Role of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system in the pathogenesis of feline idiopathic cystitis

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Abnormalities in the sympathetic nervous system as well as the hypothalamic-pituitary-adrenal axis have been reported in cats with feline idiopathic cystitis (FIC). Tyrosine hydroxylase (TH) is the rate-limiting enzyme of catecholamine synthesis. A significant increase in TH immunoreactivity has been identified in the locus coeruleus (LC) (Figure 1), an area of the brainstem that is rich in alpha adrenergic receptors and is the origin of the descending excitatory pathway to the urinary bladder; it is the most important source of norepinephrine (NE) in the feline central nervous system.[1,2] Furthermore, TH was also increased in the paraventricular nucleus of the hypothalamus in cats with FIC.[3] The increased TH immunoreactivity observed in the LC of cats with FIC may provide a clue to the observation that clinical signs of FIC in cats follow a waxing and waning course and can be aggravated by environmental stressors.[4,5]

In addition to increased LC activity, we have reported that cats with FIC also have increased plasma NE concentrations.[4,5] When evaluating various catecholamines (CCE) in both healthy cats and cats with FIC during a period of mild stress (cats were moved from their regular vivarium to a room with new cages, food, and change of external environment), we noted increased plasma and cerebrospinal fluid (CSF) concentrations of CCE and their metabolites. We found that plasma concentrations of dihydroxyphenylalanine (DOPA), NE, and

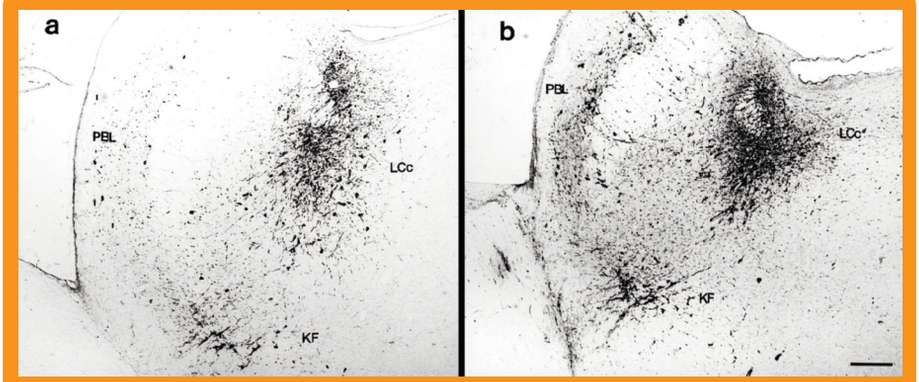

FIGURE 1 Photomicrographs of coronal sections of locus coeruleus of normal cat (a) and a cat with FIC (b), immunostained for tyrosine hydroxylase. Note increased staining density in locus coeruleus complex, parabrachial lateral (PBL) and Kolliker-Fuse (KF) nuclei of cat with FIC compared with normal cat. Scale bar: 20 pm. (From Reche AJ and Buffington CAT. Increased tyrosine hydroxylase immunoreactivity in the locus coeruleus in cats with feline interstitial cystitis. *J Urol* 1998; 159: 1045–1048)

its metabolite dihydroxyphenylglycol (DHPG), were significantly increased in FIC cats at all times during this stress protocol compared with healthy cats. Furthermore, as the healthy cats acclimated to the stress, their plasma CCE concentrations decreased, whereas even higher concentrations of plasma NE, epinephrine and their metabolites were demonstrated in cats with FIC.[4] The marked increment in DOPA concentrations suggests the possibility of a stress-induced increase in activity of TH, the rate-limiting step in CCE synthesis. In contrast, no effects on urine cortisol:creatinine was identified, suggesting an uncoupling of these two stress parameters. Plasma CCE concentrations did begin to return to baseline values after environmental enrichment strategies were employed, suggesting this therapeutic intervention may be beneficial for cats with FIC.

The acoustic startle response, a brainstem reflex in response to unexpected loud stimuli, is amplified in cats with FIC. This reflex in cats with FIC is greatest and most different from that of healthy cats during stressful situations, but is still greater in cats with FIC compared with healthy cats, even when adapted to enriched housing conditions.[6]

Enhanced stimulus-induced local NE release from the urinary bladder, could lead to a functional desensitization of the central alpha-2 adrenoceptors (α-2 AR) in cats with FIC.[7,8] In the brainstem (particularly the area of the LC), α-2 agonists inhibit NE release, whereas in the spinal cord they inhibit transmission of nociceptive input to the brain.[9] By evaluating the response of FIC cats to the selective α-2 AR agonist, medetomidine, both in vivo and in vitro studies have documented a functional desensitization of α-2 AR in affected cats.[7,8]

In addition to the sympathetic nervous system, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis have also been observed in cats with FIC. Administration of ovine corticotropin releasing factor resulted in significant increases in adrenocorticotropic hormone (ACTH), but not cortisol.[10] Administration of synthetic ACTH (125 µg) to cats with FIC resulted in significantly decreased serum cortisol responses compared with healthy cats.[11] Although no obvious histological abnormalities were identified, the areas consisting of the zonae fasciculata and reticularis were significantly smaller in sections of glands from cats with FIC than in glands from healthy cats, while the area of the zona glomerulosa was significantly larger (Figure 2). Therefore, it appears that while the sympathoneural system is fully activated in this disorder, the HPA axis is not.

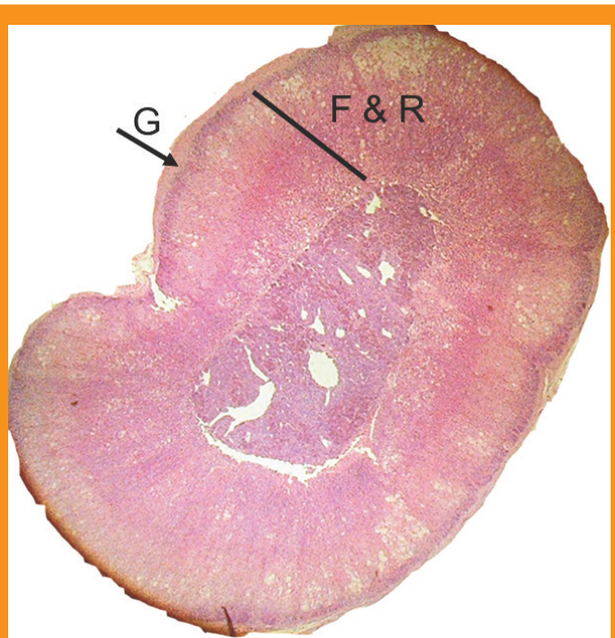

Figure 2 Histopathologic cross-section of an adrenal gland from a cat with FIC. Cats with FIC had adrenal glands with a significantly smaller zonae fasciculata and reticularis (F, R) (83% ± 2% vs 87% ± 4%, *P* = 0.03) and larger zona glomerulosa (G) (17% ± 2% vs 13% ± 3%, *P* = 0.02). No other histopathologic changes were reported

Summary

The pathophysiology of FIC likely involves complex interactions between a number of body systems. Abnormalities are not just localized to the urinary bladder, and cats can often present with various other comorbidities. In order to better treat these patients, it is important for clinicians to understand that this syndrome is not just a 'bladder disease' amenable to simple dietary or drug therapies.

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