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Interaction Between Inflammatory State and Neurochemical Changes in Major Psychiatric Disorders

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1. Introduction

Inflammation is the immunological mechanism to react against danger signal. In old days, inflammation is characterized by heat, redness, pain, swelling and loss of function in gross appearance and inflammatory cells infiltration to the affected area in microscopical appearance. Even though it is not always possible to demonstrate the inflammatory cells infiltration in certain part of brain area in patients with psychiatric disorders, there are evidences such as enhanced production of inflammatory mediators that indicated the reaction of the immune system. It is generally considered that immune reactions occur in response to a danger signal such as abnormal cell death. With time, scientists in both immunology and neuroscience fields realized that the danger signals occur not only due to microorganisms, foreign bodies or tissue injury but also some noxious situations such as psychological or emotional stress.

The involvement of immune system in psychiatric disorders is, in fact, recognized since 1927 by Wagner-Jauregg, the only psychiatrist who ever awarded Noble prize for his work on malaria inoculation in treatment of dementia paralytica (Raju, 1998) which was the treatment of psychosis by inducing fever, known as 'pyrotherapy'. That evidence indicated that the immune activation induced by infection could cure the psychotic symptoms since fever is associated to immune activation. On the other hand meningitis induced toxic psychosis without fever was reported by Fischer, 1963. Taken together, in the field of Medicine, the relation between infection, inflammation, fever and psychotic symptoms became of interest since early 20th Century. Around similar period, in the field of Biology, Selye (Selye, 1954) has reported that the neurogenic stress situation induced by forcible immobilization could effectively inhibit inflammation in the experimental granuloma-pouch under the dorsal skin of rat after chronic irritation with cotton wool and that reaction was abolished in adrenalectomized rats. That finding indicated that the anti-phlogistic effect or suppression of immune activation was largely dependent on secretion of anti-phlogistic corticoids from the adrenal glands. That was the earliest starting point indicating the effect of stress on the immune system although it was difficult to conclude if the immobilization is

physical or emotional stress, in other words, if that suppression of immune activation induced by external agent came centrally.

In 1975, Ader and Cohen reported that immune suppression could be induced by behavioural condition (Ader and Cohen, 1975). That was the clear demonstration that peripheral immune system could be influenced by emotion or behavioural manipulation. In the following years, the body and brain crosstalk through immune system became of interest in pathophysiology of psychiatric disorders. In 1987, the low natural killer cell activity in patients with depression was reported (Irwin et al., 1987). In early 1990s "sickness behaviour" was proposed as peripheral immune activation induced depressive like behaviour based on the fact that injection of bacterial toxin, lipopolysaccharide, peripherally could induce depressive like behaviour (Bluthe et al., 1992). They also reported that sickness behaviour induced by peripheral immune activation was reversed by administering the antagonist of interleukin-1 (IL1) receptor. While sickness behaviour is, unlike major depressive disorders, a short term syndrome, the symptoms of sickness behaviour such as lack of interest, inability to concentrate, loss of appetite, disturbance of sleep and social anhedonia are the similar symptoms as in depression. Thus, immune activation in the periphery was considered as part of the pathophysiological mechanisms of major depression and anti inflammatory medication or manipulation of immune system became of new therapeutic interest.

The first theory on the immune activation in psychiatric disorders proposed was "macrophage theory of depression" (Smith, 1991) in which the association between cytokine secreted from macrophage and hypothalamus activity were proposed as pathophysiological mechanism of major depressive disorder. This theory has highlighted the interaction between immune system and endocrine system which could influence the emotion and higher function of the human brain. Based on the finding related to the connection between lymphocyte function, hypothalamo-hypophysial-adrenal axis and depression which indicated the impaired lymphocyte response to mitogen stimulation (Maes et al., 1989), the macrophage theory of depression was extended to monocyte-lymphocyte hypothesis of depression (Maes et al., 1995). The same authors have also extended the hypothesis to another major psychiatric disorder, schizophrenia (Smith and Maes, 1995). It was discussed that the cytokines, such as, IL1 and IL2 in low concentration could enhance the dopaminergic neurotransmission whereas high IL2 could suppress it. Around this period, the impairment of neutrophil and macrophage phagocytoses in depressed patients was also reported (McAdams and Leonard, 1993). Changes in immunoglobulin, complement and acute phase protein levels were also reported in patients with depression (Song et al., 1994). Also in late 1080s, Nishino and colleagues has first demonstrated the prostaglandin E2 (PGE2), an enzyme involved in inflammatory process is increased in the saliva of depressed patients (Nishino et al., 1989).

Based on the different subtypes of immune cells, some studies explore the ratios between different subsets of T-lymphocytes and demonstrated the higher T-helper/T-suppressor cytotoxic cell ratio in depressed patients (Maes et al., 1992). The enhanced T-helper type 1 immune response which is associated with development of inflammation was proposed in major depressive disorders. Similar development in research related to inflammatory response and schizophrenia also occur around this later 20th Century and the beginning of 21st Century. The increased T-helper type 2 cells in the blood of patients with schizophrenia were reported and the dominance of T-helper type 2 reaction was suggested (Sperner-

Unterweger et al., 1999). Based on this finding "Th-2 hypothesis of schizophrenia" was proposed (Schwarz et al., 2001). Around the same period in the beginning of 21st Century, the tryptophan degradation induced by the indoleamine 2,3-dioxygenase (IDO) enzyme in the presence of inflammatory state became of interest as a link between immune function and serotonergic abnormalities due to reduced tryptophan availability (Capuron et al., 2002; Maes et al., 2002). A year later, the possible involvement of downstream tryptophan metabolites in terms of neurotoxic changes in major depressive disorders and further immune system and NMDA-glutermatergic neurotransmission interaction were proposed in "neurodegeneration hypothesis of depression" (Myint and Kim, 2003).

Several therapeutic strategies have been studied in the area of immune activation and psychiatric disorders. The antagonist of pro-inflammatory cytokine such as tumour necrosis factor-α (TNFα), eternacept, and n3 fatty acids are those studied and given some promising results. Recently, add-on therapy with inhibitor of cyclooxygenase-2 (COX-2) enzyme, celecoxib which was originally an anti-inflammatory medication was reported to enhance the response to both anti-depressant therapy and anti-psychotic therapy. Moreover, the possible use of inflammatory based biomarkers in diagnosis and choice of medication in major psychiatric disorders are considered.

In this chapter, brief basic immunology on inflammation, findings and mechanisms related to inflammatory state in psychiatric disorders, the immune-endocrine interaction, immune-endocrine-tryptophan metabolism interaction and inflammation-tryptophan metabolism-neurochemicals interaction network were explained and discussed.

2. Inflammatory state

2.1 A short survey of the body's defence system

The body's defense system is a complex arrangement of physical, chemical, biochemical, and cellular barriers. Here we will focus on immunity, which is the result of the interplay between two "immune" systems: the innate immune system, which is phylogenetically older, and the adaptive immune system of T and B cells (Medzhitov and Janeway-CA, 1998). The innate immune system functions in an antigen-nonspecific way, while antigen-specific mechanisms are mediated by the adaptive one. Characteristic cells of the innate immune system are e.g. granulocytes, natural killer (NK) cells, monocytes/macrophages, or dendritic cells. The innate immune system is the first line of defense against infection and it provides signals for the activation of the adaptive immune system. Innate responses serve to regulate the onset, duration, magnitude, and character of the antibody- and cell-mediated adaptive response. In contrast to the adaptive immune system, the innate immune system is not able to confer long-lasting memory, i.e. immunity against a specific pathogen.

In the late 1980s, Janeway proposed the model of the antigen-presenting cells, which are able to recognize and differentiate distinct groups of microbes by special receptors, the so-called pattern-recognition receptors (Janeway, Jr., 1989). The identification of pathogen-associated molecular patterns or microbe-associated molecular patterns by the innate immune system allows the body's defense system to discriminate between "infectious non-self" and "non-infectious self". This concept was expanded by Matzinger's hypothesis of danger signals as inducers of the body's defense system (Matzinger, 1994). According to this new concept, immunological phenomena like autoimmunity, sterile inflammation, or the acceptance of the fetus, who is immunologically 50% non-self, by the mother's immune system can be explained. Matzinger proposed that antigen presenting cells are not activated

by an infectious non-self signal, but by danger signals from injured host cells, damaged tissues, or metabolic stress. According to the term "pathogen-associated molecular patterns", she introduced the term "damage-associated molecular patterns" for these endogenous danger signals.
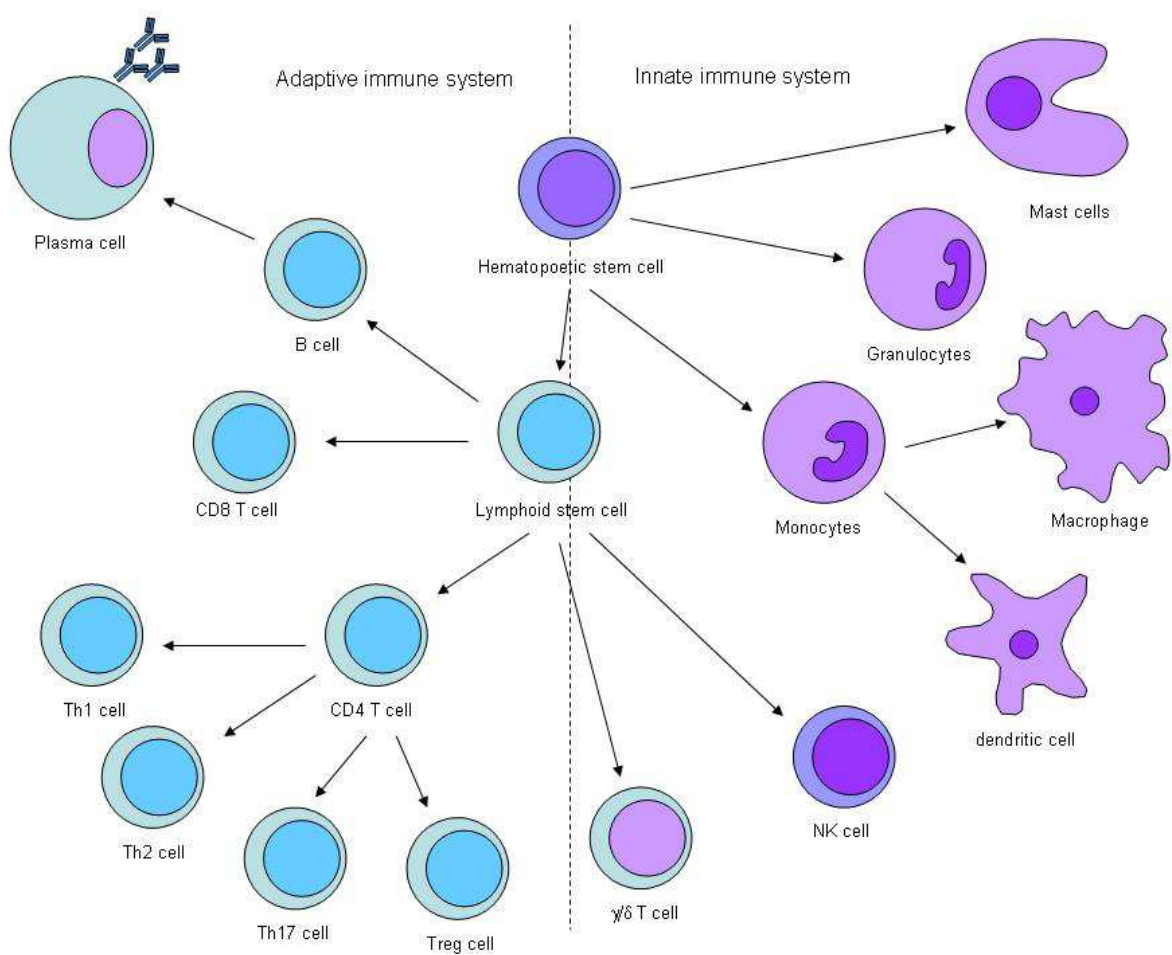

Fig. 1. Both arms of the cellular immune system (adapted from Drexhage et al., 2010).

The innate immune system provides a broad array of different receptors for the identification of both kinds of molecular patterns. The best known group of receptors is the family of Toll-like receptors (TLRs), which are able to recognize both, exogenous and endogenous molecular patterns (Medzhitov, 2009). TLR4 for example recognizes the pathogen-associated molecular pattern of bacterial lipopolysaccharide as well as the damage-associated molecular patterns of endogenous heat-shock proteins, while TLR3 is an intracellular recognition receptor of both, viral and self double-stranded DNA (Sirisinha, 2011). To limit an overshooting immune response to the minimum necessary tissue damage, the innate immune system is down-regulated by several negative regulators such as soluble decoy TLRs and intracellular TLR regulators like suppressors of cytokine signals (SOCS) and the enzyme A20 (Sirisinha, 2011).

The cells of the adaptive immune system are T cells (bearing the α/β T cell receptor) and B cells. The adaptive immune system induces T cells to change from a naive phenotype to either an effector functional type or a memory phenotype. The T cells are principally subdivided into CD4 and CD8 T cells, according to their surface receptors with affinity to

either the major histocompatibility complex II (CD4) or I (CD8). CD4, or helper T cells, are specialized to activate other cells and fall into distinct functional classes. More than twenty years ago, the dichotomy of Th1 and Th2 cells was introduced. The main function of Th1 cells (sometimes known as inflammatory T cells) is to fight against intracellular pathogens and to activate macrophages to kill the pathogens they harbor, while Th2 cells activate B cells to produce antibodies against extracellular pathogens (Janeway et al., 2001). More recently, other T helper cell subsets have been identified with Th17 cells being the most prominent ones. Th17 cells are specialized in clearing pathogens that cannot be handled by Th1 or Th2 cells including some bacteria and fungi (Jager and Kuchroo, 2010). In addition to these effector cells, CD4 T cells can also have regulatory properties; the most prominent are the regulatory T cells (Treg) cells, who are responsible for the downregulation of the T helper cell-mediated immune response. Their major function is therefore to maintain self-tolerance and immune homeostasis.

The function of CD8 T cells is to identify infected cells via the interaction of their surface protein CD8 with the antigen bearing MHC I receptor and to kill these cells by destructing their membrane. In analogy to the T helper subsets, CD8 cells can also form subsets like Tc2 and Tc17. The phylogenetically old form of T cells, characterized by the gamma/delta T cell receptor ('γ/δT-cells') is not easily subsumed to either the adaptive or the innate immune system, since it combines some characteristics of CD4 T cells, CD8 T cells, and NK cells. Cytokines and chemokines, the transmitters/hormones of the immune system, help to determine the particular type of adaptive response and the expression of costimulatory cell surface molecules that are required for efficient immune cell activation. T helper cell subsets are characterised by their respective cytokine profile. Typical Th1-like cytokines are Interferon-γ (IFN-γ), Interleukin-2 (IL-2), and IL-12, typical Th2 cytokines are IL-4, IL-10 (in the mouse, not in humans), IL-13 and others (Del Prete, 1992). IL-23 induces the subset of Th17 cells, which are characterized by the production of the partly redundant cytokines IL-17A and IL-17F; both cytokines promote tissue inflammation via induction of the production of pro-inflammatory cytokines like IL-1, IL-6, TNF and pro-inflammatory chemokines like CXCL1 and IL-8 (Jager and Kuchroo, 2010). However, the cytokines and chemokines are orchestrated in an extremely complex way and most of the effects are dependent on the simultaneous production of different cytokines. The generation of the aggressive Th17 cells, for example, requires the presence of the anti-inflammatory cytokine TGF-b together with the multifunctional cytokine IL-6, while TGF-b alone induces the development of immunosuppressive Treg cells (Jager and Kuchroo, 2010).

Besides the cellular components of the two immune systems, the humoral (i.e. soluble) components are the complement system and the acute phase proteins within the innate system and the antibodies, produced by activated B cells within the adaptive system.

2.2 The immune-brain connection

There is a strong relationship between the cytokine system and the neurotransmitter system. In vitro- and in vivo studies showed the modulating effect of interferons on the production of prolactin (Vankelecom et al., 1997) and – particularly interesting with regard to psychopathology – on the catecholaminergic, dopaminergic, serotonergic und glutamatergic neurotransmitter systems, e.g. the induction of transcriptional activity of the serotonin transporter (Kamata et al., 2000; Morikawa et al., 1998; Shuto et al., 1997; Katafuchi et al., 1995). TNF-α regulates the secretion of norepinephrine in the brain (Nickola et al., 2001).

Peripheral administration of TNF-α induces the cerebral tryptophan content (Ando and Dunn, 1999) and the synthesis of serotonin and dopamine (Hayley et al., 2002). There is experimental evidence that IL-1 can activate the serotonin transporter thereby increasing the reuptake of serotonin from the synaptic cleft (Ramamoorthy et al., 1995). Furthermore, IL-1 activates the serotonergic system (Gemma et al., 1997). The considerable overlap in biological activities of IL-1 and 5-HT indicates that the interactions between these two systems may be involved in the modulation of behaviour.

IL-2 can affect gene expression, neuronal activity and neurotransmitter release in brain regions, subserving sleep, memory and cognition, locomotion, and neuroendocrine function. IL-2 modulates neurotranmission of acetylcholine, dopamine, and norepinephrine in a biphasic manner (Petitto et al., 1997). It appears to be a potent and specific regulator of neurotransmission in frontal cortex, hippocampus, striatum, and hypothalamus (Hanisch and Quirion, 1995).

IL-6 is produced by neurons, astrocytes and microglia (Van Wagoner and Benveniste, 1999). This cytokine promotes neuronal differentiation and survival (Gadient and Otten, 1997) and modulates the above summarized neurotransmitter systems (Song et al., 1999; Qiu et al., 1995; Qiu et al., 1998). Several studies have investigated the influence of IL-6 on the production, release, and metabolism of 5-HT. Peripherally administered IL-6 increases the concentrations of tryptophan and the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) in the brain (Wang and Dunn, 1999; Wang and Dunn, 1998; Zalcman et al., 1994) and it has been proposed that the interaction between IL-6 and brain serotonin is a complex process (Barkhudaryan and Dunn, 1999).

2.3 Stress and CNS immune system

The effect of chronic stress on the peripheral immune system and its relevance for MD has extensively been discussed (O'brien et al., 2004). Recent in vivo evidence now suggests that stress-induced elevation of glucocorticoids also enhances immune function within the CNS through microglia activation and proliferation and with a loss in the number and volume of astrocytes (Czeh et al., 2005). Animal studies show that stress induces an enhanced expression of proinflammatory factors such as IL-1β (Pugh et al., 1999; Nguyen et al., 1998), macrophage migration inhibitory factor (MIF) (Bacher et al., 1998; Niino et al., 2000; Suzuki et al., 2000) and cyclooxygenase-2 (COX-2) (Madrigal et al., 2003) in the brain. Elevation of these proinflammatory factors is accompanied by dendritic atrophy and neuronal death within the hippocampus (Sapolsky, 1985; Woolley et al., 1990), which are also found in brains of subjects with MD. These detrimental effects of glucocorticoids in the CNS are mediated by a rise in extracellular glutamate (Moghaddam et al., 1994; Stein-Behrens et al., 1994) and subsequent over-stimulation of the NMDA receptor. Such an over-stimulation of the NMDA receptor results in excitotoxic neuronal damage (Takahashi et al., 2002). Nair and Bonneau could demonstrate that restraint-induced psychological stress stimulates proliferation of microglia, which was prevented by blockade either of corticosterone synthesis, of the glucocorticoid receptor, or of the NMDA receptor (Nair and Bonneau, 2006). These data show that stress-induced microglia proliferation is mediated by corticosterone-induced and NMDA receptor-mediated activation within the CNS. Moreover, NMDA receptor activation during stress leads again to increased expression of the enzyme COX-2 and its product prostaglandin E2 (PGE2), which in turn is able to stimulate microglia activation. Therefore, a vicious circle may be induced, if the stress response is not limited, as it is discussed in MD.

2.4 Inflammatory state in major psychiatric disorders
2.4.1 Schizophrenia

Several epidemiologic studies give strong evidence for urbanicity at birth and upbringing to be a major risk factor for schizophrenia (Pedersen and Mortensen, 2001; Mortensen et al., 1999; Lewis et al., 1992). Another well replicated aspect is the seasonality of birth with a 5-8% excess of winter and spring births for individuals who later develop schizophrenia (Torrey et al., 1997). Both, urbanicity and saisonality, support the idea of a pre- or perinatal exposure to a viral infection as being a risk factor for developing schizophrenia (Franzek and Beckmann, 1996; Yolken and Torrey, 1995). In recent years, accumulating data showed the significant association between maternal infection during pregnancy with a higher risk for the offspring to develop schizophrenia (Brown and Patterson, 2011). Thus, a neurodevelopmental insult resulting from a prenatal viral infection, or a latent postnatal (viral?) infection may be associated with a chronic immune activation, possibly leading to a kind of mild autoimmune reaction, or a chronic, latent 'mild encephalitis' (Bechter, 2001). Recent animal experiments strongly support this concept (Vuillermot et al., 2010).

There are several lines of evidence for a mild activation of the immune system in schizophrenia. Some investigators dealt with antibody titres, some with cellular markers and others with cytokine measurements in serum, CSF, or in vitro from stimulated peripheral immune cells. Different hypotheses have been published according to the findings, e.g. the hypothesis of dopamine receptor activating autoantibodies (Knight, 1982), activated monocytes (Smith, 1992), a predominance of the Th2 system (Schwarz et al., 2001), or a deficiency of autoimmune T cells (Kipnis et al., 2006) playing a key role in the pathophysiology of schizophrenia.

A considerable number of reports show elevated antibody titers against several antigens in schizophrenic patients. The first report on antibodies against brain tissue in cerebrospinal fluid (CSF) of schizophrenic patients was published in the 1930ies by Lehmann-Facius (Lehmann-Facius, 1937). Others followed, describing anti-neuronal and non-CNS-specific auto-antibodies, or anti-viral antibodies in schizophrenia (e.g. (Heath et al., 1989; Schwarz et al., 1999; Torrey et al., 1982), for review see (Gaughran, 2002)). Some data suggest a role for endogenous retroviruses that may be activated by endocrine changes during adolescence and early adulthood – the main age at onset – or during an exogenous virus infection (Karlsson et al., 2001; Leweke et al., 2002).

However, no disease-specific pathogen could be identified up to now. The situation is comparable with the field of Multiple Sclerosis research, where strong evidence points to an infectious/autoimmune pathogenesis, but where the causative pathogen is still unknown. Regarding the cytokine profile, Potvin and coworkers (Potvin et al., 2007) reported in their systematic review of changes in seven cytokines in patients with schizophrenia that the IL-1 receptor antagonist (IL-1RA), soluble IL-2r and IL-6 were increased in the serum of schizophrenia patients while in vitro IL-2 synthesis was decreased. IL-1 is a potent pro-inflammatory mediator, inducing febrile response, production of acute phase proteins and activating e.g. T cells, B cells; its soluble receptor antagonist blocks these effects und is therefore acting as an anti-inflammatory agent (Gabay et al., 2010). The soluble IL-2 receptor is shed from the surface of activated immune cells and blocks the pro-inflammatory action of IL-2 (Nelson and Willerford, 1998). In contrast, IL-6 is a pluripotent cytokine, which exerts not only pro-inflammatory activity, but also regulates the balance between Th17 and Treg cells (Neurath and Finotto, 2011). Since it has a broad array of functions, it is difficult to interpret its role in the presence of elevated IL-1RA and sIL-2R levels. It is important to keep

in mind that immune measures, especially measurement of cytokines, in schizophrenic patients are limited by confounding factors. Factors influencing peripheral cytokine levels are e.g. smoking, gender, age, diet, weight, physical activity, sleep disturbance, alcohol consumption, smoking and last but not least antipsychotic and other medication (Irwin, 2002; Kronfol, 2002; Hinze-Selch and Pollmacher, 2001). Thus, immunological findings based on cytokine measurements in schizophrenic patients have to be interpreted with care. An increased B cellular immune response accompanied by a reduced T cellular immunity was repeatedly described in acute schizophrenia (Maino et al., 2007; Steiner et al., 2010). Based on the currently available data, the T cell immunity cannot clearly be associated with the Th1, Th2, Th17 or the Treg subset (Drexhage et al., 2010). However, increasing evidence points to an activation of circulating monocytes in schizophrenia (Drexhage et al., 2010; Drexhage et al., 2011).

2.4.2 Depression

The so-called sickness behaviour is the non-specific reaction to infection and inflammation. Sickness behaviour is characterised by weakness, malaise, listlessness, inability to concentrate, lethargy, decreased interest in the surrounding, and reduced food intake – all of which are depression-like symptoms. Thus, sickness behaviour was proposed to be a model of major depression (Dantzer, 2001). The sickness-related psychopathological symptomatology during infection and inflammation is mediated by cytokines such as IL-1, IL-6, TNF-α, and IFNg. Their active pathway from the peripheral immune system to the brain is via afferent neurons and through direct targeting at amygdala and other brain regions after diffusion at the circumventricular organs and choroid plexus (Dantzer, 2001). Clinical evidence also shows that the changes in cognition and mood that are an integral part of major depression are also caused by these cytokines (Capuron et al., 1999). Important lessons regarding the involvement of elevated pro-inflammatory cytokines in the pathophysiology of depression can be learned from IFN-a administration in patients suffering from malignant melanoma or hepatitis C (Myint et al., 2009). Another important impact comes from rheumatoid arthritis research, where a complex pro-inflammatory immune state is frequently accompanied with depressed mood (Bruce, 2008). To underline the functional relationship between an inflammatory process and depression, several studies have demonstrated the anti-depressant effect of anti-inflammatory drugs (Tyring et al., 2006; Uguz et al., 2009). These findings resulted in clinical trials demonstrating the efficacy of non-steroidal anti-inflammatory drugs as add-on treatment of major depression (Müller et al., 2006; Akhondzadeh et al., 2009). On the other hand, antidepressants have significant anti-inflammatory effects, as recently reviewed by Janssen and colleagues (Janssen et al., 2010); they normalize elevated levels of circulating proinflammatory cytokines like IL-6, TNF-a, IFN-g, and IL-1, again indicating that the activation of the immune system may be directly involved in the pathophysiology of depression. Recent even demonstrate the possible usefulness of antidepressants to treat rheumatoid arthritis (Sacre et al., 2010).

Beside these indirect lines of evidence for the involvement of an immune process in the pathophysiology of depression, there is a large body of findings of an activation of the immune system in depressed patients. The most frequently investigated immune parameters in patients suffering from major depression is IL-6. Most of the publications report a marked increase of in-vitro IL-6 production or serum IL-6 levels in depressed

patients. Since IL-6 is a prominent marker of monocyte activity, a predominant activation of the monocyte/macrophage system in major depression was hypothesised (Smith and Maes, 1995). Recent meta-analyses have clearly pointed out the evidence for elevated IL-6 levels in patients suffering from depression (Howren et al., 2009; Dowlati et al., 2010). Regarding the elevation of the inflammatory markers C-reactive protein (CRP), IL-1, IL-1RA and TNF-a, the two meta-analyses came to diverging results.

IL-6 may be involved in the modulation of the HPA axis (Plata-Salaman, 1991). Activation of the HPA axis is one of the best-documented changes in major depression (Roy et al., 1987). Furthermore, the relationship between psychological or physical stress and an enhanced IL-6 secretion in the peripheral immune system seems to be well established (Salas et al., 1990; LeMay et al., 1990; Zhou et al., 1993; Miyahara et al., 2000). An impaired ability of stress coping is often observed in depressed patients. Thus, the high number of data showing elevated peripheral IL-6 levels in MD patients may be partly related to psychological stress. However, it should be recognized that an inherent heterogeneity exists in the aetiology of depression and different neurotransmitter systems may be disturbed. Based on the commonly accepted idea of major depression as heterogeneous group of disease entities, the group of Arolt investigated the difference between melancholic and non-melancholic major depression regarding their cytokine expression patterns (Rothermundt et al., 2001). They detected profound differences between these diagnostic subgroups: Non-melancholic patients showed increased counts of leukocytes, lymphocytes and NK-cells in the acute stage of disease and after several weeks of treatment, while their in vitro production of the cytokines was unchanged. Melancholic patients on the other hand had normal cell counts but a decreased in vitro production of IL-2, IFN-γ, and IL-10 during the acute stage of disease. Following clinical improvement, the cytokine production patterns normalised in these patients.

3. Inflammation-endocrinology and metabolism interaction

Apart from all the mechanisms discussed above regarding how inflammation itself could be detrimental to the brain and how inflammatory response system (IRS) is involved in psychiatric disorders, the interaction between IRS and endocrine system and metabolism could induce greater degree of damage to the brain. Among the different endocrine systems, this chapter will be focused on the stress hormones system which is the most involved in inflammatory reaction. In the same manner, among the different metabolic pathways, the tryptophan metabolism and glycolysis pathways will be mainly discussed in this chapter due to their significant involvement in neurochemical changes related to psychiatric disorders.

3.1 Inflammation and stress hormones interaction

Hypothalamo-pituitary-adrenal (HPA) axis is the key stress hormone axis which has interaction with immune activation and inflammation. Investigations of the role of the HPA axis in the psychopathology of depression commenced over 40 years ago when it was reported that depressed patients have a higher circulating plasma cortisol concentration than those that are not depressed (Board et al., 1957; Sachar et al., 1970). It was discovered that this synthetic glucocorticoid would normally suppress the secretion of cortisol by activating hypothalamic and pituitary glucocorticoid receptors thereby suppressing the

secretion of corticotrophin releasing factor (CRF) and adrenocorticotrophic hormone (ACTH), which in turn, reduced the activation of the adrenal cortex and the release of cortisol. The mechanism whereby these changes occurred was explained in terms of a negative feed-back loop whereby the raised plasma glucocorticoid concentration controls the further release of the steroid. However, it soon became apparent that in patients with major depression, the negative feed-back loop ceased to function due to the desensitization of the central glucocorticoid receptors. The negative dexamethasone suppression test thereby became a diagnostic marker of melancholic depression (Carroll et al., 1968a, b). As in major depression, it was reported in a systematic review that the evidence for elevated basal cortisol was consistently observed in first-episode, drug-naïve schizophrenia patients (Bradley and Dinan, 2010) although some studies reported negative finding (Strous et al., 2004).

It is frequently assumed that the synthetic glucocorticoids such as dexamethasone, act on glucocorticoid receptors in an identical manner to the natural glucocorticoids such as cortisol. This may not be the case. Dexamethasone acts primarily on the glucocorticoid receptors in the anterior pituitary, does not readily enter the brain and therefore differs substantially from natural glucocorticoids that activate both mineralocorticoid and glucocorticoid receptors (Trapp and Holsboer, 1996). There is also evidence that while dexamethasone may reduce the release of CRF, it does not suppress the release of arginine vasopressin (AVP). There is evidence that AVP, not CRF, is the main activator of the HPA axis due to chronic stress and major depression (Scott and Dinan, 1998). Although very little has been studied on CRF in schizophrenia, there are reports regarding increase AVP in schizophrenia (de Leon et al., 1994; Raskind et al., 1975). The increased action of AVP is further exacerbated by the action of IL-1β and IL-6; chronic immune activation is related more to AVP than CRF in the activation of the anterior pituitary (Raber and Bloom, 1994). In this way, chronic immune activation could induce abnormal HPA axis in both depression and schizophrenia.

On the other hand, recent in vivo evidence suggests that stress-induced elevation of glucocorticoids also enhances immune function within the central nervous system (CNS) through microglia activation and proliferation and with a loss in the number and volume of astrocytes (Czeh et al., 2006). Animal studies show that stress induces an enhanced expression of proinflammatory factors such as IL-1β (Pugh et al., 1999), macrophage migration inhibitory factor (MIF) (Bacher et al., 1998; Niino et al., 2000; Suzuki et al., 2000) and COX-2 (Madrigal et al., 2003) in the brain. Elevation of these proinflammatory factors is accompanied by dendritic atrophy and neuronal death within the hippocampus (Sapolsky, 1985; Woolley et al., 1990), which are also found in brains of subjects with major depression. These detrimental effects of glucocorticoids in the CNS are mediated by a rise in extracellular glutamate (Aucott, 1994; Stein-Behrens et al., 1994) and subsequent over-stimulation of the NMDA (N-methyl-D-aspartate) receptor. Such an over-stimulation of the NMDA receptor results in excitotoxic neuronal damage (Takahashi et al., 2002). Nair and Bonneau could demonstrate that restraint-induced psychological stress stimulates proliferation of microglia, which was prevented by blockade either of corticosterone synthesis, of the glucocorticoid receptor, or of the NMDA receptor (Nair and Bonneau, 2006). These data show that stress-induced microglia proliferation is mediated by corticosterone-induced and NMDA receptor-mediated activation within the CNS. Moreover, NMDA receptor activation during stress leads again to increased expression of

COX-2 and PGE2. Both, COX-2 and PGE2 per se are able to stimulate microglia activation. Therefore, a vicious circle may be induced, if the stress response is not limited, as in most of the psychiatric disorders.

3.2 Inflammation-stress hormones-tryptophan metabolism interaction

Not only the interaction between inflammation and stress hormones but also their further interaction with tryptophan metabolism brings the whole complex pathway to attention in psychiatric disorders. Tryptophan is an essential amino acid which has indole ring structure and is obtained from the dietary source approximately 20 nmol/day. The reference value of plasma tryptophan ranges from 45 to 60 nmol/l (Eynard et al., 1993). Of those, 50 to 85% are bound to albumin in unstable manner (Yuwiler et al., 1977). Serotonin is synthesized from about 1% of the available tryptophan in the body. Main serotonin synthesis occurred in the enterochromaffin cells in the gut and 10 to 20% occurred in the brain after crossing blood brain barrier (BBB). The central availability of tryptophan mainly depends on the competition by the large amino acids at the transport across BBB and partially depends on the cerebral demand (Fernstrom, 1977). About 99% of tryptophan is metabolized in the liver by the tryptophan 2,3-dioxygenase (TDO) (Watanabe et al., 1980). The TDO activity is mainly controlled by the tryptophan level itself and therefore, its activity is generally stable. After tryptophan is catabolised into kynurenine (KYN), it is further catabolised into 3-hydroxy-kynurenine (3HK) by kynurenine-3-monooxygenase (KMO) enzyme. After 3HK, further degradation continues to 3-hydroxyanthranilic acid (HAA) through the action of kynureninase. After that, the catabolism proceed either into complete oxidation pathway and forms adenosine triphosphate (ATP) which occurs mainly in the liver, or into quinolinic acid (QUIN) which is finally degraded into nicotinamide adenine dinucleotide (NAD). From the complete oxidation pathway, picolinic acid (PIC) is also formed in small quantity. In physiological condition, the catabolism goes mainly to ATP formation and only minor portion goes to NAD formation (Leklem, 1971). KYN can also be catabolised by the kynurenine aminotransferases (KATs) into kynurenic acid (KYNA) (Figure-2). This metabolism in the liver is more or less stable and age and gender has influence on this metabolism (Leklem, 1971) especially in terms of excretion of the metabolites of further downward KYN pathway. The formation of tryptophan to nicotinic acid and its derivatives is important and the impaired condition could result in the disease pellagra. Moreover, since ATP formation in the cells is dependent on NAD, depletion of NAD is fatal to the cells especially if the cell is under stress. In normal state, to get normal NAD requirement, QUIN synthesis occurs only transiently in the liver and QUIN does not accumulate in the hepatocytes (Bender, 1989).

Since KYN itself could be transported across the blood brain barrier, on top of the kynurenine formed in the brain by tryptophan breakdown, extra KYN is available from the periphery for further kynurenine metabolism in the brain. Sixty percent of brain KYN was contributed from the periphery (Gal and Sherman, 1980). In the brain, tryptophan catabolism occurs mainly in the astrocytes and microglia (Grant and Kapoor, 1998; Grant et al., 2000; Heyes et al., 1996). Although some neurons also posses indoleamine 2,3-dioxygenase (IDO) and/or TDO2 (Miller et al., 2004), neurons are not the main sites of kynurenine pathway in the brain. While the human astrocytes are shown to produce mainly KYNA because of lack of KMO enzyme, microglia and macrophages produce mainly QUIN (Guillemin et al., 2001; Guillemin et al., 2000; Guillemin et al., 2005a). The astrocytes

metabolize QUIN produced by the neighbouring microglia (Guillemin et al., 2001). In the brain, in physiological condition without immune challenge, as in the liver, this kynurenine pathway may serve mainly for glycogen storage and synthesis of small amount of NAD required for the central nervous system (Leklem, 1971).
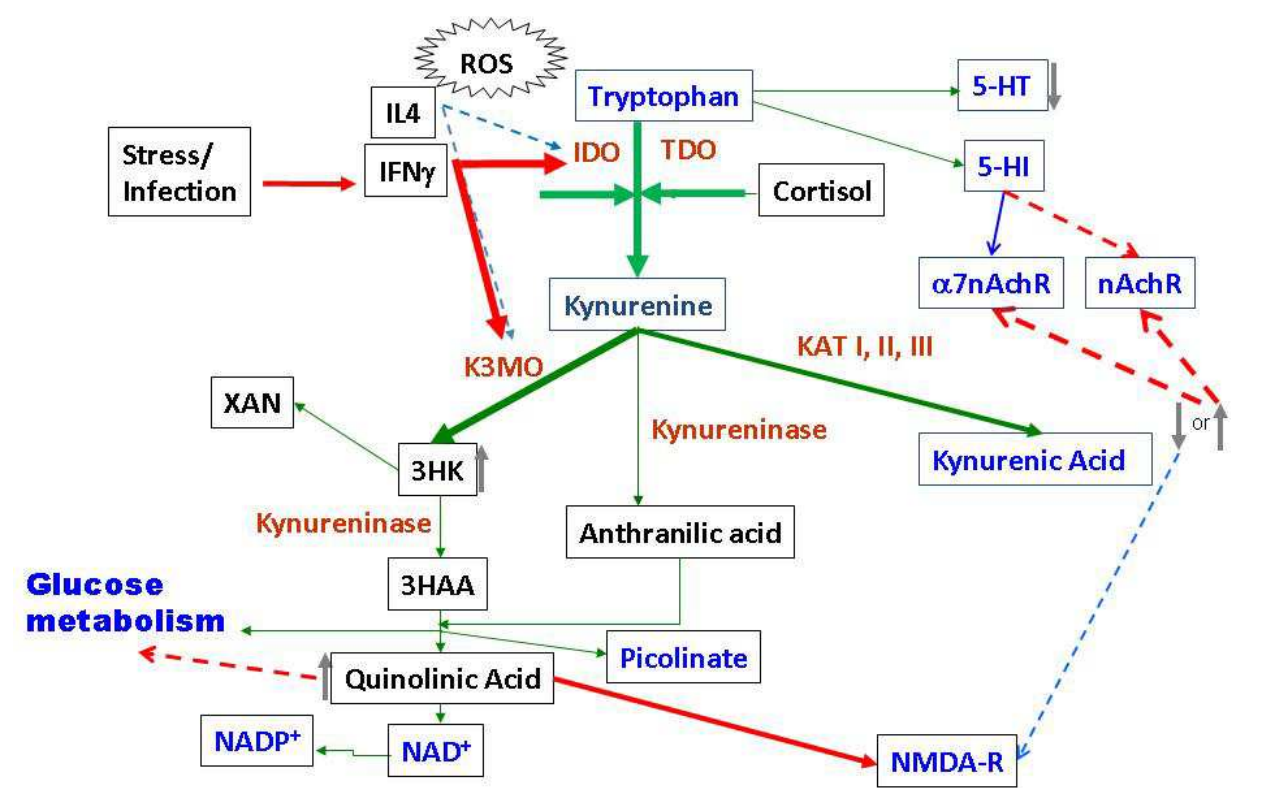

Fig. 2. Immune-NeuroEndocrine-Tryptophan Interaction (adapted from Myint et al, 2009)

In case of inflammation, infection or oxidative stress which activates the enzyme IDO in the extrahepatic tissues, such as, lungs, placenta, kidneys, spleen, blood and the brain (Heyes et al., 1993; Mellor and Munn, 1999), the extrahepatic tryptophan metabolism shifts the tryptophan metabolism away from the liver (Moffett et al., 1998). In this case, tryptophan breakdown through KYN pathway occurs mainly in the blood and lymphoid tissues (Moffett and Namboodiri, 2003). The IDO activity is enhanced by pro-inflammatory cytokines such as interferon-γ (IFNγ) (Carlin et al., 1987; Yasui et al., 1986), and inhibited by the anti-inflammatory cytokine IL4 (Musso et al., 1994). As discussed above, in case of stress or related conditions, such as inflammation, HPA axis activity will be enhanced and glococorticoid secretion is increased. In this situation, TDO activity is further enhanced by glucocorticoids (Knox, 1951; Salter and Pogson, 1985). Although not many studies have been carried out on the interaction between stress hormones or glucocorticoids and TDO, some studies have demonstrated that hepatic TDO activity can be enhanced via glucocorticoid mediated transcriptional activation (Nakamura et al., 1987), although hepatic heme is the essential requirement in this activation (Ren and Correia, 2000). This activation of TDO by stress hormone will induce further increase in tryptophan breakdown, and as a result, the KYN formation becomes much higher than physiological condition. Since the liver cell uptake of KYN is not efficient for extrahepatic KYN, the further KYN pathway mainly occurs extrahepatically. The activity of KMO is also enhanced by pro-inflammatory

cytokines (Mellor and Munn, 1999). Therefore, in case of inflammation, the formation of 3HK becomes enhanced much faster than KYNA formation and the balance between formation of 3HK and KYNA shifted to 3HK side. In the presence of inflammation, activated monocytes are found to be the robust producers of QUIN (Chiarugi et al., 2001). During inflammation, QUIN production persists till the inflammatory process is completed (Heyes and Lackner, 1990). Since some of the KYN metabolites activate inflammatory reaction, this could further prolong the QUIN synthesis (Melillo et al., 1993), whereas some of the metabolites inhibit the proliferation of T cells and NK cells (Frumento et al., 2002) and inhibit the further inflammatory process and stop further QUIN formation. In this way, immune tolerance is achieved through tryptophan depletion and homeostasis in KYN pathway is maintained.

Therefore, in case of acute inflammation, the transient disturbances in the tryptophan metabolism will take place through; (1) effect of inflammatory mediators on IDO activity and (2) interaction between glucocorticoid and TDO activity. This might be one of the reasons that could induce sickness behaviour during acute inflammation. In fact, all those changes are some how necessary for the body homeostatic mechanism to regulate the inflammatory response and to generate the energy that the body requires during acute inflammation.

4. Inflammation-tryptophan metabolism-neurochemicals interaction

The frontiers in the field of interaction between tryptophan metabolism and neurochemicals proposed that the tryptophan shunted away from the serotonin synthesis towards degradation into kynurenine as a mechanism involved in the psychiatric disorders (Lapin and Oxenkrug, 1969; Mangoni, 1974). Based on this mechanism several studies have been carried out in tryptophan and kynurenine changes in depressive disorders. One very early study on plasma kynurenine levels in depressed patients and controls demonstrated lack of significant difference between the groups (Wood et al., 1978), whereas, another study on plasma neutral amino acids and tryptophan in mania and depressed patients demonstrated reduced tryptophan availability in the patients compared to healthy controls (Moller and Amdisen, 1979). At the same time, a post mortem study was carried out on tryptophan metabolism and schizophrenia. The investigators reported the increased tryptophan and kynurenine in the brain of schizophrenia without evidence of generalized deficit in serotonin (Jospeh et al., 1979).

After the discovery of the effect of pro-inflammatory cytokines on IDO enzyme activity (Carlin et al., 1987; Yasui et al., 1986) and the interaction between glucocorticoids and TDO activity (Knox, 1951; Nakamura et al., 1987; Salter and Pogson, 1985), the link between inflammatory state, tryptophan metabolism and serotonergic neurotransmission became of interest in the field of psychoneuroimmunology. Somehow, the report of a study on QUIN and kynurenine pathway metabolism in different inflammatory and non-inflammatory neurological diseases brought this field forward although it failed to show the significant association between metabolites in the CSF and psychiatric disorder such as depression (Heyes et al., 1992). Since that time many research groups focussed on tryptophan breakdown and psychiatric disorders such as depression, anxiety disorders and schizophrenia.

4.1 Interaction with serotonergic neurotransmission

As discussed above, in the brain, the inflammatory state enhanced tryptophan breakdown and that in turn induces low availability of tryptophan for serotonin synthesis (Lapin and Oxenkrug, 1969; Mangoni, 1974). Unlike TDO, the enzyme IDO is not specific to tryptophan alone but degrades any compound with indole ring. Therefore, in case of inflammation and IDO activation, serotonin is degraded not only by monoamine oxidase (MAO) into 5-hydroxyindole acetic acid (5HIAA), but also by IDO into formyl-5-hydroxykynuramine (f5OHKYM) (Pertz and Back, 1988). This further reduces the serotonin availability for optimal serotonergic neurotransmission.

The earliest study on interaction between pro-inflammatory cytokines, tryptophan degradation and depression was carried out on patients with chronic active hepatitis C who were treated with IFNα which is a pro-inflammatory cytokine (Maes et al., 2001) . The investigators have demonstrated the association between increased in serum IL-8, serum kynurenine to tryptophan ratio that indicates increased tryptophan breakdown and depression rating scales. Unfortunately, there was no data on serotonergic neurotransmission. However, another study on IFNα therapy but in melanoma patients, also demonstrated that, in antidepressant-free patients under IFNα treatment, the decreases in serum tryptophan correlated with depressive, anxious, and cognitive symptoms, but not neurovegetative or somatic symptoms (Capuron et al., 2003). The author stated that those associations were not observed in those treated with paroxetine, a selective serotonin reuptake inhibitor (SSRI). At least, this study indirectly indicated that the development of symptoms in association with serum tryptophan level was related to insufficient serotonergic neurotransmission since paroxetine treated patients showed lack of those associations.

The occurrence of depression during pregnancy or post-partum period was also considered to be associated with inflammatory state (Maes et al., 2000) and serotonergic neurotransmission (Gu et al., 2003). A study demonstrated that the tryptophan breakdown was increased in pregnant women than non-pregnant women and the difference was more pronounced in those with anxiety and depression (Maes et al., 2002). Another study also demonstrated that low mood in post-partum period was associated with continuously low serum tryptophan after the delivery due to increased degradation into kynurenine (Kohl et al., 2005). Taken altogether, there is again, another circumstantial evidence of relationship between inflammatory state, tryptophan degradation and serotonergic neurotransmission.

There is only one study which investigated on association between complete triad of inflammation, kynurenine level and serotonin in the blood of the patients with pure major depression (Mackay et al., 2009). This study demonstrated the association between kynurenine levels and degree of depression in the patients treated with SSRI fluoxetine. Here again, there is no proof of direct association between inflammation, tryptophan degradation and serotonergic abnormalities in depression. Regarding the association between tryptophan degradation and serotonergic neurotransmission in schizophrenia, only one post-mortem study (Jospeh et al., 1979) and one CSF analyses study were carried out (Issa et al., 1994). Although the post-mortem study could show the increased tryptophan and kynurenine in the brain of the patients, and CSF study could demonstrate the reduced tryptophan level in the schizophrenia group, both studies failed to demonstrate the association with serotonergic neurotransmission.

Although there is no experimental study showing the direct relationship between increased IDO activity, tryptophan breakdown and reduced serotonergic neurotransmission, the circumstantial evidences from human studies in depression indicated the association between pro-inflammatory states, increased tryptophan breakdown and impaired serotonergic neurotransmission.

4.2 Interaction with glutamatergic and dopaminergic neurotransmission

The disturbance in glutamatergic neurotransmission is one of the common pathways involved in the pathophysiology of depression and schizophrenia. The first findings indicating the involvement of glutamatergic neurotransmission in mood disorders based on the preclinical data with N-methyl-D-aspartate receptor (NMDA-R) antagonist, ketamine (Silvestre et al., 1997). The antidepressant effect of NMDA-R antagonist, ketamine, was also reported in depressed patients (Berman et al., 2000). The hypofunctioning of glutamatergic neurotransmission as part of the pathophysiology of schizophrenia was proposed based on the finding of low glutamate concentrations the CSF of schizophrenia patients (Kim et al., 1980). Unlike in depression, NMDA-R antagonist, ketamine could enhance the neurochemical reaction of amphetamine-induced dopamine release in healthy controls mimicking the neurochemical reaction in schizophrenia patients (Kegeles et al., 2000).

As explained before, during inflammation and enhanced tryptophan breakdown, extra amount of peripheral KYN becomes available for the further KYN metabolism in the brain, since KYN can be transported across BBB. In case of pro-inflammatory state in the brain, the KYN metabolism in the astrocytes and microglia might also be enhanced. Therefore, the kynurenine pathway is highly activated in the brain. The KYN metabolites contribute directly to the neuroprotective-neuro-degenerative changes in the brain through direct effects on several neurotransmissions. The QUIN is a NMDA-R agonist (Bender and McCreanor, 1985) and accumulation of QUIN could result in excitotoxicity. It was reported in an in-vitro study that the metabolite QUIN could induce selective apoptosis to astrocytes (Guillemin et al., 2005b). 3HK causes neuronal apoptosis (Okuda et al., 1998) while QUIN causes excitotoxic neurodegenerative changes (Schwarcz et al., 1983). However, KYNA is the NMDA-R antagonist (Perkins and Stone, 1982) and is protective against excitotoxicity of QUIN (Kim and Choi, 1987).

Therefore, the pro-inflammatory status in major depression would activate not only IDO (Carlin et al., 1987; Yasui et al., 1986) but also KMO enzyme activities (Mellor and Munn, 1999) and this might in turn shift the KYN metabolism to the 3HK and QUIN arm with possible reduction in KYNA (Figure-2). The changes in NMDA-R agonist and antagonist, QUIN and KYNA might have impact on glutamatergic neurotransmission. Moreover, it was proposed that the increased in those toxic metabolites imbalanced to formation of KYNA might prime the astrocytes-microglia-neuronal network to be vulnerable to environmental factors such as stress. It was also proposed that, the imbalanced KYN pathway induced impaired glial-neuronal network might contribute to the recurrent and chronic nature of major depression (Myint and Kim, 2003). The neurotoxic metabolites might induce astrocytes apoptosis and certain neuronal apoptosis which would bring the glial-neuronal network weaker and reduction in syntheses of neurotrophic factors and prime the system to be vulnerable to stress and get psychiatric consequences. The loss of astrocytes might further induce glutermatergic abnormalities also through disturbance in glutamate-glutamine metabolism.

In patients with major depression who are drug naïve or medication free for at least 4 months, an imbalance between those neuroprotective and neurotoxic pathways with lower protective metabolite has been and demonstrated (Myint et al., 2007b). The ratio between KYNA and KYN (KYNA/KYN) which indicated how much of KYN would be degraded into KYNA was significantly lower in depressed patients than healthy controls. Moreover, 6-week medication with currently available antidepressants, mainly, selective serotonin reuptake inhibitors (SSRIs) could not reverse the metabolic imbalance in KYN pathway back to normal. We have hypothesized that such an uncorrected imbalance with higher 3HK and QUIN to KYNA ratios, in the long term, might induce further loss of astrocytes and neurodegenerative changes that in turn induces the chronicity, treatment resistance and progression of the disease. In major depression, there are evidences of neurodegenerative changes and loss of astrocytes (Rajkowska et al., 1999). In addition, the decreased glutamate and glutamine levels in pregenual anterior cingulate cortex of depressed patients with associated severity of clinical symptoms have been reported (Auer et al., 2000; Rosenberg et al., 2005).

Not only in adult depression but also in adolescent depression, the kynurenines seem to play a role. A recent study reported that in magnetic resonance (MR) spectroscopy in melancholic depressed adolescents, the choline levels which indicated the turnover of cells showed positive correlation with serum KYN and HAA/KYN ratio (Gabbay et al.). This study also demonstrated that the serum KYN and HAA/KYN ratios were significantly increased in those adolescents with melancholic depression than non-melancholic depression. Moreover, it was reported in this study that the serum KYN and HAA/KYN were positively correlated with depression scores. It could be concluded that the shift in KYN pathway more to the arm of 3HK, HAA and QUIN is involved also in adolescent melancholic depression.

In case of cytokine therapy induced depression, such as, IFNα therapy induced depression, increase in IL-6 and decrease in KYNA or increased in KYN/KYNA showed significant association with development of depressive symptoms (Wichers et al., 2005). However, another study showed that both KYNA and QUIN were increased in IFNα treated patients (Raison et al.), although the ratio between metabolites from these two arms was not reported. Nevertheless, both studies indicated the enhanced TRP degradation and change of KYN metabolites after immune challenge with IFNα and the depressive episodes were the consequences.

Further evidences also arise from animal experiments regarding the association between inflammation, tryptophan metabolic pathway abnormalities and depression. O'Connor and group demonstrated that lipopolysaccharide induced depressive behaviour through the action of enhanced IDO enzyme activity (O'Connor et al., 2009c). This group also demonstrated in the bacille Calmette-Guérin (BCG) mouse model of depression (O'Connor et al., 2009b) that immune activation using BCG could induce depressive behaviour and activation of IDO enzyme activity followed by activation 3-hydroxyanthranillic acid oxidase (HAAO) enzyme which enhance degradation of HAA and that in turn enhances the formation of neurotoxic QUIN. Moreover, blockade of IDO was demonstrated to prevent the depressive behaviour. In another study, IFNγ knock-out mice did not show the depressive behaviour when challenged with BCG since IFNγ is the inducer of IDO enzyme (O'Connor et al., 2009a). These evidences indicate that manipulating the KYN pathway could be a novel therapeutic strategy for counteracting depression.

Regarding bipolar mania, increased expression of TDO2 in anterior cingulate gyrus of post-mortem brain tissues from bipolar patients was reported (Miller et al., 2006). There is only one study reported on kynurenines changes in the plasma of bipolar mania patients (Myint et al., 2007a). It was reported that in bipolar mania patients, there was no significant reduction in KYNA, even though a trend of decrease was observed. Moreover, it was reported in that study that 6-week treatment with currently available mood stabilizers did not show any changes. Although the pro-inflammatory state in bipolar disorder was not clearly stated, there are some reports on pro-inflammatory state in bipolar disorders (Kim et al., 2007). The pro-inflammatory state induced kynurenines imbalance may also be involved in the pathophysiological mechanism of bipolar disorders. Further more detailed studies are still necessary to find out the interaction between immune status, tryptophan metabolism and neurotransmitter function in bipolar disorders.

In case of schizophrenia, a study in post-mortem brain tissue in different cortical regions revealed increased KYNA levels in schizophrenic samples compared to a control sample, particularly in the prefrontal cortex (Schwarcz et al., 2001). Another investigation in the amygdala, a small and nonsignificant increase of KYNA in medicated schizophrenics was observed (Miller et al., 2006). Those studies raised a question as to whether the increase in KYNA might be associated with antipsychotic medication. However, the increased levels of KYNA was also observed in the CSF of schizophrenic patients (Erhardt et al., 2001). Since most of the patients in this study were drug-naive first-episode patients, this increase could not be caused by antipsychotic treatment. It was hypothesized that accumulation of KYNA may lead to schizophrenic symptoms (Erhardt et al., 2003). An experiment in rat demonstrated that KYNA concentration significantly reduced in hippocampus, striatum and prefrontal cortex after one month treatment with antipsychotics, haloperidol, clozapine and raclopride (Ceresoli-Borroni et al., 2006). This study also demonstrated that one year treatment with haloperidol still continue reduction in KYNA concentration in the interstitial fluid of the rat brain.

Since prefrontal cortex area is involved in the pathophysiology of schizophrenia (Andreasen et al., 1992) the increase in KYNA might be involved in pathophysiological mechanism. Since KYNA is the NMDA-R antagonist, it could be concluded that the development of psychotic symptoms are associated NMDA-R antagonism. KYNA is the antagonist of all three ionotropic excitatory amino acid receptors (Perkins and Stone, 1982). Even though KYNA is generally considered as protective metabolite against QUIN, its abnormal accumulation beyond physiological level could induce glutamatergic hypo-functioning and might disturb cognitive function (Olney et al., 1991). Moreover, while one of tryptophan metabolites 5-hydroxy indole (5HI) activates the α7-nicotinic acetylcholine receptor (α7nAchR) and induces glutamate release (Mannaioni et al., 2003; Zwart et al., 2002), KYNA is an antagonist of α7nAchR (Hilmas et al., 2001). Since KYNA down-regulate the permissive role of 5HI activation on α7nAchR, the accumulation of KYNA could suppress α7nAchR function and induce disruption of auditory sensory gating (Shepard et al., 2003). In addition, it was reported that KYNA inversely regulates the dopaminergic tone (Wu et al., 2007). In this context, 5HI and KYNA exert synergistic action on dopaminergic neurotransmission. These interactions of KYNA with other neurotransmitters such as 5HI could contribute to some behavioural or cognitive consequences such as psychosis and cognitive impairment other than neurodegenerative changes.

Not only the positive symptoms but also the negative symptoms are part of the psychopathology of schizophrenia. There are also considerable evidences of loss of brain volume in schizophrenia (Takahashi et al., 2009). Unfortunately, the tryptophan research in schizophrenia most of the studies concentrated only on KYNA. There is only one group reported on 3HK (Condray et al., 2011; Yao et al.) although no clear change was demonstrated and no balance between potentially neuroprotective metabolite, KYNA, and neurotoxic metabolites such 3HK was investigated. Nevertheless, this group has demonstrated the association between 3HK and (1) total symptoms score at the time of recruitment, and (2) response of positive symptoms to 4-week neuroleptic treatment in first episode neuroleptic naïve schizophrenia patients. The associations between negative symptoms, brain volume changes and potentially neurotoxic metabolites in the pathophysiology have been ignored in schizophrenia research. Most of the therapeutic possibilities proposed are to manipulate KYNA (Erhardt et al., 2009). Without knowledge of interaction between different potentially neuroprotective and potentially neurotoxic metabolites, manipulation of just one metabolite would raise an issue regarding the potential untoward neurotoxic effects in the patients. Our recent finding in medication naive schizophrenia patients indicated increased 3HK and decreased KYNA in the plasma compared to healthy controls (Myint et al., 2011) and it was reversed by 6 weeks antipsychotic treatment. This would be the indirect indicator of accumulation of 3HK due to enhanced KMO activity induced by pro-inflammatory statues in schizophrenia. As discussed in depressive disorders, this might further lead to increase NMDA-R agonist QUIN in certain brain areas and excitotoxicity. To answer the question on clear interaction of inflammation, tryptophan breakdown and glutamatergic neurotransmission is more complicated.

4.3 Interaction with cholinergic and adrenergic neurotransmission

In pro-inflammatory state, although the balance between 3HK and KYNA might generally shift to 3HK arm, because of the general increase of KYN the formation of KYNA may also be higher than normal state. Since it is NMDA-R antagonist, well balanced increase may counteract the negative effects of QUIN through NMDA-R and the homeostasis will be maintained. As mentioned before, in schizophrenia, there is considerable evidence of increase formation of KYNA observed both in CSF (Erhardt et al., 2001) and at certain areas of the brain (Schwarcz et al., 2001). Also a study on IFNα treated patients show increase of both KYNA and QUIN in the CSF (Raison et al., 2010). In those cases, consequences of increase KYNA may induce negative impact on other neurotransmissions.

Apart from the interaction with α7nAchR, the metabolites 5HI and KYNA also have interaction with non-α7nAchR. The metabolite 5HI was reported to inhibit non-α7nAchR mediated release of noradrenaline (NA), dopamine (DA) and acetylcholine (Ach) (Grilli et al., 2006). Similarly, KYNA inhibit the function of the non-α7nAchR by reducing the expression of those receptors (Hilmas et al., 2001). Therefore, inhibition of non-α7nAchR by increased KYNA could also disturb cholinergic and noradrenergic neurotransmission.

Therefore, inflammatory state induced increased in KYNA could play part of the pathophysiology of noradrenergic neurotransmission in psychiatric disorders.

5. Future perspectives

The findings discussed above are the clear evidences that the interaction between immune activation and tryptophan metabolism and kynurenine pathway is involved in

pathophysiology of major psychiatric disorders. The manipulation of this metabolism is of interest for future therapeutic development and several studies are focusing on this aspect. There are some enzyme inhibitors that are already developed. However, it is important to consider the possible occurrence of imbalance between different metabolites when a particular enzyme is blocked or manipulated to enhance or reduce the particular metabolite. Therefore, such manipulation should be carried out with clear indication such as evidence of change in metabolites or ratios between metabolites as biomarkers. Moreover, close monitoring on those changes during therapy would also be necessary. Since TRP metabolism is the metabolism in which there is crosstalk between peripheral and central, use of peripheral markers as indirect evidence of central changes for diagnostic and prognostic purpose is not unrealistic.

Future studies should be carried out not only on manipulation of the metabolism for therapeutic purpose but also on the use of KYN pathway metabolites as biomarkers in evidence based management for early detection, choice of correct medication and monitoring. The normal values of those metabolites in different population are not yet known. Clear association between central and peripheral markers should be investigated. The validation of the usefulness of those biomarkers should be carried out in multicentre approach. Since currently available technologies to detect those metabolites are expensive and sophisticated, the studies on development of user-friendly and cost-effective technologies for detection of those metabolites are also necessary to be carried out.

The indirect manipulation of this pathway through anti-inflammatory medication could be considered as another therapeutic strategy. The indirect manipulation of this pathway through anti-inflammatory medication could also be another strategy. The use of COX-2 inhibitor celecoxib as add-on therapy to standard anti-depressant or anti-psychotics is a promising approach. The prevention of inflammation and oxidative stress using some medications such as n3-fatty acid which is more or less harmless or lifestyle intervention through diet, exercise and mindfulness practices could also be an option. However, this type of treatment should start timely and kynurenines could be the possible biomarkers as early indicators of immune-metabolic-neurochemical imbalances.

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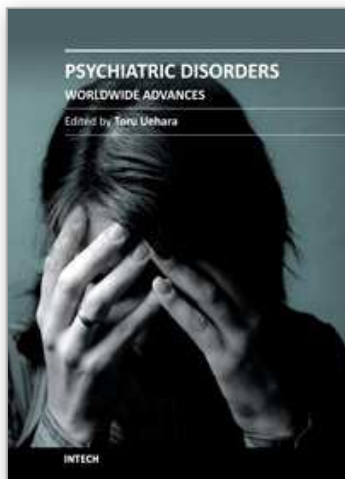
Psychiatric Disorders - Worldwide Advances

Edited by Dr. Toru Uehara

A psychiatric disorder is defined as any complex condition that involves the impairment of cognitive, emotional, or behavioral functioning. Aside from knowing the physical organic factors, its causal pathology has remained a mystery. Regarding recent advances in psychiatry and neurosciences, psychiatric disorders have been closely associated with socio-cultural, psychological, biochemical, epigenetic or neural-networking factors. A need for diverse approaches or support strategies is present, which should serve as common knowledge, empathetic views or useful skills for specialists in the filed. This book contains multifarious and powerful papers from all over the world, addressing themes such as the neurosciences, psychosocial interventions, medical factors, possible vulnerability and traumatic events. Doubtlessly, this book will be fruitful for future development and collaboration in â€œworld psychiatryâ€.

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