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**Oral presentation**

# The effect of taurine on animal behavior

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## Abstract

Taurine (TAU) is an essential or semi-essential amino acid according to the animal species. It has many basic physiological functions such as membrane stabilization, cell signaling, osmoregulation and bile acid conjugation. This review focuses on the behavioral and cognitive effects of taurine in different animal species. Taurine, found in various body tissues, is the most common amino acid after glutamate in the mammalian nervous system. It is especially common in developing brain. It is distributed in the cerebellum, cortex and hippocampus. Studies in rats and zebra fish have shown that taurine is effective in stress-related mechanisms. These effects are induced by inhibiting the hypothalamic-pituitary-adrenal axis (HPA) and activating the glycine receptor. Taurine prevents the reduction of serotonin, dopamine, noradrenaline levels in rats under chronic stress, and prevents excessive release of glutamate and corticosterone. Thus, it has anti-depressive and anxiolytic effects. A study on blue tits revealed that the amount of taurine taken during the growth period shaped long-term adulthood behaviors. It has been observed that offspring develop their spatial / spatial learning abilities and increase their risk-taking potential, especially when researching new objects. A study of zebra fish indicated that taurine use reduces the risk assessment behavior, which is a defense approach. Spatial learning ability and risk-taking tendency are influential on an individual's competitiveness and prey success. As a result, taurine affects the development of brain regions that control the HPA axis. Taurine supplementation enhances hippocampal development and function, which affects stress response and spatial learning. Interacting with learning mechanisms, taurine plays an important role in the formation of behavioral phenotypes of offspring. In the light of all this information, there is almost no scientific study on how taurine, which is widely used as a nutritional supplement in cat and dog nutrition, affects the behavior in these animals. Because of the cognitive and behavioral effects mentioned above, taurine is thought to play an active role in cat and dog breeding and training. Further research is needed to prevent depression and anxiety in pet animals.

**Keywords:** HPA axis, stress, early nutrition, risk-taking behavior, spatial learning

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## Introduction

Taurine, 2-aminoethylsulfonic acid, is produced mainly in the kidneys and liver (Karan, 1991). It is found in many other cells and tissues, including the brain, retina, heart, placenta, leukocytes and muscle (Jakaria et al., 2019). Taurine is a very important factor in various physiological processes such as brain development, neuroprotection, optic and immune systems, osmotic regulation, reproduction, stabilization of membranes and heart muscle regulation (Yeon and Kim, 2010; Park et al., 2014).

Taurine is the second most abundant amino acid in the brain after glutamate (Huxtable, 1989). TAU is common especially in developing brain (Magnusson, 1996). High taurine levels are found in the cerebral cortical regions, the hippocampus, and the cerebellum. (Jacobsen and Smith, 1968). TAU easily crosses the blood brain barrier via the taurine transporter (TAUT), commonly expressed in the central nervous system (Benrabh et al., 1995).

Milk contains taurine, and milk taurine is known to be necessary for the normal development of offspring. Taurine is considered essential in the early stages of growth; taurine deficiency in cats (Sturman, 1991), rodents (Sharma et al.,1995) and humans (Jung and Choi, 2019) were associated with lower body weights. Taurine deficiency is also associated with many neuropathological conditions such as developmental abnormalities for eyes and brain (Aerts and Assche, 2005). It is also essential to maintain normal retina (Knopf et al.,1978) and ERG function, especially in cats (Wang et al., 2017).

Taurine has been associated with growth factors such as brain-derived nerve growth factors that are related to neural plasticity (Trenkner et al., 1996). The maintenance of the proliferation and differentiation of neural stem cells are some of the crucial functions of taurine, effecting the neural physiology (Li et al., 2016). Taurine plays an essential role in modulating neurotransmission of glutamate and GABA and prevent in vitro excitotoxicity through regulation of intracellular calcium homeostasis (Louzada et al., 2004; Jakaria et al., 2019).

Taurine supplementation prevents the age-related decline of cognitive functions (Idrissi, 2019). It has been reported that taurine increased cognitive deficits in experimental demented mice to the level of normal age-matched mice but did not alter the behavior of cognitively normal mice (Kim et al., 2014).

Taurine increases the learning ability and memory; it can improve the performance of animals in memory tasks, increase exploration efficiency, and interfere with the apoptosis and neurodegeneration process (Rahmeier et al., 2016). In addition, taurine was found to have antidepressant activity and it has been speculated that this activity may be associated with the regulation of the hypothalamic-pituitary-adrenal axis and supporting the formation, survival, and growth of neurons in hippocampus (Wu et al.,2017). TAU also regulates complex behaviors such as aggression fear and anxiety, and it permanently changes hippocampal functions (Fontana et al., 2018).

Taurine is an amino acid that has recently attracted attention due to such a wide variety of neurophysiological functions. This review focuses on the behavioral and cognitive effects of taurine in different animal species. Despite taurine has a wide use as a nutritional supplement in the feeding of pet animals, there is limited scientific study focusing on its behavioral effects in these animals. The findings about the effects of taurine on depression and anxiety, make it a prominent research topic regarding the use of taurine in pet animals, especially in the frame of animal welfare.

Taurine and chronic stress-induced depression

Depression caused by chronic stress weakens the neuronal structure and function in the hippocampus. It reduces energy metabolism and brakes the negative feedback system that modulates the accumulation of corticosterone (CORT) in the hippocampus. (Erickson et al., 2003; Anacker, C. et al. 2013). Hippocampus is the main region in the brain involved in learning, memory and emotion and it is vulnerable to stress. Chronic stress and corticosterone release may develop the accumulation of glutamic acid (Glu) and disrupts the homeostasis of calcium and causes cytotoxic damage in brain tissues (Herbert, J. et al. 2006). Meanwhile, Glu accumulation may activate the HPA axis to secrete more glucocorticoids, and it exacerbates the toxic effects of Glu in the hippocampus (Compere et al., 2005;). Mutations or reductions in monoamine neurotransmitters such as 5-hydroxytryptamine (5-HT), dopamine (DA) and noradrenaline (NE) are associated with depression pathogenesis (Lopez-Munoz et al., 2009). In addition, under stress and depression, the levels of neurotrophic factors that regulate neural proliferation in the hippocampus (such as BDNF, FGF-2 and VEGF) have been found to be decreased (Bland et al., 2007; Elfving et al., 2010).

Gao-Feng Wu et al. (2017) showed that taurine had an effect on the abovementioned depression-related functions in rats exposed to chronic unpredictable mild stress (CUMS). In their research pre-administration of taurine restrained the decrease of the aforementioned neurotransmitters and neurotrophic factor levels, and the increase of glutamate and corticosterone levels. They found that both the serum and hippocampal CORT levels were low in taurine-pretreated rats; this indicates that taurine reduces the rate of corticosterone secretion by regulating HPA under prolonged stress. Their results are consistent with previous studies, which are reporting that taurine improves and regulates adult neurotrophic protein expression and neurogenesis in the hippocampus (Chen et al., 2004; Toyoda et al.,2015).

Taurine and anxiety

The GABAergic system has a vital role in regulating the anxiety behavior of animals (Idrissi and Trenkner, 2004). Taurine is capable of interacting with the GABA-Benzodiazepine system receptors, which are considered to be involved in the etiology of anxiety; taurine has been found to mimicking GABA (Kontro and Oja, 1990). Therefore taurine could be a promising agent for the treatment of anxiety-related diseases (Idrissi et al., 2013).

Exposure to various agents such as cyfluthrin (Rajawat et al., 2015), ethanol (Aragon et al.,1992) or cyhalothrin (LCT) (Prakash et al., 2015) results in reduced mobility in the open field test which indicates anxiety. Dose-based pretreatment of taurine may restore these behavioral changes. In another study on taurine and anxiety, it was observed that acute taurine treatment significantly increased the percentage of time spent on open arms in elevated plus maze test which indicates an anxiolytic effect (Chen et al., 2004). Additionally, it has been reported that, taurine resolves neuro-behavioral deficiencies caused by cisplatin which is used as a chemotherapeutic agent in cancer treatments (Owoeye et al., 2018).

Another task evaluated in these studies is muricide activity. Muricide activity or mouse killing behavior in rats is one of the most typical predatory aggressive behaviors observed in the laboratory (O'Boyle, 1974). It is thought that central serotonergic system is involved in inhibition of mouse killing behavior in rats (DiChiara et al., 1971; Gibbons et al., 1978). In a study on rats exposed to LCT (a synthetic pesticide) showed that pre-taurine administration inhibited LCT-induced muricide behavior. These results suggest that taurine’s anxiolytic effects are also associated with serotonergic system (Chakroborty et al., 2019).

Zebrafish, which has been widely used in scientific research, is a suitable model organism for studying anxiety-like behaviors. Zebrafish anxiety can be measured in different tasks, such as the response to new environments and to brightly lit environments (Stewart et.al, 2012). Anxiety-like behavior is a complex behavior in zebrafish caused by danger stimuli. It reduces their exploration behavior and typically displays as geotaxis (diving), tigmotaxis, scototaxis, increased freezing and irregular movements (Mezzomo et al., 2016). Zebrafish shoaling behavior is associated with cognitive performance and decision-making strategies (Sporns, 2010) and modulated by TAU (Jia et al., 2016). Therefore, taurine may affect the group behavior of zebrafish.

Risk assessment is a defensive behavior that involves careful investigation of new and / or potentially hazardous environments (Maximino et al., 2011; Kalueff et al., 2013). Mezzomo, et al. (2016), showed a significant decrease in the number of risk assessment behaviors in the group receiving high taurine. It has also shown that the application of taurine significantly increases the time spent in the brightly lit tank. These results suggest that TAU has an anxiolytic-like effect in zebrafish.

In another study on zebra fish, fish exposed to both TAU and ethanol showed a reduced discovery in the predatory region and decreased risk assessment sections. Also TAU-treated fish showed a significant reduction in the number of risk assessment episodes. TAU has a concentration-dependent effect on anxiety -like behavior, mobility, discovery, and aggression (Fontana et al., 2016; Rosemberg et al., 2012).

**Taurine and learning**

Studies show that learning and taurine are closely related: Taurine treatments (0.4 g / day) in pre-adult stages showed that mice can learn faster after weaning than the control group (Chen et al., 2019).

In a 2007 study at the University of Glaskow, the relationship between parental choice of prey and risk behaviors and spatial learning was investigated (Arnold et al., 2007): In some of the songbirds, there is an excessive increase in spider consumption during chick development. The researchers found that the amount of spider in the feeding of blue tits (Cyanistes caeruleus) significantly changed with the age of the chick. However, this change is not related to the season, environment or population frequency of spiders. Spiders are a food source similar to caterpillars except that they contain 40-100 times more taurine (Ramsay and Houston 2003). The period in which the amount of spider supply peaks is the period when the chicks are about 5 days old and their eyes are newly opened. At the end of the behavioral tests, it was found that providing taurine rich spiders to offspring improves their spatial / spatial learning abilities and increases their risk-taking potential while searching for new objects. These results are based on the fact that taurine influences the development of brain regions that control the HPA axis, and that taurine supplementation affects stress response and spatial learning that enhances hippocampal development and function (Koolhaas et al., 1999). In adult birds, spatial learning ability and risk-taking tendency have an impact on the individual's competitiveness and prey success. As a result of all these reasons, early feeding of the parents managed by prey selection is a mechanism that can manipulate behavioral phenotype (Metcalfe and Monaghan, 2003)

A study by McCabe, et al. (2001), provide evidence for the effect of taurine on learning mechanisms of imprinting behavior in chicks. An imprinting score was determined by a preference test applied to chicks divided into two groups; held in the dark after hatching or exposed to imprinting stimulants. Significant correlation was found between GABA and taurine levels and imprinting scores. And it has been shown that learning increased both GABA and taurine secretion. These results demonstrated that plasticity in GABAergic neurons is involved in the mechanisms of learning and memory and taurine contributes to these mechanisms.

**Conclusion**

In conclusion, all the neurophysiological properties described above shows that taurine effects anxiety, depression, learning ability, memory, risk assessment and risk taking behavior mechanisms. However, studies have reported that these effects of taurine are dose-dependent. Taurine exerts different effects under different types of stresses, as well as shows behavioral differences between acute administration and chronic treatment. The effect of taurine is varied in different developmental stages of the animals. In the light of current studies, it has a promising effect on behaviors.

Taurine is widely used as a nutritional supplement in cat and dog feeding. Because it is essential in cats and its deficiency is associated with heart disease in dogs. However, there is limited literature on the behavioral effects of taurine in these animals. Because of the cognitive and behavioral effects mentioned above, taurine can be used in behavioral disorders as it is involved with aggression mechanisms. In addition, it is thought that taurine can be used to increase animal welfare due to its anxiolytic and anti-depressive effects. Taurine is also thought to be effective in breeding programs of working dogs such as search and rescue or livestock guarding dogs. Further research is needed on the behavioral effects of taurine in pet animals.

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