Review

Atopic dermatitis and the intestinal microbiota in humans and dogs

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Abstract

The prevalence of human and canine allergic diseases is commonly perceived to be increasing. Suggested predisposing factors in people and dogs include increased allergen load, increased exposure to pollutants, reduced family size, reduced microbial load and less exposure to infection at a young age, increasingly urbanised environment, and changes in dietary habits. Genetic make-up may provide a template for phenotypic predisposition which is strongly influenced by our diet and environment leading to constant regulation of gene expression. One way in which diet can alter gene expression is via its effects on the gut flora or microbiota, the collection of microbes residing in the gastrointestinal tract. The resident microbiota is important in maintaining structural and functional integrity of the gut and in immune system regulation. It is an important driver of host immunity, helps protect against invading enteropathogens, and provides nutritional benefits to the host. Disruption of the microbiota (dysbiosis) may lead to severe health problems, both in the gastrointestinal tract and extra-intestinal organ systems. The precise mechanisms by which the intestinal microbiota exerts its effects are only beginning to be unravelled but research is demonstrating close links between gut microflora and many factors involved in the pathogenesis of atopic dermatitis (AD). AD and indeed any other 'skin disease', may be seen as a possible manifestation of a more systemic problem involving gut dysbiosis and increased intestinal permeability, which may occur even in the absence of gastrointestinal signs. Manipulation of the canine intestinal microbiota as a method for modifying atopy, may be attempted in many ways including avoidance of certain foods, supplementation with probiotics and prebiotics, optimising nutrient intake, minimising stress, antimicrobial therapy, correction and prevention of low stomach acid, and faecal microbiota transplantation (FMT).

Keywords: canine, atopic, atopy, dermatitis, dog, microbiota, dysbiosis, epigenetics, gut.

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Introduction

Allergy has long been a topic of mystery and fascination. Emperor Octavian Augustus, born in 63 BC, is believed to have had a condition resembling atopic dermatitis (AD) (Halliwell, 2009). In the 1920s, the term atopy (meaning 'strange disease'), referring to allergic asthma and hay fever, was introduced to human medicine. Canine atopy was first reported in 1941 (Wittich, 1941) in a dog with seasonal allergic rhinitis but the classical signs of canine atopic dermatitis (CAD) were not described until 30 years later (Halliwell and Schwartzman, 1971).

In the 1930s, 56.9% of all dogs seen with skin disease at the Angel Memorial Hospital in Boston, USA, were diagnosed with 'eczema' at the time believed to be allergic in origin and involving food rather than environmental allergens (Schnelle, 1933). Seasonal 'summer eczema' was attributed to flea bite allergy. In the 1970s, canine IgE was identified, purified, and characterised. It was shown to have much in common with its human counterpart (Halliwell, 1973) and to be associated with mast cells in canine skin.

Prevalence of atopic dermatitis

The prevalence (number of existing cases at a given time) of CAD is commonly perceived to be increasing, but is this actually the case or are we

simply becoming better at recognising and diagnosing this challenging condition? There are few hard data on the subject, and the true prevalence and incidence (number of new cases occurring over a period of time) of CAD in the general canine population is unknown (Hillier & Griffin 2001). In one survey conducted in UK general veterinary practices (Hill *et al.* 2006), CAD was diagnosed in 4.8% of 559 dogs with skin problems. However, in this survey, diagnosis was often incomplete (e.g. otitis, pyoderma, allergy) or not determined. CAD was diagnosed in 78% of 280 dogs in Southern England referred with a dermatological problem to the author between 2002 and 2003, and of which 85–90% were sensitive to house dust mites and/or forage (storage) mites, according to either intradermal or serological testing.

The prevalence of human allergic diseases (asthma, allergic rhinitis and AD) is believed to have risen sharply since the Second World War (Bjorksten 1997; Fennessy *et al.* 2000). Rates of reported eczema during early childhood were studied in three national cohorts of children born in 1946, 1958, and 1970 (Taylor *et al.* 1984). Overall rates rose from 5.1% in children born in 1946, to 7.3% in those born in 1958, and to 12.2% in the 1970 cohort. By 1994, 15–20% of school age British children were found to be affected with atopic eczema at some stage (Kay *et al.* 1994). The British Association of Dermatologists advised that in 2006, 'eczema' affected 20–30% of children and 2–10% of adults (Primary Care Dermatology Society Guidelines, 2006). Another study (Deckers *et al.* 2012) concluded that there was evidence of increasing prevalence of atopic eczema in Africa, Eastern Asia, Western Europe and parts of Northern Europe (i.e. UK).

Factors predisposing to atopic dermatitis

So what could be causing this increased prevalence in humans, and are similar factors likely to be at play with our pet dogs? Increased indoor allergen load; increased exposure to pollutants; reduced family size; reduced microbial load and less exposure to infection at a young age; increasingly urbanised environment;

and change in dietary habits have all been suggested (Hillier & Griffin 2001).

Although AD appears to run in families, in both dogs and people, genetics alone cannot explain its increased prevalence. Furthermore, recent advances in the science of epigenetics suggest that genetic make-up, far from dictating our destiny, merely provides a template for phenotypic predisposition (Egger *et al.* 2004; Holliday 2006) which is strongly influenced by our environment, especially diet, leading to constant regulation of gene expression (Phillips 2008; Simmons 2008). In other words, genes that code for particular proteins can be switched on and off by lifestyle choices such as what we eat, and where and how we live–with profound implications for health and disease.

Many genes and proteins are known to be upregulated in response to glucocorticoids (Tuckermann *et al.* 2005; Reddy *et al.* 2009; Miller *et al.* 2013). Might we be able to use diet to harness benefits similar to those associated with glucocorticoid therapy but without its negative consequences?

Diet, microbiota and atopic dermatitis

Intestinal microbiota and dysbiosis

Dietary sensitivities (food allergies, adverse food reactions) have long been in the differential diagnosis of canine pruritus, but food should also be seen as an important epigenetic factor in determining optimal health (Landecker 2011), which includes a healthy skin and immune system. One way in which diet can alter gene expression is via its effects on the gut flora or microbiota (Ferreira *et al.* 2014). The gastrointestinal microbiota is the collection of microbes residing in the gastrointestinal tract, and represents the largest source of non-self antigens in the human body (Brown *et al.* 2012). Its complexity has been underestimated with traditional culture techniques (Suchodolski 2011), and recent molecular-phylogenetic and metagenomic studies have revealed a highly diverse microbial community in the healthy canine gastrointestinal tract (Suchodolski *et al.* 2012).

The resident microbiota is important in maintaining the structural and functional integrity of the gut and in immune system regulation (Furusawa *et al.* 2013; Purchiaroni *et al.* 2013). It is an important driver of host immunity (Suchodolski & Simpson 2013), helps protect against invading enteropathogens, and provides nutritional benefits to the host (Maslowski *et al.* 2009; Suchodolski & Simpson 2013). Disruption of the microbiota (dysbiosis) can have far-reaching consequences on host health, not only in the gastrointestinal tract but in extra-intestinal organ systems (Sekirov *et al.* 2010; Suchodolski & Simpson 2013).

The precise mechanisms by which the intestinal microbiota exerts its effects are only beginning to be unravelled but research is demonstrating close links between gut microflora and many factors involved in the pathogenesis of AD, such as immunity and inflammation (Bowe 2011; Belkaid & Hand 2014), neuropeptide formation (Pincelli *et al.* 1990; Gueniche *et al.* 2010; Holzer & Farzi 2014), metabolism, and blood lipids and fat storage (Musso *et al.* 2010a,b).

Differences in the faecal microbiota have been demonstrated between human patients with AD and healthy control subjects (Watanabe & Nansawa 2003), and the composition and diversity of the gut microbiota from young children who later developed AD have been shown to be different from those of children who did not develop AD (Wang *et al.* 2008). Furthermore, systemic antibiotic treatment has been reported to increase the risk of AD in people (Tsakok *et al.* 2013), possibly linked to changes in intestinal microbiota. Such observations suggest involvement of the intestinal microbiota in the pathogenesis of human AD, potentially via stimulation and education of immune cell populations (Egawa & Weninger 2015). Disruptions in normal gut flora have also been found in people with other skin disorders including acne (Volkova *et al.* 2001; Katta & Desai 2014) and seborrhoeic dermatitis (Zhang *et al.* 1999).

Most research on the intestinal microbiota has, to date, been in the human field but significant differences in faecal microbiome (totality of micro-organisms and their genomic make-up) composition have been observed between healthy dogs and dogs with various acute and chronic gastrointestinal disorders (Suchodolski *et al.* 2012). Faecal microbial phylogeny and functional capacity of the canine gut have been found to be similar to the human gut (Deng & Swanson 2015) but studies investigating the effects of microbiome changes on canine physiology and health are eagerly awaited.

Intestinal permeability

Impairment of the intestinal mucosal barrier appears to be involved in the pathogenesis of human AD (Majamaa & Isolauri 1996; Rosenfeldt *et al.* 2004) and is a risk factor for canine food allergy (Verlinden *et al.* 2006), a player in a subset of dogs with AD (Chamberlain 1978; Rosser 1993).

Small intestinal biopsy samples taken to evaluate gut mucosa barrier function in children with AD, demonstrated enhanced transfer of intact and degraded proteins through the barrier relative to controls, increasing the antigenic load (Majamaa & Isolauri 1996).

The intestinal barrier, together with gut-associated lymphoid tissue (GALT) and the neuroendocrine network, controls the equilibrium between immunity and tolerance to non-self antigens (Fasano 2011). Zonulin, a human endogenous homologue of an enterotoxin elaborated by the bacterium, *Vibrio cholerae*, modulates intercellular tight junctions and thereby intestinal permeability (Fasano 2011). When the finely tuned zonulin pathway is disrupted in genetically susceptible individuals, both intestinal and extra-intestinal disorders can develop (Fasano 2011), and increased intestinal permeability has been demonstrated in people with no abdominal symptoms (Goebel *et al.* 2008).

Two powerful triggers of zonulin release are small intestinal exposure to bacteria and gluten (Fasano 2011). Wheat ingestion can cause symptoms of AD (Varionen *et al.* 2000), and AD has been found to be three times more common in patients with coeliac disease than in spouses of these patients (Ciacci *et al.* 2004). Skin lesions, generally, are reported to be common in people with coeliac disease (Saarialho-Kere 2004; Ojetti *et al.* 2006; Fasano & Catassi

2012). Eczema and skin rash have also been reported (Volta *et al.* 2012) in 'non-coeliac gluten sensitivity' a disorder in people, characterised by intestinal and extra-intestinal symptoms associated with ingestion of gluten-containing foods but without the development of coeliac-specific antibodies and villous atrophy (Sapone *et al.* 2012; Catassi *et al.* 2013).

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) has been defined as an increase in the number, and/or alteration in the type, of bacteria in the upper gastrointestinal tract (Bures *et al.* 2010). Some people with SIBO are asymptomatic whereas others develop severe malabsorption (Bowe 2011). Inappropriately located or excessive numbers of bacteria can successfully compete for nutrients, produce toxic metabolites, cause direct injury to enterocytes in the small intestine and increase intestinal permeability (DiBaise 2008; Bowe 2011).

Small intestinal bacterial overgrowth is being linked to an ever-increasing list of human health problems, including skin conditions (Bowe 2011). It is 10 times more prevalent in people with rosacea than in healthy controls, and treating SIBO in these patients has led to marked clinical improvement (Parodi *et al.* 2008). Possible reasons for skin lesion development in SIBO include nutritional deficiency; impaired lipid metabolism from deconjugation of bile acids by intraluminal bacteria; damage to GALT and impaired immune-system functioning; increased intestinal permeability, and systemic spread of lipopolysaccharide, an endotoxin derived from bacterial cell walls, with subsequent damage to epidermal structure and barrier function (Guo *et al.* 2013; Kell & Pretorius 2015). Impaired epidermal barrier function and immune system functioning have been documented in the pathogenesis of both human and canine AD (Nimmo Wilkie *et al.* 1991; Marsella *et al.* 2011).

Diagnosis of canine intestinal disease can be challenging (Batt 2000). SIBO exists as a syndrome in dogs but the term, SIBO, has been largely replaced by the term Antibiotic-Responsive Enteropathy'. The small intestinal microbiota has been analysed in dogs following administration of the macrolide antibiotic, tylosin, providing potential clues on the effect of tylosin on intestinal microbes (Suchodolski *et al.* 2009).

Inflammatory bowel disease

Skin lesions may also accompany human inflammatory bowel disease (IBD) (Ardizzoni *et al.* 2008). It has been proposed that IBD-associated skin conditions may arise from immune dysregulation resulting in a lymphocyte-mediated destructive process (Huang *et al.* 2012). Mucosal T-cells in the gut may migrate to the skin, become exposed to cutaneous antigens, and cause skin damage (Adams & Eksteen 2006).

Gut-skin axis

Although the mechanisms for how the gut and skin communicate are poorly understood, several human dermatoses, including AD, appear to have a gut-skin connection (Ali *et al.* 2014). Once the connection between skin and the gut is appreciated, AD, and indeed any other 'skin disease', may be seen as a possible manifestation of a more systemic problem involving gut dysbiosis and increased intestinal permeability, which may occur even in the absence of gastrointestinal signs. Conventional anti-inflammatory and antimicrobial therapies for skin disorders provide only temporary symptomatic relief and may potentiate associated or underlying factors such as intestinal permeability (Ünsal & Balkaya 2012) and dysbiosis as well as promoting the development of antibiotic-resistant microbes (Fujimura *et al.* 2010).

Manipulation of the canine intestinal microbiota

Manipulation of the canine intestinal microbiota may be attempted in many ways.

Avoidance of certain foods

Dogs, though not obligate carnivores, have evolved over millions of years on a diet consisting mostly of

animal protein: meat and fish (Landry & Van Ruining 1979; Coppinger & Coppinger 2001; Puotinen 2005; Brown 2010). They have been exposed to commercial dog food only in the last 150 years. Swedish researchers (Nodtvedt *et al.* 2007) found that feeding lactating bitches a diet that included non-commercial foods had a protective effective on the development of CAD in their offspring, suggesting epigenetics may be at work.

Cereal grains (seeds of specific grasses belonging to the Poaceae or Gramineae family) did not form a major part of the canine ancestral diet and yet feature prominently in many commercial dog foods. Many cereals, including wheat, rye and barley, contain gluten or equivalent toxic proteins (Sapone *et al.* 2012), and a high level of fermentable carbohydrate. Diets low in fermentable carbohydrate, which can be incompletely absorbed in the gastrointestinal tract and fermented by gut bacteria leading to dysbiosis and impairment of the intestinal barrier, have been found to be beneficial for people with functional gut symptoms (Gibson & Shepherd 2010; Barrett & Gibson 2012). Dogs have no minimum dietary requirement for simple carbohydrate or starches (Gross *et al.* 2000) and a cereal-free, low carbohydrate diet should be considered in the investigation of any chronic skin disorder, whether or not there is evidence of gastrointestinal disease.

Probiotics and prebiotics

Probiotics are live micro-organisms thought to inhibit pathogen adherence to the intestinal mucosa, improve intestinal epithelial and mucosal barrier function, produce bacteriocins, increase IgA production, enhance nutrient absorption, and downregulate pro-inflammatory cytokine secretion (Fujimura *et al.* 2010; Min-tse 2011; Plaza-Diaz *et al.* 2014). Beyond the effects on intestinal microbiota, some probiotic strains display potent immune-modulatory properties at the skin level (Gueniche *et al.* 2010). In a review of 13 randomised placebo-controlled trials (Betsi *et al.* 2008), probiotics, especially *Lactobacillus rhamnosus* GG, seemed to be effective in preventing human AD and reducing the severity of AD in

approximately half of the trials evaluated. Other studies and meta-analyses of randomised controlled trials have suggested a role for probiotics in the prevention and treatment of human AD (Kalliomaki *et al.* 2001; Kim *et al.* 2014; Panduru *et al.* 2015). Early exposure to probiotics has been shown to have long-term clinical and immunological effects in a canine model of atopic dermatitis (Marsella *et al.* 2012).

Prebiotics are selectively fermented ingredients that result in specific changes in the composition and/or activity of the gastrointestinal microbiota thus conferring benefit(s) upon host health (Gibson *et al.* 2011). They are resistant to host digestion in the small intestine but fermented in the colon (Slavin 2013). No data are available on their use in animals with SIBO (Quigley & Queira 2006). Most prebiotic research has focussed on oligosaccharides. The Japanese were the first to recognise the value of fermentable oligosaccharides, initially, in feeding piglets and later with the identification of human milk oligosaccharides (Binns 2013). Inulin and FOS (fructo-oligosaccharides) are prebiotics now widely included in commercial pet foods.

Optimising nutrient intake

Carnivores in their natural environment consume diets high in animal protein, bulk and roughage (not as plant fibre but as indigestible or poorly digestible parts of animal carcasses such as bone, cartilage, scales, fins, fur, feather, tendon, and teeth), and low in carbohydrates (Landry & Van Ruining 1979). Feeding a species-appropriate, nutrient-rich diet, most closely resembling the canine ancestral diet, would seem a sensible option if a dog is to achieve optimal general and dermatological health. In modern, western society, this is far from easy but a diet consisting mainly of good quality raw meat on the bone, skin, offal, eggs and fish is perhaps as close as we can come. Such food is high in protein, satiating, extremely palatable, and supplies prebiotic 'animal fibre' in a natural form (Depauw *et al.* 2012). Outdoor feeding may also allow dogs to ingest naturally-occurring, soil-based, 'probiotic' micro-organisms. Studies have not been conducted to assess the effects

of such diets on CAD and other skin disorders. However, optimisation of nutrient intake, microbiota and immune function could be anticipated to have beneficial effects on general health, including amelioration of skin disorders.

Minimising stress

Over 80 years ago, a gastrointestinal mechanism was proposed by two dermatologists for the overlap between depression, anxiety and skin conditions in people (Stokes & Pillsbury 1930)–the so-called gut-brain-skin axis (Arck *et al.* 2010). It was suggested that emotional states might alter the normal intestinal microflora, increase intestinal permeability and contribute to systemic inflammation. Since then, many aspects of this gut-brain-skin axis have been validated (Bowe 2011), and psychological and physical stress have been found to contribute to intestinal dysbiosis (Hawrelak & Myers 2004). Studies in mice have shown that stress can impair the integrity and protective function of the epidermal barrier, causing fewer antimicrobial peptides to be produced in the skin, and an increase in the severity of infection and inflammation in the skin (Aberg *et al.* 2007; Slominski 2007). Avoiding flare factors should be recommended for dogs with CAD (Olivry *et al.* 2010), including minimising stress and anxiety, and providing a happy, stimulating environment with an appropriate amount of exercise and a diet that satisfies psychological as well as nutritional needs.

Antibiotics

Rifaximin alone, and in combination with neomycin, has been used successfully to treat SIBO in people (Scarpellini & Gabrielli 2007; Low *et al.* 2010). Tylosin is considered the antibiotic of choice to alter gastrointestinal microbiota in dogs with chronic diarrhoea (Steiner 2013), and has been recommended for dogs with 'minimal change enteropathy' (Simpson 2013) and some subsets of dogs with chronic enteropathies (Kilpinen *et al.* 2011; Suchodolski & Simpson 2013). However, antibiotics may themselves induce gut dysbiosis (Bercik & Collins 2014).

Correction and prevention of low stomach acid

Hydrochloric acid is secreted by normally functioning gastric parietal cells. It is bactericidal, killing a large portion of bacteria ingested with the food (Faller & Schuenke 2004) and reducing the number of bacteria entering the small intestine. In the 1930s, it was proposed that changes in microbial gut flora, and bacterial colonisation of the normally sterile human small intestine may result from inadequate stomach acid (Stokes & Pillsbury 1930), and low stomach acid (hypochlorhydria) is now seen as a significant risk factor for human SIBO (Theisen *et al.* 2000; Williams 2001). SIBO, diagnosed with hydrogen breath testing, has been found in 50% of people on long-term proton pump inhibitor (PPI) treatment (Lombardo *et al.* 2010). A statistically significant association between PPI use and human SIBO was also demonstrated in a recent meta-analysis (Lo & Chan 2013). Other causes of low stomach acid include atrophic gastritis, excess intake of sugar and refined foods, nutritional deficiencies, and advancing age (Thompson 2013; Mandal *et al.* 2014).

There is no specific evidence-based treatment for hypochlorhydria but protein has been found to be the food component with the greatest effect in promoting gastric acid secretion in dogs (Saint Hilaire, 1960). Betaine hydrochloride is sometimes recommended by naturopathic practitioners for people and animals with low stomach acid.

Faecal transplants (faecal microbiota transplantation)

In the 17th century, Italian anatomist, Girolamo Fabrizio, described a technique in ruminants requiring only the transfer of chewed food from a healthy animal to a sick one to treat gastrointestinal disorders. There is now considerable interest in faecal microbiota transplantation (FMT) in people not only with chronic gastrointestinal disorders, but also with autoimmune, cardio-metabolic and other extra-intestinal conditions (Borody & Khoruts 2012; Smits *et al.* 2013). The author is not aware of any safety and efficacy data relating to FMT use in dogs.

Back to the future

We and our domestic animals have evolved over millions of years to coexist with micro-organisms. Ninety per cent of the cells that make up our bodies are in fact microbial, and we possess about 100 times more microbial-derived genetic material than the genetic material present in the human genome (Gill *et al.* 2006; Fujimura *et al.* 2010). The idea of microbes being the enemy, the cause of disease, appears now to be over-simplistic and outdated. Disruption of the microbiota may allow normally commensal or beneficial micro-organisms to overgrow and become pathogenic.

Over a decade into the 21st century, we are faced with a rising incidence of antibiotic resistance. We have an armoury of pharmaceutical interventions, with variable efficacy and risk of adverse effects. Strategies based on state-of-the-art research data and sound nutrition could provide a drug-free solution to many health disorders in man and animals, including atopic dermatitis.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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