction test are shown in Fig. 1. In the HU condition there was a significant drug-induced increase in social interaction [F (4, 25)=4.02, P<0.05]. Further analyses confirmed that both diazepam (2 mg/kg) and TA (42 mg/kg) significantly increased social interaction time compared with the control group (P<0.01). In the HF condition there was again a significant drug-induced increase in social interaction [F (4, 25)=5.31, P<0.05], due to the dose of 42 mg/kg of TA (P<0.05), although diazepam (2.0 mg/kg) had no effect on the total time spent in social interaction. Both taurine

Table 1
Effects of taurine and diazepam on exploratory behavior in rats tested on the hole-board test

Dose (mg/kg)	Head-dipping Counts	Head-dipping Duration (s)	Head-dipping Latency (s)	Rearing Counts	Rearing Duration (s)	Number of squares crossed
Vehicle	2.8±0.8	6.2±2.0	99.8±33.7	10.7±2.3	13.8±3.2	26.4±3.0
Taurine						
14	5.8±1.4	21.0±7.4	86.3±37.0	15.2±1.8	21.0±2.6	39.5±3.3
42	8.5±1.7**	28.7±6.6*	32.6±5.2	17.6±2.4*	24.5±4.0	51.9±6.4**
126	2.4±0.7	8.3±2.4	136.8±35.9	11.0±1.0	18.0±2.3	28.5±3.0
Diazepam						
0.3	5.7±0.9	17.5±4.2	44.9±14.2	16.6±1.9	23.0±3.5	48.7±6.1*
0.6	5.5±1.3	17.9±5.3	82.2±26.0	19.2±1.5**	27.2±2.2*	48.4±6.3**

Data represent mean±SEM. Taurine (14–126 mg/kg, i.p.) or diazepam (0.3–0.6 mg/kg, i.p.) was injected 30 min prior to the measurement of exploratory behavior. *P<0.05, **P<0.01 vs. vehicle-treated group (one-way ANOVA followed by two-tailed Dunnett' t-test). n=10–11.

and diazepam have no significant effect on the locomotor activity in HU and HF conditions.

4.2. Hole-board test

Data are summarized in Table 1. ANOVA (df=5,55) showed significant effects on number [F=3.58, P<0.01] and duration [F=2.80, P<0.05] of head-dipping, number of rearing [F=3.60, P<0.01], rearing duration [F=2.55, P<0.05] and number of squares crossed [F=5.04, P<0.01]. Compared with the control group, further analyses confirmed that taurine (42 mg/kg) significantly increased number (P<0.01) and duration (P<0.05) of head-dipping. Rearing counts (P<0.05) and the number of squares crossed (P<0.01) were also significantly increased. Diazepam, at both 0.3 and 0.6 mg/kg, significantly increased the number of squares crossed (P<0.05 and P<0.01). Analysis also revealed that administration of 0.6 mg/kg diazepam significantly increased number (P<0.01) and duration (P<0.05) of rearing.

4.3. Open field test

The results for the open field test are shown in Fig. 2. ANOVA demonstrated significant treatment effects on number of center entries [F (4,44)=6.57, P<0.01], time spent in central area [F (4,43)=3.47, P<0.05], and anti-thigmotactic effect score [F (4,43)=5.25, P<0.01]. Further analyses showed that taurine (126 mg/kg) and diazepam (2 mg/kg) significantly increased the number of center entries (both P<0.01) and time spent in central area (P<0.01 and P<0.05 respectively). See Fig. 2A and B. Taurine (126 mg/kg) also significantly increased the anti-thigmotactic score (P<0.01) (See Fig. 2D). Fig. 2C presents the total locomotor activity of vehicle-treated and drug-treated rats exposed to a 5-min session in the open field test. None of the drugs tested showed a significant effect on this measure.

5. Discussion

In the present study, taurine, at dose of 42 mg/kg, had apparently anxiolytic properties in rats exposed to social interaction and hole-board tests. In the open field test, the effective dose of taurine was higher (126 mg/kg) than the other two tests. These observations suggested taurine produced several clear anxiolytic effects in the battery of anxiety tests, although different tests were associated with some different outcomes.

The social interaction test was developed 27 years ago (File and Hyde, 1978) as the first animal test of anxiety that used a natural form of behavior as the dependent measure. An increase in social interaction, without a concomitant increase in motor activity, is indicative of an anxiolytic effect. Both benzodiazepines and drugs acting on the 5-HT system have been found to have effects in this test (Dunn et al., 1989). The dorsal hippocampus played an important role in controlling behavior in social interaction test. As previously stated, this animal model provides the opportunity of varying the level of anxiety that is generated by the test conditions. There is evidence for increasing endogenous serotonergic tone but decreasing endogenous cholinergic tone in the dorsal hippocampus with increasing anxiety. Thus, the dorsal hippocampal serotonergic and

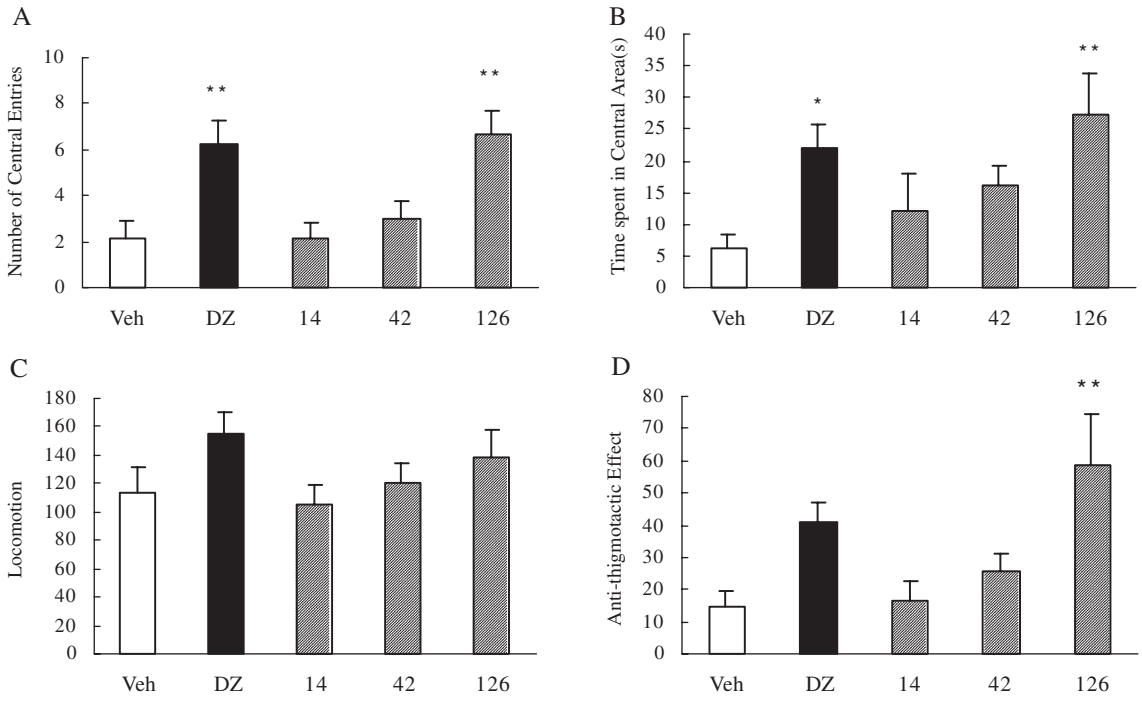

Fig. 2. The effect of taurine (14, 42, 126 mg/kg) and diazepam (2.0 mg/kg) on rats behavior in the open-field test: (A) the number of center entries; (B) time spent in the central area of the open field; (C) motor activity; (D) anti-thigmotactic effect. All drugs were injected 30 min before behavior test. Results are expressed as means± SEM. Significant differences from corresponding vehicle: *P<0.05, **P<0.01. n=8–10. Veh: □, Taurine: ▨, Diazepam: ■.

cholinergic systems are both biochemically and behaviorally tightly coupled, and appear to have an antagonistic relationship in the modulation of anxiety (File et al., 2000). Smythe et al. (1996) reported that stimulation of benzodiazepine receptors may offset the loss of cholinergic systems. In our present study, taurine (42 mg/kg, i.p.) and diazepam (2 mg/kg, i.p.) significantly increased the time of social interaction without an increase in locomotion in HU condition, the highest level of anxiety, indicating an anxiolytic effect. Based on other's studies that exogenous taurine (10^{-4} M) inhibits release and synthesis of newly formed serotonin 5-HT from tryptophan (Becquet et al., 1993) and affects the binding of ligands to the benzodiazepine site (Medina and De Robertis, 1984; Malminen and Kontro, 1986), we presumed that the anxiolytic effect of taurine in social interaction test may be due to decrease endogenous serotonin tone on the one hand and increase endogenous choline tone on the other hand while the anxiolytic effect of diazepam was mainly concerned with the increasing endogenous choline in dorsal hippocampus.

Takeda et al. (1998) indicated that head-dipping behavior was sensitive to changes in the emotional state of the animal, and suggested that the expression of an anxiolytic state in animals may be reflected by an increase in head-dipping behavior. In the present study, taurine at a dose of 42 mg/kg increased number and duration of head-dipping, the number of rearing, the number of squares crossed in the hole-board test. It could be argued that the increase of head-dipping in rats is merely an artifact of the hyperactivity induced by the drug. In order to make clear the facts, we examined the effect of taurine on the locomotor activity of mice in a separate experiment. The results in mice showed taurine had no influence on their locomotor activity at the anxiolytic doses. So we think when locomotor activity is assessed concurrently with anxiety (i.e., in the same test), sometimes the measure used is not the most appropriate because it is a biased measure, loading on both the "activity" and "anxiety" factors. In our current study, diazepam, a putative anxiolytic agent, increased the rearing behavior and the number of squares crossed as well as taurine. Therefore the increase of number of squares crossed and rearing is not only a representation of hyperactivity but also a reflection of anxiolytic effect.

During open field exposure, rats treated with 126 mg/kg significantly increased the number of center entries, the time spent in the center arena and the anti-thigmotaxis score. The number of squares entered was not significantly affected by taurine. The results of open field test seen here with 126 mg/kg taurine contrast with the finding by Sanberg and Ossenkopp (1977) that the 50 mg/kg or more of taurine decreased ambulation and increased thigmotaxis. The probable reason for this discrepancy is that the previous study tested taurine in a high light illumination field while the present study used a dim light arena. And the animals used in the present study were younger in age than those that were used by Sanberg and Ossenkopp (1977). It is well known that the effects of many drugs are dependent upon the environmental conditions under which the test is conducted and the age of test animals (Higgins et al., 1992; Serrano et al., 2002).

Additionally, there are some obvious differences on the outcomes of the three anxiety tests, such as the locomotor activity of the tested animals and the anxiolytic doses of TA. Although various experimental models of anxiety (e.g. plus-maze, social interaction, Vogel conflict, light/dark exploration, hole-board, free-exploration, and neophobia tests) have been proposed to measure different types or states of anxiety, there is some uncertainty as to whether anxiety mechanisms and anxiolytic drugs are uniformly active within and between animal models (Handley and MaBlane, 1993). They often yield variable or contradictory effects, probably as a result of differences in the target receptor or subtypes, animal models, dose range and routes of administration (Griebel, 1995).

In conclusion, the findings of the present study provide more experimental evidences to suggest taurine has anxiolytic-like effects on anxiety animal models. And this effect may be mediated by the interaction of taurine with 5-HT and GABA system, although this conclusion remains speculative in the absence of neurochemical data. Taurine may act as a modulating or anti-anxiety agent in the central nervous system but further studies investigating the mechanism underlying the behavioral actions of taurine may be necessary.

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