

EFFECT OF FELINE INTERSTITIAL CYSTITIS ON ACOUSTIC STARTLE RESPONSE

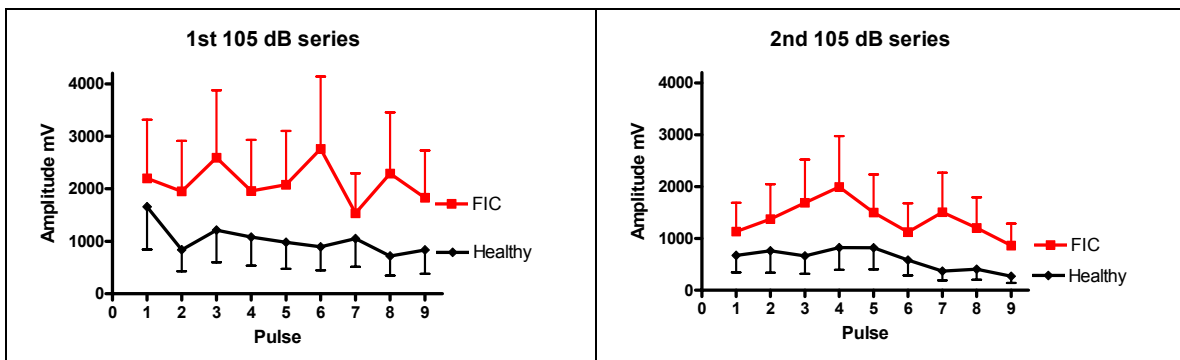
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Feline interstitial cystitis (FIC) is a naturally-occurring model of interstitial cystitis. In both species, affected individuals appear hypervigilant, and to have increased sensory and sympathetic nervous system activity and decreased adrenocortical function. To test responsiveness to environmental stimuli, we compared the acoustic startle reflex (ASR) to white noise in FIC and healthy cats. The ASR is an involuntary reaction to intense and surprising noise stimuli. It is quantifiable, and responses are comparable across species.

We employed a previously-described whole body acoustic startle protocol in cats housed in a specially designed cage. After 5 minutes of acclimatization, 9 50ms 105-dB baseline pulses were followed by 27 50 ms pulses consisting of 9@80dB, 9@80dB followed 100 ms later by 1@105dB to test prepulse inhibition, and 9-105dB pulses presented at random intervals of 50, 60, or 70 sec in pseudorandom order to avoid habituating sequences.

The ASR to both the initial ($p = 0.0002$) and the randomized 105dB pulses ($p=0.004$) were significantly greater in FIC than in healthy cats (2-way repeated measures ANOVA). No differences in ASR latency, prepulse inhibition, or response to 80dB pulses were identified.



The increased ASR responses of cats with FIC may have been due to increased sensory or sympathetic activity, reduced glucocorticoid activity, some central disorder, or some combination of these abnormalities. They also suggest that ASR could be useful as an outcome parameter for efforts to dissect the relationship of these abnormalities to the pathophysiology and symptoms of IC.

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EFFECT OF INTERSTITIAL CYSTITIS ON CENTRAL NEUROPEPTIDE AND RECEPTOR IMMUNOREACTIVITY IN CATS

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Interstitial cystitis (IC) is a chronic urological disease affecting both humans and domestic cats (FIC). Enhanced responses to external stimuli seem to play a role in the exacerbation of symptoms of IC. Corticotrophin releasing factor (CRF) release from the paraventricular nucleus (PVN) of the hypothalamus normally activates two interrelated systems, the locus coeruleus (LC)/norepinephrine system and the hypothalamic-pituitary-adrenal axis, which coordinate the stress response. To begin to evaluate the role of these systems in IC, we compared the intensity of tyrosine hydroxylase (TH), corticotrophin releasing factor (CRF) and corticotrophin releasing factor receptor-1 (CRF-R1) immunoreactivity in sections from the PVN and LC obtained from healthy cats and cats with FIC.

Four healthy cats and five cats with FIC were studied. All cats were perfused with 4% paraformaldehyde and brain sections containing the LC and PVN were collected. Frozen tissues were sectioned at 5 μ m and immunohistochemistry was performed for TH, CRF and CRF-R1. Slides were digitized and analyzed for immunoreactivity (IR).

THIR was greater in the LC ($p=0.03$) of cats with IC. CRF-R1 IR was reduced in both the LC ($p=.04$) and PVN ($p=.06$) of cats with FIC compared with healthy cats. Immunohistochemistry for CRF in the LC and PVN, and TH in the PVN, is currently in progress.

The increased THIR in the LC supports our previous finding in cats with FIC. The reduced CRF-R1 IR is consistent with ligand-mediated receptor downregulation, and we have found increased CRF in the cerebrospinal fluid of cats with FIC. These results further support the hypothesis that IC is related to persistent activation of the stress-response system.

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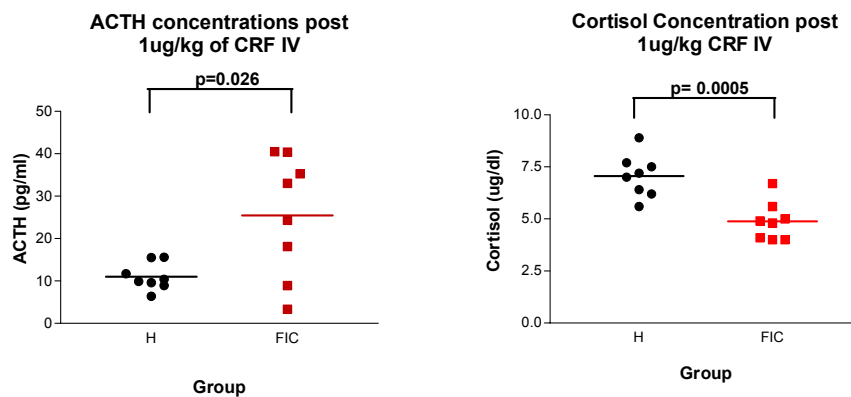
EFFECT OF A CORTICOTROPIN RELEASING FACTOR (CRF) ANTAGONIST ON HYPOTHALAMIC-PITUITARY-ADRENAL ACTIVATION IN RESPONSE TO CRF IN CATS WITH INTERSTITIAL CYSTITIS

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Based on previous results suggesting that increased corticotrophin releasing factor (CRF) may be involved in the enhanced stress responsiveness of cats with interstitial cystitis (FIC), we investigated the effects of the CRF-1 antagonist, antalarmin on response of the hypothalamic-pituitary-adrenal (HPA) axis of cats with FIC to CRF.

Antalarmin or vehicle (cremophor) was compared in 4 healthy and 4 FIC cats in a crossover design. After an overnight fast, cats were given the drug or vehicle 2.5 hours prior to blood sample collection. Cats were then subjected to a 35 minute acoustic startle paradigm, and blood was sampled again. 1ug/kg CRF was then administered intravenously to assess the magnitude of inhibition by antalarmin. Exactly 15 minutes after administration of CRF, blood was again collected and analyzed for ACTH and cortisol.



Because the effects of antalarmin were not significantly different from vehicle, results from both groups were pooled for analysis. The most significant result of this study was the effect of CRF administration on plasma [ACTH] and [Cort]. Although CRF administration significantly increased plasma [ACTH] in FIC cats compared to controls, (25.5 ± 14.3 vs. 11 ± 3.2 ; $p= 0.03$; mean \pm s.d.), the [Cort] in healthy cats were significantly greater than in cats with FIC (7.1 ± 1.0 vs. 4.9 ± 0.9 ; $p=0.0005$).

These results suggest that cats with FIC have a mild adrenal insufficiency. Our previous observation of increased CRF in the CSF of cats with FIC, and the increased ACTH response to CRF identified here argue against a hypothalamic or pituitary source, and in favor of a primary adrenal source of the abnormality.

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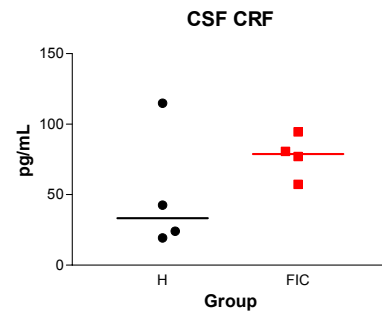
CEREBROSPINAL FLUID CORTICOTROPHIN RELEASING FACTOR AND CATECHOLAMINE CONCENTRATIONS IN HEALTHY CATS AND CATS WITH INTERSTITIAL CYSTITIS.

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We recently reported increased plasma catecholamine (CCE) concentrations in cats with interstitial cystitis (FIC) compared to healthy cats. During this same study, minimal changes were noted in the urine cortisol:creatinine ratios, suggesting a dissociation between the sympathetic nervous system and hypothalamic-pituitary-adrenal axis in FIC cats. To further investigate these observations we measured corticotropin releasing factor (CRF) and CCE concentrations ([CCE]) in the cerebrospinal fluid (CSF), and [CCE] in the plasma, of 4 healthy cats and 4 cats with FIC.

Food was removed from all cats 12 hours prior to placing them into metabolism cages. All cats were then anesthetized with isoflurane via mask induction; CSF was collected via cisternal puncture, and blood was collected through the external jugular vein. Cats were then housed in different cages and their diet was changed to simulate a mildly stressful condition. Blood was collected again on day 3, and blood and CSF collected on day 8. No significant differences were found in CSF [CRF] or [CCE] on day one. FIC cats had elevated CSF [NE] (295.3 ± 29.1 vs. 189.9 ± 68.0 ; $p=0.06$; mean \pm s.d.) and significant increases in CSF [CRF] on day 8 (77.4 ± 15.4 vs. 28.7 ± 12.3 ; $p=0.006$; mean \pm s.d.; one healthy outlier removed). Despite differences in the CSF, no differences in plasma [CCE] were found.



These results suggest that CRF and NE may be increased centrally even in the absence of alterations in peripheral [CCE]. This difference may keep these animals closer to the threshold for activation of the stress response system. If confirmed in more animals, this increase may help explain the exacerbation of symptoms observed in IC patients during stressful circumstances.

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