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Taurine Trials in Animal Models Offer No Support for Anxiolytic, Antidepressant or Stimulant Effects

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Abstract: Background: Taurine is a conditionally-essential amino acid that is found in high concentrations in the CNS and is essential for growth and survival of neurons. Taurine had been clinically tested in a number of diseases with variable results. In the context of neuropsychiatry, taurine was found to be altered in some neurological and psychiatric disorders and its levels affected by mood stabilizers and by antidepressants as well as anti-Alzheimer drugs. Taurine is also a common component in energy drinks and it is claimed (without scientific support) to have stimulant properties. The present study was designed to test taurine's effects in animal models of affective and anxiety disorders and to evaluate its properties as a stimulant. *Method*: Mice were treated with two doses of taurine with sub-chronic or chronic administration (for different experiments) and tested in the open field, the black/white box and the forced swim test. Taurine's possible stimulant effects were also tested in conjunction with amphetamine administration. *Results*: For the doses and schedules tested, taurine did not have an effect on measures of anxiety- or depression-like behaviors and did not act as a stimulant, neither alone nor in conjuction with amphetamine. In contrast, high dose taurine administration resulted in a transient decrease in activity. *Conclusion*: We suggest that any effects of taurine on affective-like behavioral measures may be very subtle (if any) and that prudence is recommended in claims regarding taurine activity as a stimulant.

Introduction

Taurine is a conditionally-essential amino acid which is not utilized in protein synthesis, but rather is found free or in simple peptides. Taurine is found in high concentrations in the central nervous system including the cerebral cortex and the hippocampus (1) as well as in other peripheral organs, it is consumed in food and also synthesized by astrocytes in the brain. It has a significant neuroprotective function and its deficiency results in neurodevelopmental pathology (2). In addition, taurine has a role as an inhibitory neuromodulator (3).

Taurine has been tried clinically for the treatment of a variety of diseases with various degrees of success including cardiomyopathy, retinal degeneration, and growth retardation, especially if deficiency occurs during development (2).

In the context of neuropsychiatric diseases, altered taurine levels had been demonstrated in a number of conditions including specific forms of schizophrenia (4), epilepsy (5) and depression (6), but the number of recent updated studies on this matter is limited.

Studies within the realm of affective disorders raise the possibility that taurine may be involved in both depression and bipolar disorder. Taurine was found to be elevated in depressed patients (7) and a significant and positive correlation was found between lymphocytes' taurine levels and the severity of depression (6). Interestingly, levels of taurine were normalized after treatment with mirtazapine (6). However, no difference in taurine levels was found in serum of treatment resistant depressed patients compared with controls, but a five-week period of antidepressant treatment in these patients did result in a reduction of taurine levels in serum (8). Taurine had also been suggested as an anticonvulsant (9) and many anticonvulsants are also mood stabilizers. However, the mood stabilizers lithium and valproate given in a therapeutically relevant chronic administration were reported to reduce taurine levels in rats (10) and humans (11). Furthermore, acute administration of high dose amphetamine, a psychostimulant that is known to induce manic episodes in susceptible individuals to rats resulted in increases in extracellular taurine brain levels as measured using

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in-vivo microdialysis (12). A recent study demonstrated a possible anxiolytic effect of acute taurine in the elevated plus-maze, a frequently used animal model of anxiety (13), and this finding may also be related to a stimulant-like effect as stimulants can induce risk-taking behaviors in animal models (14).

Taurine is a common component of many energy drinks and such drinks were reported to elevate mood and increase feelings of well being in healthy volunteers (15), but also to induce mania in susceptible individuals (16). Although taurine had been partially implicated in these effects of energy drinks, it is easily conceivable that they may be the consequences of other components such as caffeine and high sugar content (15).

Although the scientific findings regarding the effects of taurine on mood and behavior are scarce, it is frequently referred to in the non-scientific literature as having psychostimulant properties although the scientific literature is more skeptical (17). Many such references can be found in commercial advertisements for a variety of energy drinks or food supplements (e.g., http://www.thenetwork.ws/energy.doc), in mainstream media (http://abclocal.go.com/wls/story?section=special_coverage&id=3944559) and in some instructional academic material from distinguished institutions such as Texas A&M University (http://studentlife.tamu.edu/adep/FACTS/alcohol/energydrinks.htm).

Considering the data suggesting increased taurine levels in bipolar patients, raised taurine levels after psychostimulant administration, reduction in taurine levels after treatment with mood stabilizers and the non-scientific claim to its properties as a stimulant, the present study was designed to explore the effects of taurine in animal models of affective-like behavior and to evaluate its possible stimulant ability while used alone or in combination with other psychostimulants.

Methods

Animals

Adult C57bl/6 male mice (Harlan, IN) weighing 25–30g at the start of experiments served as subjects. Mice were singly housed in a colony room with constant temperature (22–23°C), 12/12 hours light/dark cycle and supplied with ad lib food and water. All experiments were performed during the light hours under standard fluorescent lights. All experiments were conducted according to NIH guidelines for the treatment and care of laboratory animals and were approved by the University of Minnesota IACUC (protocol # 0512A78028).

Drugs

Taurine (Sigma, St. Lewis, MI) at doses of 100mg or 400mg (as detailed below for the specific experiments) was dissolved in saline to a 10ml/kg volume and injected IP daily for 3 or 8 days (as detailed below for specific experiments) with the last injection 30 minutes prior to testing. These doses of taurine were selected as they were previously demonstrated to have CNS effects in animals resulting in behavioral changes (13).

Amphetamine (Sigma, St. Lewis, MI) at a 1mg/kg dose was dissolved in saline to a 10 ml/kg volume and injected acutely IP. This dose was chosen as it was repeatedly demonstrated to induce hyperactivity in mice (e.g., 18).

Order of experiments

The same mice served for more than one experiment going from less to more intrusive tests to minimize the effects of previous experience on later behavior. One group of mice was tested first in an open field, later in the Black/White Box, then in the Forced Swim Test and finally with acute amphetamine. A different group of mice served only for the taurine/amphetamine interaction test. Mice in the first group had at least a week between experiments and received taurine treatment on the last 3 days before testing.

Equipment and procedure

All experiments were performed in experimental rooms distinct from the colony room.

Open Field: Mice treated with 3 daily injections of taurine or control (n=8/group, last injection 30 minutes prior to testing) were individually placed in the center of a light grey large open field (80×80 cm with 40 cm walls) and their behavior digitally recorded for 20 minutes to a MPEG file using an overhead video camera interfaced with a computer. Files were

later analyzed for amount and distribution of locomotion using the Ethovision videotracking program (Noldus, VA). At the end of the session, mice were removed from the arena and placed back in their home cages and the open field was wiped clean with 10% alcohol solution. Beyond measuring the amount of locomotion, tests in a large open field can also provide measures related to anxiety-like behavior that are based on the distribution of activity in the arena (19). As done previously (19), the center area of 40×40 cm of the open field was defined as "center" for the purposes of analysis of distribution of activity.

Black/White Box: The black/white box test is a frequently used model for anxiety-like behavior (20). A wooden box (60 X 25 cm with 30 cm walls) was divided into two compartments: black (one-third of the box) and white (two-thirds of the box) with a separating door that can be open to allow free transitions between the compartments. Each mouse was placed in the white part of the box, with the separation door open, and allowed to freely locomote for a 10 minute session. Behavior was digitally recorded (as described above) and manually scored for measures of time and frequency of visits to the white part of the box. At the end of the session mice were returned to their home cages and the area was wiped clean with a 10% alcohol solution.

Forced Swim Test: The forced swim test is a relatively validated model for antidepressant activity. For the present experiment, transparent Plexiglas cylinders, 35 cm high with a diameter of 17 cm, served for the forced swim test. The cylinders were filled with tap water at 22–23°C to about 20 cm in a way that mice, when placed in the water, were not able to touch the floor or escape. Each mouse was placed individually into the water for a single 6 minute session and behavior was videotaped for later analysis. At the end of each session, each mouse was taken out of the water and replaced in its home cage. Water was replaced after each mouse. As done before (e.g., 21), the measures of immobility versus activity during the last 4 minutes of the session (first 2 minutes excluded) were manually scored for later analysis where immobility was defined as lack of activity except for movements needed to keep the body afloat.

Amphetamine Hyperactivity: The amphetamine-induced hyperactivity model is representative of the aroused activity levels of manic patients (for review see 22). The present experiments were conducted in transparent OptoM3 automated activity monitors (Columbus Inst, OH) measuring 45×25 cm with 25 cm walls. For both experiments (3 days taurine single exposure and 8 days taurine repeated exposure), for the final test session mice were injected with amphetamine and immediately placed in the activity monitor for 60 minutes. The automated monitors are equipped with 6 infrared beams and collect data on beam crossings. The number of crossings during the session was used for later analysis. For the single exposure experiment, mice (n=8/group) received 3 daily injections of taurine 100mg/kg or vehicle in their home cages. Thirty minutes after the last taurine injection animals were administered amphetamine and tested in the activity monitors. For the repeated exposure experiment mice received 8 daily injections of taurine (400 mg/kg) or vehicle (n=16/group) and tested in the activity monitors every second day (30 minutes after injection, without amphetamine; days 2, 4, 6). On the last day of testing (day 8 of the experiment), 30 minutes after the last taurine/vehicle injection, mice were administered amphetamine or saline and tested in the activity monitors. This design resulted in 4 groups (n=8/group) with taurine and amphetamine as variables.

Statistics: Tests based on 2 groups were analyzed using student's t-tests or repeated measures ANOVA with time as the repeated measure (for the locomotion measures in the large open field). The test for continuous exposure, amphetamine-induced hyperactivity was analyzed using repeated measures factorial ANOVA with time as the repeated measure and amphetamine and taurine as factors of the ANOVA. Since the analysis resulted in significant interaction within and across sessions, it was followed by t-test analyses for the specific time sessions. For all analyses, significance level was set at $p<0.05$.

Results

Activity levels

High dose of taurine resulted in a transient reduction

in spontaneous activity during the first 20 minutes of testing in test day 1 [Figure 1a; ANOVA, drug effect $F(1,27)=1.38$, N.S.; Time effects $F(5,23)=52.5$, $p<0.001$; Drug x Time Interaction $F(5,23)=2.86$, $p<0.02$; specific analysis of time sessions, minutes 0–10 $t(16)=2.1$, $p<0.05$; minutes 10–20 $t(16)=2.3$, $p<0.05$] and the first 10 minutes in test day 2 [Figure 1b; ANOVA, drug effect $F(1,27)=1.41$, N.S.; Time effects $F(5,23)=37.8$, $p<0.001$; Drug x Time Interaction $F(5,23)=2.81$, $p<0.02$; specific analysis of time sessions, minutes 0–10 $t(16)=3.0$, $p<0.01$]. This effect was, however, tolerated within sessions (Figure 1a & 1b) and across sessions as it was not apparent in test day 3 (Figure 1c). This initial reduction in locomotor activity was not observed with a lower dose of taurine (Figure 1d).

Depression and anxiety-like behavior

Taurine administration did not affect the behavior of mice in the Forced Swim Test, a frequently used model for antidepressant-like effects (Table 1). Taurine did not influence the behavior in the Black/White Box or the distribution of activity between center and periphery in a large open field, two measures for anxiety like behavior (Table 1).

Interactions with psychostimulant

Neither acute (Figure 2a) nor repeated (Figure 2b) taurine administration affected mice response to amphetamine suggesting that taurine does not augment amphetamine activity and does not cross sensitize with amphetamine. As expected, amphetamine treatment by itself (regardless of co-administration of taurine) significantly increased activity levels [Figure 2b; ANOVA taurine effect $F(6,23)=0.6$, N.S.; Amphetamine effect $F(6,23)=3.3$ $p<0.02$; Taurine X Amphetamine interaction $F96,23)=0.8$, N.S.].

Discussion

Some lines of evidence suggest the involvement of taurine in affective and anxiety disorders including major depression (6, 7), bipolar disorder (9–11) and anxiety (13). Taurine is also a component of energy drinks and is regarded as a stimulant. The available data regarding taurine effects are not consistent. For example, taurine levels were found to be elevated in depressed patients and were normalized after antidepressant treatment (6) but taurine was also elevated after amphetamine administration (12) and amphetamine has an antidepressant or pro-manic effect. The inconsistent findings may indicate that a variety of pathological processes may be affecting taurine levels via different pathways.

It is, however, interesting that most of the previous findings suggest a correlation between increased taurine and pathology, decreased taurine and treatment. Yet, taurine has an important role as a neuroprotective agent, essential for neuronal growth and survival (23). This introduces a complexity in any possible interpretation as antidepressants and mood stabilizers had been repeatedly demonstrated to increase neuroprotection and cellular resilience (24, 25). Moreover, substrates that enhance neuroprotection were shown to have antidepressant activity (26) and disruption of neuroprotective

Table 1. *Taurine administration in models for depression and anxiety*

Test	Measure	Control (mean±SE)	Taurine (mean±SE)	Statistics
Forced Swim Test	Immobility (sec)	222.6±5.7	221.7±3.4	$t(14)=0.1$, N.S.
Black/White Box	Time in white (sec)	82.6±12	70.4±9.5	$t(14)=0.8$, N.S.
	Frequency in white	12.9±2.1	12.6±0.9	$t(14)=0.1$, N.S.
Distribution of open field activity	Time in center (sec)	148.5±8.7	153.1±16.5	$t(14)=0.3$, N.S.
	Frequency in center	50.1±4.2	54.3±5.0	$t(14)=0.5$, N.S.

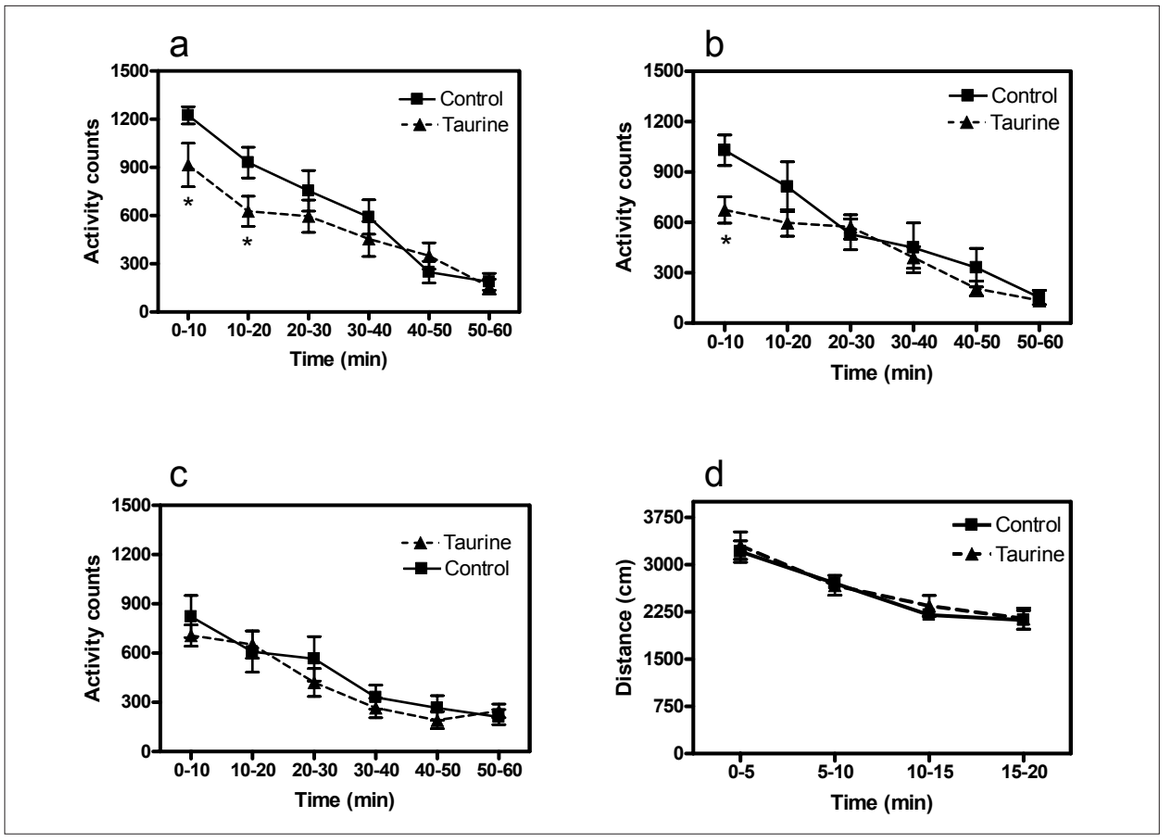

Figure 1: Effects of taurine on spontaneous locomotion

High dose taurine administration resulted in an initial decrease in locomotion after the first (a) and second (b) injections but this effect was tolerated by injection 3 (c). The lower dose of taurine did not affect locomotion levels (d). Filled squares represents control animals and filled triangles represent taurine treated mice. * represents statistically significant difference at $p<0.05$.

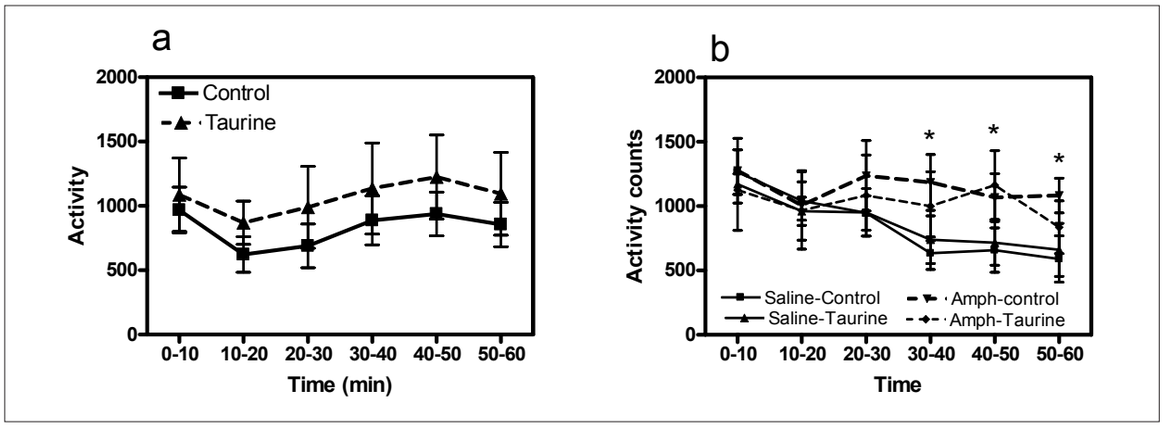

Figure 2: Effects of taurine on amphetamine-induced locomotion

Neither acute (a) nor repeated (b) administration of taurine affected amphetamine-induced locomotion. Amphetamine, regardless of taurine administration increased locomotion (b).
* in (b) signifies statistically significant effects ($p<0.05$) for the amphetamine versus control analysis.

mechanisms results in emotional-like pathology in animal models (for review see 27).

Based on these previous findings and the apparent incongruity between effects and possible mechanisms, the present study was designed to evaluate the possible effects of taurine in a number of models of affective- and anxiety-like behaviors as well as possible stimulant activity.

Two doses of taurine were tested, 100mg/kg and 400mg/kg. The choice of these doses was based on previous experiments showing their effects on CNS related behavioral measures (13). These doses are significantly higher than the ones present in energy drinks. For example, a can of Red Bull, a commonly marketed drink, contains 1000mg of taurine which, for a 70kg person is a dose of approximately 14mg/kg. It is, therefore, theoretically possible that at lower doses taurine may have some stimulatory activity. Yet, considering the different metabolism of rodents and humans, it is commonly accepted to treat mice with significantly higher doses of drugs compared to humans (e.g., 21).

If indeed taurine had a stimulatory effect, this may have influenced the results of a number of the tests described above. We would have expected taurine to increase activity levels in the open field spontaneous activity task decrease immobility time in the forced swim test (28) and increase the response to amphetamine in a cross sensitization mechanism (e.g., 29). Yet, none of these happened and no evidence was found to support a stimulatory activity of taurine.

Neither sub-chronic (3 doses) nor chronic (8 doses) taurine resulted in a stimulant effect. Additionally, the sub-chronic administration did not show potential antidepressant or anxiolytic activity. The present findings may be in contrast with a previous report showing that 60mg/kg taurine induced increases in the time spent in the open arms of an elevated plus maze, an anxiolytic-like response (13). However, even in that earlier report the authors note that taurine action may be different than classical anxiolytics as only one measure (time in open arms) in the test was influenced whereas anxiolytic drugs (as well as SSRIs) influence a number of measures. Furthermore, the conditions of testing in this study were significantly different from the present study. A different strain of mice (Swiss mice compared with C57bl/6 in the present study) were used, the mice were probably somewhat younger (tested at 20g compared with 25–30g in the present study) and, most importantly, the previous study was conducted under dim red light (compared with standard fluorescent lights in the present study); therefore the differences between the open and closed arms of the maze may have been less significant and the open arms less stressful than in the equivalent situations in the present study (the white area of the black/white box and the center area of the open field). It is therefore possible that taurine may have a very mild anxiolytic effect that can be observed when anxiety levels are low but not when they are somewhat higher. This is not uncommon that a compound may have an effect only when anxiety levels are either high or low but not at all times. For example, inositol treatment was demonstrated to have anxiolytic properties when anxiety levels are high but not when they are low (30). The present results do not support an antidepressant-like effect in the forced swimming test. Previous work clearly demonstrated that forced swimming in rats results in significant and lasting increases in taurine in the hypothalamus and that this increase is related to downstream vasopressin release (31). These data suggests that taurine may be related to stress response and it is therefore possible that its administration can have some effects in situations of repeated stress. However, the present study did not explore such situations and no effects were observed in the standard forced swim test as used to screen for antidepressant-like behavior.

The only observed effect of taurine was a transient reduction in locomotor activity levels but this effect tolerated across time and across repeated administration. This effect is similar to previous reports in rats (32) and mice (33) and was suggested to be related to taurine possible role as a stabilizing modulator at the central nervous system (32). These previous results may not be enough to exclude stimulant activity of taurine as some stimulants induce an initial reduction in activity followed by a steep increase (34), yet the present findings do not show such a pattern but only an initial decrease in activity levels. Some data suggest that taurine may have behavioral (35) and physiological (36) effects in combination with caffeine and the present results cannot negate this possibility. Yet, the focus of this study was

to explore the possible effects of taurine in the context of affective disorders and amphetamine-induced behavior is the most frequently used model in this context (37).

In summary, the present study demonstrates that at the doses and administration schedules tested, effects of taurine on C57BL/6 mice were very limited. These data therefore do not support the non-scientific literature related to energy drinks. Whereas it is possible that the taurine in these drinks may have some other beneficial effects to drinkers, or some effects in the combination with caffeine, it is our contention, based on the results, that its described role as a stimulant is speculative at best.

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