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The new '5-HT' hypothesis of depression: Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression

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ABSTRACT

This paper reviews the body of evidence that not only tryptophan and consequent 5-HT depletion, but also induction of indoleamine 2,3-dioxygenase (IDO) and the detrimental effects of tryptophan catabolites (TRYCATs) play a role in the pathophysiology of depression. IDO is induced by interferon (IFN)γ, interleukin-6 and tumor necrosis factor-α, lipopolysaccharides and oxidative stress, factors that play a role in the pathophysiology of depression. TRYCATs, like kynurenine and quinolinic acid, are depressogenic and anxiogenic; activate oxidative pathways; cause mitochondrial dysfunctions; and have neuroexcitatory and neurotoxic effects that may lead to neurodegeneration. The TRYCAT pathway is also activated following induction of tryptophan 2,3-dioxygenase (TDO) by glucocorticoids, which are elevated in depression. There is evidence that activation of IDO reduces plasma tryptophan and increases TRYCAT synthesis in depressive states and that TDO activation may play a role as well. The development of depressive symptoms during IFNα-based immunotherapy is strongly associated with IDO activation, increased production of detrimental TRYCATs and lowered levels of tryptophan. Women show greater IDO activation and TRYCAT production following immune challenge than men. In the early puerperium, IDO activation and TRYCAT production are associated with the development of affective symptoms. Clinical depression is accompanied by lowered levels of neuroprotective TRYCATs or increased levels or neurotoxic TRYCATs, and lowered plasma tryptophan, which is associated with indices of immune activation and glucocorticoid hypersecretion. Lowered tryptophan and increased TRYCATs induce T cell unresponsiveness and therefore may exert a negative feedback on the primary inflammatory response in depression. It is concluded that activation of the TRYCAT pathway by IDO and TDO may be associated with the development of depressive symptoms through tryptophan depletion and the detrimental effects of TRYCATs. Therefore, the TRYCAT pathway should be a new drug target in depression. Direct inhibitors of IDO are less likely to be useful drugs than agents, such as kynurenine hydroxylase inhibitors; drugs which block the primary immune response; compounds that increase the protective effects of kynurenic acid; and specific antioxidants that target IDO activation, the immune and oxidative pathways, and 5-HT as well.

Abbreviations: 5-HT, serotonin; TDO, tryptophan 2,3-dioxygenase; IDO, indoleamine 2,3-dioxygenase; TRYCATs, tryptophan catabolites; LPS, lipopolysaccharides; SSRIs, selective 5-HT reuptake inhibitors; HPA, hypothalamic–pituitary–adrenal; CAA, competing amino acids; O&NS, oxidative and nitrosative; IL, interleukin; TNF, tumor necrosis factor; NFκB, nuclear factor κB; IFN, interferon; APPs, acute phase proteins; CARS, counter inflammatory response syndrome; IL-1RA, IL-1 receptor antagonist; ROS, radical oxygen species; RNS, radical nitrogen species; NO, nitric oxide; IO&NS, inflammatory, oxidative and nitrosative stress; mCPP, meta-chlorophenylpiperazine; PET, positron emission tomography; ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; CRF, corticotropin-releasing-factor; sIL-2R, soluble interleukin-2 receptor; GPX, glutathione peroxidase; SAR, superoxide anion radical; F&S, fatigue and somatic symptoms; RM, repeated measurements; UCMS, unpredictable chronic mild stress; 5-HTP, 5-hydroxy-L-tryptophan; ICV, intracerebroventricular; BCG, bacille Calmette–Guérin; SERT, serotonin transport activity; BHT, butylated hydroxytoluene; I&ND, inflammatory and neurodegenerative; NMDA, N-methyl-D-aspartic acid; GABA, gamma-aminobutyric acid; GDF, glia depressing factor; EGCG, Epigallocatechin-3-gallate; STAT1, signal transducer and activator of transcription 1.

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1. Introduction

The bioactive neurotransmitter serotonin or 5-hydroxytryptamine (5-HT) is derived from the essential amino acid tryptophan. The synthesis of 5-HT in the brain is highly dependent on the bio-availability of tryptophan in the plasma (Fernstrom, 1983). Catabolism via the oxidative or the so-called kynurenine pathway may divert tryptophan from the 5-HT synthetic route. This pathway, shown in Fig. 1, is the major catabolic route for tryptophan degradation. Ultimately, catabolism of tryptophan leads to the synthesis of nicotinamide and generation of energy via the glutarate pathway. The first step of this pathway, conversion of tryptophan to kynurenine is rate-limiting. Two enzymes catalyze this first step: tryptophan 2,3-dioxygenase (TDO, tryptophan pyrolase EC 1.13.11.11) and indoleamine 2,3-dioxygenase (IDO, EC 1.13.11.52), both leading to kynurenine.

Following induction of IDO or TDO, by stimuli to be discussed, various metabolites are formed from tryptophan, particularly, kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid (see Fig. 1). These tryptophan catabolites (TRYCATs) have multiple effects, e.g. they may act as pro- or antioxidants, are neurotoxic or neuroprotective, may induce apoptosis, and are depressogenic and anxiogenic (Lapin, 2003; Mackay et al., 2006). Since along this pathway many TRYCATs are formed that all have significant (patho) physiological effects, we label this pathway the TRYCAT pathway instead of the classical term kynurenine pathway or other terms, such as quinolinic acid or IDO pathway. The TRYCAT pathway may be activated through TDO that is stimulated by glucocorticoids, or through IDO that is stimulated by pro-inflammatory cytokines, lipopolysaccharides (LPS) and free radicals.

Early antidepressant drugs like iproniazid, imipramine and selective 5-HT reuptake inhibitors (SSRIs) suggested a role for biogenic monoamines, their receptors and transporters in the etiology of mood disorders, the so-called 5-HT hypothesis of depression (Coppen, 1967; Maes and Meltzer, 1995). This '5-HT hypothesis of depression' considered that a diminished synthesis of 5-HT, and hence central diminished stimulation of various 5-HT receptors, e.g. 5-HT1A, 5-HT2C, 5-HT3 etc., and hyposerotonergic activity is associated with the onset of depression (Maes and Meltzer, 1995).

There is now abundant evidence that depression is accompanied by hyperactivity of the hypothalamic–pituitary–adrenal (HPA)-axis, as indicated by increased levels of glucocorticoid levels (Carroll, 1980), and systemic inflammation and cell-mediated immune activation, with increased production of pro-inflammatory cytokines (Maes, 1993, 1995, 2008, 2010). Consequently, these factors would be expected to induce TDO and IDO, respectively, leading to lowered plasma tryptophan in depression.

The aims of the present paper are to review whether a) the lowered availability of plasma tryptophan in depression is caused by increased HPA-axis activity or to systemic inflammation or cell-mediated immune activation, neither or both; b) TDO and/or IDO activation is associated with clinical depression; c) tryptophan depletion and/or the production of TRYCATs are associated with the onset of depression; and d) the same pathways can be detected in animal models of depression. Finally, we review the molecular pathways that may account for the detrimental effects of TRYCAT formation and novel drug targets in the TRYCAT pathway.

2. Plasma tryptophan and brain 5-HT

5-HT synthesis depends on the dietary intake of tryptophan; tryptophan circulates in the blood with a major fraction loosely bound to albumin (around 70–90%), whereas the remaining circulates as free tryptophan (Curzon and Sarna, 1984; Fernstrom, 1984; Yuwiler et al., 1977). Tryptophan is actively transported over the brain blood barrier via the large chain amino acid transporter and thus has to compete with other amino acids like tyrosine, valine, leucine, isoleucine and phenylalanine for transport to the brain (Fernstrom, 1984) and therefore are called competing amino acids (CAA). The extraction of plasma tryptophan by the brain depends in part on the competition of the brain transport site with plasma albumin that is stripped off as the complex passes through the brain capillaries (Yuwiler et al., 1977; Pardridge, 1979). All in all, the influx of tryptophan into the brain depends on plasma total and free tryptophan, the CAA and albumin concentrations as well (Curzon and Sarna, 1984; Pardridge, 1979; Yuwiler et al., 1977).

After entering the brain, tryptophan is actively taken up in the serotonergic neurons. The first and rate limiting step in 5-HT synthesis is hydroxylation to 5-hydroxytryptophan by the action of tryptophan hydroxylase (tryptophan 5-monooxogenase, EC 1.14.16.4.). Since this enzyme is not ordinarily saturated by its substrate, changes in tryptophan availability determine the synthesis of 5-HT (Moir and Eccleston, 1968; Fernstrom et al., 1976).

3. Cell-mediated immune activation and oxidative and nitrosative stress (O&NS) pathways

In this section we will briefly review the key components of the inflammatory response, cell-mediated immunity, O&NS, and translocation of LPS from gram negative bacteria because these factors play a role in depression and are related to IDO activation.

Inflammatory responses are a self-defense mechanism that is triggered following various insults and consist of cellular and humoral responses, and complement and cytokine cascades (Burdette et al., 2010). Primary cell-derived mediators of the inflammatory response are macrophage-derived cytokines, e.g. interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα). Those cytokines or the presence of LPS from gram-negative bacteria leads to activation of nuclear factor κB (NFκB), which induces the production of T-cell-derived cytokines, e.g. interferon (IFN)γ, IL-6 and IL-8 (Burdette et al., 2010). IL-6, but also IL-1β and TNFα, modulate the synthesis of acute phase proteins (APPs), i.e. positive APPs, like haptoglobin and C-reactive protein, and negative APPs, like albumin and transferrin (Maes, 1993). The initial inflammatory response may be downregulated by a counter inflammatory response syndrome (CARS), which involves the synthesis of immunosuppressive substances, e.g. the IL-1 receptor antagonist (IL-1RA) (Burdette et al., 2010).

That part of the immune system not involving antibodies but interactions between T lymphocytes and macrophages/monocytes is called cell-mediated immunity. A first step in cell-mediated immune responses is activation of T lymphocytes and the production of T lymphocytic cytokines, like IFNγ and IL-2. The latter activate monocytes/macrophages to produce a) other cytokines, like IL-1β, that in turn will activate T lymphocytes (Wachter et al., 1992); and b) T cell activation markers, such as neopterin (Fuchs et al., 1992; Wachter et al., 1992). IL-2 stimulates the activation, proliferation and/or differentiation of T cells and natural killer cells (Robb, 1985; Smith, 1982). IL-12 is produced by macrophages, dendritic cells, phagocytes, B cells and other antigen-presenting cells and stimulates the production of IFNγ and differentiates naive T into Th0 cells, activates the function and growth of T cells and natural killer cells, plays an important role in the development of Th-1-like responses, and increases the cytotoxic activity of CD8+ cytotoxic T lymphocytes (Trinchieri, 2003).

Systemic inflammatory responses are frequently accompanied by induction of oxidative and nitrosative stress (O&NS) pathways (review: Maes et al., 2010). O&NS pathways entail the generation of radical oxygen species (ROS) and radical nitrogen species (RNS), which can be measured, for example, by nitric oxide (NO) production and increased xanthine oxidase activity. ROS and RNS can react with proteins, fatty acids, and DNA, and cause damage to the cell wall and the mitochondria, which eventually results in apoptosis and cell death (Maes et al., 2010; Gardner and Boles, 2010). Oxidation of lipid structures and nitration of proteins may change the functions and chemical structure of these substrates. The latter may generate