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Review

The complex interplay between stress and bacterial infections in animals

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ABSTRACT

Over the past decade, an increasing awareness has arisen of the role of neuroendocrine hormones in the susceptibility of mammalian hosts to a bacterial infection. During a stress response, glucocorticoids, catecholamines and neuroendocrine factors are released into the circulation of the host. For a long time the effects of stress on the course of an infection have been exclusively ascribed to the direct effect of stress-related hormones on the immune system and the intestinal barrier function. Chronic stress is known to cause a shift from T helper 1-mediated cellular immunity toward T helper 2-mediated humoral immunity, which can influence the course of an infection and/or the susceptibility to a microorganism. Bacteria can however also respond directly to stress-related host signals. Catecholamines can alter growth, motility, biofilm formation and/or virulence of pathogens and commensal bacteria, and as a consequence influence the outcome of infections by these bacteria in many hosts. For some bacteria, such as *Salmonella*, *Escherichia coli* and *Pseudomonas aeruginosa* it was shown that this influence is regulated by quorum sensing mechanisms. In this manuscript an overview of how and when stress influences the outcome of bacterial infections in animals is provided.

Contents

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1. Introduction

Stress is a concept that has multiple meanings, leading to different definitions (Murray et al., 1996). According to Dhabhar and McEwen (1997), "stress is a constellation of events, consisting of a stimulus (stressor) that precipitates a reaction in the brain (stress perception), which activates physiological fight-or-flight systems in the body (stress response)".

Stress is essential for the survival of an organism as it forms the basis of the innate fight-or-flight response, a fundamental survival mechanism that prepares the body to either challenge or flee from a threat (Dhabhar, 2009; Hughes et al., 2009). The term stress often has a negative connotation since chronic stress suppresses the immune system and increases the susceptibility to infections (Dhabhar and McEwen, 1997). A period of stress results in the release of a variety of neurotransmitters, peptides, cytokines, hormones, and other factors into the circulation or tissues (Freestone et al., 2008b; Dhabhar, 2009). The most important mediators of the stress response are the fast-acting catecholamines epinephrine and norepinephrine, which are released by the sympathetic nervous system, and the slow-acting glucocorticoids cortisol and corticosterone, which are secreted by the adrenal gland after activation of the hypothalamic-pituitary-adrenal axis (Dhabhar, 2009).

For a long time, the effects of stress on the course of an infection have been exclusively ascribed to the effect of these stress-related hormones on the immune system. However, during the past decade a new perspective has been introduced which implies that stress-related hormones directly affect the infectious microorganism itself or the host–pathogen interaction (Lyte, 2004). These new insights led to the development of a research area named microbial endocrinology where microbiology and neurophysiology intersect. Recent work from this field shows that bacteria, either from the gastrointestinal tract, the respiratory tract or the skin, can exploit the neuroendocrine alteration due to a stress reaction of the host as a signal for growth and pathogenic processes (Lyte, 2004; Freestone et al., 2008b). Both humans and animals are susceptible to the effects of stress on the outcome of an infectious disease. Current animal production practices contain several potentially stressful periods (like inadequate housing conditions, overcrowding, heat, cold, feed deprivation before slaughter and transportation). These stress factors have been linked to increased pathogen carriage, disease susceptibility, carcass contamination and pathogen shedding (Burkholder et al., 2008; Rostagno, 2009).

As some bacteria like *Salmonella* spp. are present in silent carriers, stress induced pathogen shedding could result in an increased transmission of the bacterium and as a consequence interfere with risk assessments. Therefore, it is of great importance to be aware that stress can alter the outcome of an infection in animals. The intent of the current review is to summarize the recent literature on how and when stress influences bacterial infections in animals.

2. Stress and stress-related hormones in animals

The factors causing physical or psychologic stress are different, but they generally result in similar responses, such as the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. This results in the rapid and transient release of catecholamines. Subsequently glucocorticoids are released into the circulation, as summarized in Fig. 1 (Webster Marketon and Glaser, 2008).

Besides these stress mediators, other neuroendocrine factors can be released following stress, including prolactin, vasoactive intestinal polypeptide, cholecystokinin, growth hormone, nerve growth factor, substance P, neuropeptide Y and serotonin (Joëls and Baram, 2009).

2.1. Activation of the sympathetic nervous system: catecholamines

Stress induces the secretion of acetylcholine from the pre-ganglionic sympathetic fibers in the adrenal medulla via the activation of the sympathetic nervous system. This induces the rapid secretion of epinephrine from the adrenal medulla into the bloodstream and the rapid secretion of norepinephrine from the sympathetic nerve terminals into lymphoid organs, as illustrated in Fig. 1. The close association of nerve terminals with immune cells in lymphoid organs facilitates the effects of norepinephrine (Yang and Glaser, 2002).

Catecholamines are synthesized from tyrosine and exert their effects by binding to adrenergic receptors. These adrenergic receptors are G-protein coupled receptors which can be subdivided in α- and β-adrenergic receptors, that comprise α_1 and α_2 subtypes, and β_1, β_2 and β_3 subtypes, respectively. Virtually all lymphoid cells express β-adrenergic receptors, with β_2-adrenergic receptors being the most important receptors in terms of the immune system (Elenkov et al., 2000; Webster et al., 2002). When epinephrine and norepinephrine bind the β_2-adrenergic receptors, conformational changes of these receptors take place and G-proteins become activated through the exchange of guanosine diphosphate (GDP) for guanosine triphosphate (GTP). This in turn stimulates enzymes to induce the production of cyclic adenosine 5′-monophosphate (cAMP), which for example can modulate cytokine expression, as illustrated in Fig. 2 (Elenkov et al., 2000; Webster et al., 2002). Catecholamines play an important role in many functions in eukaryotic organisms such as energy balance, thermoregulation, cardiovascular function, behaviour and immunity (Thomas and Palmiter, 1997).

2.2. Activation of the hypothalamic-pituitary-adrenal axis: glucocorticoids

Besides the activation of the sympathetic nervous system, the hypothalamic-pituitary-adrenal axis becomes activated during a stress response, which results in the secretion of corticotropin releasing factor from the paraventricular nucleus of the hypothalamus (Webster Marketon and Glaser, 2008). Next, corticotropin releasing factor binds to corticotropin releasing factor subtype 1

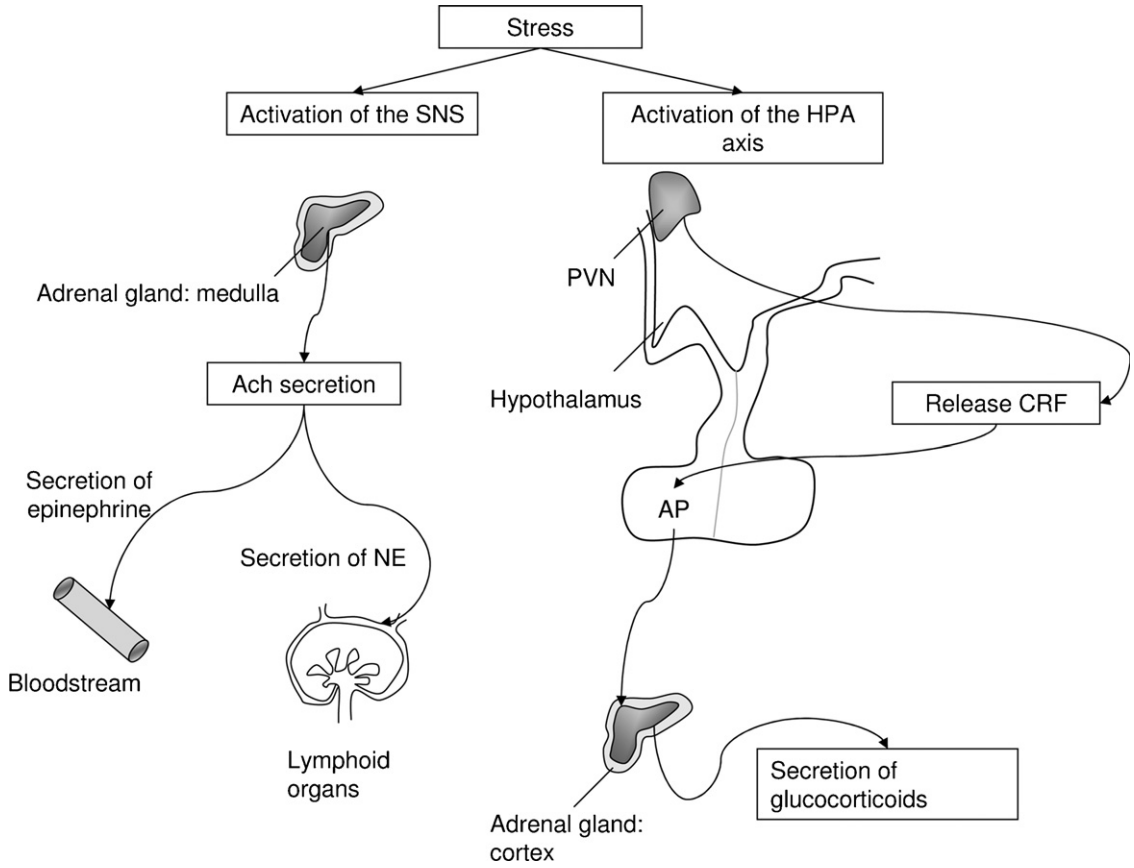


Fig. 1. Stress activates the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal axis (HPA), resulting in the release of respective catecholamines and glucocorticoids. The activation of the sympathetic nervous system induces the secretion of acetylcholine (Ach) from the pre-ganglionic sympathetic fibers in the adrenal medulla. This results in the secretion of epinephrine from the adrenal medulla into the bloodstream and the secretion of norepinephrine (NE) from the sympathetic nerve terminals into lymphoid organs. Besides the activation of the sympathetic nervous system, the hypothalamic-pituitary-adrenal axis becomes activated during a stress response which results in the secretion of corticotropin releasing factor (CRF) from the paraventricular nucleus (PVN) of the hypothalamus. Then, corticotropin releasing factor binds to corticotropin releasing factor subtype 1 receptors, located on membranes of anterior pituitary (AP) corticotrope cells, which results in the secretion of the adrenocorticotropine hormone (ACTH) from the anterior pituitary into the systemic circulation. This triggers glucocorticoid secretion from the adrenal glands.

receptors, located on membranes of anterior pituitary corticotrope cells (Taché and Brunnhuber, 2008). This subsequently results in the secretion of the adrenocorticotropic hormone from the anterior pituitary into the systemic circulation, which than forms the trigger for glucocorticoid secretion from the adrenal glands, as illustrated in Fig. 1. Most mammals secrete cortisol as the predominant glucocorticoid, whereas in most rodents and birds, corticosterone is the most important glucocorticoid secreted during a stress reaction. Both are synthesized from cholesterol and besides a minor degree of binding to albumin, in unstressed animals approximately 90% is bound to corticosterone-binding globulin, which is the major transport protein for glucocorticoids in the plasma of mammalian species (Petersen et al., 2006). Only the unbound cortisol or corticosterone can easily cross cell membranes via passive diffusion. Cortisol and corticosterone generally exert their effects by binding to the glucocorticoid receptor or the mineralocorticoid receptor. In the absence of glucocorticoids these receptors reside in the cytoplasm as a multiprotein complex (Webster et al., 2002). Binding to the mineralocorticoid receptor occurs with a 10-fold higher affinity than to the glucocorticoid receptor. This implies that, under basal resting conditions, the glucocorticoids preferentially bind to the mineralocorticoid receptor and during periods of stress substantial glucocorticoid receptor binding occurs (de Kloet et al., 1993). Upon ligand binding, the glucocorticoid receptor dissociates from its multiprotein complex and is translocated into the nucleus where it acts as a transcription factor via the interaction with genes whose promoter regions contain glucocorticoid respons elements (Webster et al., 2002). Furthermore, it can directly interact with transcription factors including nuclear factor (NF)-κB and AP-1, to inhibit their activation. This results in the inhibition of numerous genes encoding immune effector and pro-inflammatory cytokines (Belgi and Friedmann, 2002). Moreover, there is some evidence that the ligand/receptor complex can interact with protein kinases involved in intracellular signalling, which results in the phosphorylation of various signal transducing kinases and Annexin-1 (Belgi and Friedmann, 2002). In general,

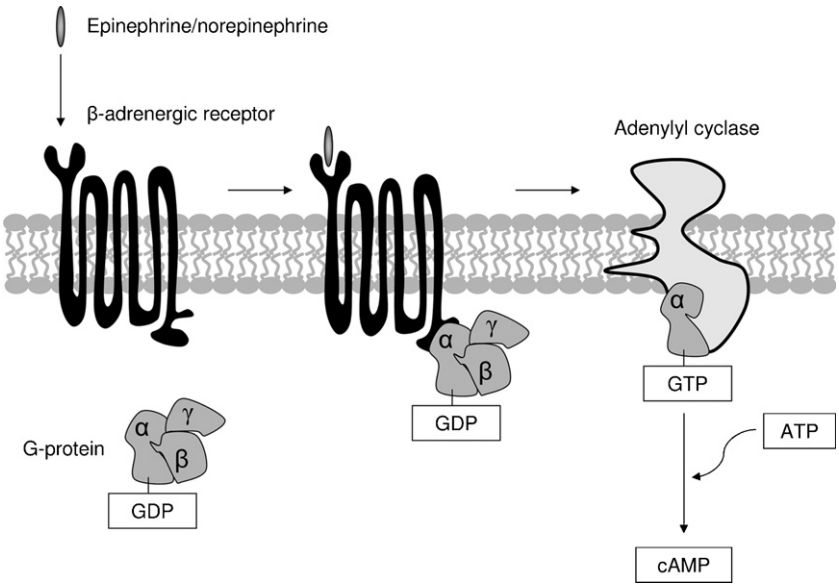
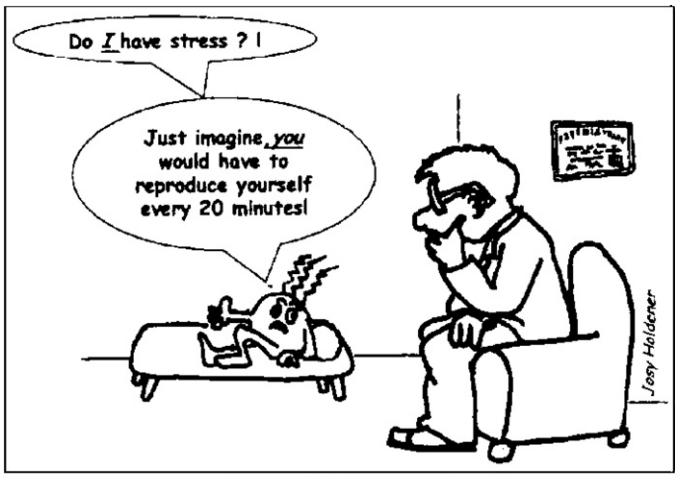


Fig. 2. The binding of epinephrine or norepinephrine to a β-adrenergic receptor causes conformational changes of the receptor that allow the association of the trimeric G-protein (G_α, G_β and G_γ subunit) with the receptor. The G_α subunit is bound to guanosine diphosphate (GDP), but the interaction between the G-protein and the β-adrenergic receptor results in the exchange of guanosine diphosphate for guanosine triphosphate (GTP). As a result, the G_α subunit detaches from the complex and binds to adenylyl cyclase. Consequently adenylyl cyclase becomes activated and catalyzes the formation of the secondary messenger cyclic adenosine 5′-monophosphate (cAMP) from adenosine-5′-triphosphate (ATP).

glucocorticoids regulate a wide variety of functions, ranging from growth, metabolic functions, and cardiovascular functions, to immune modulation (Sapolsky et al., 2000; de Kloet et al., 2008).

3. The effects of stress-related hormones on the host immune response and the intestinal barrier

Neuroendocrine stress hormones can modulate various aspects of the immune system. Almost all cells of the immune system have receptors for one or more of the hormones that are released during a stress response. This implies that stress hormones can have direct effects on all cells of the immune system. However, the modulation of the immune response due to a stress reaction can also occur via secondary effects, for example by interfering with cytokine production (Glaser and Kiecolt-Glaser, 2005; Radek, 2010). The effects of stress hormones on the immune system have been extensively reviewed elsewhere (Elenkov and Chrousos, 1999; Webster et al., 2002; Dhabhar, 2009). A short overview of the current knowledge is provided below.



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3.1. Effects of stress on the innate and acquired immune system

Stress hormones regulate a wide variety of functions in cells of the immune system and influence the expression of various cytokines (Webster et al., 2002). Glucocorticoids suppress the production of interleukin (IL)-12 by antigen-presenting cells and down-regulate the expression of IL-12 receptors on natural killer and T-cells. As the main inducer of T helper (Th) 1 responses is down-regulated, the secretion of interferon (IFN)-γ, which normally further promotes Th1 responses, is inhibited (Elenkov and Chrousos, 1999; Webster Marketon and Glaser, 2008). It is also known that besides IL-12, glucocorticoids suppress other proinflammatory cytokines and immunoregulatory cytokines including IL-1, IL-2, IL-6, IL-8, IL-11 as well as granulocyte macrophage colony-stimulating factor (Webster et al., 2002). Furthermore, glucocorticoids cause an upregulation of the production of the anti-inflammatory cytokines IL-4 and IL-10 (Webster et al., 2002). Catecholamines enhance these effects by inhibiting and increasing IL-12 and IL-10 production, respectively (Elenkov and Chrousos, 1999). In addition, stress increases the production of IL-10 by Th2 cells (Webster Marketon and Glaser, 2008). Furthermore, stress hormones modulate trafficking, maturation and differentiation of cells of the immune system, the expression of adhesion molecules, chemoattractants and cell migration factors, and the production of inflammatory mediators (Yang and Glaser, 2000; Webster et al., 2002; Yang and Glaser, 2002).

In conclusion, chronic stress stimulates the humoral immunity and inhibits the cellular immunity by altering the cytokine balance from type-1 to type-2 cytokine driven responses, which can influence the course of an infection and/or the susceptibility to a microorganism (Elenkov and Chrousos, 1999).

3.2. Effects of stress on the intestinal barrier

The gastrointestinal tract is controlled by the enteric nervous system, that innervates the gut and is bidirectionally linked with the central nervous system by sympathetic and parasympathetic pathways that form the brain–gut axis (Bhatia and Tandon, 2005; Rostagno, 2009). The gastrointestinal tract has the challenge of responding to pathogens while at the same time remaining relatively unresponsive to food antigens and the commensal microbiota (Macdonald and Monteleone, 2005). The ability to control the uptake of nutrients across the gut mucosa and to protect the gastrointestinal tract against noxious substances is defined as the intestinal barrier function, which comprises several first line defense mechanisms such as commensal bacteria, the gut mucous lining, the gut epithelium, the lamina propria and the intestinal propulsive motility. Commensal intestinal bacteria can inhibit the colonization of pathogens via the production of antimicrobial substances (bacteriocins), alteration of the pH and competition for binding sites and nutrients required for their growth (Keita and Söderholm, 2010). The mucus layer protects the gut epithelium and serves as a physical barrier to inhibit and entrap invading microorganisms (Moran et al., 2011). The enterocytes of the gut epithelium are connected to each other by junctional complexes, such as tight junctions, which are important for epithelial transport. Under normal conditions, the intestinal epithelium secretes antimicrobial peptides and constitutes an effective barrier to invading microorganisms (Keita and Söderholm, 2010). Furthermore, the lamina propria includes the enteric nervous system, endocrine system and cells of the innate and acquired immunity and together with the intestinal motility, it can protect the host from invading pathogens (Keita and Söderholm, 2010).

A disruption of the intestinal barrier function can lead to an increased antigen and pathogen passage, and subsequently to altered host–pathogen interactions. The intestinal barrier has many cellular targets for catecholamines and glucocorticoids, including epithelial cells, enteroendocrine cells, leukocytes, mast cells and enteric neurons (Lyte et al., 2011). This implies that stress mediators can alter the mucosa–bacterial interactions and so affect the commensal microbiota and/or the outcome of a bacterial infection (Lyte et al., 2011).

During stress, the release of norepinephrine from sympathetic nerves that innervate the myenteric plexus, the submucosa and mucosa of the intestine, can accelerate intestinal motility, colonic transit and transepithelial ion transport, which can influence the microbial population of the gut (Enck et al., 1989; Mizuta et al., 2006; Freestone et al., 2008b). As commensal bacteria inhibit the colonization of pathogens, a stress-induced alteration of the gut microbiota may alter host susceptibility to pathogenic bacteria (Bailey et al., 2004; Keita and Söderholm, 2010). Furthermore, stress can modulate the intestinal permeability and promote the luminal attachment of pathogenic bacteria (Zareie et al., 2006; Lyte et al., 2011).

4. The effects of stress-related hormones on the course of bacterial infections

Apart from the effect of stress hormones and other indirect effects on the immune response, the course of an infection can also be altered by the direct effect of stress mediators on bacteria. Catecholamines stimulate growth and virulence of many Gram-negative and Gram-positive bacteria. Possibly, bacteria sense the increased concentrations of stress hormones and respond with an increased growth and enhanced potential to cause disease, resulting in an increased transmission to a new healthy host (Freestone et al., 2008b). For a number of specific bacterial pathogens for which it has been demonstrated that stress can alter the susceptibility to infection and have a serious impact on animal health, the present knowledge on stress–pathogens–host interactions is presented in Table 1.

4.1. Escherichia coli

E. coli is a normal inhabitant of the intestinal tract of numerous hosts such as mammals, birds and reptiles. Both for commensal *E. coli* and some strains equipped with specific virulence factors, such as enterotoxigenic *E. coli* (ETEC) and enterohemorrhagic *E. coli* (EHEC), information

Table 1
The effects of stress or stress hormones on responsive bacteria.

Pathogen	Effects of stress or stress hormones on bacteria	References
Mycoplasma hyopneumoniae	Norepinephrine down-regulates the general metabolism of *M. hyopneumoniae*, resulting in reduced growth.	Oneal et al. (2008)
Bordetella bronchiseptica	Norepinephrine promotes the growth of *B. bronchiseptica* and facilitates iron acquisition by this organism from transferrin.	Anderson and Armstrong (2006, 2008)
Pseudomonas aeruginosa	Experiments *in vitro* have shown that norepinephrine enhances growth of *P. aeruginosa* by supplying iron from transferrin, production of virulence factors (pyocyanin, elastase and PQS), invasion of epithelial cells and swimming motility. All these mechanisms are mediated primarily through the *las* quorum sensing pathway.	Hegde et al. (2009); Li et al. (2009)
Vibrio species	Norepinephrine stimulates growth of *V. parahaemolyticus* and *V. mimicus*, but not of *V. cholerae* and *V. vulnificus*.	Nakano et al. (2007a)
	Norepinephrine modulates both the cytotoxic activity and enteropathogenicity of *V. parahaemolyticus* via its type III secretion systems.	Nakano et al. (2007b)
	Physiological changes imposed by stress or stress hormones can influence the host–pathogen interactions in oysters and increase the susceptibility to *V. splendidus.*	Lacoste et al. (2001)
Listeria monocytogenes	Norepinephrine induces growth of *L. monocytogenes*. The bacterium itself can not produce any siderophores, but it uses the capacity of catecholamines to bind iron via their catechol moiety. After binding, the ferric catecholamine complex is reduced via a cell-surface bound ferric reductase and finally the ferrous iron becomes available for utilization. This implies that norepinephrine functions as a sideophore-like compound in *L. monocytogenes* in a catecholamine receptor independent way, but via a cell-bound ferrireductase activity of the bacteria.	Coulanges et al. (1997, 1998)
	Alterations in corticosterone and norepinephrine levels can influence murine host resistance to *L. monocytogenes.*	Kim et al. (2004)
	Although the exact mechanism is not known, cold stress can increase the colonization of *L. monocytogenes* in the liver and synovial tissues in turkeys.	Huff et al. (2007); Dutta et al. (2008)
Borrelia burgdorferi	Human epinephrine and norepinephrine are recognized and bound specifically by *B. burgdorferi*, which results in increased expression of the outer surface protein A (OspA). Normally OspA is up-regulated as the bacterium enters the tick vector where it mediates attachment of the bacterium in the tick gut, and down-regulated when the bacterium is in a mammalian host. Therefore, the recognition of catecholamines, likely to be present at the site of a tick bite, may inform *B. burgdorferi* of local changes and prepare it for recolonization of uninfected ticks feeding on infected mammals.	Scheckelhoff et al. (2007); Battisti et al. (2008)

For a number of specific bacterial pathogens the present knowledge on stress–pathogens–host interactions is presented.

is available which shows that stress or stress hormones can influence the outcome of the infection.

ETEC infections are a significant cause of watery diarrhea in animals (especially piglets, calves and lambs) and humans. Norepinephrine induces an increase in growth of ETEC and it induces the expression of F5 fimbrial adhesion, which mediates the attachment of the bacterium to receptors on the small intestinal epithelium (Lyte et al., 1997a,b; Nagy and Fekete, 2005).

However, more is known about EHEC, a zoonotic pathogen that causes hemorrhagic colitis and haemolytic uremic syndrome in infected humans (Ferens and Hovde, 2010; Zoja et al., 2010). Healthy cattle carrying EHEC in their large intestine are the main reservoir for this agent. The ability to cause disease, colonize the bovine gastrointestinal tract, and survive in the environment, requires several virulence factors, including virulence plasmids and pathogenicity island encoded factors (Moxley, 2004; Lim et al., 2010; Pennington, 2010).

Iron is an essential nutritional element needed for the growth and survival of the majority of bacteria. Therefore, limiting iron availability is part of the host defense against bacterial infections. Catecholamines, especially norepinephrine, remove iron from the host high-affinity ferric-iron-binding proteins transferrin and lactoferrin, and make the iron ions available to the bacterial cells. The increased availability of iron subsequently enhances the growth of EHEC and commensal *E. coli* (Lyte and Ernst, 1992, 1993; Lyte et al., 1996b, 1997a; Freestone et al., 2002; Chen et al., 2003; Sandrini et al., 2010).

Bacterial cells respond to stress hormones via quorum sensing, through the use of small hormone-like molecules (autoinducers) to regulate gene expression within their own species and other bacterial strains in the microenvironment (Asad and Opal, 2008; Boyen et al., 2009; Pacheco and Sperandio, 2009). Bacteria do not express homologues of mammalian adrenergic receptors to respond to catecholamines, but they sense these hormones through

histidine sensor kinases. Two histidine sensor kinases characterized in EHEC, QseC and QseE, have been reported to sense epinephrine, norepinephrine and autoinducer 3 (Hughes et al., 2009).

It has been suggested that epinephrine and norepinephrine exacerbate EHEC infections because they attract EHEC, increase EHEC motility and cause an upregulation of genes involved in virulence (Lyte et al., 1996a; Bansal et al., 2007; Dowd, 2007). It is thought that EHEC uses histidine sensor kinases to activate expression of metabolic, virulence and stress response genes, synchronizing the bacterial cell response to these stress hormones (Sperandio et al., 2003; Hughes et al., 2009). Furthermore, catecholamines increase biofilm formation by EHEC, cause an upregulation of genes involved in surface colonization, and increase adherence to cecal and colonic mucosa (Chen et al., 2003; Green et al., 2004; Chen et al., 2006; Bansal et al., 2007). Norepinephrine increases the uptake of EHEC, but not of non-pathogenic *E. coli*, into jejunal Peyer's patches (Green et al., 2003). Additional *in vivo* research showed that exposure to various stressors, such as feed withdrawal and handling, increases fecal shedding of *E. coli* in beef cattle (Brownlie and Grau, 1967; Reid et al., 2002), sheep (Grau et al., 1969), or young piglets (Dowd et al., 2007), as well as shedding of EHEC in calves (Brown et al., 1997; Cray et al., 1998). The increased growth, motility and altered virulence probably provide only a partial explanation for the *in vivo* effects. The role of glucocorticoids or the interplay between different stress hormones still remains unknown.

According to Moro et al. (1998) cold stress significantly increases the resistance of *E. coli* from the intestinal tract of swine to ampicillin and tetracycline. Mathew et al. (2003) showed that the prevalence of *E. coli* resistant to apramycin increases upon exposure to various stressors, such as cold stress, crowding and intervention with oxytetracycline. Furthermore, Moro et al. (2000) demonstrated that heat stress in swine results in the increased propulsion of resistant bacteria from the upper- to the lower gastrointestinal tract. This implies that stress can increase the resistance of *E. coli* to antimicrobial agents and the shedding of resistant bacteria, as a defense mechanism against the increased state of readiness in stressed and sick animals.

4.2. *Salmonella enterica*

Salmonellosis is one of the most important zoonotic bacterial diseases. *Salmonella* Typhimurium is the predominant serovar isolated from slaughter pigs and *Salmonella* Enteritidis is the major cause of egg contamination without causing discernible illness in infected birds (Boyen et al., 2008; Gantois et al., 2009).

It has been shown that norepinephrine promotes growth, (due to increased iron availability to the bacterial cell) and motility of *S. enterica in vitro* (Bearson and Bearson, 2008; Bearson et al., 2008; Methner et al., 2008). A possible *in vivo* result of this could be the recrudescence of *Salmonella* in carrier animals, increased colonization of the gut due to its increased motility, increased shedding and consequently an increased contamination of the environment and other animals. In fact, Toscano et al. (2007) established that pretreatment of *Salmonella* Typhimurium with norepinephrine *in vitro* is associated with increased replication of this microorganism in various tissues of experimentally infected pigs. However, conflicting results have been obtained by Pullinger et al. (2010b) who showed that pre-culture of the bacteria with norepinephrine does not alter the outcome of a *Salmonella* Typhimurium infection in pigs.

Norepinephrine and epinephrine interact with quorum sensing systems of *Salmonella* and it was shown that epinephrine alerts the bacterial defenses against oxidative stress, but that norepinephrine and epinephrine also act in favour of the host by inducing a reduction in bacterial antimicrobial peptide resistance and by down-regulation of bacterial virulence (Karavolos et al., 2008; Spencer et al., 2010). According to Pullinger et al. (2010a), bacterial adrenergic sensors may not be the essential link between stress and the increased susceptibility to *Salmonella* Typhimurium infection. This is because QseC and QseE, two histidine sensor kinases that play a role in quorum sensing, are not required for norepinephrine-enhanced enteritis, intestinal colonization in calves or norepinephrine dependent growth in iron-restricted medium. Nor do they influence expression or secretion of enteritis-associated virulence factors. Furthermore it was shown that the excretion of a Δ*qseC* mutant of *Salmonella* Typhimurium in pigs was diminished in comparison to the parent strain, albeit not significantly (Pullinger et al., 2010b). In contrast, Moreira et al. (2010) demonstrated that QseC plays an important role in flagellar motility, invasion of epithelial cells, survival within macrophages and in the systemic infection of mice. Additionally, a Δ*qseC* mutant displayed decreased colonization of the gastrointestinal tract and decreased fecal shedding in a porcine host (Bearson and Bearson, 2008; Bearson et al., 2010). These conflicting data underscore the need for further studies to evaluate the exact role of QseC in stress-related pathogenesis.

Early studies in mice have established that stress causes an increased frequency and persistency of *Salmonella* infections (Miraglia and Berry, 1962; Previte et al., 1970, 1973; Kuriyama et al., 1996). Pre-treatment of mice with norepinephrine resulted in an enhanced systemic spread of *Salmonella* Typhimurium in mice (Williams et al., 2006).

Environmental stressors such as feed withdrawal and heat cause changes in the normal intestinal microbiota of poultry and the intestinal epithelial structure. This can lead to increased attachment of *Salmonella* enteritidis (Burkholder et al., 2008). Stressed chickens have higher intestinal and circulating levels of norepinephrine and this stress hormone increases the colonization and systemic spread of *Salmonella* in chicken models (Knowles and Broom, 1993; Cheng et al., 2002; Methner et al., 2008). *In vivo* experiments showed that stress associated with forced molting of egg-laying flocks increases *Salmonella* enteritidis shedding and that feed withdrawal before slaughter causes an increase of crop contamination by *Salmonella* as well as an enhanced colonization frequency of *Salmonella* in broiler chickens (Holt et al., 1994; Line et al., 1997; Ramirez et al., 1997; Corrier et al., 1999). In contrast, according to Rostagno et al. (2006), preslaughter stress practices (feed withdrawal, catching, loading,

transportation and holding) do not significantly alter the prevalence of *Salmonella* in market-age turkeys.

Although a *Salmonella* Typhimurium infection in pigs can result in enterocolitis, the infection most often passes asymptomatically (Boyen et al., 2008). Pigs infected with these bacteria may carry *Salmonella* in their tonsils, gut and gut-associated lymphoid tissue for weeks or even months and excrete them in very low numbers. It is thought that stress can increase *Salmonella* shedding in infected pigs and even cause a re-excretion of *Salmonella* in silent carriers (Hurd et al., 2002). This results in an increased cross-contamination during transport and lairage and as a consequence in a higher level of pig carcass contamination (Berends et al., 1996; Hald et al., 2003). An early study by Williams and Newell (1970) pointed out that transportation of pigs may lead to increased shedding of *Salmonella*, however conflicting results have been published (Morrow et al., 2002; Rostagno et al., 2005; Scherer et al., 2008). In more recent studies it was also shown that feed withdrawal and transportation stress is associated with increased shedding of *Salmonella* Typhimurium (Isaacson et al., 1999; Martín-Peláez et al., 2009). In addition, it was established that due to stress, sows become more susceptible to "new" *Salmonella* infections and that carrier sows are more likely to start shedding the pathogen (Nollet et al., 2005). This was confirmed in our laboratory by demonstrating that feed withdrawal increases the *Salmonella* Typhimurium load in pigs, which is associated with cortisol induced increased intracellular proliferation in porcine macrophages (unpublished results).

In beef cattle, marketing- and transportation stress induced fecal excretion of *Salmonella* and transportation stress increased the frequency of *Salmonella* infections (Corrier et al., 1990; Barham et al., 2002; Reicks et al., 2007; Dewell et al., 2008). Systemic infections in cattle by *Salmonella* may result in encephalopathy. According to McCuddin et al. (2008), norepinephrine can play a role in these neurological manifestations by *Salmonella* since norepinephrine is needed for *Salmonella* to gain access to the systemic circulation and to induce encephalopathy.

As different types of natural stress factors can result in an increased susceptibility to *Salmonella* infections and a higher colonization and shedding of these bacteria, stress could also result in an increased contamination of other animals, carcasses and the environment.

4.3. Campylobacter jejuni

C. jejuni colonizes the intestine of a wide range of hosts like chickens, turkeys, ducks and pigs as a commensal organism. The bacterium has emerged as the most common bacterial cause of food-borne disease in many industrialized countries (Dasti et al., 2010). The effects of stress in animal carriers on the pathogenesis of this bacterium are unknown. There are indications that stress can increase the susceptibility of broiler chickens for colonization by *C. jejuni* (Stern et al., 1995).

Cogan et al. (2007) provided evidence that norepinephrine potentiates the growth of *C. jejuni*, and Zeng et al. (2009) partially elucidated the mechanism for this norepinephrine-mediated growth promotion. *C. jejuni* expresses the ferric enterobactin receptor CfrA for the utilization of ferric enterobactin (siderophore) as an iron source. Inactivation of the *cfrA* gene impaired norepinephrine-mediated growth, whereas complementation of the *cfrA* mutation completely restored norepinephrine-mediated growth promotion. Although the exact mechanism is not known, this implies that CfrA is at least partially responsible for the norepinephrine-mediated growth promotion of *C. jejuni* (Zeng et al., 2009). Whether the norepinephrine-induced increased growth of *C. jejuni* explains the *in vivo* outcome of stress, remains unknown. There is always danger in extrapolating the results obtained in an oversimplified model to the *in vivo* situation, since other factors for example the host immune system, commensal bacteria or the age of the host, can also influence the outcome of a bacterial infection. Thus, animal models must be created in order to study the effects of stress and stress hormones on bacterial infections.

As in the case for *E. coli* and *Salmonella*, motility plays an important role in colonization by *C. jejuni* because the bacterium has to penetrate mucus to adhere to surface epithelial cells. Cogan et al. (2007) established that norepinephrine increases the motility and invasion of *C. jejuni*, which implies that norepinephrine causes an increase in virulence-associated properties of *Campylobacter*. This suggests that stress in an animal and the release of norepinephrine, can increase the colonization efficacy of *C. jejuni* (Everest, 2007). Indeed *in vivo* trials showed that transportation stress causes an increase in colonization and shedding of *Campylobacter* in broiler chickens (Stern et al., 1995; Line et al., 1997; Whyte et al., 2001; Wesley et al., 2005). Furthermore, Byrd et al. (1998) demonstrated that preharvest feed withdrawal increases the frequency of *Campylobacter* crop contamination in broiler chickens. Wesley et al. (2009) confirmed these results in turkeys by demonstrating that transportation stress increases the number of *Campylobacter* bacteria in crop contamination.

Infected livestock, free-living animals and the environment are potential sources and vectors for contamination with *Campylobacter* (Hermans et al., 2011). As stress can result in an increased colonization and shedding of the bacterium in broiler chickens, this can result in increased horizontal transmission of *Campylobacter*.

4.4. Mycobacteria

Macrophages play an important role in the first line of defense against these facultative intracellular pathogens. The ability of activated macrophages to restrict the growth of mycobacteria will determine the outcome of an infection (Boomershine et al., 1999). It has been shown that the treatment of resident peritoneal macrophages with epinephrine and norepinephrine causes α_2-adrenergic stimulation of these macrophages, resulting in an increased inhibition of mycobacterial growth and an enhanced production of peroxynitrite (Miles et al., 1996; Chen et al., 1999; Weatherby et al., 2003). However, according to Boomershine et al. (1999), stimulation of IFN-γ primed macrophages with epinephrine, at the time of a *M. avium* subsp. *avium* infection, inhibits the anti-mycobacterial

activity of these macrophages via the activation of the β_2-adrenergic receptors and results in a decreased nitric oxide production. These reports suggest that catecholamines can suppress or activate macrophages, depending upon their state of activation and perhaps on the differential expression of adrenergic receptors (Boomershine et al., 1999). In addition to this, hypothalamic-pituitary-adrenal axis activation or exogenous treatment of macrophages of mice with corticosterone, suppresses the ability of macrophages to control the growth of *M. avium* subsp. *avium* (Zwilling et al., 1990, 1992; Brown et al., 1998). Since stress hormones can influence the macrophage–pathogen interactions, they probably can affect the outcome of mycobacterial infections. In fact, cortisol enables *M. tuberculosis* to grow more rapidly in severely immunodeficient mice and their immunocompetent counterparts (North and Izzo, 1993).

Infections with *M. avium* subsp. *paratuberculosis* occur mainly in ruminants and following infection they may shed the bacteria without any clinical signs. Only after a long incubation period, clinical signs appear which are characterized by loss of milk production, significant weight loss, and diarrhea (Marcé et al., 2010). It has been acknowledged that stressors, such as calving or change of feed, accelerate the development of clinical sings in infected animals (Chiodini et al., 1984; Kudahl et al., 2007). Thus stress can aggravate mycobacterial infections.

4.5. *Staphylococcus epidermidis*

The coagulase-negative staphylococci usually have a benign relationship with their host (Duguid et al., 1992; Otto, 2009). According to Lyte et al. (2003), norepinephrine stimulates the proliferation and biofilm formation of *S. epidermidis*. This highlights the fact that the stress response is a universal phenomenon which is not limited to pathogenic bacteria, but that also affects commensal bacteria. Neal et al. (2001) showed that the principal mechanism by which norepinephrine promotes the growth of coagulase-negative staphylococci is by the provision of iron via the removal of iron from iron-saturated transferrin. Furthermore, Freestone et al. (2008a) provided evidence that inhibition of staphylococcal growth by rifampin and minocycline could be reversed by exposure to dopamine or norepinephrine, via the increased provision of iron.

It has been proposed that coagulase-negative staphylococci have a probiotic function by preventing the colonization of other more pathogenic bacteria, like *S. aureus* (Otto, 2009). This might implicate that stress indirectly affects the outcome of a *S. aureus* infection. The importance of norepinephrine in the pathogenesis of other coagulase-negative staphylococcal infections, for example in subclinical mastitis in cattle is not yet known and therefore further research concerning this topic is required.

5. Conclusion

Stress may influence the outcome of many bacterial infections. Drawing a general conclusion on how and when this occurs covering all bacterial infections is, unfortunately, not possible because the mechanism of how stress can alter the course of a bacterial infection is still poorly known and is probably bacterium and host dependent. During a stress reaction, the sympathetic nervous system and hypothalamic-pituitary-adrenal axis become activated, which results in the release of catecholamines and glucocorticoids, respectively. Besides the effects of these stress hormones on the host immune response, *in vitro* studies have shown that catecholamines can alter the growth and/or virulence of many pathogens, and as a consequence may influence bacterium–host interactions. The duration of stress plays a significant role in the complex interplay between stress, the host immune system and the infectious microorganism. The quick bacterial response to stress hormones coincides with enhanced host cell-mediated immunity during acute stress. However, chronic stress suppresses cell-mediated immunity. Therefore the outcome of a bacterial infection is altered by the chronic exposure to stress.

For many pathogens, such as pathogenic and commensal *E. coli*, *S. enterica*, *Campylobacter*, *B. bronchiseptica*, *P. aeruginosa*, *L. monocytogenes* and coagulase-negative staphylococci, the increased growth has been attributed to the capacity of catehcolamines to supply the bacterium of iron. The increased availability of iron, which is supplied through the intervention of stress hormones, probably plays a key role in the effects of stress on the outcome of an infectious disease.

Certain pathogens, such as EHEC and *S. enterica*, sense norepinephrine and epinephrine through histidine sensor kinases (QseC and QseE), as a quorum sensing signal to regulate virulence gene expression and enhance its potential to cause disease. Therefore, these receptors could be considered as regulators of multiple virulence factors, making them a possible target to combat bacterial infections. However, there are different mechanisms of quorum sensing. Norepinephrine enhances the growth and virulence of *P. aeruginosa* through the *las* quorum sensing pathway. It is possible that these receptors vary depending on the type of pathogen, the host or the type of stress hormone. In the search toward possible antimicrobials against these receptors, more research is needed to further identify these targets.

For some bacteria, *in vivo* studies have confirmed that stress may influence the outcome of an infection. However, such studies are scarce and sometimes contradictory results have been reported (Cray et al., 1998; Kudahl et al., 2007; Dutta et al., 2008; Martín-Peláez et al., 2009; Wesley et al., 2009). In order to understand the interplay between different types of stress, the host immune system and bacteria, it is of utmost importance that animal models are created and field studies are conducted to investigate the effects of stress and stress hormones (individually or simultaneously) on bacterial infections in different hosts.

There is increasing evidence that stress promotes the colonization of farm animals by enteric pathogens such as *E. coli*, *S. enterica* and *Campylobacter* (Rostagno, 2009). Exposure to various stressors has been shown to increase fecal shedding of these pathogens. This could lead to an increased cross-contamination during transport and lairage and to a higher degree of carcass contamination. Since these pathogens are major causes of food-borne diseases

worldwide, not only animal, but also human health could be affected.

Some studies showed that stress can increase the resistance of *E. coli* to antimicrobial agents and the shedding of resistant bacteria (Moro et al., 1998, 2000; Mathew et al., 2003). This not only limits the use of antimicrobial agents in the treatment of bacterial infections, but could also result in the increased transfer of resistant bacteria or resistance genes to the environment, animals and humans. The mechanism underlying the increased resistance has not been elucidated yet, highlighting the need for further research concerning this topic. Biofilm formation of pathogenic bacteria such as EHEC and commensal bacteria such as *S. epidermidis* can be stimulated by norepinephrine. Biofilms are communities of bacterial cells attached to a surface that are enclosed in a self-produced polymer matrix. Within these biofilms, the bacteria are less susceptible to antimicrobial agents. Therefore, increased biofilm formation could also lead to an increased resistance to antibiotics.

Glucocorticoids and catecholamines are widespread throughout the body and are frequently used in human and animal medicine, for example the use of artificial glucocorticoids as anti-inflammatory agents (Behrend and Kemppainen, 1997; Lowe et al., 2008). That is why not only the effects of natural glucocorticoids and catecholamines, but also those of their synthetic related derivatives on bacterial infections need further examination. Furthermore, besides these stress mediators, other neuroendocrine factors can be released following stress. Until now, most of the research remains limited to the catecholamines.

Not only the question how bacteria respond to stress remains partly unknown, but also why bacteria respond to stress and stress hormones. What is the advantage of pathogenic and commensal bacteria to respond to these stress hormones? How come that norepinephrine causes a reduced growth of *M. hyopneumoniae*, while many pathogens respond with an increased growth? Possibly some bacteria respond with an increased growth to escape a sick or dying host in order to infect new and healthy host, while other bacteria respond with a reduced growth in order to cause a redistribution of energy sources. Although there is still a long way to go and many questions remain unknown, this review emphasizes that stress can influence the outcome of a bacterial infection. Since stress also reduces the fitness of animals, it is important to optimize animal welfare and to minify stressful conditions during their lives. In addition, the elucidation of the mechanisms by which stress and its hormones alter the susceptibility to an infection would help us to improve the prevention and treatment of infectious diseases.

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