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Immune changes and neurotransmitters: Possible interactions in depression?

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ABSTRACT

A disturbed metabolism of catecholamines and other neurotransmitters appears to play a major role in the pathogenesis of neurospychiatric symptoms, such as changes in mood and depression. This symptomatology is common in patients with chronic inflammatory disorders such as infections, autoimmune diseases, or cancer. The pathogenesis of these symptoms is still unclear. Pro-inflammatory stimuli interfere not only with the neural circuits and neurotransmitters of the serotonergic system but also with those of the adrenergic system. The pro-inflammatory cytokine interferon-γ stimulates the biosynthesis of 5,6,7,8-tetrahydrobiopterin (BH_4), which is a co-factor for several aromatic amino acid mono-oxygenases and is rate-limiting for the biosynthesis of the neurotransmitter serotonin and the catecholamines dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline). Interferon-γ triggers the high output of reactive oxygen species in macrophages, which can destroy the oxidation-labile BH_4. Recent data suggests that oxidative loss of BH_4 in chronic inflammatory conditions can reduce the biosynthesis of catecholamines, which may relate to disturbed adrenergic neurotransmitter pathways in patients.

1. Introduction

1.1. Epidemiological and pathophysiological aspects of depression

Major depressive disorder (MDD) is a heterogeneous disease characterized by low mood and anxiety, loss of interest and pleasure in normally enjoyable activities, as well as loss of energy. Neurocognitive impairment, neurovegetative and somatic symptoms are also common clinical symptoms of MDD.

In high income countries, the average lifetime prevalence of MDD is approximately 15% countries. Approximately 5.5% of the general population has been diagnosed within the past 12 months (Bromet et al., 2011). The World Health Organization (WHO) ranks MDD as the fourth leading cause of disability worldwide and projects that by 2030, it will be the second leading cause (Mathers and Loncar, 2005). MDD represents a serious and often recurrent disorder. Depressed patients experience reduced general functioning and quality of life, as well as increased physical morbidity and mortality (Spijker et al., 2004; Üstün et al., 2004). Several studies have shown that MDD predicts the onset and the progression of both physical and social disability (Bruce et al., 1994; Penninx et al., 1998). The 12-month prevalence rates of mental disorders, especially MDD, are 1.5 to 2 times higher in patients with chronic somatic diseases compared to the general population (Harter et al., 2007). In general hospitals, depressive disorders are present in 10 to 60% of somatically ill patients, depending on the somatic diagnosis. In the first month after myocardial infarction, the incidence for MDD increases between 15% and 30% (Strik et al., 2004) and systematic reviews of prognostic studies have identified co-morbid depression as a consistent predictor of adverse outcome, including mortality (Kuper et al., 2002; Strik et al., 2004).

In contrast to this significant burden of disease, rates of diagnostic recognition of MDD are poor (35%–45%) (Hansen et al., 2001; Hardman et al., 1989; Harter et al., 2004; Ormel et al., 2008; Wancata et al., 2000). Furthermore, only a part of diagnosed patients are provided with adequate treatment. Ormel et al. (2008) found that in high-income countries severely disabling mental disorders are only half as likely to be treated, compared to serious disabling physical disorders (35.3% *vs.* 77.6%).

Although the exact pathophysiological mechanism of MDD is still not known, dysfunction in the monoamine systems of neurotransmitters 5-HT, NE and DA appears to be involved in the pathogenesis when monoamine depletion was found to influence mood. Evidence for this hypothesis came from clinical observations and animal experiments, which showed that the antihypertensive drug reserpine,

Abbreviations: BH_4, 5,6,7,8-tetrahydrobiopterin; DA, Dopamine; L-DOPA, L-3,4-dihydroxyphenylalanine; GCH, GTP cylohydrolase I; HIV, human immunodeficiency virus infection; HUVEC, human umbilical vein endothelial cells; IDO, indoleamine 2,3-dioxygenase; IFN-α -ß -γ, interferon-α, -ß, -γ; Kyn/Trp, kynurenine to tryptophan ratio; LPS, lipopolysaccharide; NA, noradrenaline; NET, norepinephrine transporter; NO, nitric oxide; $ONOO^-$, peroxinitrite; O_2^-, superoxide anion; PAH, phenylalanine 4-hydroxylase; Phe/Tyr, phenylalanine to tyrosine ratio; PKU, phenylketonuria; ROS, reactive oxygen species; 5-HT, Serotonin; TDO, tryptophan 2,3-dioxygenase; TNF-α, tumor necrosis factor-α.

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which causes a depletion of presynaptic stores of NE, 5-HT, and DA, induced a syndrome resembling depression. In contrast to the effects obtained with reserpine, euphoria and hyperactive behavior were observed in some patients being treated with iproniazid, a compound synthesized for the treatment of tuberculosis, which increased brain concentrations of NE and 5-HT by inhibiting the metabolic enzyme MAO. These findings were the basis for the development of tricyclic antidepressant agents to influence the monoaminergic neurotransmission in the 50s, followed by the design of serotonergic reuptake inhibitors in the 80s; more recently substances inhibiting the noradrenergic reuptake have become available.

Research on the pathophysiology of MDD revealed that acute monoamine depletion did not decrease mood in healthy controls but only in individuals with a family history of major depressive disorder (Ruhé et al., 2007). This indicates that a monoamine deficiency itself is not sufficient for the development of the clinical syndrome of depression.

MDD represents a complex psychiatric disorder, which is also influenced by psychosocial, environmental, and genetic conditions (Fig. 1). Although it has been difficult to identify single candidate genes, the influence of genetic factors on the development of MDD has been proven in numerous studies, *e.g.* the promoter region of the 5-HT transporter gene (5-HTTLPR) (Caspi et al., 2003; Cervilla et al., 2007; Eley et al., 2004; Kaufmann et al., 2004; Wilhelm et al., 2006) and 5-HT receptor polymorphisms (Kamata et al., 2011). Furthermore, gene–environment interactions showing a relationship between stressful life events and serotonergic genotypes have been reported (Surtees et al., 2006; Uher and McGuffin, 2008). In this context, it has been found that individuals who are homozygous for the short allele of the 5-HTTLPR polymorphisms have an increased activity of the hypothalamic–pituitary–adrenal axis due to psychosocial stress (Gotlib et al., 2008; Jabbi et al., 2007). Present research also focuses on genetic polymorphisms of different enzymes catalyzing the catecholaminergic pathways. Kim et al., 2006 showed that the monoamine transporter gene polymorphisms, 5-HT transporter, and NET are associated with a response to antidepressants with homologous monoamine transporter targets. Combinations of polymorphisms were informative for response and non-response.

Until recently, the role of DA in the etiopathology and treatment of depression (Bottiglieri et al., 2000; Kapur and Mann, 1992; Stein, 2008) was largely ignored. This occurred despite a dopaminergic theory of depression which was proposed more than 35 years ago (Braestrup et al., 1975).

Aside from the dysfunction in the neurotransmitter systems of 5-HT, NE and DA, MDD is associated with a hypothalamic–pituitary–adrenal (HPA) "hyperdrive". Signs and symptoms characteristic for depression include changes in the setpoint of the HPA-system, which in the majority of patients result in an altered regulation of corticotropin (ACTH) and cortisol secretory activity. Knowledge on the functioning of the HPA axis under acute or chronic challenge is also a key to understand the intimate link between stress response and the pathogenesis of depression (Charney and Manji, 2004). Despite the fact that observed changes of HPA regulation are so far not specific for the diagnosis of depression or for any of its clinical syndromes (Holsboer, 2008), altered HPA-axis parameters are considered important biomarkers, particularly in preclinical studies (Fig. 1).

2. Depression and inflammation

During the past 20 years the relationship between depressive symptoms and somatic conditions such as cardiovascular disease, diabetes, cancer, and neurodegenerative disorders has received increasing attention in research. Depressive symptoms may be a secondary reaction to the development of the disease, the disease itself, or to complications and aversive symptoms of the disease; in addition, they may also be related to side effects of medications administered to treat the illness. Aside from these indirect effects, as well as disease-specific direct pathophysiological effects on the brain (*i.e.* stroke or multiple sclerosis), inflammation is the common underlying condition of these chronic somatic diseases (Haroon et al., 2012). Thus, patients who suffer from chronic inflammatory processes due to autoimmune syndromes, infections, or cancer, *etc.*, have an increased risk of developing neuropsychiatric deviations such as fatigue and depression (Dantzer et al., 2008). Similar clinical abnormalities can develop as side effects in patients under treatment with pro-inflammatory cytokines such as interleukins, interferons (IFNs) or tumor necrosis factor-α (TNF-α) (Raison et al., 2006). These observations indicate that cytokine-induced biochemical changes can play a substantial role in the precipitation of neuropsychiatric symptoms (Kim et al., 2007). Genetic studies of polymorphisms in the promoter region of the 5-HT transporter gene 5HTTLPR have indicated an association with

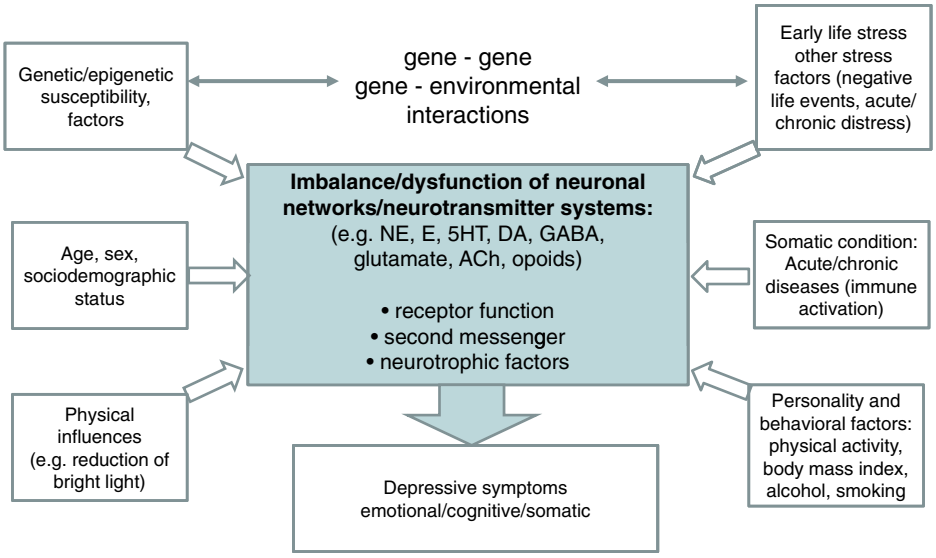

Fig. 1. Etiology and pathophysiology of depressive symptoms. Depression is a heterogenous disease and its development depends on different interacting causes such as genetic and epigenetic factors, which might be influenced by early-life experiences as well as personality and behavior factors but also by somatic conditions like chronic diseases *e.g.*, cardiovascular disease, diabetes, and cancer.