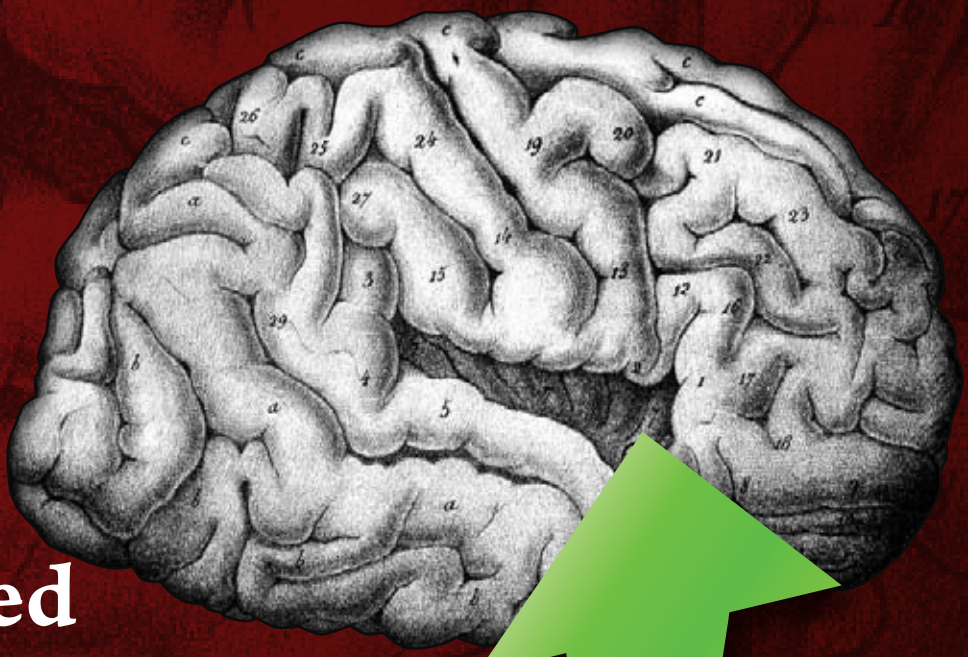
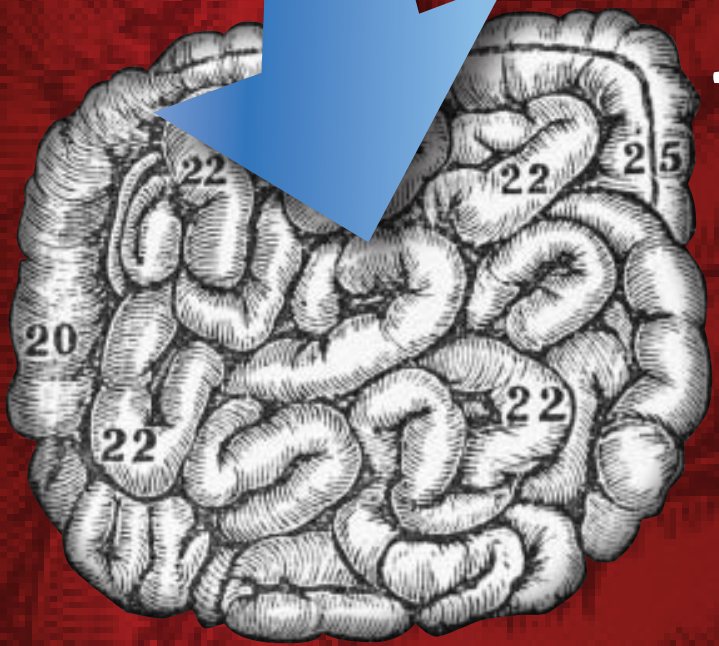


# The Stressed GUT

# [axis]

# The Depressed BRAIN



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# The Stressed Gut: The Depressed Brain:
# The Immune Link and the Gut Brain Axis

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***The human immune system, its response to triggers and its subsequent local and systemic impact on human function is an expanding area of research. The mucosal immune tissues represent the largest immune interface with the external world, which includes environment, food, bacteria and emotion.***

***As conditions as diverse as cardiovascular disease, inflammatory bowel disease and mental health are increasingly understood to be impacted upon by inflammation (cytokines), interest in the management of immune responsiveness is growing. The innate immune system whilst incapable of developing a memory and traditionally regarded as the unsophisticated arm is now understood to determine adaptive immune activity. The gastrointestinal tract represents the greatest area of interaction between the two components of immune function and natural therapeutics have a legitimate and effective role to play in this area for the management of human health.***

There have been increasing amounts of data published in last few years confirming and exploring the role of the immune system in the pathophysiology of depression and allied symptoms.[1] Whilst it is now well understood, if not yet universally recognised, that one of the downstream consequences of depression is an altered capacity and function of the affected individuals humoral and cellular immune systems.[2] Contemporary psychoneuroimmunology opinion has turned this concept upside down creating a paradigm shift; exploring the evolving model that depressive disorders can now be characterised as a set of symptoms driven by hyperactivation of the innate immune systems inflammatory responses.[3]

## Increased inflammation in depressed people.

This profound change has occurred as part of a collective information sharing amongst differing fields of investigative medical specialties, as inflammation has become inextricably linked to conditions such as cardiovascular disease, diabetes, neurodevelopmental problems and cancer.[4,5,6,7] This cross fertilisation is driven in part by the need to uncover the relationship between these medical illnesses and major depression.

The overarching discovery has been the comprehension that communication occurs between the immune, endocrine, autonomic and central nervous system and that immune activation, or the products of this activation – cytokines, profoundly influence neuroendocrine and central neurotransmitter processes.[8,9]

Cytokines are low molecular weight, soluble proteins produced by immunocompetent cells that then communicate with other cells to regulate innate and adaptive immune function. They act via specific receptors and depending on the particular cytokine and the cell it binds to they can up or down regulate the activity of other cells. There are in excess of 150 cytokines but a select few have been linked to altered mood state. These are IL6, IL1 and TNFα.[10,11,12]

Inflammation is the ***sine qua non*** of illness, so the proposal that proinflammatory cytokines may contribute to the 5 fold increase of risk of developing depression in the medically ill is understandable.[13] But there are also many presumed healthy individuals who present with depression. Psychological stressors are commonly cited as the initiating event and are known to induce proinflammatory cytokines. They may also

represent an amplifying trigger as may other events that induce an immunological change or affect microbial innate immune defenses, leading to persistent low level immune activation.[14,15] This in turn reactivates cytokine sensitive receptors of the limbic system sensitised from a prior stressor, inducing a change in psychological function referred to as 'sickness behaviour', single depressive events and mild depressive symptoms.[16,17]

Individuals have individual responses to inflammation and allied cytokine activation. This variation in responsiveness has been attributed to events such as in utero toxin exposure and post natal infections.[18] There are also gene related variations in cytokine sensitivity, where single nucleotide (SNP's) variations in individual gene pools have an effect on cytokine receptor sensitivity. Considered from a clinical perspective the large variation in activation and receptors as well as lifestyle differences (esp. sleep patterns)[19] and developmental events combine to provide a complex interface between the environment, microbiome and immune interactions.[20,21]

## Depression

Depression is a leading cause of disability worldwide.[22] It is the third most common reason for consultation in primary care.[23] The enhanced management of depression in primary care is central to the World Health Organisation strategy for mental health.[24]

Yet the precise definition of depression remains elusive and other than providing advantages to pharmacological intervention its increasing use as a 'defining condition' may prove to be an oversimplification of the multifactoral 'state of being'.[26] Increasingly the western societies suppose that if 'feelings' fall short of contentment and ease they simply become unacceptable and require remediation. In the mid 1980s research suggested that some 50% of people with depressive symptoms do not consult their medical practitioner, and even if they did the GP may not recognise the symptoms.[25] Since then the prescription practices of GPs seem to reflect an increasing willingness to recognise and or medicate their mood altered patients.

Classification of the depressive disorders has long been contentious, with three principle models argued for on the basis of the presumed number of types; one, two, and many.[26]

The binary model posited two principle types (i.e. "endogenous / psychotic" and "neurotic / reactive") and is perhaps a predictable combination, for as the American humorist Benchley observed, there are two classes of people in the world: - 'those who divide the people in the world into two classes and those who do not.'[27]

Nevertheless, it had its influential proponents, including St. Paul, who, according to Altschule,[28] determined two types of depression: one "from God" and the other "of the world".

In 1926, however, British psychiatrist Prof Edward Mapother argued that the long-standing binary distinction made in clinical practice was pointless because both "psychotic" and "neurotic" forms of depression lie along a continuum accordingly, he espoused the Unitarian position (i.e. there is only one type of depression, which varies by severity). [29]

In the latter part of the 20th century and up to now, there has evolved a regular use of the term 'depression' without qualification both by qualified professionals and lay people. In practice the term depression may now be used to describe a symptom or a full blown disorder and in general represents a cultural incorporation into a title of affects of energy, guilt, fatigue and stress.[30]

This is reflected in the significant and corresponding change in the prescribing figures for medications to treat. In Britain the prescription for Selective Serotonin Reuptake Inhibitors (SSRI's) rose from 9 to 21 million during the 1990s, mirroring somewhat the marketing and production of these medicines as well as the pervasive medicalisation of different mood states.[31]

This increased medicalisation of depression seems at odds with the UK guidelines for clinical care recommended by the National Institute of Clinical Excellence (NICE) as their guidelines do not recommend the use of anti depressants as a primary intervention in mild to moderate cases.[32]

Perhaps the application of SSRI's, which have their critics, has been driven by patients seeking assistance for alterations in affect that are not so clearly defined as depressive episodes, but for which the clinician has noted a symptomatic improvement following prescription, not because of the serotonin reuptake, but because of suppression of cytokine driven inflammation.[33,34]

This beneficial side effect of SSRI's would fit the evolving view which incorporates more sophisticated interactions within the body. In this view depression may be a component of 'sickness behaviour'[35] and that alterations in our immune function provide distinct levels of personality traits and disorders, of which sickness behaviour meets the broad distinctions and variations in mental health.[36]

'Sickness behaviour' involves a set of central responses to an immune challenger which has promoted the release of the proinflammatory cytokines IL-1, TNFά and IL6. These cytokines can impact on the hypothalamic pituitary adrenal (HPA) axis and induce symptoms. The characteristic symptom pattern of sickness behaviour comprises pyrexia, fatigue, somnolence, psychomotor retardation, anhedonia (lack of ability to experience pleasures such as eating and sex) and impaired cognitive functioning.[37, 38, 39] In other words the syndrome of sickness behaviour matches almost exactly the standard diagnostic descriptions of major depressive disorder.[40] The only apparent differences, that of somnolence and pyrexia can be explained, since daytime somnolence typically leads to secondary insomnia with nocturnal sleep disruption, and the presence of pyrexia has not yet been extensively evaluated in depression.[41]

Tempting though it may be to prescribe SSRI's in the hope that patterns of affect disruption may be targeted, SSRI's are not risk free and the clinical use of other agents or strategies with no or negligible risk, but similar modes of action and benefit are attractive.[42]

## Do your patients have the guts to be happy?

The gastrointestinal tract is a long tube from mouth to anus that in effect exists within our bodies and yet it's contents are excluded in a time and content sensitive manner from our inner being by a single columnar epithelial cells thickness. It's 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 lymphoid immune system – purportedly the largest collection of immune tissues in the body. These mucosal tissues, by virtue of their location are directly exposed to the external environment and challenged with antigenic loads consisting of commensal bacteria, dietary antigens, and viruses at far greater quantities on a daily basis than the systemic immune system faces in a lifetime.[43]

These mucosal barriers are not simply the first line of defence; they are also the site of greatest clinical opportunity to influence physical and mental health through the ingestion of foods and microbes. Over thousands of years the bacteria that coexist with our body have developed highly specialised skills to survive and modify our health through altering gene expression and overall function.[44] This mutual relationship is the most dynamic and least understood aspect of integrated nutritional health care.

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.[45] The overall effect is to induce altered proinflammatory chemical output.[46] This can result in chronic inflammatory conditions including autoimmune diseases, allergy, cancer and depression.[47]

## The Mucosal Immune System

Is the area of most relevance for this short review, so a summary of it's 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.[48]

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.[49]

Embedded within and also lying below the lamina propria are the Peyers Patches. These act as discrete filtration systems where Microfold cells (M Cells) direct microbial specimens for assessment and ultimate inactivation by macrophages. Then T (thymus) cell derived lymphocytes identify unique coded patterns on and in the organism using a highly specialised identification system called Toll Like Receptors (TLR).[50]

These codes, depending on their source material, are passed to the elaborate immune tissues in the mucosal immune system. Uniquely, this information may be assessed by either the cellular or humoral or both of these systems to determine a response. It is sent to the naive T cells for activation or to the beta cells which cause them to develop into plasma cells. These plasma cells then migrate to various mucosal tissue sites in the body, including the GIT, Lungs and Genitourinary Tract.[51]

Induction via these plasma cells leads to the release of the greatest secreted (60mg/Kg daily) immune protein in the body called Secretory Immunoglobulin A (sIgA). This then migrates to the apical surfaces acting as a three point intervention immune substrate and immune modulator held in mucins which act as an immunoglobulin reservoir, or washed away in peristaltic actions.

This protein is involved in mood management as an effector and affector of mood.[52] sIgA deficiency is also associated with food allergy/sensitivity and its absence or deficiency may have immunomodulatory effects on mood via food antigen stimulation.[53] It is also linked to alterations in the microbial eco system in the gastrointestinal tract, and may precipitate or participate in the ongoing production of proinflammatory cytokines but not via complement activation.[54]

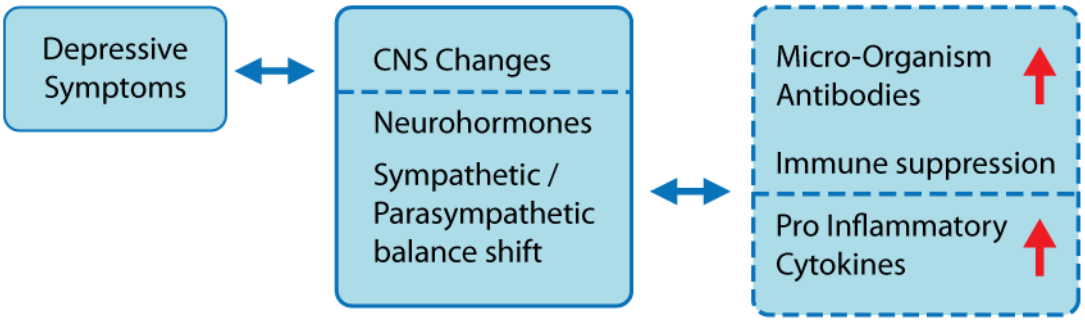
sIgA inhibits adhesion by unwanted microbes, 'no adhesion - no inflammation'. Proinflammatory cytokines such as Tumor Necrosis Factor Alpha (TNFa) and Interleukins-1, 6, 8 (cyto/chemokines) are not produced and tolerance is achieved. In addition there is increasing evidence that it helps to support a neutral immune response to commensals.[55]

In the face of constant immunological stimulation in the gastrointestinal tract there is an ongoing requirement for a homeostatic balance, which in its most essential form is an attempt to maintain the "constancy of the internal state" in response to perturbations resulting from environmental fluctuations. This is arguably the most acute in the gastrointestinal tract, which covers an area of approximately 100m2 and relies on a constant state of immunosuppression rather than activation to achieve this.[56]

## Cytokines

Cytokines from the body's immune system send signals to the brain via several mechanisms, including crossing the brain-blood barrier via the bloodstream. This permeability is essential for communication with the brain. Cytokines 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.[57]

Cytokines can also signal the brain via direct nerve routes, (e.g. the vagus nerve) and a multitude of connections with the abdominal organs result. The activation of the brain by cytokines from the peripheral parts of the body induces the behaviours 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.[58]




## The Brain-Gut Axis

The Brain-Gut Axis describes the bi-directional neural pathways linking cognitive and emotional centres in the brain to the neuroendocrine centres, the enteric nervous system, and the immune system.[59]

It plays a major role in the physiology of a frequently encountered functional gastrointestinal problem called Irritable Bowel Syndrome (IBS).[60] IBS is associated with visceral hypersensitivity and with a high co-occurrence of psychiatric symptoms, in particular affective dysregulation.[61,62,63]

The scientific evidence emerging over the past several decades strongly suggests that psychosocial factors, from emotional states such as depression and behavioural dispositions, ranging from hostility to psychosocial stress, can directly influence both physiologic function and health outcomes.[64]

Mediating this connectivity are the intimately involved inflammatory responses which in turn are modulated by their bidirectional communication flow between the neuroendocrine, immune systems and the brain. Many lines of research have established multiple pathways by which the immune system and the central nervous system communicate bidirectionally.[65]

The 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. These modalities can impart a positive influence on homeostatic balance.

In a healthy individual this bidirectional regulatory system forms a principley negative feedback loop that keeps the immune system and central nervous system in homeostatic balance, that is, it keeps it anergic and yet capable of immediate response.

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.[66,67,68]

## The Gastrointestinal Tract and Mood

Most have experienced at first hand the effects of stress on the digestive systems. As early as 1833, Beaumont 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.[69]

The impact of psychological, physical, and immunological stressors on gastrointestinal secretion, motility, epithelial permeability, and inflammation is now thoroughly documented, and stress is understood to have a major influence on digestive diseases.[70]

Stress has also long been implicated in the aetiology of psychiatric disorders. Alterations in immune system function have been suggested to play a role in the pathophysiology of psychiatric conditions such as major depression and anxiety.[71,72,73,74]

The ability of cytokines released in response to stressors to alter brain function and lead to depressive-like behaviours has implicated them in psychiatric diseases. [75,76,77] Experiencing stressful life events can exaggerate the release of proinflammatory cytokines to immune challenge? suggests the possible importance of cross-sensitisation in the aetiology of affective disorders.[78] It also adds to the understanding that prior stressful experiences sensitise individuals to future events.

As the gastrointestinal tract is the site of greatest immune tissues, disturbances to it's eco system, the loss of tolerance and immunological anergy will lead to the production of proinflammatory cytokines. The physiological and psychological effects of immune activation (collectively termed *sickness behaviour*) are then mediated by cytokines derived from activated immune and other cells. [79,80,81]

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 IL1 and TNF-α, which serve as neurotransmitters and neuroregulators. [82]

## Nuclear Factor Kappa B (NF-B)

NF-κB is a transcription factor residing in the cytoplasm of every cell and translocates to the nucleus when activated. It's activation is induced by a wide variety of agents including stress, cigarette smoke, viruses, bacteria, inflammatory stimuli, cytokines, free radicals, carcinogens, tumour promoters, and endotoxins. Of particular note for the gut-brain axis, is that pathogenic microbes initiate NF-κB activation and that dysbiosis, the loss of ecological microbial tolerance, is also implicated in activating NF-κB.[83]

On activation, NF-κB regulates the expression of almost 400 different genes involved in inflammation, 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.[84]

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. [85] In the brain NF-κB is known to alter socialisation and affect appetite, as well as reducing neuronal plasticity, reflecting patterns found in depressive's brains.[86,87]

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.[88,89,90]

Because of the strong link of NF-κB with different stress signals, it has been called a "smoke-sensor" of the body. In the management of conditions of mood the management and control of increased but inappropriate NF-κB production represents a therapeutic window due to its disruption of glucocorticoid receptors.[91,92]

## 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.

If the gut is under stress from a pathogenic microbe or from a loss of ecological balance, in an attempt to reduce the available stores of tryptophan being ingested as food by the bacteria, the body activates the enzyme Indolamine 2-3 dioxygenase, which degrades serotonin and tryptophan limiting nourishment but potentially contributing to depressive and anxiety states as well as cognition, memory appetite, sleep and body temperature disturbances.[93]

Neuroendocrine (NE) cells are found in a majority of the body organs. In the gastrointestinal (GI) tract, EC cells 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 and Depression

The suggestion that the immune system may play a role in the aetiology of certain psychiatric disorders including depression is not a recent discovery, it was seriously explored by Dr Wagner-Jauregg in 1887, for which he won the Nobel Prize in 1927. [94]

However, contemporary views on the mechanisms by which peripherally released cytokines can act on the brain to induce behavioural effects have been profoundly modified by the understanding that cytokine receptors are expressed in the brain.[95] Also, that administration of cytokine receptor antagonists annuls the central effects of peripherally administered cytokines.[96] These findings have been complemented by the demonstration of the existence of a central cytokine compartment that is inducible by peripheral cytokines.[97]

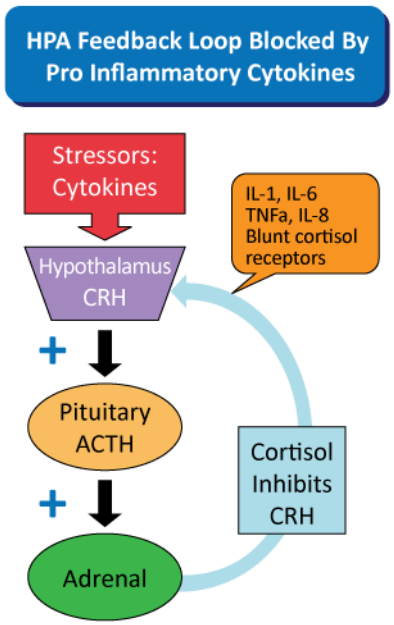
The discovery that cytokines affect the central nervous system in major depression is a significant opportunity for cytokine mediated antidepression therapy. Cytokines contribute to the development and/or maintenance of major depression via a multidimensional route.

**First:** IL-6, and in some models IL-1 and TNFά, appear to be increased in persons exposed to chronic stress, including emotional stress[98].

**Second:** IL-1 and IL-6 have been shown to stimulate the secretion of Corticotrophin Releasing Hormone (CRH) from the hypothalamus. CRH, in turn, stimulates the anterior pituitary secretion of Adrenocorticotropic hormone (ACTH) and ultimately cortisol from the adrenal cortex. [99]

**Third:** Hormones of the hypothalamic-pituitary-adrenal (HPA) axis are associated with anxiety and mood swings.[100] Depression has been suggested to develop as a result of dysregulation of the CRH-ACTH-cortisol negative feedback cycle.

A persistent mild to moderate HPA axis activation associated with depressive illness is a well-documented phenomenon and can be demonstrated in approximately half of patients suffering from a major depression.[101]




The bulk of available evidence indicates this phenomenon is related to a hypersecretion of hypothalamic CRH.[102] Clinical studies have shown that during periods of depression this results in persistent hypercortisolism of varying degrees that is sufficiently chronic to induce adaptive changes in hypothalamic-pituitary-adrenal axis function.[101] These include adrenal hypertrophy and diminished pituitary corticotroph responsiveness to stimulation with CRH.

Although less well studied, evidence from several studies also suggests that resolution of depressive episodes is accompanied by resolution of HPA axis hyperactivity and restoration of more normal hormonal secretion patterns.[103]

In the normal feedback cycle between these hormones, when external and internal stressors induce increased levels of the cytokines IL1, IL6 and TNFά they cause an elevation of CRH leading 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.

Persistent or even acute elevations in these proinflammatory cytokines have been suggested to disrupt this feedback cycle by blunting the receptors for cortisol on the hypothalamic cells,[104] resulting in an elevated CRH in spite of elevated cortisol, leading to increased levels of cortisol and the risk of conditions associated with this. IL1 has also been implicated in interfering with the production of the neurotransmitter serotonin in the brain.[105]

A reasonable clinical intervention is therefore to mitigate adverse immune activation of the mucosal tissues and down regulate the production of proinflammatory cytokines to reduce inflammation induced depression and sickness behaviour via bystander suppression and systemic immunological tolerance.

## How to use the gastrointestinal tract to mediate inflammation induced depression

Combining immunological management of NF-κB together with other antiinflammatory strategies such as appropriate dietary restriction (where adverse immune responses have been identified,) suitable food selection and selected probiotics represents a plausible evidence based route for resolving inflammation-related depression via the mucosal immune system.

## NF-κB Inhibition

The use of NF-κB inhibitors, such as the use of vitamins C, E and N-acetylcysteine,[106] cat's claw extract,[107] green and black tea polyphenols,[108] the spice curcumin,[109] citrus flavanoids,[110] and others have all shown NF-κB inhibiting effects.[111]

## Probiotics

Antiinflammatory cytokines are used and produced by commensal bacteria, sometimes referred to as 'old friends,' to maintain immune tolerance in the gastrointestinal tract. They do this by using codes in their membranes that are recognised by the innate immune system as being friend rather than foe. These codes include lipopolysaccharides and lipoteichoic acids and others, then identified by many types of cells on the surface of the intestine; epithelial cells, lymphocytes between the epithelial cells, subepithelial mesenchymal cells, macrophages, and dendritic cells via Toll Like Receptors (TLRs.)[112] Both commensal (mostly gram negative) and probiotics (mostly gram positive) have the necessary codes to carry signals to the immune system. Understanding which species and strain does this, helps to determine the appropriate delivery of selected bacteria.

Knowing that certain types of bacteria induce antiinflammatory responses allows us to introduce bacteria into the gastrointestinal tract to affect inflammation both locally and systemically via 'bystander suppression' and thereby affect mood.[113] Certain bacteria also reduce activation of NF-κB providing a double edged benefit in their use of this transcription factor to maintain mucosal tolerance.[114]

Controlling inflammation in this manner appears to also increase the ability of the brain to repair itself and resolve effects linked to mood disorders. Probiotics have also been linked to increased levels of an essential growth factor in the brain, brain derived neuro (BDNF) that assists more rapid repair of neurons damaged by stress.[115]

The quickest way the body transfers immunological information from the gastrointestinal tract to the CNS is via the vagal nerve. Using this large nerve as the conduit, means that immunological activation in the gut has an immediate correlate in the brain and vice versa. There is evidence that food selection can influence the cholinergic nerve signals and this has implications for the management of CNS activity.[116] The vagus nerve is a paired structure that arises in the brainstem and traverses the neck, thorax, and abdomen to innervate visceral organs. It was named as such for its wandering and meandering course.

Its fibres contain sensory and motor components that control organ functions as varied as heart rate and digestion. Evidence now shows that in addition to controlling these physiological functions, the vagus nerve also prevents the release of inflammatory chemicals including TNFa, (High mobility group box 1) HMGB1, IL-1, and other proinflammatory cytokines.[117] As the activity of this pathway is controlled by neural signals, it provides a way for the brain to regulate the cytokine response in a localised, controlled, and organ-specific manner and seems to use the selection of dietary fats to achieve this in the gut. Increasing the intake of fats in the diet can activate the cholinergic anti-inflammatory pathway.[118]

## Probiotics are inflammation controllers.

Depressed patients have increased oxidative stress, altered gastrointestinal function including increased permeability, lowered micronutrient and omega-3 fatty acid status. It is also understood that stress, a significant factor in depression, alters the balance of intestinal bacteria by lowering the levels of lactobacilli and bifidobacterium.[119,120] Research suggests that bacteria in the gastrointestinal tract can communicate with the central nervous system, even in the absence of an immune response.[121]

Probiotics have the power to lower systemic inflammatory cytokines, decrease oxidative stress, and improve nutritional status, and when used correctly have the potential to be significant players in the management of inflammation-induced depression.

They also play an important role in the production of a special immune cell called a regulatory T cell. [122,123] These cells act as the 'peace keepers' of the immune system. They are made in small numbers in the thymus, but in great numbers in the gastrointestinal tract. The cells can travel from the gastrointestinal tract around the body, calming down inflammation and also act to encourage the production of anti-inflammatory cytokines through their controlling influence over our gastrointestinal bacterial composition and their support of the adaptive immune system.[124]

> Understanding there does not need to be an infection in the gastrointestinal tract, merely a loss of microbial balance and or an ongoing stressful experience to keep releasing depression inducing chemical to the brain suggests that correcting this or harnessing the gastrointestinal tract's immune system may lend itself to a treatment for immune induced depressive behaviour.

Probiotics have also been shown to have even more significant effects on the HPA axis, providing the appropriate stimuli to allow the effects of separation stress to be normalised in animal models.[125,126] Probiotics are able to correct gut disturbances induced by stress through multiple points of interaction, resulting in a long gut-brain neuroimmune reflex pathway. This is done via a trophic effect on epithelial tissues, normalisation of gut microbiota, the prevention of adherence of luminal bacteria and the enhancement of barrier integrity.

Then by their secretion of soluble immune stabilising factors, or by the direct activation of TLR's or mannose receptors, or the release of dendritic cell adhesion molecules which in turn stimulate immune cells such as mast cells, T lymphocytes to normalise the ratio of pro versus anti inflammatory cytokines.
Then they also, via a cytokine neurohumoral route, indirectly stimulate afferent nerve fibres, especially vagal nerve afferents, which results in a reduction of systemic corticosterone and adrenocorticotrophic hormone.[127,128]

## sIgA

Our bodies produce only one type of anti-inflammatory immunoglobulin and this is called secretory IgA (sIgA). We manufacture more of this than any other immune chemical and it is produced mainly in the gastrointestinal tract. It acts to inhibit attachment of bacteria and viruses to the underlying epithelium, and agglutinate antigens, trapping them in the essential mucus layer to help remove provocative food components and limit responsiveness.[129,130]

As well as modifying inflammation, it is essential in helping bacteria to survive and also to deliver their encoded messages to TLR's and epitheilial cells. However, sIgA production is very susceptible to overt

emotion and frustration, characteristic symptoms of depression which can result in a significant reduction of output.[131] The use of probiotics and friendly yeast called Saccharomyces Boulardii will enhance sIgA production so reducing immune promoted inflammation in the mucosal tissues.[132]

## Indoleamine and mood

When our immune system is activated against infection, trauma or under stress, we release Indoleamine 2,3-dioxygenase (IDO), a 'metabolic' enzyme that has been part of immune defence for the past 600 million years of evolution. This enzyme has a key role in controlling adaptive immune responses, chronic infections, allergy and autoimmunity and has a role to play in depression.[133, 134,135]

During inflammation, IDO inhibits tryptophan conversion to the mood aiding neurotransmitter serotonin. Whilst the aim of this process is to starve certain bacteria of tryptophan as food, the consequence is prolonged inflammation and a loss of available serotonin further contributing to depressive behaviour. At the same time another inflammatory chemical blocks the re-uptake of serotonin, so that the longer the inflammation remains the less serotonin remains available.

Persistent parasitic infection, leads to decreased tryptophan inhibition and increased risk of persistent infection and inflammation and risk of mood changes.[136]

In addition, the IDO potent neurotoxin by-products – quinolinic, picolinic acid and kynurenines are also implicated in altered neurological function as well as depression.[137,138] One final relevant role it has is limiting the biosynthesis of nicotinic acid (B3) a vitamin essential for adrenal hormones and serotonin production, further contributing to risk of stress, inflammation and depression.

Folate and B12 deficiency,[139] common through poor food selection also contributes to the symptoms of depression[140] and poor response to antidepressants;[141] a Vitamin B complex supplement containing all the B vitamins therefore has clinical justification.

The use of essential fatty acids has been found to have a variety of effects on mood and depression, but one role that these fats can play is in the specific reduction of depression linked to proinflammatory cytokines.[142] The consumption of cold pressed olive oil has also been linked to a reduction of key inflammatory molecules.[143]

## A Summary of Practical Approaches

**Avoid:** Rancid, polyunsaturated and partly hydrogenated fats and oils. These fats lead to the production of proinflammatory prostaglandins (another inflammatory chemical) and should be eliminated from the diet. These fats are found in most processed foods or fast foods and are hard to avoid, meaning that food selection and meal planning should exclude an excess of pre-prepared foods.

Olive oil can be used as an alternative to margarine or shortening. Olive oil contains omega-9 fatty acids, which work with omega-3 essential fatty acids to increase it's benefits on the body, including the reduction of depressive symptoms.

**Include:** Omega-3 fatty acids, found mainly in fish of cold-water origin, such as mackerel, salmon, sardines, anchovies and herring. Omega-3 fatty acids are also found in walnuts, Brazil nuts, almonds, pumpkin seeds and sunflower seeds.

Other foods that have anti-inflammatory properties include fruits, vegetables and whole grains. Fruits and vegetables included are blackberries, strawberries, raspberries, kiwi, peaches, mango, melon, apples, carrots, squash, sweet potato, spinach, kale, greens, broccoli, cabbage and brussel sprouts. Grains include lentils, chickpeas, brown rice, wheat germ and non-instant oatmeal. These food items are all high in vitamins A, C and E.

Two other important components to the anti-inflammatory diet include ginger and turmeric.

**A suggested list of supplements/strategies**

Consume probiotics of the following type: Bifido Bacteria and Lactic Acid bacteria. Continue taking these for many months as it takes considerable time for the immune system in the gastrointestinal tract to be reprogrammed.

1. Saccharomyces Boulardii
2. EPA oils
3. Natural inhibitors of NF-κB
4. Eat an anti-inflammatory diet
5. Remove any intestinal pathogens
6. Correct intestinal dysbiosis
7. Use strain specific bacteria to deliver the correct immune message to the systemic immune system.

It is highly recommended that advice from a suitably qualified and experienced nutritional therapist is sought prior to trying out any of the above recommendations

## Author

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