Chapter 20
Functional Implication of Taurine in Aging

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Abstract Age-related impairment of central functions is though to result from alterations of neurochemical indices of synaptic function. These neurochemical modifications involve structural proteins, neurotransmitters, neuropeptides and related receptors. Several studies demonstrated that GABA receptors, glutamic acid decarboxylase (GAD65&67), and different subpopulations of GABAergic neurons are markedly decreased in experimental animal brains during aging. Thus, the age-related decline in cognitive functions could be attributable, at least in part, to decrements in the function of the GABAergic inhibitory neurotransmitter system. In this study we show that chronic supplementation of taurine to aged mice significantly ameliorated the age-dependent decline in memory acquisition and retention, and caused alterations in the GABAergic system. These changes include increased levels of the neurotransmitters GABA and glutamate, increased expression of glutamic acid decarboxylase and the neuropeptide somatostatin and increased in the number of somatostatin-positive neurons. These specific alterations of the inhibitory system caused by taurine treatment oppose those naturally-occurring during aging, and suggest a protective role of taurine in this process.

Increased understanding of age-related neurochemical changes in the GABAergic system will be important in elucidating the underpinnings of the functional changes of aging. Taurine might help forestall the age-related decline in cognitive functions through interaction with the GABAergic system.

Abbreviations *Tau*, taurine; *GAD*, glutamic acid decarboxylase; *IRB*, infrared beam

20.1 Introduction

Aging of the brain is characterized by several neurochemical modifications involving structural proteins, neurotransmitters, neuropeptides and related receptors (Marczynski 1998). Alterations of neurochemical indices of synaptic function have

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been considered as indicators of age-related impairment of central functions, such as locomotion, memory and sensory performances.

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system and is present in neurons in all brain regions. A number of GABAergic parameters have been reported to undergo changes during senescence (Araki et al. 1996). Several studies demonstrated that GABA receptors are markedly decreased in experimental animal brains during aging (Govoni et al. 1980; Hunter et al. 1989; Milbrandt et al. 1996). Significant age-related decreases in glutamic acid decarboxylase (GAD65&67), the enzyme responsible for GABA synthesis, were observed in the cortex and hippocampus of aged rats relative to their young adult cohorts, suggesting an age-dependent down-regulation of normal adult inhibitory GABA neurotransmission (Marczynski 1998). Consistent with this, functional studies in primate visual and auditory cortices demonstrated sensory coding changes suggestive of altered inhibitory processing in aged animals. Such age-related loss of normal adult GABA neurotransmission in the auditory cortex would likely alter temporal coding properties and could contribute to the loss in speech understanding observed in the elderly. Thus the age-related central sensory processing deficits could be attributable, at least in part, to decrements in GABA inhibitory neurotransmission (Caspary et al. 1990, 2002). Indeed, the auditory midbrain shows significant age-related changes related to GABA neurotransmission (Banay-Schwartz et al. 1989; Caspary et al. 1990, 1995; Gutiérrez et al. 1994, Milbrandt et al. 1996; Raza et al. 1994). Furthermore, different subpopulations of GABAergic neurons such as somatostatin- and parvalbumin-containing neurons are reduced in aged rats (Kuwahara et al. 2004). These observations seem to indicate that age-related changes in GABAergic function may be an important determinant of cognitive function. In the present study, therefore, we focused on GABA, the major inhibitory neurotransmitter system.

The neonatal brain contains high levels of taurine (Huxtable 1989; Huxtable 1992; Sturman 1993; Kuriyama and Hashimoto 1998). As the brain matures its taurine content declines and reaches stable adult concentrations that are second to those of glutamate, the principal excitatory neurotransmitter in the brain. Taurine levels in the brain significantly increase under stressful conditions (Wu et al. 1998), suggesting that taurine may play a vital role in neuroprotection. A possible mechanism of taurine's neuroprotection lies in its calcium modulatory effects. We have shown that taurine modulates both cytoplasmic and intra-mitochondrial calcium homeostatsis (El Idrissi et al. 1999; El Idrissi et al. 2003; El Idrissi and Trenkner 2004). Furthermore, taurine acts as an agonist of $GABA_A$ receptors (Quinn and Harris 1995; Wang et al. 1998; del Olmo et al. 2000; Mellor et al. 2000; El Idrissi et al. 2003; El Idrissi and Trenkner 2004). Thus, we hypothesize that the age-dependent deterioration in GABAergic function and the resulting decline in cognitive function could be ameliorated by supplementing exogenous taurine.

We found an age-dependent decline in learning and memory as measured by acquisition and retention of a passive avoidance task between young and old mice. Young mice (2 months) learned at a significantly quicker rate and much greater amplitude than aged mice (16 months). Furthermore, the young group of mice

performed significantly better on a recall test than aged mice. Interestingly, when aged mice were supplemented with taurine in drinking water for four weeks, they showed a significant increase in acquisition and retention of a passive avoidance task as compared to age-matched controls. On the other hand, young mice supplemented with taurine learned to the same extent as their age-matched controls. Furthermore, we found several biochemical changes that accompanied the increased performance in memory tasks of taurine-fed mice. The brains of these mice have elevated levels of both the excitatory and inhibitory neurotransmitters (glutamate and GABA, respectively) and the GABA synthesizing enzyme, glutamic acid decarboxylase (GAD). The levels of somatostatin and somatostatin-positive neurons were increased in the brain of taurine-fed mice. These chances seem to be opposing those naturally-induced by aging. Interestingly, electrophysiological recordings from hippocampal slices prepared from the brain of taurine-fed mice showed an increased in the amplitude and duration of population spikes recorded from CA1 in response to Schaefer collaterals stimulation. Such increased excitability of hippocampal slices of taurine-fed mice is consistent with lower threshold for LTP induction, which would explain the increased learning in these mice.

Using this paradigm of taurine treatment we will gain significant understanding of the mechanisms by which taurine influences the inhibitory GABAergic systems in the brain and explore the potential of taurine in reversing the age-dependent alteration in the inhibitory system. Most importantly, the identification of specific age-dependent alterations in the GABAergic system will enhance our understanding of the basis for the long-lasting altered cellular and synaptic properties that contribute to the decline in cognitive function, characteristic of senescence.

20.2 Methods

20.2.1 Passive Avoidance Test

We conducted the repetitive training passive avoidance test when the animals were 2 months or 16 months old. The test was carried out during the light phase (13:00–17:00 hrs), and each animal was housed individually during the test. The apparatus has a bright and a dark compartment with a computer-controlled door between them. The delivery of electric shocks (0.5 mA for 2 sec) and the raising and lowering of the door and the latencies at which the animals stepped into the dark from the bright compartment were con-trolled by the computer. Each animal was gently placed in the light compartment for 10 sec, after which the guillotine door was raised and the time the animal waited before crossing to the dark (shock) compartment was re-corded as the latency. The trial ended when an animal waited more than 180 sec to cross to the dark side, or if it received an electrical shock in the dark side after crossing. Once the animal crossed with all four paws to the dark compartment, the door was closed and a 0.5 mA foot shock was de-livered for 2 sec.

This shuttle box apparatus has 8 infrared sensors on each side that allow to measure locomotor activity by measuring the number of infrared beams breaks.

20.2.2 Statistic Analysis

Multifactorial analyses of variance was used to identify overall condition effects. Significant changes were determined by post hoc comparisons of means using the Tukey HSD test. Significance was set at a confidence level of 95%. Data are presented as mean ± SEM.

20.3 Results

20.3.1 Taurine Improves Acquisition and Retention in Aged Mice

Taurine has been shown to act as an agonist of GABAA receptors (del Olmo et al. 2000; El Idrissi and Trenkner 2004; Wang et al. 1998). Since senescence is characterized by a decline in the GABAergic neurotransmission, we supplemented taurine in drinking water to determine if chronic taurine intake alleviates the age-dependent decline in cognitive function. Using the passive avoidance paradigm, we tested the acquisition and retention in both young (2 months-old FVB/NJ males) and aged (16 months-old FVB/NJ males) mice supplemented with taurine (0.05%) in drinking water. Mice were given six trials a day for five days and after repetitive training, the level of learning was measured on the fifth day. Figure 20.1 shows that the performances of young and old mice during the last day of training. The apparatus has a bright and a dark compartment with a computer-controlled door between them. The delivery of electric shocks, the raising and lowering of the door and the latencies at which the animals stepped into the dark from the initial bright compartment were controlled and measured by the computer. Each animal was gently placed in the light compartment for 10 sec, after which the guillotine door was raised. The amount of time the animal waited before crossing to the dark (shock) compartment was recorded as the latency. The trial ended when an animal waited more than 180 sec to cross to the other side, or if it received an electrical shock in the dark side after crossing. Once the animal crossed with all four paws to the next compartment, the door was closed and a 1.5 mA foot shock was delivered for 5 sec. Young mice were supplemented with taurine for four weeks and old mice were fed taurine for 8 months prior to, and during testing. Figure 20.1 shows that taurine had no significant effects on young mice. However, aged mice supplemented with taurine showed a significant increase in learning when compared to aged-matched controls (Fig. 20.1). Furthermore, aged mice approached learning levels observed in the young group after repetitive training. When we tested retention two weeks later, the performance of every experimental group correlated with learning. However, the aged control group showed the highest decline in the retention of previously learned

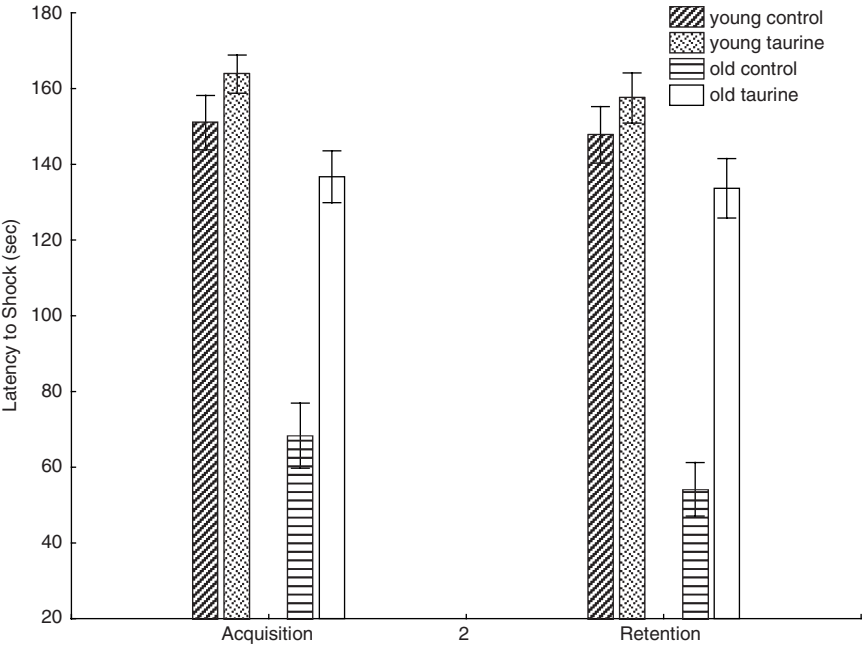

Fig. 20.1 Acquisition and retention of a passive avoidance task in young and old mice. Each animal was familiarized with the behavioral apparatus for 2–3 min the day before the training session and 10 sec before the test. All training and testing was carried out between 08:00 and 12:00 h. Mice (FVB/NJ males) were individually housed throughout the testing. Young group (2 months-old), aged group (16 months-old). Data represent the mean ± SEM of latencies to the end of the trial on the fifth day of training (acquisition) and two weeks after the last day of training (retention). Each group consisted of 10 mice. $^{*}p < 0.01$

task (extinction) when compared against all groups. Though, this decrease did not reach significance.

20.4 Discussion

We found an age-dependent decline in learning and memory as measured by acquisition and retention of a passive avoidance task between young and old mice. Taurine supplementation in drinking water for eight months significantly increased the performances of aged mice as compared to untreated controls. We have previously shown that chronic taurine supplementation in drinking water resulted in several biochemical changes in the inhibitory system. These taurine-induced alterations oppose those observed during aging. The brains of taurine-fed mice have elevated levels of both the excitatory and inhibitory neurotransmitters (glutamate and GABA, respectively) and the GABA synthesizing enzyme, GAD (El Idrissi and Trenkner 2004). The levels of somatostatin and somatostatin-positive

neurons were increased in the brain of taurine-fed mice (Levinskaya et al. 2006). Numerous experimental and clinical studies have demonstrated that somatostatin neurotransmission plays an important role in the modulation of several brain functions, including learning and memory processes. Expression of somatostatin in the brain declines during aging (Dournaud et al. 1996). A prominent decrease in this neuropeptide also represents a pathological characteristic of Alzheimer disease (Saito et al. 2005). Furthermore, one of the most consistent neurochemical abnormalities in Alzheimer's disease is a reduction in cortical somatostatin (Davies et al. 1980; Rossor et al. 1980). This may be attributed to the loss of intrinsic cortical neurons or could be caused by a decrease in synthesis or an increase in degradation of the peptide. In our previous study, we reported that taurine supplementation resulted in a significant increase in the number of somatostatin-positive neurons in the cortex and hippocampus (Levinskaya et al. 2006). Therefore, within the GABAergic population of interneurons, somatostatin-positive neurons seem to be more vulnerable in aging. Taurine supplementation selectively enhances the survival of this population of GABAergic neurons (somatostatin-positive). Although the mechanisms mediating this observation are not currently understood, it is possible that taurine may have a trophic effect on this subpopulation of GABAergic neurons.

These biochemical changes resulting from taurine supplementation are opposing those naturally-induced by aging and suggest that taurine improves learning and memory in aged mice through amelioration of the age-dependent decline in GABAergic function. In the central nervous system, the effects of taurine are not limited to interactions with the inhibitory GABAergic system. Taurine also activates glycine receptors (Häusser et al. 1992), acts as anti-oxidant (Aruoma et al. 1988) and regulates intracellular calcium homeostasis (El Idrissi and Trenkner 1999). Therefore, these neuroprotective effects of taurine could also contribute to the improvement of cognitive functions observed after chronic supplementation with taurine. Young mice on the other hand showed no improvement in learning and retention above controls. This could possibly be due to the limited sensitivity of the behavioral test used in this study that could not detect subtle differences between the two groups of mice. However, taurine induced several biochemical changes to the inhibitory GABAergic system at early ages that could be beneficial in aging.

20.5 Conclusion

In summary, this study shows that supplementation of taurine in drinking water to senescent mice significantly improved their ability to learn and retain memory tasks. Taurine induces biochemical changes in the inhibitory system opposing those naturally occurring during aging.

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