

Clinical Evidence Review

Scientific Insights



STRESS – Its role in Feline Idiopathic Cystitis (FIC) and aids to help manage it

KEY POINTS

- Accumulating evidence suggests that stress plays an important role in the development of FIC via a blunted cortisol response and exaggerated catecholamine release
- L-Tryptophan and milk protein hydrolysate have been shown to decrease anxiety and stress-related behavioural signs in cats, and may be helpful in managing FIC

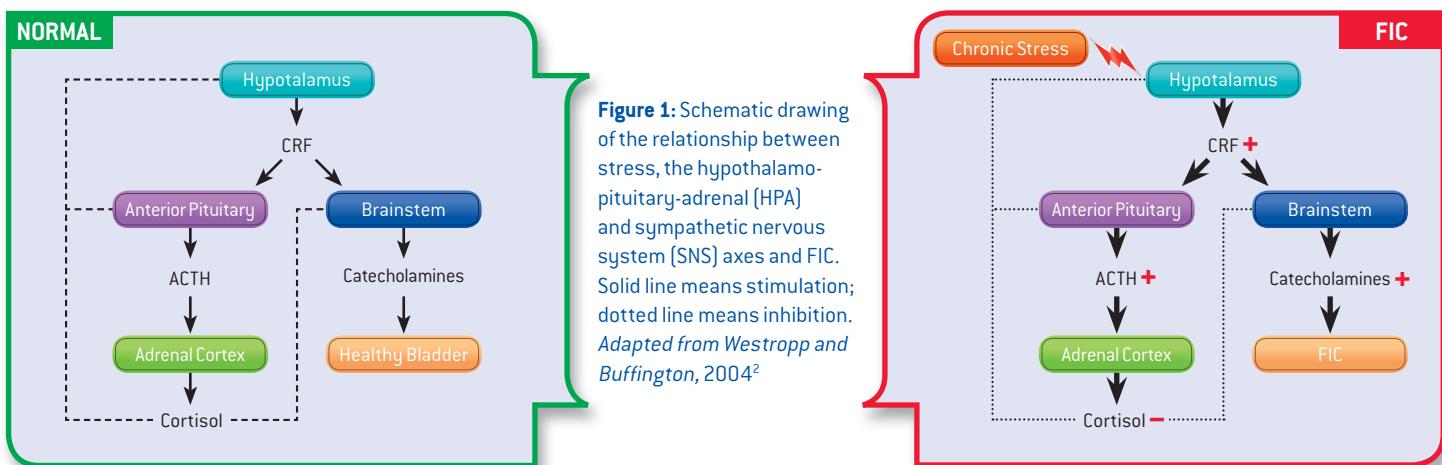
INTRODUCTION

Current evidence published to date suggests that stress (defined as 'the nonspecific response of the body to any demand made on it') is involved in the pathogenesis of feline idiopathic cystitis (FIC). A theory to this effect from the Ohio State University² postulates that chronic stress in these cats leads to disturbances in the hypothalamo-pituitary-adrenal axis, resulting in enhanced sympathetic nervous system outflow, which in turn causes increased sensory stimulation and altered urinary bladder permeability in affected cats (Figure 1). Indeed, in cats with FIC as compared with healthy cats:

- Corticotrophin releasing factor (CRF) in cerebrospinal fluid was higher³
- In response to an injection of CRF, the plasma adrenocorticotropic hormone (ACTH) response was higher and the cortisol response was lower⁴
- The adrenal glands were smaller⁵
- Plasma catecholamine concentrations were higher and urinary bladder permeability was increased⁶

Therefore, besides managing FIC nutritionally with foods enriched with ω-3 fatty acids from fish oil and antioxidants, which has been clinically proven to reduce the recurrence of episodes of FIC⁷, interventions to reduce stress and/or anxiety in cats with FIC seem warranted. It has been shown that environmental enrichment in cats with FIC significantly reduces signs of FIC and anxiety⁸.

Positive effects of various nutrients on anxiety and stress-related behaviours in various mammals (including cats) have been reported, notably of the essential large neutral amino acid L-Tryptophan and of milk protein hydrolysate (also known as hydrolysed casein or alpha-casozepine).



L-Tryptophan is the precursor for serotonin synthesis. Serotonin cannot cross the blood brain barrier so it is important to have an adequate dietary supply of L-Tryptophan for serotonin synthesis in the brain. Serotonin in the central nervous system is generally regarded to influence mood, satiety, cognition, and learning ability. Increased concentrations of serotonin have been associated with a feeling of happiness and decreased anxiety in people and animal models.⁹

Milk protein hydrolysate (such as casein hydrolysate, which is formed by trypsin hydrolysis) has been associated with significant alleviation of stress in models of anxiety in rodents and people. The exact mechanism of these anxiolytic effects is unknown but may be mediated through the gamma amino butyric acid (GABA)/benzodiazepine receptor complex.¹⁰

EFFECT OF DIETARY INTAKE OF L-TRYPTOPHAN SUPPLEMENTATION ON MULTI-HOUSED CATS PRESENTING STRESS RELATED BEHAVIOURS¹¹

Pereira CG, Fragoso S, Pires E. British Small Animal Veterinary Association, April 2010 [Abstract]

STUDY DESIGN

A randomized, placebo-controlled, double-blinded study of 25 cats (mean age 8 years; 10 males and 15 females) housed in multi-cat households was conducted to evaluate the effect of L-Tryptophan supplementation on behavioural signs of anxiety and stress-related disorders.

Cats received a physical examination prior to enrolment and at the end of the study. Cats were observed for 10 minutes/day (5 days/week) over 3.5 months by a trained observer. The first 2 weeks of observation were used to familiarise the cats with the observer. The cats received no supplementation for the next 4 weeks of observation to establish a baseline. Starting in week 7, cats were randomly assigned to receive either 12.5 mg/kg body weight of L-Tryptophan or a placebo control with their daily meal. Behavioural observations continued for the next 8 weeks.

RESULTS

Cats in the L-Tryptophan supplemented group had significantly decreased displays of stress-related behaviours (e.g., stereotypic, agonistic and sustaining behaviours) associated with anxiety and stress compared with the placebo group ($P<0.05$ for each).

CONCLUSION AND CLINICAL IMPORTANCE

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



EFFECT OF ALPHA-CASOZEPINE (ZYLKENE) ON ANXIETY IN CATS¹²

Beata C, Beaumont-Graff E, Coll V et al. *J Vet Behavior* 2007;2:40-6.

STUDY DESIGN

A multicentre, randomized, double-blinded, placebo-controlled trial was conducted to evaluate the efficacy of oral α -casozepine as an anxiolytic in cats.

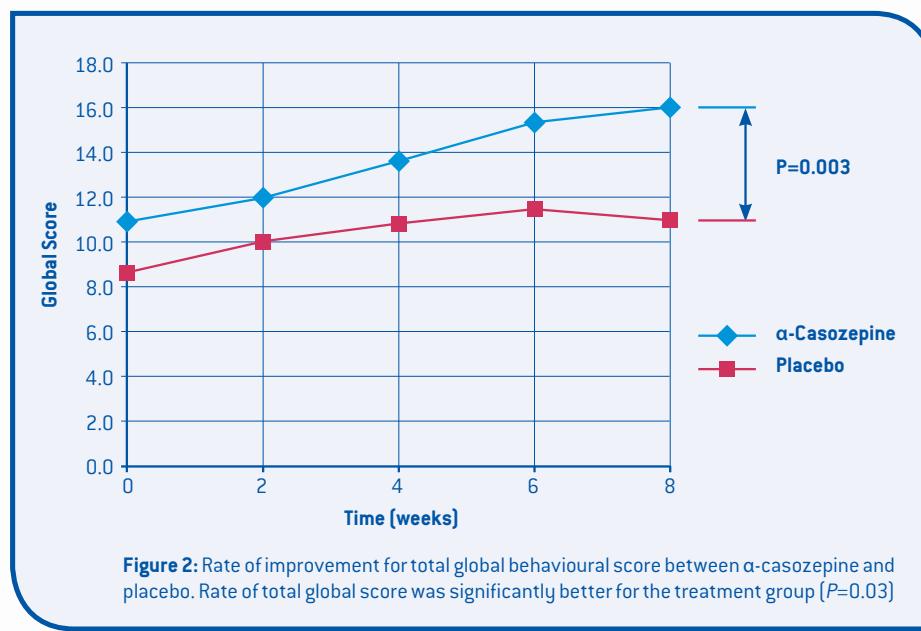
Cats were evaluated for anxiety by using a validated cat emotional scale. Owners evaluated five behaviours using a scale from 0 to 5 (0 indicated a behaviour indicative of high anxiety and 5 indicated low anxiety). Cats were included in the study if they had a total score of <15 on the evaluation or a score of zero on any one behaviour. Owners also subjectively scored their impression of improvement or not.

Thirty-four cats (21 female, 13 male) were enrolled in the study and randomly assigned to test or placebo group. The test group received 15 mg/kg BW of α -casozepine by mouth once a day. Each cat was evaluated 5 times. Evaluations were performed initially and at weeks 4 and 8 in the hospital. Telephone evaluations occurred 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 subjective evaluation of change. Positive results for the three categories were defined as overall objective global score ≥ 16 , no behaviours scored as zero, and owner's subjective evaluation score $\geq 6/10$. Successful treatment was defined as having attained criterion for both the objective global score and subjective score by week 8.

RESULTS

No significant difference existed between the groups at the beginning of the study. By week 8, 10/17 cats (59%) in the α -casozepine group and 4/17 (23%) in the placebo group had responded positively, which was a significant difference ($P=0.02$). In addition, total global score rate of improvement over time was significantly greater in the α -casozepine group than in the placebo group (Figure 2).



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.

SCIENTIFIC INSIGHTS SUMMARY

Stress is postulated to play an important role in the development of FIC, and stress reduction is recommended as a key component of multimodal management for these cats. L-Tryptophan and milk protein hydrolysate have been shown to decrease anxiety and stress-related behavioural signs and may be helpful for cats with FIC. Foods containing these ingredients to help control stress, such as Prescription DietTM c/dTM Feline Urinary Stress, can play an important role in the management of cats with FIC.



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