Chapter 25
Host Neuroendocrine Stress Hormones Driving Bacterial Behaviour and Virulence

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Abstract In recent years there have been striking advances in our understanding of not only intra-bacterial communication but also the existence of inter-kingdom crosstalk between bacterial pathogens and their eukaryotic hosts. The intimate co-evolution of host and bacterial chemical communication systems appears to have generated an array of specialised signalling molecules which enable this dialogue. Bacterial pathogens are able to eavesdrop on their host and constantly adjust their metabolic and virulence status in order to survive and cause disease. Host neuroendocrine stress hormones like adrenaline and noradrenaline play a key role in modulating the response of many pathogens during host infection. The huge benefits of unravelling such a complex interplay in inter-kingdom signalling merits additional efforts in reaching the ultimate goal of decoding and interfering with the dialect of hormones.

25.1 Introduction

Bacterial pathogens use an array of molecular sensors to perceive and facilitate adaptation to changes in their environment. Mechanisms which allow bacterial pathogens to eavesdrop on mammalian host signalling systems such as neuroendocrine (NE) stress hormones may aid towards their successful adaptation and survival within the host (Pacheco and Sperandio 2009). Upon entering the host, pathogens come in contact with a wide range of chemical signals including the NE stress hormone noradrenaline which is abundant in the gut as well as adrenaline which is

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found mostly in the bloodstream (Aneman et al. 1996; Eisenhofer et al. 1996; Furness 2000). Interestingly, bacterial lipopolysaccharide has the ability to signal the formation of adrenaline and noradrenaline by macrophages in the bloodstream (Flierl et al. 2007, 2009). It was therefore suggested that the phagocytic system represents a diffusely expressed adrenergic organ (Flierl et al. 2007, 2009).

Faced with such a wide repertoire of host signals and environments, bacteria employ collective decision making, synchronizing their responses efficiently, in order to circumvent host defences and survive. Successful pathogens have, therefore, evolved a communication protocol which employs producing and sensing the concentration of autoinducer molecules in a process called quorum sensing (QS) (Pacheco and Sperandio 2009; Williams 2007). Following detection of the autoinducer, bacteria coordinate their gene expression in such a way as to behave in a "multicellular" fashion. Thus, organised bacterial attack against host defences ensures maximum chances of survival. More recently, a bacterial autoinducer, AI-3, was shown to cross talk with the host NE stress hormones adrenaline and noradrenaline (Sperandio et al. 2003).

Host-pathogen interactions are extremely important in determining the overall outcome of an infection. There is increasing evidence to suggest that bacteria can sense host NE stress hormones such as adrenaline and noradrenaline to modulate their virulence (Karavolos et al. 2008b, 2011a, b; Pacheco and Sperandio 2009; Spencer et al. 2010). In this chapter we will present the latest evidence supporting this inter-Kingdom signalling hypothesis and discuss aspects of the newly evolving concepts of bacterial-host communication.

25.2 Autoinducers and Hormones

In Gram-negative bacteria QS is usually mediated by *N*-acylhomoserine lactones (AHLs), 2-alkyl-4-quinolones (AQs) and furanones such as autoinducer-2 (AI-2) (Bassler et al. 1994; Winson et al. 1995). QS presents an advantage to the bacteria in terms of allowing coordinated expression of mechanisms aiding bacterial survival whilst simultaneously modulating metabolic fitness (Fuqua and Greenberg 1998; Miller and Bassler 2001; Winzer et al. 2002, 2003; Winzer and Williams 2001).

AHLs represent a class of freely diffusible autoinducers produced solely by Gram-negative bacteria. AHLs mediate signalling via critical concentration-mediated activation of LuxR family transcriptional regulators via the LuxNUO signal transduction system (Taga and Bassler 2003; Xavier and Bassler 2003). In Gram-positive bacteria, the autoinducers are actively secreted, post-translationally modified, autoinducing peptides resulting from the cleavage of larger precursors. Signalling is achieved by interaction with membrane receptors using the classical two-component signal transduction system, or intracellularly following internalisation by oligopeptides permeases (Dunny and Leonard 1997; Lazazzera 2000; Lyon and Novick 2004; Schauder and Bassler 2001).

AI-2 is a signal molecule deriving from rearrangement of 4,5-dihydroxy-2,3-pentanedione (DPD) which is itself a by-product in a reaction catalysed by the enzyme LuxS (Surette et al. 1999). It has been suggested that different bacteria use a variety of rearranged forms of DPD as AI-2 (Xavier and Bassler 2005). For example, in *Vibrio harveyi* AI-2 is a furanosyl borate diester (Chen et al. 2002), while *Salmonella enterica* serovar Typhimurium (*S*. Typhimurium) produces a different form of AI-2, (2R,4S)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran (*R*-THMF), lacking boron (Miller et al. 2004). In *S*. Typhimurium, AI-2 is thought to freely diffuse and accumulate extracellularly where upon reaching a critical concentration it is internalised and activated by phosphorylation via the Lsr system (Xavier and Bassler 2005). LuxS-dependent AI-2 activity has been detected in spent culture supernatants of a wide variety of bacteria leading to the hypothesis that AI-2 represents a "universal" bacterial communication signal (Miller and Bassler 2001; Xavier and Bassler 2005). In a number of species studied so far LuxS and AI-2 have been shown to affect the regulation of genes encoding a wide variety of virulence factors, motility, cell division, antibiotic production, biofilm formation, and carbohydrate metabolism (Sircili et al. 2004; Vendeville et al. 2005; Xavier and Bassler 2003, 2005). In *S*. Typhimurium, AI-2 only affects the expression of the Lsr system involved in its own uptake (De Keersmaecker et al. 2005; Taga et al. 2003; Xavier and Bassler 2003). LuxS exhibits quorum sensing-independent activity in *S*. Typhimurium by modulating flagellar phase variation to favour expression of the more immunogenic phase-1 flagellin (Karavolos et al. 2008a).

The LuxS enzyme, due to its pleiotropic effects on bacterial metabolism, has also been indirectly implicated in the production of another autoinducer (AI-3) in *Escherichia coli* (Sperandio et al. 2003; Walters et al. 2006). In enterohemorrhagic *Escherichia coli* (EHEC), AI-3 acts synergistically with adrenaline and noradrenaline to regulate motility and virulence via the two-component signal transduction systems QseBC and QseEF (Pacheco and Sperandio 2009; Rasko et al. 2008). In spite of AI-3 being described almost 10 years ago, its structure is still unknown, and its role in quorum sensing is currently under investigation.

25.3 Role of Host Neuroendocrine Stress Hormones in Bacterial Growth and Virulence

The mammalian endocrine system represents a very fine and sensitive tool that synchronises the responses of host cells to a vast array of internal or external signals. Many forms of stress have profound effects on the functions of the gastrointestinal tract (Elenkov and Chrousos 2006). The intestinal mucosa, therefore, with its large commensal bacterial population, represents a highly interactive niche where bacteria-host communications can potentially thrive (Freestone et al. 2008; Lyte et al. 2011).

NE stress hormones have been shown to influence the growth of bacteria (Freestone et al. 2007, 2008). Indeed, recently it was demonstrated that NE stress hormones, can contribute to the ability of Gram-negative pathogens to replicate in iron-restrictive media that may reflect the conditions of the gastrointestinal tract (Freestone et al. 2007). This action of NE stress hormones is related to their natural ability to remove iron from mammalian iron-sequestering proteins like transferrin and lactoferrin and hence make it available for bacteria to use in growth-related processes (Freestone et al. 2000; Sandrini et al. 2010). NE stress hormones improve growth of coagulase-negative *Staphylococci* but have no significant effect on the growth of the important Gram-positive pathogen *Staphylococcus aureus* (Beasley et al. 2011; Neal et al. 2001).

While there has been extensive coverage in the literature of the ability of NE stress hormones to affect bacterial growth, this is by no means the only effect of NE stress hormone exposure on bacterial physiology and ability to cause disease. In enterotoxigenic *Escherichia coli*, NE stress hormones influence the expression of the virulence-associated K99 pilus adhesin (Lyte et al. 1997). Additionally, NE stress hormones affect expression of Shiga-like toxins produced by *Escherichia coli* O157:H7 (Lyte et al. 1996). Bacterial exposure to NE stress hormones increases the adherence of EHEC to bovine intestinal mucosa (Vlisidou et al. 2004) and upregulates Type 3 secretion in *Vibrio parahaemolyticus* (Nakano et al. 2007). Exposure of *Campylobacter jejuni* to NE stress hormones increases invasion of epithelial cells and breakdown of epithelial tight junctions (Cogan et al. 2007). Furthermore, there is evidence to suggest that *Borrelia burgdorferi* may intercept host NE stress hormone signalling to modulate its virulence (Scheckelhoff et al. 2007). Most recently, exposure of *Porphyromonas gingivalis* to NE stress hormones increased expression of the protease arg-gingipainB, a major virulence factor (Saito et al. 2011). These observations put forward a possible role of NE stress hormones in the establishment of infection via the induction of bacterial virulence factors.

In *S*. Typhimurium NE stress hormones have been reported to affect motility (Bearson and Bearson 2008; Moreira et al. 2010) and Type 3 secretion (Moreira et al. 2010). These observations have introduced a measure of controversy in the field since other groups have been unable to replicate such findings (Karavolos et al. 2008b, 2011a; Pullinger et al. 2010). It is possible that these observations may constitute an indirect effect of the natural ability of NE stress hormones to provide iron to the cells and hence affect motility and Type 3 secretion (Bearson et al. 2010; Ellermeier and Slauch 2008; Teixidó et al. 2011; Troxell et al. 2011).

The major feature of the *S.* Typhimurium adrenaline response is the upregulation of genes involved in metal homeostasis and oxidative stress (Karavolos et al. 2008b). When *S*. Typhimurium, is exposed to NE stress hormones there is an induction of key metal transport systems within 30 min of treatment (Karavolos et al. 2008b). The oxidative stress responses employing manganese internalisation were also elicited. Cells lacking the key oxidative stress regulator OxyR showed reduced survival in the presence of adrenaline and complete restoration of growth upon addition of manganese. Hence, through iron transport, adrenaline may affect the oxidative stress balance of the bacteria requiring OxyR for physiological growth. Adrenaline

sensing may therefore provide an environmental cue for the induction of the *Salmonella* stress response in anticipation of imminent host-derived oxidative stress.

Furthermore, a significant reduction in the expression of the *pmrHFIJKLM* antimicrobial peptide resistance operon reduced the ability of *Salmonella* to survive polymyxin B following addition of adrenaline (Karavolos et al. 2008b). Resistance to antimicrobial peptides has been shown to contribute to persistence of *S*. Typhimurium in a variety of niches ranging from the phagosomes within macrophages to the *C. elegans* intestine (Alegado and Tan 2000; Prost et al. 2007). In *S*. Typhimurium, the *pmr* locus is under the control of the BasSR two component system (Gunn et al. 1998; Hagiwara et al. 2004). According to the above, we have a direct reduction of bacterial antimicrobial peptide resistance by a mammalian hormone and hence a novel "antibacterial" role for adrenaline. However, we note that *Salmonella* may have adapted to this negative effect of adrenaline within mammalian hosts by increasing lipid A deacylation and palmitoylation, thus favouring survival via reduced TLR-4 receptor-based bacterial signalling (Kawasaki et al. 2004b, 2005). Systemic or macrophage produced adrenaline may therefore regulate the fine balance between the host and *Salmonella* defence mechanisms, and impact upon the development of disease.

To add to the above observations, treatment of *S*. Typhimurium with NE stress hormones reduces its resistance to the peptide cathelicidin LL-37, a human antimicrobial peptide. LL-37 is produced in the gastrointestinal tract, bone marrow and macrophages, and has antimicrobial activity against many Gram-positive and Gram-negative bacteria (Bals et al. 1998). A NE stress hormone-mediated increase in sensitivity to LL-37 may act as a host defence system to combat infection, suggesting that bacterial sensing of stress hormones may be a double-edged sword: although bacteria can sense and exploit these molecules, the host can use the same signals to manipulate the bacteria (Spencer et al. 2010).

Exposure of *S*. Typhimurium to NE stress hormones also affects expression of *virK* and *mig14*, two genes involved in survival and persistence within the host. Genetic deletion of either gene reduces the virulence of *S*. Typhimurium in a mouse infection model, and also reduces survival in macrophages, signifying a possible role in the late stages of infection (Brodsky et al. 2005; Detweiler et al. 2003). The down-regulation of *mig14* by NE stress hormones may hence reduce levels of persistent infection and promote clearance of bacteria (Spencer et al. 2010). All the above paradigms highlight the dual role of NE stress hormones in mediating host-bacterial interactions.

Salmonella enterica serovar Typhi (*S*. Typhi) is an exclusively human pathogen causing typhoid fever which is physiologically non-haemolytic (Huang and DuPont 2005). Exposure of *S*. Typhi to NE stress hormones marks a significantly increase in haemolytic activity (Karavolos et al. 2011a, b). The haemolytic response is specific to outer membrane vesicles containing the haemolysin HlyE. Mechanistically, NE stress hormones interact with the CpxAR putative adrenergic sensory system to downregulate outer membrane protein A (OmpA) levels via upregulation of the sRNA *micA*. Reduced OmpA levels increase outer membrane vesicle shedding and hence haemolysis via increased release of HlyE (Karavolos et al. 2011a, b).

The significantly increased ability of this important systemic pathogen to produce haemolysis upon interaction with NE stress hormones, may ultimately aid in enhancing its host invasiveness and survival.

25.4 Signaling Through Bacterial Adrenergic Receptors

In EHEC adrenaline and noradrenaline can substitute for the bacterial autoinducer AI-3 implying the existence of cross talk between the two signalling systems (Sperandio et al. 2003). This observation raised the possibility of the presence of adrenergic receptors in bacteria (Sperandio et al. 2003).

Indeed, the sensor kinase QseC is autophosphorylated on binding either adrenaline or noradrenaline, demonstrating the existence of adrenergic receptors in bacteria (Clarke et al. 2006). Furthermore, these adrenergic responses can be inhibited by mammalian α- and β-adrenergic antagonists like phentolamine and propranolol. Remarkably, there is strong specificity in the antagonistic effect with QseC only being blocked by phentolamine (Clarke and Sperandio 2005). In *Escherichia coli* O157:H7 and *Salmonella* the QseBC system has been proposed as the adrenergic receptor. However, new emerging evidence supports the existence of alternative adrenergic receptors. For example, in *S*. Typhimurium it has been demonstrated that QseBC is not required for norepinephrine-enhanced enteritis or intestinal colonisation in calves (Pullinger et al. 2010).

In another example of adrenergic receptor antagonist inhibition, increased expression of *virK* and *mig14* in *S*. Typhimurium was reversed by the addition of the β-adrenergic antagonist propranolol. Some adrenergic phenotypes in bacteria are associated with altered iron uptake via the siderophore enterobactin (Burton et al. 2002; Freestone et al. 2003). A *tonB* mutant, defective in siderophore uptake, showed the same differential gene regulation upon exposure to NE stress hormones as the parent strain, suggesting that the adrenergic regulation is mediated through a mechanism independent of TonB. Furthermore, in *S*. Typhimurium, QseBC does not mediate the adrenergic signalling cascade leading to increased sensitivity to the antimicrobial peptide LL-37 (Spencer et al. 2010). Hence, it is likely that a different putative adrenergic receptor is involved in this response.

Additionally, the adrenaline-induced reduction in the ability of *Salmonella* to resist polymyxin B was fully reversible by the β-adrenergic blocker propranolol. This effect was dependent on the BasSR two component signal transduction system which is the likely putative adrenaline sensor mediating the antimicrobial peptide response (Karavolos et al. 2008b). Adrenaline may, therefore, exert its effect on the *pmr* locus of S. Typhimurium via the reversible interaction of the β-adrenergic blocker with the BasS membrane sensor in a manner similar to the interaction of adrenaline with QseC in *E. coli*. The low (31 %) amino acid sequence identity between BasS and QseC may provide a clue as to why we observe β-blockage in *Salmonella* as opposed to α-blockage in *E. coli*.

The physiological phenotypes of NE stress hormones described above are not linked with QseBC or QseEF signalling (Karavolos et al. 2008b, 2011a, b; Spencer et al. 2010). This may reflect differences in pathogenesis between *S*. Typhimurium, an invasive pathogen infecting macrophages and epithelial cells and *E. coli*, a mainly non-invasive pathogen which remains in the host intestine. The significant divergence in niches occupied by these two pathogens requires different gene expression patterns for maximum infection efficiency; hence NE stress hormones may modulate different genetic pathways to the advantage or disadvantage of the pathogen.

The inhibition of NE stress hormone-mediated haemolysis by the adrenergic β-blocker propranolol in the exclusively human pathogen *S*. Typhi is another example of the existence of an additional putative novel bacterial adrenergic receptor. In *S*. Typhi, NE stress hormone-mediated haemolysis is clearly independent of the known *E. coli* O157:H7 adrenergic receptor QseBC and is mediated via the CpxAR two component system (Karavolos et al. 2011a, b)

Based on the above observations, it is evident that natural selection has ensured that there is no monopoly in bacterial adrenergic signalling. Millions of years of evolution have culminated in a fine tuned bacterial sensing system composed of different adrenergic receptors, which through their fastidious specificities, orchestrate the strategic responses of pathogens within their host milieu.

25.5 Conclusions

In response to acute stress, the sympathetic nervous system is activated due to the sudden release of NE stress hormones in a response known as the "fight-or-flight" reflex (Cannon 1915 – for more details see Chap. 2). This stress reaction evolved from our ancestral survival needs and causes immediate physical reactions in preparation of the muscular activity needed to fight or flee an imminent threat.

Recently, a number of groups, including ourselves, have made compelling observations that bacteria can also sense and respond to these host stress signals. Specifically, work from our laboratory has shown that *Salmonella* has evolved multiple specialised systems for directly sensing NE stress hormones. We have demonstrated that even brief exposure of *Salmonella* to physiological concentrations of stress hormones can result in marked changes in expression of virulence factors. These combined observations are summarised briefly in Fig. 25.1.

The effects of adrenaline and noradrenaline are likely to be complex, involving multiple effects on both bacteria and host gene expression signatures to actively influence the outcome of the infection. It is possible that the adrenergic modulation of these genes may confer an advantage to the bacteria under certain *in vivo* conditions but an unavoidable disadvantage in others; for example down-regulation of the lipopolysaccharide (LPS) modifying enzymes PmrF and PagL causes an increase in sensitivity to polymyxin B, but also concomitantly reduces activation of the TLR-4 Toll-like receptors, reducing the host inflammatory response to infection (Kawasaki et al. 2004a; Miller et al. 2005).

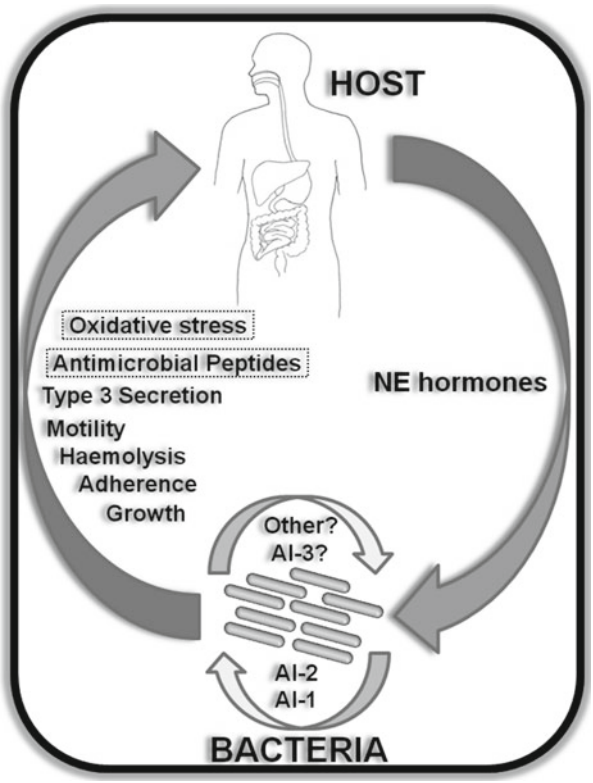

Fig. 25.1 Host-Pathogen communication via NE hormones. Host-produced NE stress hormones are sensed by bacterial pathogens which use them as environmental cues and, in combination with intrabacterial signalling through autoinducers (AIs), adjust their pathophysiology to their benefit. Bacterial sensing of NE stress hormones can also be a double-edged sword since it may exert a detrimental effect by weakening pathogen defences against the host arsenal (*dotted text boxes*)

Thus, host NE stress hormones can provide vital environmental cues for bacterial pathogens to navigate their way through their specific infectious cycle. On the other hand, NE stress hormones can provide the host with a unique tool to manipulate bacterial pathogens. The observations described in this Chapter provide important insights into the intriguing pathways leading to host-pathogen cross-talk and illustrate some of the unique ways bacterial pathogens intercept host communication signals to their advantage or detriment.

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