



Microbe-Endocrine Hormone Interactions



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Introduction

The influence of hormones on human cells is very well characterized, yet much less understood is the response to those chemical signals of the 10¹³-10¹⁴ bacteria and fungi that are co-resident within the human frame [1]. Microbial Endocrinology is a research area which seeks to understand the role of microbial interactions with mammalian hormones in conditions of health and disease [2-4]. It takes the view that through their long evolutionary relationship with animals microorganisms have evolved systems for sensing hormones which they use as an indicator that they are within the proximity of a potential host. This article considers what happens when the human microbiota

come into contact with the chemical signals of their host, and the health significance of this inter-kingdom-encounter.

Hormones can be classified on the basis of their chemical structures: amino acid, peptide and protein and cholesterol based, and the receptor location by which the hormonal signal is transduced. The function of each hormonal type will be described, and the health implications to the host when the hormone is encountered by potentially infectious bacteria and fungi. Structures of the hormones covered and the microbes which recognize them can be found in Table 1, respectively [5-39].

Table 1: Hormone responsive microorganisms.

Species	Hormone/Metabolite	Growth	Virulence	Reference
<i>Aeromonas hydrophila</i>	NE	+	+	Kinney et al. [5]
<i>Acinetobacter lwoffii</i>	NE	+		Freestone et al. [6]
<i>Bordetella bronchiseptica</i> , <i>B. pertussis</i>	NE, Adr, Dop	+	+	Anderson & Armstrong [7]
<i>Borrelia burgdorferi</i>	NE		+	Scheckelhoff et al. [8]
<i>Brachyspira pilosicoli</i>	NE	+	+	Naresh & Hampson [9]
<i>Campylobacter jejuni</i>	NE	+	+	Cogan et al. [10]
<i>Citrobacterfreundii</i> , <i>C. rodentium</i>	NE	+		Freestone et al. [6], Bailey et al. [11]
<i>Enterobacter agglomerans</i> , <i>E. sakazaki</i>	NE	+		Freestone et al. [6]
<i>Enterococcus faecalis</i> , <i>E. cloacae</i>	NE	+		Freestone et al. [6]
<i>Escherichia coli</i> (commensal and pathogenic)	NE, Adr, Dop, Iso, Dob, DHPG, DHMA	+	+	Lyte & Ernst [12], Freestone et al. [6,13-15], Green et al. [16], Vlisidou et al. [17], Sandrini et al. [18]
<i>Hafnia alvei</i>	NE	+		Freestone et al. [6]
<i>Helicobacter pylori</i>	NE	+		Doherty et al. [19]
<i>Klebsiella oxytoca</i> , <i>K. pneumoniae</i>	NE	+		Freestone et al. [6]
<i>Listeria monocytogenes</i>	NE, Adr, Dop	+		Coulanges et al. [20], Freestone et al. [6]
<i>Morganella morganana</i>	NE	+		Freestone et al. [6]
<i>Mycoplasma hyponeumoniae</i>	NE		+	O'Neal et al. [21]
<i>Proteus mirabilis</i>	NE	+		Freestone et al. [6]

<i>Pseudomonas aeruginosa</i>	NE, Adr, Dop	+	+	Alverdy et al.[22], Freestone et al. [6,23]
<i>Salmonella enterica, Salmonella Typhimurium</i>	NE, Adr, Dop	+	+	Freestone et al. [6,24] Methner et al. [25], Pullinger et al. [26]
<i>Shigella sonnei, S. flexneri</i>	NE	+		Freestone et al. [6,27]
<i>Staphylococcus aureus</i>	NE, Dop	+		Freestone et al. [27]
<i>Staphylococcus epidermidis, S. capitis,</i>				
<i>S. saprophyticus, S. haemolyticus, S. hominis</i>	NE, Adr, Dop, Iso, Dob	+	+	Freestone et al. [6,27]
<i>Streptococcus dysgalactica</i>	NE	+		Freestone et al. [6]
<i>Vibrio parahaemolyticus, V. mimicus, V. vulnificus</i>	NE, Adr, Dop	+	+	Nakano et al. [28]
<i>Xanthomonas maltophilia</i>	NE	+		Freestone et al. [6]
<i>Yersinia enterocolitica</i>	NE, Adr, Dop,	+		Freestone et al. [6,29]
<i>Periodontal pathogens</i>	NE, Adr	+		Roberts et al. [30]
<i>Actinomyces gerenscseriae, A. naeslundii, A. odontolyticus, Campylobacter gracilis, Capnocytophaga sputigena, C. gingivalis, Eikenella corrodens, Eubacterium saburreum, Fusobacterium periodonticum, F. nucleatum subsp. Vincentii, Leptotrichia buccalis, Neisseria mucosa, Peptostreptococcus anaerobius, P. micros, Prevotella denticola, P. Melaninogenica, S. intermedius, S. gordonii, S. constellatus, S. mitis, S. mutans, S. sanguis</i>				
<i>Burkholderia pseudomallei</i>	Insulin		+	Wood et al. [31]
<i>Candia albicans</i>	Oestrogen			
<i>Progesterone</i>				
<i>Luteinising hormone</i>	+			
+	+			
+				
+	Kinsman et al. [32], White & Larsen [33], Tarry et al. [34]			
<i>Banerjee et al. [35]</i>				
<i>Bramley et al. [36,37]</i>				
<i>Chlamydia trachomatis</i>	Oestrogen			
<i>Progesterone</i>		+		
+	Sonnex [38]			
<i>Sonnex [38]</i>				
<i>E. coli</i>	ACTH		+	Schreiber & Brown [39]

The '+' indicates that the hormone shown, or their metabolites have induced enhancement of growth or virulence of the bacterial species shown. Key: NE, noradrenaline; Adr, adrenaline; Dop, dopamine; Iso, isoprenaline; Dob, dobutamine; DHPG, dihydroxy phenylglycol; DHMA, dihydroxy mandelic acid, ACTH, adrenocorticotrophic hormone.

This table was adapted with permission from Freestone [3].

Amino Acid-Derived Hormones

These are commonly derived from dietary tyrosine and tryptophan, and comprise two main types: thyroid hormone such as thyroxine and the catecholamines dopamine, noradrenaline and adrenaline [5]. Catecholamines are well studied as they possess a diversity of signaling functions and are widely

distributed throughout the tissues and organs of the human body [5]. Noradrenaline and adrenaline are neurotransmitters but also play an integral role in the flight or fight response. In terms of the infection significance of catecholamine release, the field of psychoneuroimmunology has long reported that stress hormone elevations in humans and animals increases their risk of developing an infection. This is in part due to

stress-released catecholamine and glucocorticoid hormones reducing the functionality of the immune system [6,7]. More recently, Microbial Endocrinology studies have shown that like immune cells many bacteria involved in human infections recognize catecholamines which they appear to use as an indicator that their host is stressed, and possibly less able to mount a defense to the invading microbe [3,4]. Table 1 shows the catecholamine-responsive microbes that have been identified so far. Most analyses of bacterial stress hormone interactions have looked at growth effects using serum- or blood-based culture media, chosen to more closely reflect the host environment in which the hormone will be encountered [40]. Blood or serum containing media is iron limited due to the presence of ferric iron sequestering proteins such as transferrin or lactoferrin which inhibits the growth of most bacterial pathogens [41]. Because iron is so essential for the *in-vivo* growth of bacteria [42], its limitation by transferrin and lactoferrin represents a key immune defense against infection. However, bacteria can directly use catecholamines as a kind of siderophore to steal transferrin and lactoferrin Fe which enables up to 100,000-fold increases in bacterial cell numbers in what normally should be highly bacteriostatic host tissue fluids [14,15,18,23].

Dopamine, noradrenaline and adrenaline exposure can also induce pathogenic bacteria to become even more virulent by inducing expression of genes in toxin release [43], increasing biofilm formation [18] and enhancing attachment to host epithelial tissues [16,17]. Catecholamines can even catalyze recovery of bacteria severely damaged by antibiotic treatment [18,27], and rapidly promote exchange of genetic material between different bacterial species [44]. In terms of the infection significance of catecholamine-microbe interactions, catecholamines are used therapeutically in acutely ill patients to maintain heart and kidney function [5]. Catecholamines at the levels infused down intravenous catheter lines were found to massively increase staphylococcal biofilm formation on the same plastic, while clinically attainable levels of catecholamines also increased *P. aeruginosa* biofilm formation on endotracheal tubing (used to maintain an open airway in ventilated patients) as well as enabling the pathogen to resist antibiotic treatment [18].

Peptide and Protein Hormones

There are reports of peptide-like hormones affecting the infectious potential of pathogenic bacteria. Melioidosis is an infectious disease caused by the Gram-negative bacterium *Burkholderia pseudomallei*, which tends to be found in soil and water of tropical climates such as Vietnam and parts of Australia. It has been observed that type I diabetes mellitus is an apparent risk factor for the development of the septicemic form of melioidosis [20]. Woods and co-workers found that *B. pseudomallei* can directly bind human insulin and that each bacterial cell expressed around 5000 surface-associated insulin receptors. Woods et al. [31] showed that insulin inhibited the growth of *B. pseudomallei* and suggested that the deficiency

of the hormone at least in part explained the higher risk of melioidosis in insulin-dependent diabetics [31].

Adrenocorticotrophic hormone (ACTH) is a peptide hormone that induces the adrenal cortex to produce corticosteroid hormones such as cortisol which contribute to regulation of systemic glucose levels. It is therefore interesting that Schreiber and Brown found that exposure to ACTH increased attachment of *E. coli* O157:H7 to gut epithelia, though the underlying mechanism for this response is not clear [39]. Thyrotropin is a pituitary hormone that induces the thyroid gland to produce thyroxine followed by triiodothyronine which stimulates oxidative respiration and organ development. Interestingly, use of radiolabelled thyrotropin has showed the presence of receptor for thyrotropin in *Yersinia enterocolitica* [45,46]. The thyrotropin specificity of the *Y. enterocolitica* binding activity was similar to that of the thyrotropin receptor in human thyroid tissue. This binding activity is thought to have implications for Graves' disease, which is an autoimmune disease in which thyroid-stimulating antibodies to the thyroid-stimulating hormone receptor mimic thyroid-stimulating hormone, which activates the receptor leading to hyperthyroidism. Thyrotropin binding sites on have been shown to be recognized by antibodies from humans with Graves' disease, and prior infection by *Y. enterocolitica* has been implicated in the pathogenesis of Graves' disease [46]. The outer membrane porins Omp A,C and F have been identified as the *Y. enterocolitica* targets recognized by Graves' patient antibodies, though their role in contributing to development of Graves' disease remains to be shown [47].

Candida albicans is a dimorphic opportunistic fungal pathogen of females and the immunocompromised which has been shown to interact with several human peptide hormones. Luteinizing hormone is required for ovulation and the formation of a corpus luteum in the female menstrual cycle. *C. albicans* has been shown to bind human luteinizing hormone and chorionic gonadotropin [36]. Bramley et al. [36] used (125I)-labeled luteinizing hormone and chorionic gonadotropin to demonstrate the presence of specific binding sites for both hormones in *C. albicans*, and *C. tropicalis* [36]. The binding activity was found to be highly specific and was not surface associated instead being at greatest levels in microsomes and cytoplasmic fractions. Also, of considerable relevance to *C. albicans* infectivity, interaction with the luteinizing hormone was found to stimulate germination of *Candida* spores and germ tube formation [32].

Cholesterol-Derived Hormones

Cholesterol is the chemical basis of steroid hormones such as oestrogen, progesterone and testosterone which regulate aspects of the metabolism, tissue differentiation and reproductive cycles of females and males. Investigations from a variety of researchers have shown that exposure of some bacteria and fungi to steroid hormones can elevate infection risk in certain patient groups. For instance oestrogen have been shown to increase the likelihood of urogenital infections, particularly during

pregnancy, or in women taking high oestrogen contraceptives or hormone replacement therapy [38]. *Chlamydia trachomatis* is an important sexually transmitted pathogen, especially in young women; Sonnex [38] reported that treatment of *C. trachomatis* with physiological levels of oestrogen increased infection of human endometrial cells, and enhanced Chlamydia colonisation of female mice. *C. trachomatis* infection of female mice was also increased following pre-treatment with progesterone. *C. albicans* is a major source of fungal infections in women of reproductive age [38] which has been shown to possess an oestrogen binding protein of high affinity and specificity [32,33,34]. Contact with oestrogen has been reported to increase *C. albicans* growth as well as its infectivity, causing the yeast to shift into to a more invasive hyphal morphology [33]. Tarry et al. [34] showed that *C. albicans* vaginal colonization in a rat model of infection was increased over 8-fold when a physiological level of oestrogen was present [38]. Banerjee et al. [35] investigated the effects of progesterone on *C. albicans* gene expression and found that expression of 99 genes was differentially affected by the hormone. Most changes were metabolism associated such as protein synthesis and cellular transport. Of relevance to infection risk was the finding that expression of virulence associated genes such as those involved in hyphal induction, pathogenesis and multi-drug resistance genes were significantly increased in progesterone-treated *Candida* [48-50].

Conclusion

The effects of endogenous hormones on mammalian cell are well understood, yet although microbes within the human body will repeatedly encounter their host hormones the biological significance to the host of these interactions is only now becoming apparent. This review examined only a few of the many hormones within the human body, but still revealed that there are considerable health implication for some of the microbe-hormone encounters. Table 1 revealed that the most extensively studied area of microbial endocrinology is catecholamine-related, largely because of the long held view of stress increasing infection risk. However it is clear that other types of contact the human microbiota may have with mammalian hormones has health implications. It will be interesting to discover if additional signals within our hormonal milieu are being sensed by the thousands of other species of microbes we host.

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