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Stress and Feline Health

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Keywords

coping; early life stress; epigenetic modulation of gene expression; perception of control; perception of threat; resilience; threat response system

Introduction

Veterinarians strive to improve the health of their patients, and recently there has been a more concentrated effort to understand the relationship between stress, physical health, and emotional health. Recent research has investigated how the effects of stressful environments manifest in cats, expanding from and connecting to research in other species.[1,2]

What is stress?

The term stress can be defined in various ways. From the perspectives of health and disease, stress is often defined in terms of *stressors*, which are events in the internal and external environment that result in a *stress response*. We think of stressors as events that are perceived as threats to one's perception of control. From this perspective, a stressor is anything that activates the central threat response system (CTRS).[3] Stressors can vary along a continuum: positive to negative, duration, acute to chronic, and intensity, (mild to toxic). For the purposes of this chapter, we have adapted the "ecobiodevelopmental" framework proposed by the American Academy of Pediatrics, "to stimulate fresh thinking about the promotion of health and prevention of disease across the lifespan."[4], which provides a helpful way to begin to think about stressors and stress responses. This framework acknowledges that all events that activate the CTRS are not equally threatening, and proposes a conceptual taxonomy comprising three distinct types of CTRS responses: mild

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"Everyone knows what stress is, but nobody really knows." Hans Selye

(positive), moderate (tolerable), and severe (toxic). The taxonomy is based on the differences in their potential to cause enduring physiologic disruptions as a result of the intensity and duration of the response.

Mild stress responses, defined as brief in duration and mild-to-moderate in magnitude, can help develop stress coping skills. Mild stress responses are part of normal development when they occur in the safe, predictable environments of stable and supportive relationships. Examples of events resulting in positive stress responses in young animals include non-threatening veterinary visits and exposure to novel environments and foods.

Moderate stress responses result from exposure to experiences that present greater threats, such as lack of stimulation/boredom or household instability, illness or injury, or exposure to a natural disaster. As with mild stress responses, when the event occurs in an otherwise safe environment, recovery to normal is likely. Thus, the essential feature that makes moderate stress response tolerable is the extent to which one's protective surroundings permit retention of sufficient perception of control to permit adaptive coping to occur.

In the most threatening circumstances, severe stress responses can result. Toxic stress responses, strong, frequent, or prolonged, are the most dangerous to long-term health and welfare. Examples of events that can result in severe stress responses include chronic abuse, severe or chronic disease, and adverse early life events like nutritional deprivation,[5] maternal separation, or significant maternal threat during pregnancy (more on this later).[6]

Stress and the Lower Urinary Tract (LUT)

Abnormal signs referable to the lower urinary tract (LUTS) of domestic cats include variable combinations of increased voiding urgency and frequency, decreased volume, blood in the urine, and urination outside the litter box. Although there are many possible causes of these signs, the most common causes include: "idiopathic cystitis"; a stone, usually calcium oxalate or magnesium ammonium phosphate; or a urinary tract infection (usually in older cats with upper tract disease). In addition to infection and inflammation, stress responses also can activate the LUT, although some of the fundamental neural mechanisms and pathways linking psychosocial stress to altered behaviors and physiological disorders are still unclear. Holstege[7] has pointed out that micturition plays a much more important role in the context of the survival of individuals and species in most mammals than it does in humans. For most mammals, urine also signals important messages such as the demarcation of territory of a specific individual[8] and estrus.[9] These urine functions demonstrate that voiding can occur for reasons other than to empty a full bladder, including the contexts of perception of threat and reproduction. Micturition responses in these situations require, and imply, supraspinal control of micturition.[7]

Part of the interest in feline stress biology arose from studies of cats with severe, recurrent chronic LUTS. Lower urinary tract signs have long been recognized in domestic cats, being described as "very common" in Kirk's 1925 veterinary textbook.[10] Clinicians historically interpreted signs referable to the LUT to suggest an external (e.g., infectious agent, urinary stone) or structural disorder of the LUT (e.g., stricture or incontinence), although

environmental conditions were recognized as a risk factor by Kirk in 1925, and subsequently confirmed to be relevant by other investigators.[11,12]

In 1996, Osborne et al., summarized the literature on feline LUTS, identifying some 30 distinct causes of LUTS.[13] That so many potential causes result in similar LUTS demonstrates that the signs in themselves only represent the limited repertoire available to the LUT to respond to any insult. During this time, a syndrome described as "feline interstitial cystitis" (FIC) also was being studied.[14] These studies found that additional problems outside the lower urinary tract were commonly present in these cats, and could be mitigated by multimodal environmental modification (MEMO).[15] Subsequent research has revealed the complex nature of this condition. For example, some cats with severe, chronic LUTS seem to have a functional, rather than a structural, lower urinary tract disorder,[1] and that LUTS can occur even in presumably healthy cats exposed to stressful circumstances.[12,16]

These findings suggest that terms such as "feline urological syndrome",[17] "feline lower urinary tract disease",[18] and "feline interstitial cystitis"[14] historically used to describe patients with this syndrome do not describe the extent of the problems occurring in many afflicted cats. Conversely, the narrow focus on the LUT may have precluded thorough evaluation of the entire patient, which might have revealed variable combinations of clinical signs referable to other organ systems such as the gastrointestinal tract, skin, lung, cardiovascular, central nervous, endocrine, and immune systems.[15,19] These comorbidities include some of the most common problems in feline medicine. They also lack a predictable pattern of onset across patients, and often precede the appearance of LUTS. This situation is similar in human beings with "central sensitivity syndromes"[20], suggesting that individual patterns of comorbidities may represent an amplification of underlying familial sensitivities.[21]

Perception of threat—The inconsistency of comorbidities observed in cats with chronic LUTS suggests that they may be variable manifestations of a common underlying problem.[22,23] The underlying problem in these patients appears to be a sensitized CTRS,[1] which results in a relative predominance of sympathetic to parasympathetic nervous system responses,[25,26] increased hypothalamic-pituitary – but not adrenal – activity,[24] as well as variable alterations in immune[25] and endocrine function.[26] Chronic activation of the CTRS seems to result in chronic "wear and tear" on body and brain systems, which can eventually progress to clinical signs referable to those organs most vulnerable in a particular individual.[27]

In addition to alterations in the components of the CTRS distal to the hypothalamus, brain structures that modulate activity of the CTRS also appear to be affected.[28] For example, cognitive factors such as classical and operant conditioning, attention bias, and memory have been shown to play roles in the onset, development, and maintenance of chronic health problems.[28] Moreover, studies have shown that the individual's expectations and ability to cope with potentially traumatic events are more important than the physical events *per se* for determining the immediate and long term consequences for health.[29]

The sensitization of the CTRS appears to result from genetic disorders, developmental events, environmental threats, or variable combinations of these.[30] A variety of polymorphisms in genes that affect stress responsiveness, including catechol-O-methyltransferase,[31] serotonin transporter,[32] and alpha-2 adrenergic receptor, have been identified in humans.[33,34] In cats, a genetic polymorphism of the alpha-2 adrenergic receptor that appears to enhance stress susceptibility has been reported.[35]

During the last two decades, the science of Developmental Origins of Health and Disease[36] has emerged to investigate the role of early life experiences on the sensitivity of the CTRS. Evidence from clinical, epidemiological, and experimental observations has shown how evolutionarily conserved developmental processes can interact with environmental cues, often transmitted from the mother via the placenta to the offspring, to attempt to match the physiology of the developing organism to its post-natal environment. The sequence of events that has emerged from this research proposes that when a pregnant female is exposed to a sufficiently severe stressor, the neuro-endocrine products of the ensuing stress response may cross the placenta and affect the course of fetal development.[37] The biological ”purpose” of transmitting such environmental cues to the fetus may be to guide the development of the fetal CTRS and associated behaviors to increase the probability of survival. The fetus may “use” information in its *in utero* environment to make predictive adaptive response “decisions”. If a threatening or nutrient-limiting environment is perceived, the developmental trajectory of the fetus may change in response to the available information to enhance reproductive fitness in the predicted *ex utero* environment.

Studies of the enduring effects of stressful developmental experiences on health have now been published in a wide variety of mammalian species, from rodents to primates.[6] Problems can arise when the actual *ex utero* environment does not match the predicted one. Studies in multiple species have found that cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome, and respiratory, gastrointestinal, lower urinary tract, dental, and mood disorders all can result from a mismatch between the predicted and actual environment the individual inhabits.[38] Cognitive function, too, is affected by both genetic and developmental influences. Impaired coping to stressful situations, increased fear and anxiety-related behaviors, and dysregulation of the CTRS all have been found in adults exposed to adverse early life experiences.[6]

Recent research also has shown that one mechanism underlying the sensitization of the CTRS involves a process called epigenetic modulation of gene expression.[39] This general biological process results in such commonplace outcomes as sex- and organ-specific patterns of gene expression that lead to the final phenotype of the organism by silencing genes not appropriate to the particular tissue environment. The molecular mechanisms of epigenetics are beyond the scope of this review, but detailed explanations are freely available.[40]

The effects of stressors on sensitization of the CTRS seem to depend both on the timing and magnitude of exposure to products of the maternal stress response in relation to the activity of the developmental “programs” that determine the maturation of the various body systems during gestation and early postnatal development. For example, the small adrenal cortices found in some cats with FIC suggest that the event occurred during a time when

adrenocortical maturation was occurring.[41] If the developing fetus had been exposed to a stressor before adrenocortical maturation, the effect may not have been observed, whereas if it had occurred later in development adrenal size and subsequent adrenocortical responses to stress might have been increased. Given the number of orphaned or abandoned kittens obtained from shelters, the risk for sensitization of the CTRS in client-owned cats may be high.

While sensitization of the CTRS is more likely to occur during growth and maturation of the neural, endocrine, and immune systems, it is not restricted to the developmental period. Moreover, sensitization of the CTRS may be unmasked by another adverse experience later in life, possibly associated with another round of epigenetic modulation of gene expression.[24] Subsequent rounds of alterations in gene expression may be quite stable and resistant to current medical interventions. Additionally, sensitization of the CTRS may be part of a more general "survival phenotype" that includes smaller (or larger) size at birth.[42]

Perception of control—Activation of the CTRS appears to depend on the balance between perceptions of threat and perceptions of control. Other recent research has focused on the roles of resilience and choice on stress responsiveness. The American Psychological Association's website "The Road to Resilience" (https://www.apa.org/helpcenter/road-resilience) defines resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats, or significant sources of stress. It means "bouncing back" from difficult experiences." A recent (September 15, 2019) special issue of Biological Psychiatry addressed the topic of the neurobiology of resilience from basic, clinical, and translational perspectives to summarize current knowledge of this important and rapidly expanding topic.[43] For example, Cathomas, et al.,[29] reviewed the physiological and transcriptional adaptations of specific brain circuits, the role of cellular and humoral factors of the immune system, the gut microbiota, and changes at the interface between the brain and the periphery on the neurobiological mechanisms of stress resilience. They proposed viewing resilience as a process that integrates multiple central and peripheral systems.

Belief in one's ability to exert control over the environment and to produce desired results is essential for wellbeing, and probably a psychological and biological necessity. Converging evidence from animal research, clinical studies and neuroimaging suggests that the need for control is a biological imperative for survival. The ability to choose permits animals to increase their perception of control over their surroundings, which helps reduce activation of the CTRS.[44,45] In fact, one of the Five Freedoms, freedom from fear, recently has been operationalized as the opportunity for choice and control.[46] And Rochlitz has declared that, "Provided extremes are avoided, if the cat has a variety of behavioural choices and is able to exert some control over its physical and social environment, it will develop more flexible and effective strategies for coping with stimuli."[47]

The negative effects of adverse early life events mediated by severe stress responses on the long-term health and welfare of cats demonstrate the importance of identification of risk factors and provision of effective education of clients by clinicians about appropriate environments for indoor or otherwise confined cats throughout their lives.[48] From this perspective, initial vaccination appointments are anything but "routine", and may in fact be

the most important appointments of the animal's life. This is because such visits present opportunities to teach husbandry appropriate for the animal based on the environment it is confined to at a time when owners are likely to be most motivated and responsive to recommendations. (See also Environment and Feline Health: At Home and in the Clinic by Heath). These needs remain but modifications may be required as cats age. (See Feline Ageing: Promoting Physiological and Emotional Wellbeing by Gunn-Moore)

Shonkoff et al.,[4] described three foundational domains to promote long-term health and welfare that can be adapted to preventive veterinary care for confined cats. These include:

1. A stable and responsive environment that provides consistent, nurturing, and protective interactions that enhance learning and support development of adaptive capacities (resilience and coping) that promote a well-regulated CTRS;
2. A safe and supportive physical, chemical, and built environment that is free from toxins and fear, allows active exploration without significant risk of harm, and offers support for families caring for the cat; and
3. Satisfactory nutrition for the cat's age, including feeding management practices that maintain an appropriate body condition (beginning with the future mother prior to conception if possible) while providing safety, choice, and mental stimulation to the extent possible.[49] (See also Feeding Cats for Optimal Mental and Behavioral Well-Being Part 2 by Dantas and Delgado)

Consideration of the role of a sensitized CTRS also has important therapeutic implications. For example, drugs to modulate gene expression are under active investigation in oncology[50] and psychiatry[51] that may become available in veterinary medicine. Given that these drugs also may modulate expression of other genes in potentially unpredictable ways, the availability of a naturally occurring animal model of a disease likely influenced by these mechanisms offers the opportunity to test these compounds before they are introduced to human medicine.[21] Recent research also suggests that drugs like some of the psychedelics[52] and low doses of ketamine[53] might prove therapeutic for patients with central sensitivity syndromes.

Environmental modification also can modulate gene expression,[54,55] which may explain the effectiveness of behavior-based approaches for treatment in humans[56] and multimodal environmental modification for therapy of cats with FIC.[12,15] Effective environmental modification has been found to result in significant resolution of signs of comorbid disorders as well as LUTS in treated cats suffering from FIC,[12,15] and to reverse the effects of maternal separation on stress reactivity in rodents.[57]

The roles of environmental modification on feline health and welfare can be visualized in the illustration (Figure 1). Cats' perceptions of threat may be reduced by increasing safety through provision of separate sets of resources, opportunities to express species-typical behaviors, and elimination of conflict,[58] and their perception of control can be enhanced by offering resources as choices, and providing only those the cat chooses.[59] Changing the environment changes the context and the cat's expectations, which over time changes its history, permitting it to cope with its environment and benefitting its health and welfare.

Summary/Discussion

Changing our view of some chronic diseases from that of isolated organ-originating diseases in otherwise healthy individuals to one that considers the role of a sensitized CTRS (and the potential roles of early adverse experiences) has at least two important implications. First, it provides a more parsimonious explanation for many findings that previously were quite difficult to account for, including the unfortunate lack of beneficial effect of therapies directed at the peripheral organ of interest by a particular medical subspecialty, the presence of multiple comorbid disorders in many patients with chronic disorders, but not in patients with other individual organ diseases, the unpredictable order of appearance of the comorbidities, and the altered functioning of the CTRS. Second, and more importantly, it opens whole new areas of therapy that may escape consideration from the individual medical specialty perspective. The currently available data only suggest this possibility, however, but they do permit generation of the hypothesis.

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KEY POINTS

1. Stress is often defined in terms of *stressors* – events in the internal and external environment that result in a *stress response*. Stressors increase the ratio of one's perception of threat/perception of control.
2. The central stress response system can be sensitized by early adverse experiences, which can leave the individual more susceptible to perceive events in the environment as threats.
3. Environmental modifications to reduce perceptions of threat and enhance perceptions of control can promote resilience, which can improve health and welfare.

SYNOPSIS

The term stress can be defined in various ways. In the health sciences stress often is defined in terms of *stressors*; events that are perceived as threats to one's perception of control. From this perspective, a stressor is anything that activates the central threat response system (CTRS). Recent research has found that the CTRS can be sensitized to environmental events through a process called epigenetic modulation of gene expression. Sensitization may result from adverse early life experiences, or by sufficiently severe events at any time of like. When CTRS activation is chronic, as can occur in confined individuals, health and welfare may be harmed. Environmental modification can mitigate the harmful effects of chronic CTRS activation by reducing the individual's perception of threat and increasing its perception of control, which improves health and welfare.

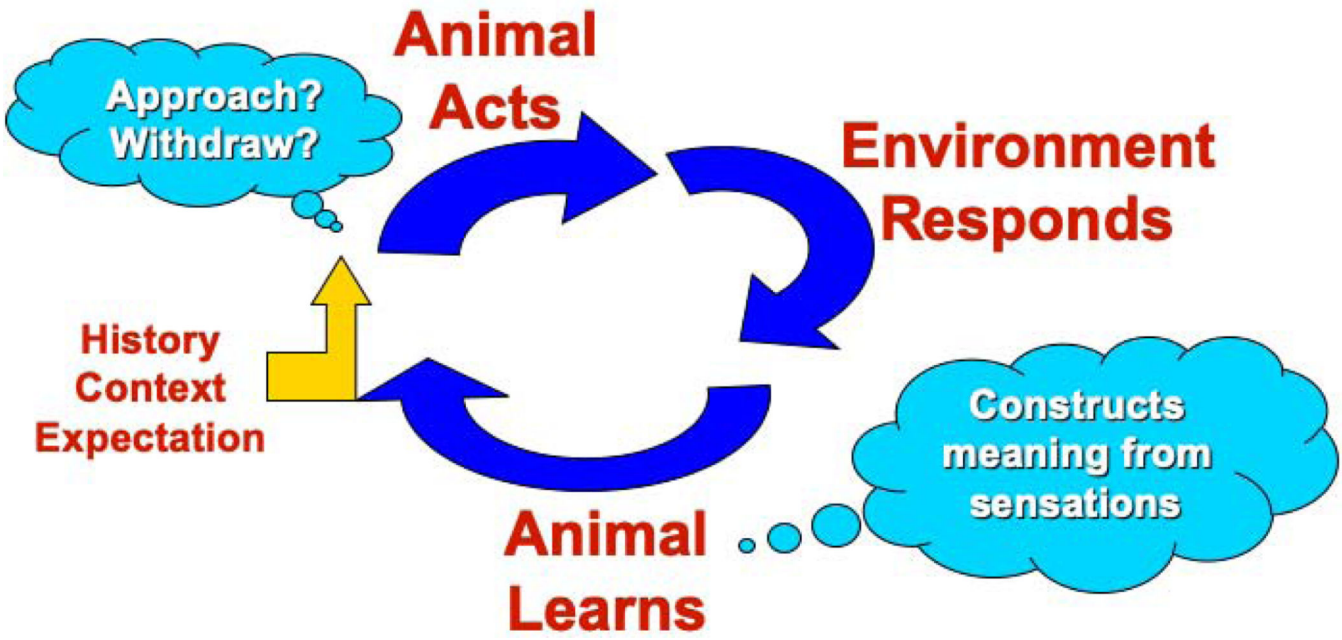

Figure 1.

The “circle of behavior” illustrating how animals sense and respond to events in the environment. Starting at the top, when an animal acts (e.g., a cat jumps up onto a counter), the environment may respond (e.g., a shout or swat from a person to remove the cat from the counter). The sensations arising in the cats nervous system enter the cat’s brain to form a perception of the response, which is then compared to events in the cat’s history (genetic,epigenetic and environmental), the context in which the response was received, and its expectation of future events. These result in subsequent acts, depending on the threat or reward potential of the response. The circle is completed on a time constant of milliseconds throughout the life of the animal.