A short review of the relationship between chronic
inflammation and psychological disorders

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Abstract: Chronic inflammation is closely related to a variety of psychological
disorders such as anxiety, depression, sleep disorders and attention disorders, and even
suicide. On the other hand , the psychological disorders may be also one of risk factors
for triggering and aggravating chronic inflammation. This article mainly reviews the
researches on the relationship between chronic inflammation and psychological disorders
in recent years.

Key words: Chronic inflammation; psychological disorders; anxiety;depression

Introduction

Up to date,it’s believed that chronic inflammation may intertwine with psychological disorders,and then may form a bidirectional loop between them,in which psychological disorders positively facilitated inflammatory responses and chronic inflammation conversely promoted psychological disorders.

Chronic inflammation may be a characterized part of some systemic diseases,such as cardiovascular diseases,diabetes,metabolic syndrome,rheumatoid arthritis,asthma,multiple sclerosis,chronic pain, psoriasis and so on [1].These patients had a higher risk for psychological disorders (such as anxiety and depression) than general population.According to the bio-psycho-social model of diseases,psychological factors play a more and more important role in some chronic diseases.And in clinical,physicians gradually pay more attention on the psychological factors other than the physical ones.On the other hand,chronic inflammation may closely relate to a variety of psychological disorders,such as anxiety, depression,sleep disorders,attention disorders,and so on.The psychological disorder may be a direct reason

for some chronic inflammation,and an important factor for disease aggravation.However,it remained unkown how do the inflammation and psychologies affect each other.So this article was aimed to review the relationship between chronic inflammation and psychologies.

A vicious circle between chronic inflammation and psychological disorders

Psychological disorders are one of the most prevalent diseases in the world,especially depression and anxiety,which more than 300 million people are suffering from [2].Clinical studies have confirmed that anxiety and depression are associated with a range 39

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of inflammatory diseases such as gastrointestinal inflammation and autoimmune diseases.Depression may be a manifestation of external neuropsychiatric symptoms of the chronic inflammatory syndrome, which is most commonly found in gastrointestinal mucosal damage,usually due to mucosal flora disorders and the damage of mucosal repair.On the

other hand,it’s also very common in clinical practice that many patients with chronic gastrointestinal inflammation are often accompanied by manifestations of autonomic dysfunction(such as fatigue,dizziness, headache,and insomnia).The chronic gastrointestinal inflammation may cause systemic effects via cytokines, neuropeptides and eicosanoids,and then impact various organ functions(such as the brain).

Recently many researchers have focused on the role of “brain-gut axis” in the comorbidity between intestinal diseases and psychological symptoms, such as the role of inflammatory bowel disease (IBD)and irritable bowel syndrome(IBS)in the development of central comorbidities.On the contrary, anxiety and/or depression may increase the grade of intestinal inflammation and may result in IBD recurrence [3-6].Psycho-neuro-endocrine-immune regulation via the brain-gut axis may not only play a key role in psychological disorders,but also in chronic inflammation of the gastrointestinal tract.In clinical practice,many patients with severe ulcerative

colitis(UC)presents depressive symptoms or mental stress.Previous studies had found that the incidence of anxiety and depression was significantly higher in patients with functional gastrointestinal disease or organ damages than in the general population. Konturek.et al [7] conducted a questionnaire survey including 1 641 patients with gastrointestinal diseases, in which 1 379 cases of psychological disorders,1 098 cases of anxiety and 442 cases of depression have been notified respectively.And Logistic regression analysis showed that patients with gastrointestinal diseases are more likely to develop anxiety and depression.

These findings indicates that chronic gastrointestinal inflammation may directly result in anxiety and depression.

Possible mechanisms of the interac-tion between chronic inflammation and psychological disorders

In a state of chronic inflammation,the immune system responds by producing various proinflammatory cytokines and metabolites,several of which are detected in the blood

[8]

.These molecules cross the blood-brain barrier(BBB)and signal the brain which eventually leads to psychological disorders

[9]

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Previous studies have suggested that the mechanisms of interaction between chronic inflammation and psychological disorders are complex and may involve multiple interactions such as neural,humoral,cellular and carrier route.

1.Neural pathway

Vagus pathway is very important in the regulation of gastrointestinal motility and secretion.And now it was found that stimulation of the vagus nerve could significantly inhibit cytokine production,and this discovery had led to the recognition of the concept of cholinergic anti-inflammatory pathways

[10-11]

.In the presence of systemic inflammation,the central nervous system(CNS)can be activated by the afferent fibers of the vagus nerve.These signals are integrated in CNS,and fire the efferent nerves of the CNS,and then regulate the splenic immune response via the superior mesenteric ganglia.And the

activation of splenic cholinergic nerves results in the release of norepinephrine,which positively trigger more acetylcholine release.In fact.acetylcholine decreases the expression of TNF-α,IL-1,IL-18,and other proinflammatory factors.O’Mahony,et al [12] found that dextran sodium sulfate(DSS)induced UC animal were more severely exacerbated by cutting the vagus nerve.And the acetylcholinesterase inhibitors(such as neostigmine and physostigmine) significantly alleviated the severity of colitis induced by trinitrobenzenesulfonic acid(TNBS) [12-13] .Animal models with depression had got a reduction of intestinal acetylcholine level.Interestingly,this depression model was more likely to TNBS-induced UC.And this phenomenon can be reversed by antidepressants [14] .

Once presence of chronic intestinal inflammation,the vagus nerve is activated by proinflammatory cytokines and other metabolites released by immune cells,40

neurons or intestinal bacteria [15] .This cascade activates

hypothalamic-pituitary-adrenal axis(HPA)which

increases cortisol(stress hormone)levels and decreases

brain-derived neurotrophic factor(BDNF)levels [16]

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Cortisol has a strong negative impact not only on the

hippocampus and amygdala,but also on the function

of the prefrontal cortex;whereas the traditional brain

derived neurotrophic factor hypothesis suggests that

BDNF is an important regulator of nerve growth.The

reduction of BDNF levels leads to increased neuronal

apoptosis,which will cause depressive symptoms.

Cortisol levels in patients prone to be unpleasant

are higher than those in healthy controls [15,17]

.Other

studies have shown that plasma/serum BDNF levels

were lower in patients with acute major depression

(MDD)compared with healthy controls,and both

antidepressant therapy and electroconvulsive therapy

can significantly increase the plasma/serum BDNF

level [18]

.At the same time,hyperactivity of the HPA

is also the reason of dysregulation of the kynurenine

pathway.The basic role of the kynurenine in healthy organisms is to convert tryptophan into two basic compounds involved in mood regulation,namely serotonin and melatonin [19].

Sympathetic nervous fibers are not only distributed in the intestinal plexus,but also in intestinal mucosa and intestinal-associated lymphoid tissue [20].Sympathetic nerves release norepinephrine,neuropeptide Y,ATP, and purine,and then regulate the movement,secretion, sensory and immune activities of the gastrointestinal tract [20].Intestinal inflammation interferes with the above sympathetic nervous process.The previous studies on arthritis found that the inflamed region showed absence of sympathetic nerve fibers [21-23].

Patients with Crohn's disease(CD)showed as well as the absence of sympathetic nerve fibers in the intestinal mucosa and the submucosa.The similar phenomenon was also found in DSS-induced colitis mice [24-25],with a decreased secretion of sympathetic neurotransmitters

such as norepinephrine and catecholamines [26] .

However,there are some contradictions.For instance, 6-hydroxydopamine,blocking the sympathetic nerve function,significanty aggravated chronic colitis induced by DSS in mice,and also raised the intestinal inflammation in IBD mice by IL-10 gene knockout.

But it alleviates intestinal inflammation in IBD rats induced by DSS or TNBS [27] .Therefore,the sympathetic nerve may have both the proinflammatory and anti inflammatory effects,and the role of sympathetic nerve in IBD pathogensis remained uncertain and need further studies.

2.Humoral pathway

Leukocytes have the ability to pass or migrate into tissues,and this ability is extremely crucial for the performance of the host in terms of physiology, immunopathology and host defense.The classical theory is that due to the presence of the blood-brain barrier(BBB)and the lack of lymph drainage,the central nervous system is relatively homeostatic and the accessing of white blood cells to the CNS are limited.Circumventricular organs(CVOs)are a group

of structures within the brain that are rich in blood vessels,but lack of the integrated BBB.They can be divided into two categories according to the functions, that’s sensory organ and secretory organ.The sensory CVOs include the posterior marginal zone,subfornical organ and the organum vasculosum laminae teminalis. These structures are able to identify those molecules in the plasma and transmit information to other areas of the brain and directly get involved in the regulation of the circulatory system by the autonomic nervous system.The secretory CVOs include subcommissural organ,posterior lobe of the pituitary gland(also referenced as neurohypophysis),pineal gland,median carina and intermediate lobe of hypophysis of some animals.These structures are in charge of the secretion of hormones and glycoproteins into the blood during feedback regulation of the brain’s reaction to internal and external stimuli.CNS can communicate with peripheral blood circulation via CVOs.Meanwhile, CVOs are also an important part of neuroendocrine function.The humoral pathway is that the peripheral

inflammatory factors and related metabolites affect the CNS and induces psychological disorder by acting on CVOs [28] .These peripheral inflammatory factors and related metabolites are often induced by chronic inflammation.

3.Cellular route

The cellular route involves cytokine receptors,such as receptors for TNF-αand IL-1β,expressed on non neuronal cells in the brain,such as microglia and 41

astrocytes [29-30] .TNF-αand IL-1βenter the brain via CVOs and/or other pathways,and bind to their receptors in the brain,and then activate the cerebral NF-κB signaling pathway and induce the production of secondary cytokines,which can aggravate the depressed mood [31] .In fact,a great amount of data showed that increased levels of cytokines in peripheral circulation have dose-dependent effects on psychological symptoms and the severity of depression.

Proinflammatory cytokines such as IFN-γ,IL-2,IL-6, TNF-αand inflammatory markers such as CRP are associated with a higher risk of depression

[32-33]

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4.Carrier route

The blood-brain barrier(BBB)prevents unrestricted migration/transportation of peptides and proteins between the brain and blood.However,some peptides and regulatory proteins can access the brain via the energy-and carrier-dependent active transport system or via no energy-dependent carrier-mediated facilitated diffusion system to cross the BBB

[32,34]

.Such as the way how tryptophan access the CNS.Generally speaking, tryptophan can access the CNS under the transport of a carrier to synthesize 5-hydroxytryptamine.In the state of systemic inflammation,the neutral amino acid transporter(LAT-1)on the blood-brain barrier can transport kynurenine from the peripheral blood circulation to the CNS and produces downstream cascade metabolites with the stimulation of central glial cells

[35]

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5.Others

Psychological disorders can cause or aggravate chronic inflammation,in addition to the above mentioned systemic interactions,including the effects

of stress,poor nutrition,physical inactivity,obesity, smoking,gut permeability,microbiota disturbances, mitochondrial dysfunction,autoimmunity,and sleep disturbances [36-38] .In a meta-analysis,Howren,et al [32] suggested that higher CRP level in MDD with obesity is a risk factor for the development of diabetes and cardiovascular disease,and these chronic diseases are significantly associated with increased morbidity and mortality of psychotic disorders [39] .

Progress in the treatment of chronic inflammation and psychological dis-order

Inflammation is a reaction of the body against infection,injury and immune stimuli.Moderate inflammatory reaction is essential for repairing damage and maintaining homeostasis.On one hand, the local inflammation can be transmitted to the CNS through the“brain-gut axis”,and induces changes of the CNS activities and functions,which may lead to development of psychological disorders.This suggests

that reasonable intervention in certain phases of the inflammatory has a positive effect on the disorders of the CNS.On the other hand,long-term psychological disorders will also affect the recurrence and progression of chronic inflammation through multi-pathway interactions.

1.Anti-inflammatory drugs

Several studies had found that some anti-inflammatory drugs showed an antidepressant effect.Recently, COX-2 inhibitors(such as celecoxib),minocycline (microglia inhibitors)and anakinra(IL-1R1 receptor antagonist)were studied respectively.They exerted a variety of antidepressant effects on various depression.

Celecoxib can relieve the HPA dysregulation induced by removing olfactory bulbs,and relieve pleasure loss as a result of unpredictable chronic mild stress [40,41] .

Minocycline can normalize the behaviors of mouse, which are depression models with learning helpless and forced swimming [42,43] .Anakinra also relieves the symptoms of depression in rats [44,45] .

2.Antidepressants

Antidepressants have also been found have the

ability to anti-inflammatory in animal models of chronic inflammation.Different anti-inflammatory mechanisms have been established for different types of antidepressants,including selective serotonin reuptake inhibitors(SSRIs,such as sertraline and citalopram),tricyclic antidepressants(such as pamin and imipramine)and atypical antidepressants(such as agomelatine melatonin receptor inhibitor) [46-48] .

Cognitive behavioral therapy not only improves psychological symptoms,but also alleviates the gastrointestinal symptoms [49] .The therapy stimulates

the vagus nerve and then activates the cholinergic anti inflammatory pathway and exerts its anti-inflammatory effects,which has been widely used in drug-dependent epilepsy and depression [47] .Animal studies had shown that activation of the vagus nerve can relieve symptoms,alleviate intestinal inflammation and reduce histological score in colitis rats [50] .These also suggested that cognitive behavioral therapy and stimulation of

the vagus nerve may become potential therapeutic measures for human inflammatory diseases(such as IBD and arthritis etc).

Conclusions and outlooks

There is an interaction between chronic inflammation and psychological disorders.Those patients with chronic inflammatory inflammation often are affected by psychological disorders,such as depression and anxiety.These symptoms have an adverse effect on the progression and morbidity of chronic inflammation and treatment outcome by various mechanisms.However, the most studies were still stuck in phenomenological correlations as well as in the investigation of the effects after specific molecular interventions.For some exact mechanisms,more convincing experimental verification is necessary.In particular,It is worthy of searching biomarkers to assist in the diagnosis and prediction of the treatment effect of psychological disorders.The collaboration between clinicians and psychologists is essential and encouraged in clinical practice.

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