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The effect of stress on microbial growth

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Abstract

The neurophysiological response of an animal to stress involves the production of a number of stress-related neurochemicals including the catecholamines norepinephrine and epinephrine. It is generally believed that such neurochemicals belong exclusively to the animal kingdom and that any role such neurochemicals play in the infective process is largely confined to host physiology and immunology-related parameters. This, however, is wholly incorrect as many of the bacterial species that are known to cause infections possess the capacity to not only recognize neuroendocrine hormones produced by the host in response to stress, but also synthesize the very same neurochemicals. Given this, infectious microorganisms are capable of directly responding to the neurochemical outflow resulting from a stress event and initiating pathogenic processes. Although the neuroendocrine environment of the lung following a stress event is not fully understood, it most likely possesses abundant levels of stress-related neurochemicals due to its rich blood supply and rich noradrenergic tissue innervation. The ability of microorganisms to recognize and produce neurochemicals that can influence the host, known as *microbial endocrinology*, provides for a mechanistic basis with which to examine the ability of stress to influence health and susceptibility to disease.

Keywords: stress, bacteria, pathogens, microbial endocrinology.

Microbial endocrinology: intersection of microbiology and neurophysiology

The environmental factors within the lung that may influence the ability of bacterial pathogens to initiate and maintain an infective process are still incompletely understood. The recognition that bacteria possess the ability to both produce and recognize the very same neurochemicals that are present within the mammalian neurophysiological system strongly indicates that the commonly shared neurochemicals represent a mechanistic pathway by which these two kingdoms can interact. This intersection of mammalian neurophysiology and microbiology has been termed microbial endocrinology (Lyte, 2004, 2010).

The range of both hormone-like materials and the variety of microorganisms in which they have been identified are very large. For example, gamma amino butyric acid (GABA), which is the primary inhibitory neurotransmitter found in the mammalian brain and which possesses immunomodulatory properties (Song *et al.*, 1998; Bjurstom *et al.*, 2008; Bhat *et al.*, 2010), is produced in large quantities by a number of commensal and pathogenic microorganisms (Minuk, 1986; Guthrie *et al.*, 2000; Di Cagno *et al.*, 2010). Numerous other neurochemicals that are usually associated only with mammalian nervous and endocrine systems, such as histamine and acetylcholine, as well as the presence of the corresponding putative receptor, have also been demonstrated in various microorganisms (Roshchina, 2010). Interestingly, the catecholamine biosynthetic pathway that exists in bacteria is precisely the same as that which exists in animals; this has led to the theory that the acquisition of cell–cell signaling pathways in animals is due to late horizontal gene transfer from bacteria (Iyer *et al.*, 2004).

Investigators have debated the significance of such hormones in microorganisms for decades. The most widely accepted theory concerns the use of such hormones as a form of intercellular communication (Leroith *et al.*, 1986). Indeed, studies have shown that the growth of colonies of *Escherichia coli* involves a high degree of specialization of function by individual bacteria (Budrene and Berg, 1991) and presumably the need for some form of intercellular communication to accomplish this goal. This concept of microorganisms both producing and responding to endocrine hormones has been expanded to the realm of infectious disease and been termed microbial endocrinology (Lyte, 1993). According to a microbial endocrinology-based

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approach, microorganisms entering into a host, whether through an intravenous catheter, wound, lung or any other entry point, could utilize the endocrine hormones present within the host to serve as environmental cues by which they would sense their surroundings. The development of pathogenicity would then, in part, depend on the ability of the particular microorganism to respond to the type of endocrine hormonal environment that it encounters upon entrance into the host.

Stress and infection: the response of bacteria to stress-related neurochemicals

At its beginnings, the demonstration that the neurochemical outflow resulting from a stress event, namely the elaboration of the catecholamines norepinephrine and epinephrine, could *directly* affect the growth and expression of virulence-related factors in pathogenic bacteria was investigated in the gut-related pathogens such as *Yersinia enterocolitica, E. coli* and various *Salmonella* and *Shigella* species (Lyte and Ernst, 1992; Lyte *et al.*, 1996, 1997; Nguyen and Lyte, 1997). Other laboratories have noted the similar ability of stress-related neurochemicals not only to increase bacterial growth and virulence factor production (Rahman *et al.*, 2000; Belay and Sonnenfeld, 2002; Nakano *et al.*, 2007; Bearson *et al.*, 2008), but also to increase the rate of conjugative gene transfer between enteric bacteria, thereby increasing the evolution and adaptation of pathogens to new environments through, for example, transfer of drug resistance genes (Peterson *et al.*, 2011). From a historical viewpoint, it must be noted that the description of the ability of catecholamines to affect bacterial growth and virulence was noted as early as 1930 (Renaud and Miget, 1930), although the prevailing thought was that such ability must be due to inhibitory effects on immune cells (Miles *et al.*, 1957). The possibility that the bacteria were directly interacting with the catecholamine was not envisioned until many years later (Lyte, 2004).

Stress and the bovine lung

The lungs are extensively innervated by nerves belonging to the autonomic nervous system (ANS). For example, adrenergic and cholinergic components of the ANS have been demonstrated to extensively innervate pulmonary tissue in the pig (Wojtarowicz *et al.*, 2003). The ANS innervation serves a number of functions in the regulation of normal pulmonary homeostasis such as control of smooth muscle tone, secretion of mucus from submucosal glands and blood flow within the lungs themselves (Belvisi, 2002). Although there is understandably a large body of literature on ANS-related receptors in the human, and the relevance of these receptors to treatment of a number of pulmonary-related disease states, there is little knowledge of the neural innervation of the bovine lung, and correspondingly few if any reports of the neuroendocrine environment within the bovine lung following a stress-related event. Given the extensive blood flow in the lung as well as the abundant noradrenergic innervation, it can reasonably be assumed that stress-related events result in release of substantial amounts of catecholamines within the lung space that are available to interact with any bacterial pathogens that might also be present. One study which indicated that this would indeed be the case was performed in sheep where endotoxin-mediated injury to the lung resulted in elevated plasma levels of both norepinephrine and epinephrine, presumably originating from the lung space (Hofford *et al.*, 1996).

If concentrations of catecholamines such as norepinephrine are indeed elevated within the stressed lung, it is likely that they contribute to the infective process by directly interacting with bacterial pathogens. Anderson and Armstrong (2008) have shown that the *in vitro* growth of the respiratory pathogen *Bordetella bronchiseptica* is greatly increased in the presence of norepinephrine and that this ability is, in part, mediated by the ability of norepinephrine to increase acquisition of transferrin-bound iron by *B. bronchiseptica*. That the interaction of stress-related neurochemicals with the bovine lung may be an area worth investigating can best be seen in a study which examined the interaction of the *Mycoplasma hyopneumoniae* with norepinephrine. Global transcriptional analysis of *M. hyopneumoniae* following exposure to norepinephrine revealed numerous changes with the overall pattern of up-regulation of protein expression and down-regulation of general metabolism (Oneal *et al.*, 2008).

In conclusion, considering that microbial endocrinology-based interactions between host and pathogen are well recognized across a wide spectrum of clinical-related infections (Lyte *et al.*, 2003), it may be of scientific merit to investigate the role of these interactions in the development of bovine lung infections.

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