The Stressed Gut: The Depressed Brain : The Immune Link

Michael Ash BSc (Hons) DO, ND, Dip ION
Fellow of The Royal Society of Medicine

The gastro intestinal tract is a long tube from mouth to anus that in effect exists within our bodies and yet its contents are excluded in a time and content sensitive manner from our inner being. Its principle roles are the digestion and absorption of our foods, the management of an ecologically co dependant community of bacteria and the development and maintenance of the mucosal immune system - the largest collection of immune tissues in the body.

The mucosal barriers of our body are not simply the first line of defence; they are also the site of greatest clinical opportunity to influence physical and mental health. Over thousands of years the bacteria that co exist with the host have developed highly specialised skills to survive and modify the hosts health through altering gene expression and function. This mutuality relationship is the most dynamic and least understood aspect of integrated health care

The largest mass of immune tissue is present in the Gastro Intestinal Tract (GIT), where it is exposed to exogenous antigens at the rate of up to 1 ton per year; as such it has to be able to meet a vast array of potentially provocational antigens with an appropriate and controlled response. Problems with the gastrointestinal immune system normally result in a change or loss of mucosal tolerance and a subsequent up or down regulation of key immune responses.[1] The overall effect is to induce altered inflammatory chemical output.

The Mucosal Immune System

Is the area of most concern for this short review, so a summary of its sections may prove to be helpful. The small intestine is the tissue where the greatest volume of exchange between the contents of the gut and the mucosa, lamina propria and the gut associated lymphoid tissue (GALT) takes place.[2]

The lamina propria is home to specialised plasma cells and many other immune system components. The GALT actually contains a greater number of immune cell elements than all of those contained in the bone marrow, spleen and lymph nodes combined.[3]

Embedded within and also lying below the lamina propria are the Peyers Patches, these act as specialised filtration systems where Microfold cells direct microbial specimens for assessment and ultimate inactivation by macrophages. Then T (thymus) cell derived lymphocytes identify specialised patterns on the organism using a sampling system called Toll Like Receptors (TLR). This information is passed to the nieve T cells for activation and or to the beta cells which will cause them to develop into plasma cells; these then migrate to various mucosal tissue sites in the body, including the GIT, Lungs and Genitourinary Tract.[4]

Induction via these plasma cell leads to the greatest secreted immune protein in the body called Secretory Immunoglobulin A being released which then migrates to the surface acting as a three point intervention immune substrate and immune modulator.

This fluid will inhibit adhesion by unwanted microbes, ‘if there is no adhesion there is no inflammation’. Pro inflammatory cytokines such as Tumor Necrosis Factor Alpha (TNFa) and Interleukin 1,6,8 are not activated (cytokines) and tolerance is achieved.

This immune response is an elegant surveillance mechanism that is finely tuned in a series of cascade cellular events whose ultimate goal is to protect the organism from foreign substances, such as bacteria and viruses. The discovery of the small protein

molecules known as cytokines (e.g., interleukin-1 and interleukin-2), which are elaborated by different types of white blood cells, has allowed for further understanding of how the immune response is structured and coordinated.

Cytokines from the body's immune system can send signals to the brain via several mechanisms, including crossing the brain-blood barrier via the bloodstream. This permeability is essential for communication with brain areas. Cytokines can attach to their receptors in the lining of blood vessels in the brain and stimulate the release of secondary chemical signals in the brain tissue around the blood vessels.

Cytokines can also signal the brain via direct nerve routes, (e.g., the vagus nerve) and a multitude of connections with abdominal organs result. The activation of the brain by cytokines from the peripheral parts of the body induces the behaviors of anxiety depression, mood changes and cautious avoidance associated with the stress response's principle activity - maintaining the organism's integrity during recovery from stressful activities or from traumatic injury.[5]

The "brain-gut axis"

Describes the bi-directional neural pathways linking cognitive and emotional centres in the brain to neuroendocrine centres, the enteric nervous system, and the immune system, and plays a major role in the concept of a frequently encountered functional gastro intestinal problem called Irritable Bowel Syndrome (IBS).[6] IBS is associated with visceral hypersensitivity and with a high co-occurrence of psychiatric symptoms, in particular affective dysregulation.[7 8 9]

The scientific evidence emerging over the past several decades strongly suggests that psychosocial factors from emotional states that include depression and behavioral dispositions ranging from hostility to psychosocial stress can directly influence both physiologic function and health outcomes.[10]

Intimately involved inflammatory responses are modulated by a bidirectional communication flow between the neuroendocrine and immune systems and the brain. Many lines of research have established multiple pathways by which the immune system and the central nervous system communicate. Hormonal and neuronal mechanisms by which the brain regulates the function of the immune system and, conversely, cytokines, which allow the immune system to regulate the brain, provide the basis for mind-body medicine modalities such as relaxation and meditation that impart a positive influence on homeostatic balance.

In a healthy individual this bi-directional regulatory system forms a negative feedback loop that keeps the immune system and central nervous system in homeostatic balance. Changes to these regulatory systems have been postulated to potentially lead to overactive immune response, inducing inflammatory disease and disorders including disturbances to the psyche, or over suppression of the immune system and increased susceptibility to infectious disease.[11 12 13]

The Gastro Intestinal Tract and Mood

Most of us have experienced at first hand the effects of stress on our digestive systems. As early as 1833, Beaumont [14] described that fear and anger influenced acid secretion from the stomach of his patient Alexis St. Martin, a Canadian trapper with a permanent gastric fistula caused by a gunshot wound. The impact of psychological, physical, and immunological stressors on gastrointestinal secretion, motility, epithelial permeability, and inflammation is now thoroughly documented, and stress has a major influence on digestive diseases.

As the site of greatest immune tissues, disturbances to the eco system, loss of tolerance and immune anergy can lead to the production of pro inflammatory cytokines.

The physiological and psychological effects of immune activation (collectively termed

sickness behavior) is then mediated by cytokines derived from activated immune and other cells. [15 16 17]

Most immune challenges produce their initial effects in the periphery, but information regarding their presence is almost immediately transmitted to the brain, in a sensory-like process. Within the brain, this immune-related information activates several areas, and induces glial cells and neurons to release cytokines, such as interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α), which serve as neurotransmitters and neuroregulators. [18].

Nuclear factor-kappa B (NF-κB)

Is a transcription factor that resides in the cytoplasm of every cell and translocates to the nucleus when activated. Its activation is induced by a wide variety of agents including stress, cigarette smoke, viruses, bacteria, inflammatory stimuli, cytokines, free radicals, carcinogens, tumor promoters, and endotoxins.

On activation, NF-κB regulates the expression of almost 400 different genes, which include enzymes (e.g., cyclooxygenase (COX-2), 5 Lipoxygenase (5-LOX), and Inducible Nitric Oxide (iNOS), cytokines (such as TNFa, IL-1, IL-6, IL-8, and chemokines), adhesion molecules, cell cycle regulatory molecules, viral proteins, and angiogenic factors. The constitutive activation of NF-κB has been linked with a wide variety of human diseases, including depression, asthma, atherosclerosis, AIDS, rheumatoid arthritis, diabetes, osteoporosis, Alzheimer's disease, and cancer.

Several agents are known to suppress NF-κB activation, including Th2 cytokines (IL-4, IL-13, and IL-10), interferons, endocrine hormones, phytochemicals, corticosteroids, and immunosuppressive agents. Because of the strong link of NF-κB with different stress signals, it has been called a "smoke-sensor" of the body.

Serotonin

Is a widespread neurotransmitter formed by hydroxylation and decarboxylation of the dietary amino acid tryptophan. Approximately 2% of the body's serotonin resides in the brain, 2% resides in the platelets, and the majority of the remainder resides within the enterochromaffin cells (EC cells) of the gut. Neuroendocrine (NE) cells are found in a majority of the body organs. In the gastrointestinal (GI) tract, (EC) constitute the largest NE cell population and they are distributed from the cardia (The gastric cardia is the uppermost part of the stomach that connects the bottom of the esophagus to the stomach to the anus).

Cytokines

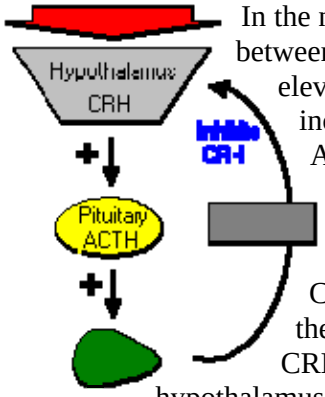
The suggestion that the immune system may play a role in the etiology of certain psychiatric disorders including depression is an old one, first suggested by Wagner-Jauregg in 1887, and for which he won the Nobel Prize in 1927.

The discovery that cytokines affect the central nervous system in major depression is a significant opportunity for cytokine mediated anti depression therapy. Many of the symptoms of depression mirror those of cytokine-induced sickness behavior, including fatigue, anorexia, anhedonia, and withdrawal from social situations. Cytokines contribute to the development and/or maintenance of major depression via a multidimensional route.

First, IL-6, and in some models IL-1 and TNFa, appears to be increased in persons exposed to chronic stress, including emotional stress (Watkins and others 1999).

Second, IL-1 and IL-6 have been shown to stimulate the secretion of CRH from the hypothalamus. Corticotrophin Releasing Hormone (CRH), in turn, stimulates the anterior pituitary secretion of Adrenocorticotropic hormone (ACTH) and ultimately cortisol from the adrenal cortex (Turnbull and Rivier 1995; Sternberg and Gold 1997). These hormones of the

hypothalamic-pituitary-adrenal (HPA) axis are associated with anxiety and mood swings (Sternberg and Gold 1997; Angeli and others 1999). Depression has been suggested to develop as a result of dysregulation of the CRH-ACTH-cortisol negative feedback cycle.



In the normal feedback cycle between these hormones, elevated CRH leads to increased production of ACTH, which in turn stimulates the adrenal gland to produce cortisol. Cortisol then inhibits the further release of CRH from the hypothalamus. Elevations in the pro-inflammatory cytokines have been suggested to disrupt this feedback cycle by down-regulating the receptors for cortisol on the hypothalamic cells (Dantzer and others 1999; Maes 1999; Miller and others 1999), resulting in elevated CRH in spite of elevated cortisol.

Interleukin-1 also has been implicated in interfering with the production of the neurotransmitter serotonin in the brain (Ramamoorthy and others 1995; Licinio andWong 1999). Serotonin is an important neurotransmitter, the lack of which is known to contribute to the development of depression.

How to mitigate adverse immune activation of the mucosal tissues and down regulate the production of pro inflammatory cytokines to reduce inflammation induced depression and sickness behaviour.

Complementary and Alternative Approaches

Enthusiasm for CAM use and research is clearly growing. Medline citations for alternative medicine have steadily increased from 69 citations in the 1970s to 423 citations since 2000. Unfortunately, a growing percentage of these articles are reviews, rather than original research (20% reviews since 2000 compared with 10% in 1970–1979). However whilst the traditional prejudices against CAM therapies begin to decline, the major obstacle to these studies still remains one of funding.

The development of the National Center for Complementary and Alternative Medicine at the National Institute of Health has increased such funding in the USA, with a budget of over 100 million dollars in 2005. Other government and private foundations such as the Kings Trust are increasingly investing in CAM research, although the proportion of gastrointestinal research funding dedicated to CAM is quite small.

In addition to overcoming economic barriers, collaboration of gastrointestinal physiologists, researchers, and clinicians with experienced CAM providers internationally will be necessary, particularly in the areas of nutrition, microbiology, immunology, acupuncture, Chinese herbal medicine, Ayurvedic medicine, and other traditional practices.

"Enthusiasm for CAM use and research is clearly growing"

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