AN ASSESSMENT OF TAURINE AS A NOOTROPIC IN AGED MALE RATS IN THE ATTENTION SET-SHIFT TEST

Sam, G.R. 1,2, Ulloa, A.L. 2,3, Mian, M. 1,2, Traficante, M.T. 2,3, Vasquez, M.A. 2,4, Emenike, B.U. 4, & Neuwirth, L.S. 2,3,

Biology Department 1, SUNY Neuroscience Research Institute 2, Psychology Department 3, Department of Chemistry & Physics 4, SUNY Old Westbury, Old Westbury, NY 11568

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ORAL PRESENTATION
Overview:

- **Part I:** Background on Aging

- **Part II:** Implications of Taurine Offering Neuroprotection

- **Part III:** Attention Set-Shift Test (ASST)

- **Part IV:** Implications of Taurine as a Nootropic to Recover Age Related Cognitive Deficits/Impairments
It is predicted that by the year 2050, nearly 20-25% of the world's population will be 65 years of age or older (Martini et al., 2007).
As the world’s population ages, it also increases the risk for more people suffering from age-related disorders such as Alzheimer’s Disease as a single example (Martini et al., 2007).
Taurine has been suggested to function as a neuroprotective compound.

Taurine is theorized that through modulating the NMDA$_R$ through the glycine/strychnine binding cite that it increases the probability for activating the NMDA$_R$ to increase learning and memory to enhance cognition.

Additionally, it is also theorized that taurine can substitute for GABA and is a partial agonist for the GABA-A$_R$ to increase the probability for inhibition.

Thus, taurine may serve as a nootropic in an aged brain having cognitive deficits/impairments and poor decision making/impulsivity due to reduced inhibition as a function of senescence (Lam et al., 2021; Neuwirth & Emenike, 2021; Neuwirth et al., 2019a; 2019b).
Part III: Attentional Set-shifting: From Human Cognition to Using Rodents to Model Human Age-Related Disabilities
The Brain Regions Responsible for Attention are Comparable Across Species

Translational & Comparative Cross-Species Neuroanatomy of Fronto-executive Functions

Human

Rat

dorsomedial
Prelimbic
Infralimbic
ventromedial

Brodman Area 32 = rational thought processes, social and/or contextual judgment
Brodman Area 25 = memory formation, self-esteem, and emotional valence

(Adapted from Gass & Chandler, 2013)
The Rodent ASST is a Construct & Face Valid Model for Frontoexecutive Impairments & Psychopharmacotherapeutic Testing

Assessment of intradimensional/extradimensional attentional set-shifting in rats

David S. Taita, Eric M. Bowman, Lorenz S. Neuwirth, Verity J. Brown

School of Psychology and Neuroscience, University of St Andrews, St Mary’s Quad, South Street, St Andrews, Fife, KY16 9JP, UK
Department of Psychology, SUNY Old Westbury, Old Westbury, NY, 11568, USA
SUNY Neuroscience Research Institute, Old Westbury, NY, 11568, USA

ABSTRACT

The rat intradimensional/extradimensional (ID/ED) task, first described by Pavlov and Brown 18 years ago, has become the predominant means by which attentional set-shifting is investigated in rodents: the use of rats in the task has been described in over 135 publications by researchers from nearly 90 universities and pharmaceutical companies. There is variation in the protocols used by different groups, including differences in apparatus, stimuli (both stimulus dimensions and exemplars within), and also the methodology. Nevertheless, most of these variations seem to be of little consequence: there is remarkable similarity in the profile of published data, with consistency of learning rates and in the size and reliability of the set-shifting and reversal ‘costs’. However, we suspect that there may be inconsistent data that is unpublished or perhaps ‘failed experiments’ that may have been caused by unintended deviations from effective protocols. The purpose of this review is to describe our approach and the rationale behind certain aspects of the protocol, including common pitfalls that are encountered when establishing an effective local protocol.
Methods & Experimental Design

- **Treatment Groups**
  - Aged Control
    - Aged up to 1-year
      - Aged Control
      - Taurine Treatment 1-month
        - Taurine 0.05% in water
          - Control Rat’s That Failed Underwent Taurine Treatment To Assess Cognitive Recovery
            - ASST 1 week
  - Aged Control
    - Aged Control
      - Taurine 0.05% in water
        - ASST 1 week
  - Aged Control
    - Aged Control
      - Taurine 0.05% in water
        - ASST 1 week
  - Young Control
    - Aged up to 3-8 Months
      - Young Control
        - ASST 1 week
        - Testing 3-8 Months

- **Behavioral Testing**
  - 12-13 months
    - Young Rats Served As a Healthy Cognitive Reference Group
Flavor of the Froot Loop™ is the same regardless of color, but varied color to prevent it being used as an associative cue.
Neuwirth-Brown™ 2022
Attention Set-Shift Test (ASST) Experimental Apparatus

Right Choice Chamber
(Styrofoam with R+)

Left Choice Chamber
(Shredded Paper)

Neutral Chamber

Start Chamber
Attention Set-Shift Test Stimulus Sets: Training Phase MD & OD
Attention Set-Shift Test Stimulus Sets: Training Phase SD, CD, CD-Rev
Attention Set-Shift Test Stimulus Sets: Training Phase CD-Re-Acq, ID, ID-Rev
Attention Set-Shift Test Stimulus Sets:
Training Phase ID-Re-Acq, ED, ED-Rev
Results

Figure 4. Illustrates the ASST training profiles for Control Young (Blue), Control Old (Black), and Control Old + Taurine (Grey) treatment groups for their latency (A) and their trials-to-criterion (B). The data revealed that Control Old rats had difficulty in completing their training, whereby only 2 of 6 rats (33.33%) were able to complete the MD and OD training conditions. The data show that Control Old rats too substantially longer latencies to make cognitive decisions indicative of a intellectual deficit/delay \( (p < 0.01^{**}; \ A) \) and took longer trials to meet the criterion for the MD \( (p < 0.05^{*}; \ B) \). In contrast, the Control Old +Taurine rats performed their training similar to control and it appears that taurine treatment reversed theses aged-induced training intellectual delays/deficits. Data are shown as the mean ± SEM for each bar graph from a One-way ANOVA.
Results (Continued)

Taurine Treatment Reversed The Deficits in Fronto-executive Function Due to Aging And Made Older Rats Perform the ASST Equivalent to Younger Rats

**Figure 5.** Illustrates the ASST testing profiles for Control Young (Blue), Control Old (Black; data not shown as these rats were unable to complete the SD and therefore were disqualified from subsequent testing), and Control Old + Taurine (Grey) treatment groups for their latency (A) and their trials-to-criterion (B). The data revealed that Control Young rats took more time to complete the CD stage of the ASST ($p < 0.001***$; A), when compared to the Control Old + Taurine group. In contrast, the Control Young rats took more trials to complete the SD, CD-Rev, and ED stages of the ASST ($p < 0.01**$; B), when compared to the Control Old + Taurine group. The data show that Older rats fronto-executive functions can be recovered, their information processing speed increased, and their accuracy of responding to be equivalent to or better than Control Younger rats. This evidence suggests that taurine serves as a nootropic in aged rats to reduce age-dependent effects on attentional learning, cognitive flexibility, and working memory. Data are shown as the mean $\pm$ SEM with for each bar graph from a One-way ANOVA.
Discussion: Implications of Taurine as a Nootropic to Recover Age Related Cognitive Deficits/Impairments

- Notably, 66.67% of Control Old Rats failed the Training Phase and the remaining rats (33.33%) could not complete the SD to continue the ASST.

- The present study is one of the first to report using a clear aging model in rats, that taurine treatment given in the later years of life can prevent the naturally occurring age-dependent declines in fronto-executive functions (i.e., attention, cognitive flexibility, adaptive responding, working memory, goal-directed behaviors, and their associated motor planning) using the ASST.

- These neuroprotective effects in recovering the ASST fronto-executive dysfunctions in older rats support the claim that taurine may also serve as a nootropic compound as an explanation for its neuroprotective properties.
Discussion (Continued)

- The improvements in fronto-executive functions observed in older rats treated with taurine, reversed their fronto-executive profile to that of a younger rat (i.e., a comparison of having the working memory of a 6-month younger rat). All the taurine rats completed the ASST unlike their age-matched counterparts.

- Moreover, taurine treatment also sped up the cognitive information processing speed in the older rat’s decision making profiles observed in their latencies.

- These findings provide new insights into how taurine might serve to increase better rates of GABAergic inhibition in aged rats. It is well-established that taurine increases GABA-A receptor inhibition and this inhibition/disinhibition is critical for normal cognitive processes. Aging is associated with reduced GABAergic tone in the brain and perhaps taurine is re-establishing more GABAergic tone in older rats. This would explain why and how the older rats have fronto-executive profiles that resemble younger rats.
Conclusions, Future Outlook, & Limitations

■ The present study only evaluated male aged-rats and these findings may not be observed to occur in the same way in female aged rats. More work is needed in order to establish the aging and sex-based differences in fronto-executive function and the role taurine might play in females as a nootropic.

■ This current study suggests, at least for males, that taurine may serve as a viable nootropic for increasing more efficient and accurate fronto-executive functions in aged rats. Whether this finding is generalizable from rats-to-humans seems promising, but requires more testing and supporting translational evidence.

■ Nevertheless, this is the first study that offers an approach to use taurine specifically as a nootropic to improve fronto-executive functions through the ASST in normal rats that only experience the natural effects of aging. There are may reports of taurine showing neuroprotective effects in neurological, psychiatric, and other developmental disorder/disability models, but less is known about its neuroprotective role in the aging brain. More work in this area may complement and/or supplement what has been reported to update the field on the prospects of taurine psychopharmacotherapy and its potential therapeutic value in humans.
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