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How Does Stress Affect the Immune Response?

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It has been well established that the immune and neuroendocrine systems interact and communicate with each other, a relationship that contributes to the regulation of cell-mediated and humoral responses [1-4]. The effect of stress on immune responses has been noted for centuries; observations that psychological stress influences the body's ability to respond to infection and the recovery from wounds in battle have been recorded throughout history. Recently, short-term stress has been shown to enhance immune responses whereas long-term stress leads to suppression. Although the mechanisms responsible for these observations have still not been fully elucidated data from this laboratory indicate that molecules produced in response to stress may play a major role. More surprisingly, it appears that the active moieties are extremely small peptides cleaved from larger neuroendocrine molecules.

Recently it was recognized that the neuroendocrine system and immune cells produce peptide hormones, which interact through shared ligand receptors [1,5-6]. These bidirectional molecules include endogenous peptide opioids, such as endorphins and enkephalins, which function as natural analgesics [2,7]. A lthough the enkephalins share amino acid homology with the endorphins and dynorphins (i.e. the first five amino acids of β-endorphin are identical to methionine-enkephalin; the first five amino acids of dynorphin A are identical to leucine-enkephalin), these molecules are though to be derived from different precursors. Thus, β-endorphin and several other bioactive peptides including adrenocorticotropic hormone (ACTH), lipotropins and melanotropins are derived from pro-opiomelanocortin (POMC), a product of the pituitary and the hypothalamus [8,9]. The dynorphins are derived from prodynorphin, also a pituitary hormone [10,11]. The enkephalins (methionine enkephalin, Tyr-Gly-Gly-Phe-Met and leucine-enkephalin, Tyr-Gly-Gly-Phe-Leu), are derived from proenkephalin A and are thought to be synthesized at various locations including the adrenals [2,7,8]. It was also discovered that immune cells could also produce β-endorphin, dynorphins and enkephalins [9,12,13].

Several investigations have shown that endogenous peptide opioids, such as endorphins, dynorphins and enkephalins, are capable of modulating immune activities *in vivo* and *in vitro* [1,2,14-19]. Reports describing many of these immunomodulatory effects have been conflicting in that some show only dose-dependent suppression whereas others describe dose-dependent enhancement of the same function [20-23]. In some cases, a biphasic response was observed in the same system, the resultant response dependent on concentration - for example lower concentrations of the enkephalins enhanced while higher concentrations suppressed the activity or function [23-32].

Data from this laboratory has demonstrated that methionine-enkephalin (met-enkephalin, Tyr-Gly-Gly-Phe-Met [YGGFM]) and certain of its peptide derivatives (Tyr-Gly-Gly [YGG] and Tyr-Gly [YG]) modulate immune responses in a biphasic manner with suppression at high doses and enhancement at low concentrations. These data showed *in vivo* (via delayed-type hypersensitivity responses, [33] and *in vitro* (via cytokine production, [34]) that met-enkephalin, YGG and YG modulated immune responses in a concentration-dependent biphasic manner without affecting the overall number of cells. Met-enkephalin, YGG and YG modulated the production of IFN-γ biphasically. Furthermore, at higher concentrations met-enkephalin and YG suppressed the production of IL-2 and IL-4. The di- and tri-peptides showed a higher specific activity than the parent molecule with YG being the smallest active moiety: Tyr alone did not show activity although the terminal Tyr was required on the peptide since GGFM [des-tyr met-enkephalin] was inactive. We initially proposed that met-enkephalin must be cleaved to YG to be active since we had found YG and YGG were more potent than met-enkephalin in immune enhancement. However, we subsequently found that an analog of met-enkephalin resistant to peptidase activity (D-Ala_2, D-Met enkephalin [DADME]) enhanced responses in our system but did not induce suppression at any concentration. Thus, while cleavage of YGGFM to YG may be required for induction of immune suppression it is not required for immune enhancement. Naloxone (an opioid receptor antagonist) only blocked the enhancing effects of met-enkephalin and not the suppressive ones. Thus, it appears that binding to classical opiate receptors is involved in the initiation of enhancement by met-enkephalin while cleavage to YG and an unidentified, nonopioid receptor may be associated with suppression.

This is consistent with negative feedback such that when the concentration of YG rises to sufficient levels, a suppressor mechanism is stimulated to down regulate immune responses. The nature of this suppression is yet to be elucidated. The following model/hypotheses is proposed to account for these observations:

- Neuroendocrine cells produce met-enkephalin (either directly or via cleavage of β-endorphin) in response to stress. During immune stimulation lymphoid cells also produce met-enkephalin.
- Low concentrations of met-enkephalin enhance the immune response possibly via modulation of an inflammatory type 1 response. This effect appears to be mediated by classical opiate receptors (most likely δ) on T cells.
- Met-enkephalin is cleaved into YGG and YG by proteases present in serum or via membrane-bound ectoenzymes on cells; YGG is further cleaved to YG. At low concentrations, YG continues to stimulate type 1 responses possibly through unidentified, nonopioid receptors.
- As the level of YG rises, a feedback mechanism is initiated that suppresses the immune response (cytokine-mediated/regulatory cell-mediated?).
- The activity of YG and the other bioactive molecules is then curtailed by cleavage of the terminal Tyr by membrane-bound or secreted aminopeptidases.

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Because others have shown that stress stimulates the endogenous synthesis and release of opioid peptides our data could thus provide a mechanism for understanding why immune responses in highly stressed individuals have frequently been found to be lower than in their unstressed counterparts. It also explains why short-term stress is associated with enhanced immunity. Further understanding of how opioid peptides are able to modulate the immune system may provide a basis for monitoring the endogenous immunomodulatory parameters of patients, enhancing immune reactions that are suppressed (such as due to stress) and suppressing those that are deleterious (such as allergic or inflammatory responses). Additionally, these studies may identify a novel immunoregulatory mechanism heretofore unrecognized and given that the enkephalins are conserved throughout nature, it may represent one of the oldest means of regulating immune responses in phylogeny.

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