Clinical Evidence Review

Scientific Insights

Evaluation of nutritional options for managing anxiety or stress in cats.

KEY POINTS:

- Accumulating evidence suggests that the urinary bladder of cats with feline idiopathic cystitis (FIC) is secondarily affected by an exaggerated sympathetic nervous system response to perceived stress.
- Stress reduction (e.g., environmental enrichment) is recommended as a key component of management for FIC.
- Tryptophan and a milk protein hydrolysate (hydrolyzed casein) have been shown to decrease anxiety and stress-related behavioural signs and may be helpful for cats with FIC.

GENERAL BACKGROUND

The term "stress", as it is currently used, was coined by Hans Selye in 1936 when he published in *Nature* the article "A syndrome produced by diverse nocuous agents"[1]. His initial definition of stress was "The nonspecific response of the body to any demand made on it". Selye's proposed General Adaptation Theory (1950)[2] described three responses of the body to stressors: alarm, resistance and exhaustion. Chronic stress would lead to exhaustion as manifested by disease and death.

Although the effects of stress in cats have not been extensively evaluated, recently published evidence shows that stress increases the risk of upper respiratory tract infections[3] and is involved in the pathogenesis of FIC[4]. The importance of providing an enriched environment for cats in domestic settings has recently led to recommendations from the American Association of Feline Practitioners and the International Society of Feline Medicine. They supported a provision of 5 pillars of needs for cats to minimize perceived stressors, and thus stress[5]. However, this monograph did not include any recommendations regarding the potential influence of nutrition for the management of stress in cats. Below is a summary of recently reported studies in cats describing the effects of nutritional supplements on anxiety and stress-related behaviours.

EFFECT OF DIETARY INTAKE OF L-TRYPTOPHAN SUPPLEMENTATION ON MULTI-HOUSED CATS PRESENTING STRESS-RELATED BEHAVIOURS.

Pereira GG, Fragoso S, Pires E. Effect of dietary intake of L-tryptophan supplementation on multi housed cats presenting stress related behaviours, in *Proceedings*. BSAVA 2010.

BACKGROUND

Tryptophan is an essential amino acid that has multiple metabolic fates. In most species it may be incorporated into proteins, converted to glucose and oxidized for energy, serve as a precursor to partially fulfill the niacin requirement and finally be converted to the neurotransmitter serotonin. Cats are unique from other species in that their ability to convert tryptophan to niacin is negligible and thus they have a requirement for preformed niacin in their diet.

Tryptophan is the precursor for serotonin synthesis and requires two enzymes to complete the conversion: the first and rate limiting enzyme is tryptophan hydroxylase, which produces 5-hydroxytryptophan, and the second step involves 5-hydroxytryptophan decarboxylase, resulting in the production of serotonin. Serotonin cannot cross the blood brain barrier so it is important to have an adequate supply of tryptophan to serve as the precursor for its synthesis **(Figure 1)**.

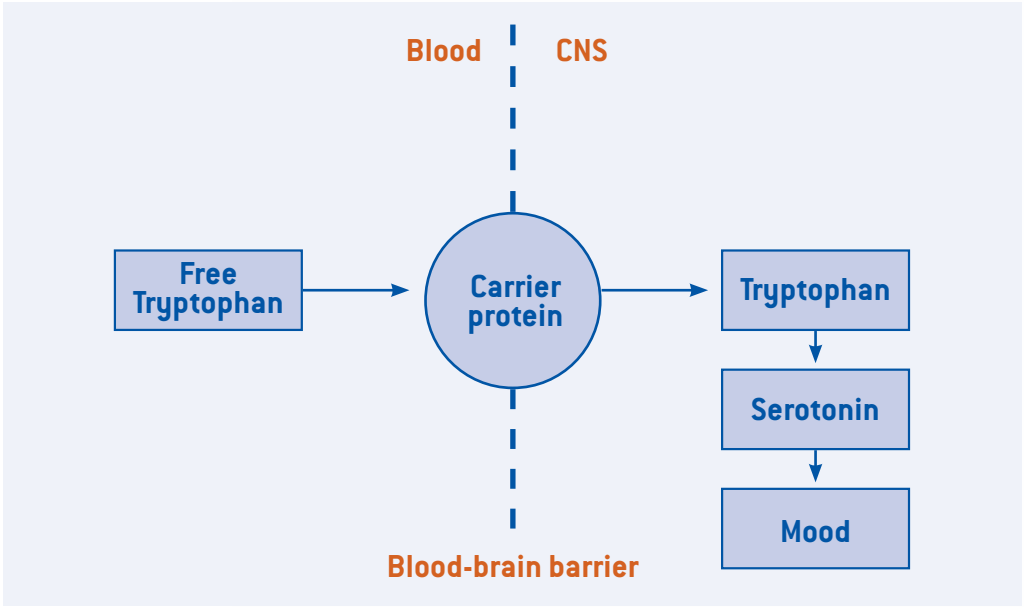

Figure 1. Tryptophan and other amino acids use a transporter (carrier protein) to move across the blood-brain barrier. In order to increase the amount of tryptophan available in the central nervous system (CNS) for serotonin synthesis, it is important to increase the amount of free tryptophan in the blood.

Serotonin is an important neurotransmitter that is found in the gastrointestinal (GI) system, platelets and the central nervous system (CNS) of animals. The majority of serotonin is found in the enterochromaffin cells of the GI system and is involved in the regulation of gut motility. Serotonin in the CNS generally is regarded to influence mood, satiety, cognitive and learning ability as well as multiple other physiologic functions. Increased concentrations of serotonin have been associated with a feeling of happiness and decreased anxiety in people and animal models[6].

STUDY DETAILS

WHAT

This was a randomized, placebo controlled, double blinded study of 25 multi-cat households conducted to evaluate the effect of dietary tryptophan supplementation on behavioural signs of anxiety and stress-related disorders. A total of 10 male and 15 female cats were included as part of the study group with one cat representing each household.

HOW

Cats received a health examination prior to enrollment and at the end of the study. Cats were observed for 10 minutes a day for 5 days a week for 3.5 months by a trained observer. The first 2 weeks of observation were habituation (getting used to the observer), and in the next 4 weeks' observations for baseline prior to intervention were obtained without any supplementation. Starting in week 7, cats were randomly assigned to receive either 12.5 mg/kg body weight of tryptophan or a placebo control with their daily meal and behavioural observations continued for the next 8 weeks.

RESULTS

Cats in the tryptophan supplemented group had significantly decreased displays of behaviour associated with anxiety and stress [stereotypes (repetitive movements), vocalization, antagonistic (fighting), affiliative, exploring and sustaining behaviour] compared with the placebo group ($P<0.05$ for each).

CONCLUSION AND CLINICAL IMPORTANCE

Supplementation of cats from multi-cat households with dietary tryptophan may be a beneficial adjunct to decrease signs of stress and anxiety and improve animal welfare.

EFFECT OF ALPHA-CASOZEPINE (ZYLKENE) ON ANXIETY IN CATS.

Beata C, Beaumont-Graff E, Coll V, et al. *J Vet Behav.* 2007;2(2):40-46.

BACKGROUND

Caseins, the major proteins in ruminant milk, may undergo hydrolysis secondary to the effects of trypsin in the digestive tract. This results in production of peptides of varying length that are subject to either further digestion or have biological activity. One such decapeptide, α-casozepine [generally recognized as a safe (GRAS) ingredient] has been associated with significant improvements in alleviation of stress, using models of anxiety in rodents and people[7]. The original mechanism of action was proposed to be through effects on the gamma amino butyric acid (GABA) receptor. The exact mechanism of the anxiolytic effect is unknown and may be mediated through effects on the serotonin, dopamine, or GABA receptor systems[8].

GABA receptors bind GABA and usually are considered to produce inhibitory responses within the CNS. Activation of GABA receptors helps to blunt anxiety signals in the brain. Serotonin has been associated with alleviation of depression and general increases in happiness. Serotonin in the CNS generally is regarded to influence mood, satiety, cognitive and learning ability as well as multiple other physiologic functions. Increased concentrations of serotonin have been associated with a feeling of happiness and decreased anxiety. Dopamine is a member of the catecholamine family and its release is considered a reward signal for the brain. If α-casozepine or smaller peptides from α-S-casein have biologic activity through modulation of any of these systems, it could result in an anxiolytic effect **(Figure 2)**.

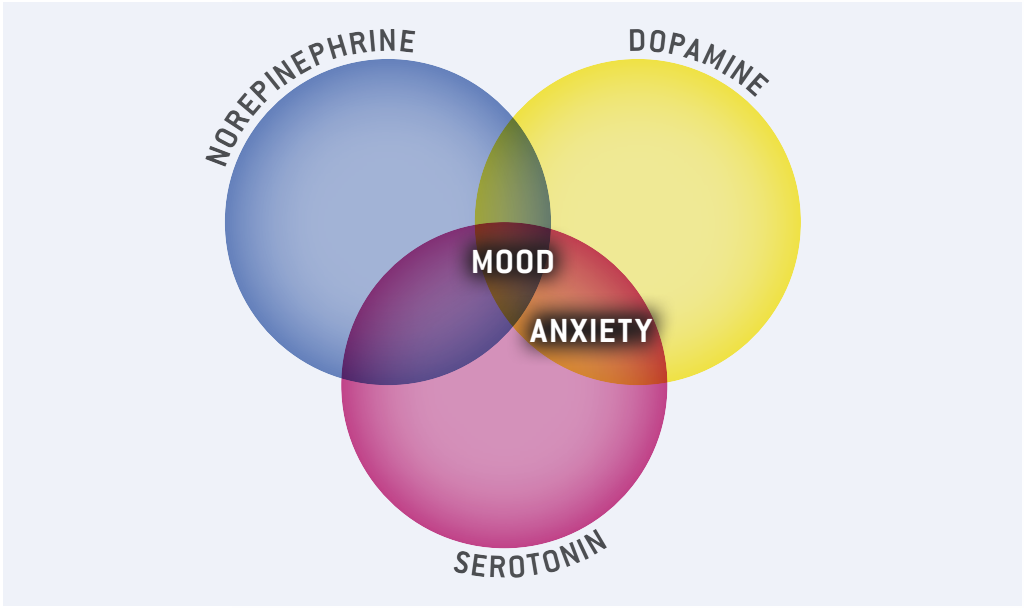

Figure 2. Influence of different receptor pathways on the brain.

STUDY DETAILS

WHAT

A multicentric, randomized, double-blind, placebo controlled trial was conducted to evaluate the efficacy of oral α-casozepine as an anxiolytic in cats. Alpha-casozepine is a 10 amino acid peptide produced by trypsin hydrolysis from ruminant αS-casein milk protein.

HOW

Cats were evaluated for anxiety by using a validated cat emotional scale. Owners evaluated five behaviours using a scale from 0 to 5; a score of 0 indicated a behaviour indicative of high anxiety and 5 was low anxiety. Cats were included in the study if they had a total score of <15 on the evaluation or a score of 0 on any one behaviour. There was also a subjective evaluation score performed by owners for an impression of improvement or not.

Thirty-four cats (21 female, 13 male) were enrolled in the study and randomly assigned to a placebo or test group. The test group received 15 mg/kg of α-casozepine by mouth once a day. All cats were evaluated 5 times during the study, including an initial hospital visit followed by visits at weeks 4 and 8, and subsequent telephone evaluations at weeks 2 and 6. Three separate categories were tracked at each evaluation: overall score; number of items with a score of 0, and owner's evaluation of change. Positive results for the three categories were defined as: overall objective global score ≥ 16, no behaviours scored as 0, and owner's subjective evaluation score ≥ 6/10. Successful treatment was defined as having attained criterion for both the objective global score and subjective score by week 8.

RESULTS

There was no significant difference between the groups at the beginning of the study. By week 8, 59% (10 of 17) of cats in the α-casozepine group and 24% (4 of 17) in the placebo group had responded positively. These results **(Figure 3)** were significantly different by comparison with a chi-square test (P=0.02). In addition, total global score rate of improvement over time **(Figure 4)**, an objective measure, was significantly greater in the α-casozepine group (P=0.003).

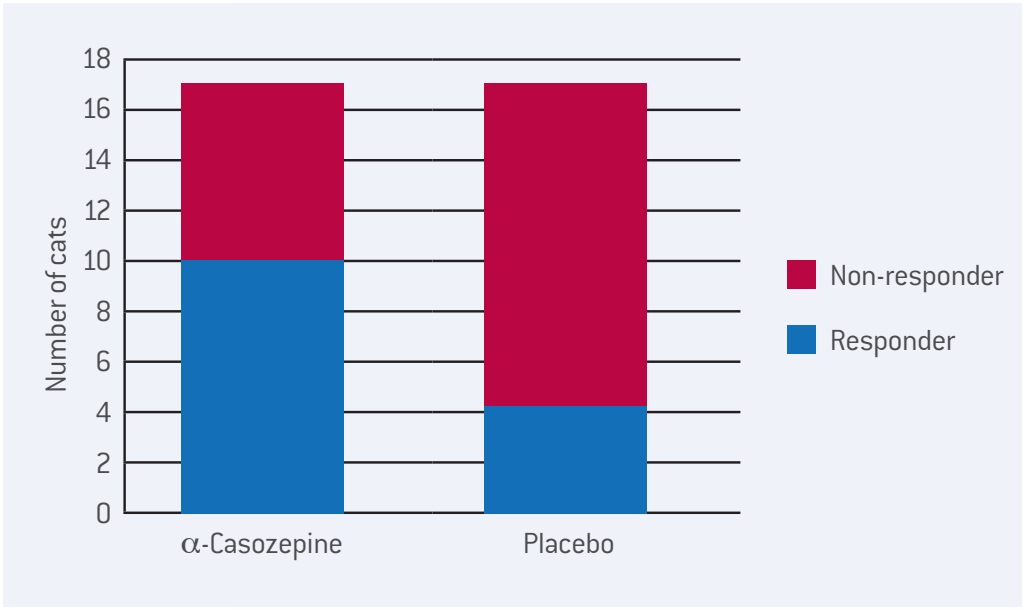

Figure 3. Effect of α-casozepine on successful resolution of behavioural signs of anxiety and stress compared to a placebo control. The treatment group had significantly more responders than the control group (*P*=0.02).

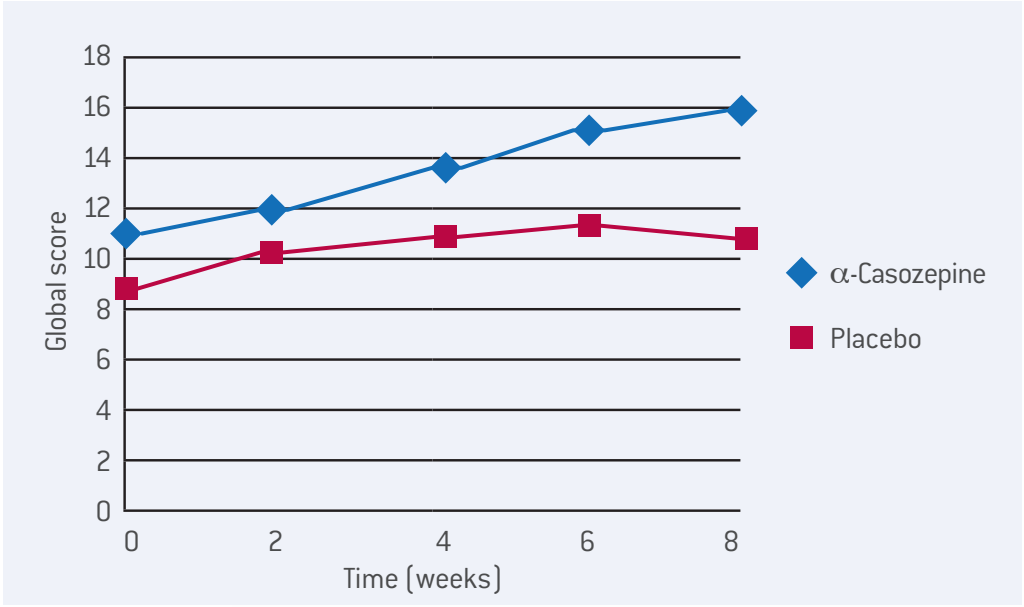

Figure 4. Rate of improvement for total global behavioural score between α-casozepine and placebo. Rate of total global score was significantly better for the treatment group (*P*=0.003).

CONCLUSION AND CLINICAL IMPORTANCE

The study provides positive Grade 1 evidence for the efficacy of α-casozepine in the management of cats exhibiting behaviours attributable to stressful social environments.

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