Veterinary Dermatology
Dermatologie vétérinaire

Itch in dogs and cats

Frédéric Sauvé

Definition

The definition of itch (or pruritus) seems obvious: a sensation provoking a specific reaction of scratching behavior (1–3). However, the neurobiological pathway behind itch is less obvious! This sensation, originating from the skin and mucosal surfaces, is usually considered useful to relieve the skin of irritants (insects, chemicals, poisonous plants) — especially when acute (1,3–5). This is a reflex mechanism that can be considered a first line of defense (3).

The International Forum for the Study of Itch has defined chronic itch as pruritus lasting for longer than 6 wk (1). Chronic itch is more complex, at least in humans, and can be associated with various etiologies (*e.g.,* atopic dermatitis, chronic renal failure, cholestatic liver disease, pregnancy, and endocrine disease) (1,5,6). In veterinary medicine, chronic itch is usually secondary to inflammatory skin diseases, mainly hypersensitivities. The clinical manifestation of this behavior in dogs and cats can vary from obvious signs such as scratching, rubbing, or licking excessively; to subtle signs such as self-induced alopecia or alesional pruritus (2). Behind this simple behavior, there is a complex pathophysiology that is not entirely understood. It is even more complex in animals since there is no objective method to evaluate the sensation of itch (1).

In humans, itch is usually considered a mix of sensations, including itch itself and burning, prickling, or stinging sensations (1). We assume that itchy pets feel the same way and that

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The CAVD has partnered with Royal Canin, Zoetis, and Ceva to present the 4th annual Empathy for Itch campaign. This campaign is designed to create awareness and empathy for pets suffering from itchy skin. The theme this year is "dermatology is a team sport." The team includes the veterinary team, pet parents, and groomers. For more details, visit: https://www.cavd.ca/empathy-for-itch

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Dr. Sauvé is a Board-certified Veterinary Dermatologist and Immediate Past President of the Canadian Academy of Veterinary Dermatology (CAVD).

Département de sciences cliniques, Faculté de médecine vétérinaire, Université de Montréal, 3200, rue Sicotte, Saint-Hyacinthe, Quebec J2S 2M2.

Address all correspondence to Dr. Frédéric Sauvé; email: f.sauve@umontreal.ca

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the pathophysiology of itch is similar. Considering the clinical patterns of pruritus in dogs, and more specifically in cats — especially if chronic, further studies will be required to better define the underlying pathophysiology of this behavior and thereby define whether it is identical to that in humans. Interestingly, although itch is mainly defined as an unpleasant sensation that can seriously affect quality of life, especially when chronic, it has also been associated with pleasant and rewarding behavior (1,5).

Physiologic itch

It is well-known that cutaneous pruritus and pain travel through similar pathways, explaining why pain following scratching can relieve pruritus (4,7–9). However, some studies have concluded on specific neuronal itch pathways that are distinct from pain. For example, a distinct subgroup of mechanically insensitive C-fibers, not the most common type, are excited by pruritic substances such as histamine (7,8). In addition, identification of specific transmembrane receptors on pruriceptive afferent neurons [Mas-related G protein-coupled receptor (Mrgpr) family] and pruritogenic mediators [*e.g.,* interleukin (IL)-31, IL-13, thymic stromal lymphopoietin (TSLP)] seem more often specifically associated to pruritus perception (1,8,10). Itch-specific central neurotransmitters [*e.g.,* gastrin-releasing peptide (GRP)] have also been reported (1,8,10). Regardless, some studies have not been conclusive to support a specific itching pathway, rather suggesting that nociceptors can give both itch and pain signals. This can explain why itch may sometimes be partially painful, or pain partially itchy (10).

There are 2 distinct neurophysiological pathways for itch: one involving mechano-insensitive primary afferent neurons stimulated by histamine; and another, independent of histamine, induced by activation of cutaneous nociceptors (central activation pattern). Pruritus induced by the spicules covering seedpods of the plant *Mucuna pruriens* (cowhage; itching powder) is a classic example of a central activation pattern (1,4,7).

The perception of pruritus is initiated by stimulation of cutaneous pruriceptors by environmental triggers (allergens, irritants, and other pruritogen substances). The pruriceptors are primary afferent fibers (selective unmyelinated C fibers) relaying the perceived sensation to cell bodies localized in the dorsal root and trigeminal ganglia in the dorsal horn of the spinal cord (1,4,10). Histaminergic neurons (mechano-insensitive C fibers, activated by histamine) and nonhistaminergic neurons (mechanosensitive C and A fibers, activated by pruritogens other than histamine) use different tracts (1,11,12). Then, the message reaches the thalamus *via* the contralateral spinothalamic tract, following synapses with a second set of neurons involving excitatory and inhibitory activities. The excitatory-inhibitory activities give the gradation of the signal transmitted to the brain by the spinothalamic tract. Activation of the thalamus also varies depending on the neurons activated (histaminergic or nonhistaminergic). Ultimately, interpretation of the signal in the thalamus results in a motor response: the behavior of scratching (1,4,10,11).

Pathophysiology of itch

The pathophysiology of itch may differ based on the type of itch (acute, chronic, neurogenic, neuropathic, pruritoceptive, or psychogenic) or clinical classification (dermatologic, systemic, neurologic, psychogenic, mixed, or other) (1,6,9,13). Although a detailed description of the pathophysiology of itch is beyond the scope of this article, it is interesting to highlight some mechanisms and molecules triggering the sensation of itch.

Acute itch following a sudden epidermal insult results in activation of sensory free nerve endings (pruriceptors). Indeed, a myriad of pruritogenic substances (*e.g.,* histamine, cytokines, proteases, chemokines) are released by local cells — in particular, the keratinocytes, mast cells, and basophils — secondary to the insult. Histamine, the most important molecule in acute itch, binds H1 and H4 receptors on histaminergenic ending nerves (3,4,11,13). The scratching reflex and inflammatory mediators released in the skin aim to control the aggressor and repair the insulted epidermis. Both peripheral and central mechanisms are involved in stimulation, conduction, and interpretation of the message initiated by cutaneous stimuli (5,13). If the aggressor is controlled, acute itch should not persist for longer than a few days (13). Most types of chronic itch are chemically or mechanically induced (nonhistaminergic) secondary to a systemic or dermatological disease. They are characterized by a complex, constant liberation of pruritogenic mediators, and a series of events not fully understood in all pathologies (1,3,5).

Classic examples of chronic itch in dogs and cats are atopic dermatitis and feline atopic skin syndrome, respectively. Among cytokines released or expressed in canine atopic dermatitis, TSLP, IL-4, IL-13, IL-31, and IL-33 have critical roles in inducing itch (1,13–17). Most of these cytokines are strongly associated with a Type-2 [T helper 2 (Th2)] immune cascade. A major cytokine in canine skin allergic diseases that has recently received more attention is IL-31. Cytokine IL-31, belonging to the IL-6 family of cytokines, is mainly produced by Th2 cells (13,15,18). Other inflammatory cells (*e.g.,* macrophages, dendritic cells, eosinophils) can also express IL-31 (18). The pruritus results from IL-31 binding to its receptor on sensory neurons and the activation of the Janus kinase (JAK)-signal transducer and activation of transcription (STAT) signaling pathway (18).

In cats, there is currently less evidence of the molecules triggering pruritus. Considering the various feline clinical patterns associated with cutaneous allergic diseases (self-induced alopecia, head/neck pruritus, eosinophilic granuloma complex, and miliary dermatitis), we can even ask the question of whether pruritus is the only skin sensation perceived by affected cats. Mast cells containing numerous granules with a high potential to initiate itch, especially histamine, are abundant in the lesional skin of allergic cats, but the clinical significance of this finding is still unclear. A potential role of IL-4 and IL-31 has also been suggested in the pathogenesis of feline atopic skin syndrome (14,19,20).

Interestingly, chronic itch can induce peripheral and central neural sensitization, defined by a change in the degree of sensitivity of the itch-neural pathway (1,3,11). These phenomena are not well described in dogs and cats but would represent patients more sensitive to mild or non-pruritic stimuli. These patients are suffering from either alloknesis, which refers to a nonpruritogenic stimulus perceived as pruritic; or hyperknesis, which refers to pruritic triggers that would not normally cause itch (or would

cause only mild itch) (1,3,5,11). Following chronic exposure to inflammatory mediators associated with allergic disorders and self-traumas, some peripheral modifications leading to neuronal sensitization (or decreased threshold of itch sensation) are observed in the skin: increased intraepidermal pruritoceptors, increased mast cells, upregulated pruritogenic substances and receptors, and abnormal innervation (1,3,7,9,11,21).

Central sensitization is caused by a prolonged and sustained pruritic disease; this results in modification in transmission of the pruritogenic signal in the spinal cord and spinothalamic tract, and an alteration in the function and structure of the brain (9,11,21). Several sites along the itch-neural pathway can be affected. Upregulation of some neurotransmitters secreted by activated neurons localized in the spinal cord may partially explain central sensitization. The inhibitory control of pruritus (*e.g.,* following scratching or a pain stimulus) in the spinal cord can also be dysfunctional (fewer inhibitory neurotransmitters secreted by neurons) (1,11,21). Specific changes in the itch-related cortical brain areas are noted in patients with chronic itch, which may contribute to central sensitization (11). The itch signal would also travel through a descending inhibitory pathway from the brain along the spinothalamic tract. This inhibitory pathway may be attenuated, which can amplify the signal of itch (11,21).

Table 1. Canadian-approved veterinary topical drugs for skin containing a glucocorticoid.

Topicals	Ingredients	GC potency (North American classification)[a]
Theraderm Cream (Bimeda-MTC Animal Health, Cambridge, Ontario)	Neomycin (AB) Gramicidin (AB) Nystatin (AF) Triamcinolone acetonide (GC)	3
Isaderm Gel (Dechra, Pointe-Claire, Quebec)	Fusidic acid (AB) Betamethasone valerate (GC)	3
Topagen Spray (Merck Animal Health, Kirkland, Quebec)	Gentamicin (AB) Betamethasone valerate (GC)	3
Cortavance Spray (Virbac, Cambridge, Ontario)	Hydrocortisone aceponate (GC)	4 to 5
CortiPro Spray (ProConcepts/Can-Vet Animal Health Supplies, Guelph, Ontario)	1% hydrocortisone (GC)	7

[a] Topical GC are divided into 7 classes based on their potency (1 is the highest potency and 7 is the lowest). The potency of the GC is aligned with its efficacy to control inflammation, but also to cause local and systemic side effects (22).
AB — Antibiotic; AF — Antifungal; GC — Glucocorticoid.

Treatment of itch

A better understanding of the physiology and pathophysiology of itch helps explain the erratic responses of some dogs and cats to antipruritic treatments, and helps clinicians to choose a therapeutic approach that targets more specifically the factors contributing to this sensation. For example, chronic itch in atopy (or atopic-like dermatitis) is mainly driven by nonhistaminergic neurons, which reflects the weak clinical efficacy of antihistamines.

The therapeutic approach to itch may encompass topical and/or systemic therapies (3). However, some types of haircoat or grooming behavior in cats present obstacles for topical therapies, especially if large areas have to be treated (15,22). Moreover, few topical therapeutic molecules have been investigated in veterinary medicine. Most studies that have investigated antipruritic properties of various therapies were designed for allergic skin diseases. Creams, ointments, gels, or sprays containing glucocorticoids (GC) are certainly among the best topical options to control inflammation and pruritus (4,14,15,22,23). By acting on various aspects of the inflammation and pruritogenic pathway, GC (topical or systemic) are drugs of choice for controlling pruritus of inflammatory origin. Although topical GC have fewer side effects than systemic ones, they have to be used diligently since local and even systemic side effects may be secondary to prolonged use, especially with a highly potent GC (4,14,22,23).

Canadian-approved veterinary topical drugs with GC are listed in Table 1. A topical calcineurin inhibitor, such as 0.1% tacrolimus (0.1% Protopic; Leo Pharma, Toronto, Ontario), may be a safer alternative to GC when chronic administration is required (4,15,24). Similar to the oral calcineurin inhibitor cyclosporine (Atopica; Elanco Canada, Mississauga, Ontario), tacrolimus is a slow-acting medication (7 to 10 d before beneficial effects are apparent) (4,15).

Systemic antipruritic therapies are often required since veterinarians frequently need to control generalized itch, and these therapies are also often more convenient for pet owners (Table 2). Glucocorticoids are still an effective and inexpensive treatment for pruritus, especially in the presence of skin inflammation. However, with newer and safer antipruritic therapies available, veterinarians use GC for controlling pruritus less often than in the past (4,14,16,23). Glucocorticoids can be considered to control acute flares of skin allergies or be used in conjunction with other antipruritic therapies when the primary therapy alone does not adequately control the pruritus (23). However, it is important to be aware of potential drug interactions or immunosuppression when GC are used in combination with other antipruritic therapies. Long-acting injectable GC are not recommended due to a high risk of side effects (23). Short-term and/or low doses or frequencies of administration should be prescribed to reduce side effects. Prednisone (in dogs), prednisolone, or methylprednisolone are the preferred oral GC (4,23).

Oclacitinib (Apoquel; Zoetis, Kirkland, Quebec), a jakinib (inhibitor of the JAK-STAT signaling pathway), interferes with key mediators in the itch pathway — especially IL-31, but also IL-4 and IL-13 (25). Rapidly absorbed, oclacitinib reaches peak plasma concentrations within 1 h (26). Oclacitinib has been approved in dogs for the control of pruritus secondary to allergic skin diseases and the control of atopic dermatitis. This treatment can be used for acute flares, with short- or long-term administration in dogs more than 12 mo of age.

Oral cyclosporine is also a potent antipruritic therapy, but it requires more prolonged administration before controlling clini-

Table 2. Common systemic antipruritic therapies for dogs and cats (4,15,23).

Antipruritic therapies	Dosage	Notes
Predniso(lo)ne Methylprednisolone	0.5 (D) or 1 to 1.5 (C) mg/kg, PO, q24h, until remission of clinical signs; then taper to the lowest dosage and frequency required to maintain comfort while reducing side effects	If the animal requires daily administration to be maintained comfortable or if adverse effects are noted, another alternative must be considered.
Oclacitinib (Apoquel; Zoetis, Kirkland, Quebec)	0.4 to 0.6 (D) mg/kg, PO, q12h for 14 d, then q24h	In milder cases, oclacitinib can be administered q24h from the beginning. Not approved for cats.
Cyclosporine (Atopica; Elanco Canada, Mississauga, Ontario)	5 (D) or 7 (C) mg/kg, PO, q24h for 4 to 6 wk; then find minimal daily dose or reduce frequency of administration	Cyclosporine administered concomitantly to prednisolone 1 mg/kg, q24h for 7 d, then q48h for 14 d, can accelerate control of skin lesions and pruritus in dogs. Administering frozen capsules or refrigerated oral solution reduces gastrointestinal side effects.
Lokivetmab (Cytopoint; Zoetis)	2 mg/kg (D), SC, every 4 wk or as needed	Approved at 1 mg/kg in some countries. Must not be used in cats.
Chlorpherinamine	0.4 mg/kg (D) or 2 to 4 mg/cat (C), PO, q12h	Limited and variable benefits for all antihistamines. Should be considered as an adjunctive treatment, in mild cases, or to prevent flare-ups.
Hydroxyzine	2 mg/kg (D), PO, q12 to 8h	
Cetirizine	0.5 to 1 mg/kg (D), PO, q24h	

C — Cats; D — Dogs.

cal signs; treatment for 4 to 6 wk is usually necessary to reach at least a 30% decrease in pruritus in dogs (4,23,27). Clinical experience suggests a quicker response in cats. Cyclosporine acts by blocking transcription of cytokines, especially the major pro-inflammatory cytokine IL-2, by CD4+ T lymphocytes (28). Overall, the antipruritic effects of cyclosporine are mainly due to the reduction of IL-4 synthesis; inhibition of skin mast cell counts and their response, as well as their histamine content; inhibition of eosinophil survival and function; and reduction in serum IL-31 (28,29). Cyclosporine is approved for treatment of canine atopic dermatitis; as well as allergic dermatitis, miliary dermatitis, eosinophilic plaque, and self-induced alopecia in cats. Considering its mode of action, cyclosporine would not be indicated to rapidly control acute itch.

Lokivetmab (Cytopoint; Zoetis), a caninized monoclonal antibody targeting specifically only circulating IL-31, is approved for the control of canine atopic dermatitis and canine allergic dermatitis (30). This biological therapy is effective to control pruritus by its neutralizing action on a key cytokine for itch signal, IL-31 (30). Considering its safety profile and its action on pruritus within 3 d, it represents an option for both acute and chronic management of itch (15). This treatment should only be administered to dogs.

As previously mentioned, the beneficial effect of antihistamines for controlling itch is modest, and they should probably be prescribed only in mild cases, as adjunctive treatment, or in chronic itch when the acute phase is controlled (4,23).

Other treatments reported to be effective in treating pruritic allergic skin diseases include misoprostol, phosphodiesterase inhibitors (arofylline, pentoxifylline), and azathioprine; but more studies are required to support their usefulness (4).

Depending on which type or clinical presentation of itch the animal presents, other classes of drugs may be more useful than one targeting inflammatory cytokines. If central sensitization or neurologic itch is suspected, then anticonvulsants, especially gabapentin or pregabalin, could be options for treatment (1,3,7,11). Antidepressants, such as serotonin reuptake inhibitors (*e.g.,* fluvoxamine, fluoxetine) may alleviate psychogenic pruritus (3,11). The tricyclic antidepressant amitriptyline has been studied in dogs, with control of at least 50% of the pruritus achieved in ~32% of dogs (31). However, it is unclear if the efficacy of amitriptyline is related to the antidepressant properties of the molecule, its antihistamine effect, or both (3,11).

The μ-opioid receptor antagonist (MORA) (*e.g.,* naltrexone) and κ-opioid receptor agonist (KORA) (*e.g.,* nalfurafine), as well as butorphanol (with MORA and KORA properties), were useful in humans to control itch originating from various pruritic disorders — especially systemic diseases (3,11).

The neurokinin-1 (NK-1) receptor antagonists, used for their antidepressant, anxiolytic, and antiemetic properties, have also demonstrated some efficacy in treatment of pruritus (11,32). In veterinary medicine, the NK-1 receptor antagonist maropitant (Cerenia; Zoetis) was effective in controlling pruritus in cats (32). Maropitant likely controls pruritus by inhibiting binding of substance P, a pro-inflammatory and pruritogenic molecule, on NK-1 receptors (11,32). In humans, cognitive-behavioral therapy was effective to decrease pruritus in some patients (11). Perhaps by reducing stress in dogs and cats, a similar effect might be noticed.

Conclusion

Clearly, further investigations are required to better define the neuronal pathways of itch. Improving our understanding of the various peripheral and central mechanisms involved in itch will help to develop new therapeutic modalities. But more importantly, we must recognize that, for dogs or cats and their owners, quality of life is highly affected by chronic pruritic

disorders (33,34). Veterinarians must realize the physical and emotional impact of this chronic unpleasant sensation for both pets and their owners, as well as the financial burden it places on owners. Any discussion with an owner about their pet's allergy should include the fact that various treatments are available to help control pruritus, and that it is realistic to expect an improvement in the quality of life of affected animals with ongoing therapy. Several tools created by the Canadian Academy of Veterinary Dermatology (CAVD) and their collaborators for the Empathy for Itch campaign are available online to rise awareness about itchy pets, and also to help owners and veterinary teams dealing with itch (for veterinary professionals: www.cavd.ca/empathy-for-itch ; for pet parents: www.cavd.ca/empathy-for-itch-pet-parent).

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