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Review article

Anaerobes in human infections (dental/oral infections)

Stress hormone epinephrine (adrenaline) and norepinephrine (noradrenaline) effects on the anaerobic bacteria

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A B S T R A C T

Microbial endocrinology is a relatively new research area that already encompasses the anaerobes. Stress hormones, epinephrine and norepinephrine, can affect the growth of anaerobic bacteria such as *Fusobacterium nucleatum, Prevotella* spp., *Porhyromonas* spp., *Tanerella forsythia* and *Propionibacterium acnes* and can increase virulence gene expression, iron acquisition and many virulence factors of some anaerobic species such as *Clostridium perfringens, Porphyromonas gingivalis* and *Brachyspira pilosicoli.* Epinephrine and norepinephrine effects can lead to a growth increase or decrease, or no effect on the growth of the anaerobes. The effects are species-specific and perhaps strain-specific. Discrepancies in the results of some studies can be due to the different methods and media used, catecholamine concentrations, measurement techniques and the low number of strains tested. Biological effects of the stress hormones on the anaerobes may range from halitosis and a worsening of periodontal diseases to tissue damages and atherosclerotic plaque ruptures. Optimizations of the research methods and a detailed assessment of the catecholamine effects in conditions mimicking those in affected organs and tissues, as well as the effects on the quorum sensing and virulence of the anaerobes and the full spectrum of biological consequences of the effects are interesting topics for further evaluation.

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1. Stress and stress hormones

Stress is commonly described as experiences of physiological or psychological challenges [1]. There is a wide range of stressors in life, which can be physical (e.g., radiation, cold and heat), psychological (like fear), social (e.g., death of a partner) or disease-related (e.g., a hemorrhage or hypoglycemia) [2].

Exposure to stress elevates sympathetic nervous system activity and excites chromaffin cells of the adrenal medulla, thereby leading to an increased release of neuroendocrine hormones called catecholamines such as epinephrine (adrenaline), dopamine, and norepinephrine (noradrenaline) [3,4]. The catecholamines are nitrogen-containing organic compounds derived from the amino acid tyrosine and possess a benzene ring with two hydroxyl groups and a terminal amine side chain [5].

Normal epinephrine and norepinephrine concentrations in plasma are 0–900 pg/mL and 0–600 pg/mL, respectively, although the usual plasma concentrations most often are 23–85 pg/mL of epinephrine and 176–386 pg/mL of norepinephrine [4,6–8]. However, during or following stress, the catecholamine levels rise very sharply (often 5- to 20-fold) [8]. Concentrations of 177 pg/mL of epinephrine and 578 pg/mL of norepinephrine were found in patients undergoing endotracheal tube and proseal laryngeal mask airway [7]. In patients with postoperative pain, the epinephrine concentration was 235 pg/mL and that of norepinephrine reached 1084 pg/mL [9]. In patients with severe traumatic brain injury undergoing a "neurological wake-up test", the levels of epinephrine and norepinephrine increased to 750 and 2800 pg/mL, respectively [10]. Notably, under severe stress conditions, the norepinephrine levels in plasma can reach high values (9.24 μM = 1.6 μg/mL), [1].

In vivo catecholamine concentrations in some organs and tissues are, however, difficult to measure accurately. For instance, in the intestinal tract, several factors such as different catecholamine contents in foods and fast enzymatic changes of the stress hormones impede the accurate measurement of their levels [1]. In one study, the salivary norepinephrine levels (approximately 0.1 pmol/mL in healthy volunteers) did not parallel those in serum, but showed a 10-fold increase under stress conditions [11]. Therefore, for studies on periodontal bacteria, the lower catecholamine concentrations appear to be more relevant than the higher concentrations.

On the other hand, catecholamines have been used therapeutically. Norepinephrine and dopamine have been recommended as first-line vasopressor drugs in septic shock, and epinephrine has been included in the second-line agents [12,13]. Epinephrine is also used in dentistry practice as a component of local anesthetics for dental analgesia. For instance, epinephrine hydrogen tartrate is incorporated in Xylocaine and epinephrine is used in Ultracaine DS [14].

In the human organism, catecholamines affect almost all tissues, exert many important cardiovascular, metabolic, endocrine and neuronal effects, and affect the intestinal barrier and the immune system [3]. For example, chronic stress induces a shift from T helper 1-linked cellular immunity toward T helper 2-linked linked humoral immunity, thereby changing the infection course [15]. However, microbes, including anaerobic bacteria, can also respond to human stress hormones, and these responses are the subject of a relatively new research area.

2. Microbial endocrinology and some aerobic/facultative bacterial species

In 1992, Lyte and Ernst [16] evaluated stress hormone effects on bacterial growth and introduced the "microbial endocrinology" term, thus indicating the bi-directional interplay between microbes and human neuroendocrine factors. Microbial endocrinology is a relatively young scientific area as, for many decades, catecholamine activities have been associated only with the host's immune response and vasoconstriction, with no attention to the direct effects on the bacteria [17], including the anaerobes.

Interkingdom signaling involves a hormonal communication between the bacteria and the human host. Several bacterial species in the gut use two bacterial adrenergic sensors: the membrane-bound histidine kinases, QseC and QseE, to sense the host hormones epinephrine and norepinephrine. QseC also detects the bacterial signal autoinducer-3 produced by both the host and the intestinal bacteria [18]. Strikingly, the bacterial stress hormone receptor and a global regulator, QseC, can modulate the expression of many (>400) genes, including virulence, metabolic and stress response genes, in enterohemorrhagic *Escherichia coli* [18].

Quorum sensing is a crucial mechanism of bacterial cell-to-cell signaling, allowing the bacteria to respond to autoinducers and thus to change their gene expression [19]. In several bacterial species such as enterohemorrhagic *E. coli*, the QseC quorum-sensing sensor kinase has been associated with changes in bacterial motility as well as with virulence gene activation [19–21]. Epinephrine sensing of *Salmonella enterica* serovar Typhimurium has been linked to induction of metal transport systems and reduced resistance to antimicrobial peptides and stress responses [20].

Some stress hormones such as norepinephrine can be used as siderophores by some bacteria and, moreover, the hormones can change bacterial outer surface proteins and cytotoxic activity [14]. Epinephrine can up-regulate the gene encoding for superoxide dismutase and can enhance *S. enterica* susceptibility to polymyxin B [20].

By modifying bacterial motility, growth, quorum sensing, virulence and biofilm formation of some aerobic/facultative bacteria such as *E. coli*, *Salmonella* spp. and *Pseudomonas aeruginosa*, the catecholamines can modify the course and the outcome of associated infections [15]. Some authors did not find any antimicrobial activity of commercially prepared epinephrine or norepinephrine products against various species of aerobic/facultative bacteria and fungi [12]. Nevertheless, according to other authors, *Staphylococcus aureus*, coagulase-negative staphylococci, many species within the family Enterobacteriaceae, involving *E. coli*, *Salmonella, Shigella, Proteus, Citrobacter* and *Yersinia* spp. as well as species of the genera *Helicobacter*, *Campylobacter* and *Listeria* have been found to be stress hormone responsive bacteria [1,5].

It has been reported that norepinephrine exerts a stronger growth enhancing effect on *P. aeruginosa, Klebsiella pneumoniae* and *E. coli* compared with epinephrine and that norepinephrine has a stronger growth enhancing activity on Gram-negative bacteria compared with some Gram-positive bacteria such as *Staphylococcus aureus* [22].

Nonetheless, the effect of catcholamines on the growth and virulence of anaerobic bacteria is not well evaluated.

3. Microbial endocrinology and anaerobic bacteria

The first study of the stress hormone activity on the growth of the anaerobes was published by Roberts et al. [23]. The authors observed different *in vitro* growth responses to epinephrine and norepinephrine in periodontal bacteria and suggested that *in vivo* composition of subgingival biofilms could change under stress conditions [23].

At present, there are a number of studies on microbial endocrinology of the anaerobic bacteria, mostly periodontal pathogens (see below). Some discrepancies in the results of the studies may be due to the dissimilar methods used, including differences in various