Medical Hypotheses 85 (2015) 506–511

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Correspondence

Integrated theory to unify status among schizophrenia and manic depressive illness

K. Fukuda *

Soka Clinic of Psychosomatic Medicine, Fujimoto Bld. 4F, 2-18-16 Takasago, Soka, Saitama 340-0015, Japan

ARTICLE INFO

Article history:
Received 19 February 2015
Accepted 17 June 2015

ABSTRACT

Tryptophan hydroxylase 1 is primarily expressed in the gastrointestinal tract, and has been associated with both schizophrenia and depression. Although decreased serotonin activity has been reported in both depression and mania, it is important to investigate the interaction between serotonin and other neurotransmitter systems.

There are competitive relationships between branched-chain amino acids, and tryptophan and tyrosine that relate to physical activity, and between L-3,4-dihydroxyphenylalanine (L-DOPA) and 5-hydroxytryptophan (5-HTP), both highly dependent on intracellular tetrahydrobiopterin concentrations.

Here, I propose a chaos theory for schizophrenia, mania, and depression using the competitive interaction between tryptophan and tyrosine with regard to the blood–brain barrier and coenzyme tetrahydrobiopterin.

Mania may be due to the initial conditions of physical hyperactivity and hypofunctional 5-HTP-producing cells inducing increased dopamine. Depression may be due to the initial conditions of physical hypoactivity and hypofunctional 5-HTP-producing cells inducing decreased serotonin. Psychomotor excitation may be due to the initial conditions of physical hyperactivity and hyperfunctional 5-HTP-producing cells inducing increased serotonin and substantially increased dopamine. The hallucinatory-paranoid state may be due to the initial conditions of physical hypoactivity and hyperfunctional 5-HTP-producing cells inducing increased serotonin and dopamine.

Introduction

Two isoforms of tryptophan hydroxylase (TPH) have been discovered: TPH1, primarily expressed in the gastrointestinal tract, and TPH2, expressed exclusively in neuronal cells. Excluding the brain, large amounts of serotonin (5-HT) are produced in enterochromaffin (EC) and mast cells, and stored in platelets. TPH1 expression was expected to be confined to EC and mast cells in the intestine, but unexpectedly was also found in 5-hydroxytryptophan-producing cells (5-HTP cells) in normal enterocytes lining the small intestine epithelium. 5-HTP cells are differentiated mucosal villous epithelial cells that express positive TPH1 staining and secrete intermediate 5-hydroxytryptophan (5-HTP) into the mesenteric vein circulation, although as stored 5-HT is not identified within them, they show no 5-HT immunoreactivity [1–3]. 5-HTP is regarded as a 5-HT precursor, and 5-HTP cells are essentially thought to shunt 5-HT production in 5-HT-producing cells (5-HT cells) in both the periphery and brain. Although TPH1 is not detected in the brain, it has been associated with schizophrenia [4–6]. Furthermore, a considerable number of genetic studies have shown that TPH1 is associated with depression or the responsiveness of depression to antidepressant medication [7–10]. As for schizophrenia, overactive 5-HTP cells (reflecting TPH1 hyperfunction) produce excess amounts of 5-HTP. Abundant 5-HTP increases 5-HT within the brain, and leads to negative feedback of 5-HT synthesis at the rate-limiting step catalysed by TPH2. Owing to this negative feedback, brain tryptophan is further metabolized via the kynurenine pathway (Fig. 1). Increased kynurenic acid (KYNA), similar to systemic administration of phencyclidine or ketamine, contributes to decreased glutamate function and increased firing rates and burst firing activities of midbrain dopamine neurons, all known causes of schizophrenia [11,12]. Thus, schizophrenia is postulated to result from overactive 5-HTP cells.

Conversely, it is possible that hypofunctional 5-HTP cells in the periphery (reflecting TPH1 dysfunction) lead to deficient 5-HTP, low 5-HT, and concomitant compensatory TPH2 activation in the brain, and may cause depression (Fig. 2) [13].

* Tel./fax: +81 48924 6257.
E-mail address: katsu853@theia.ocn.ne.jp

http://dx.doi.org/10.1016/j.mehy.2015.06.012
0306-9877/

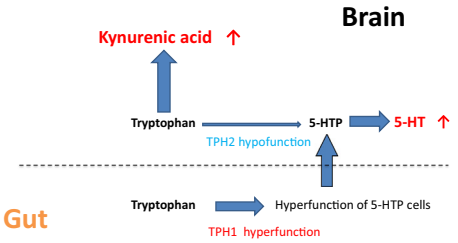

Fig. 1. Overactive 5-HTP cells increase 5-HT and kynurenic acid in the brain. TPH, tryptophan hydroxylase; 5-HTP, 5-hydroxytryptophan.

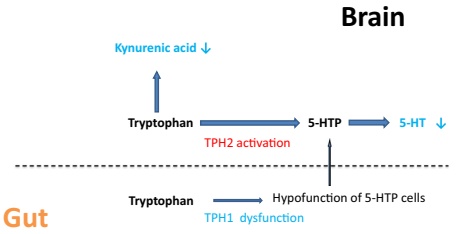

Fig. 2. Hypofunctional 5-HTP cells decrease 5-HT and kynurenic acid in the brain.

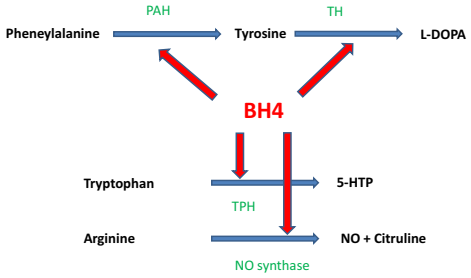

Fig. 3. Tetrahydrobiopterin (BH4) cofactor roles. PAH, phenylalanine hydroxylase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; NO, nitric oxide.

Enzymes known to depend on tetrahydrobiopterin (BH_4) include phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), TPH, and all three types of nitric oxide (NO) synthase (Fig. 3) [14]. TH and TPH are rate-limiting enzymes for catecholamine and 5-HT biosynthesis. In schizophrenic patients, a mean reduction to 34% of control values has been reported for plasma BH4 [15]. Moreover, there is impaired PAH function in schizophrenia, leading to higher phenylalanine and phenylalanine:tyrosine ratio [16]. Conversely, BH4 levels in patients with affective disorders are significantly elevated at the symptomatic phase compared with normal controls [17]. Therefore, it is possible that hyperfunctional 5-HTP cells exhaust BH4, while hypofunctional 5-HTP cells do not. Because of this, schizophrenia would be the opposite of depression for 5-HTP cell activity, and may be due to hyperfunctional 5-HTP cells, compared with hypofunctional 5-HTP cells in depression.

Depression is symptomatically antithetic to mania. In addition, there are mixed mood episodes, with both mood "poles" (mania and depression) occurring simultaneously or in rapid sequence, which correlates with dangerous behaviour including self-injury or suicide. Decreased serotonergic activity may be present in both depression and mania, as suggested by cerebrospinal fluid, postmortem, platelet, neuroendocrine challenge, and tryptophan depletion studies [18,19]. Therefore, it is important to investigate the interaction between 5-HT and other neurotransmitter systems.

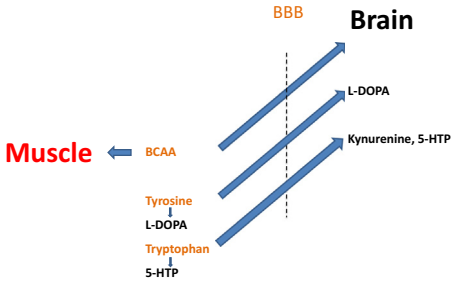

Fig. 4. Competitive relationship between branched-chain amino acids (BCAA) and tryptophan and tyrosine in crossing the blood–brain barrier (BBB).

With regard to crossing the blood–brain barrier (BBB), there is a competitive relationship between the branched-chain amino acids (BCAA) and tryptophan and tyrosine (Fig. 4) [20]. As a single type of transport carrier mediates transcapillary movement of structurally related large neutral amino acids (LNAA), elevation in plasma concentration of one will inhibit uptake of the others. In particular, BCAA modify tryptophan and tyrosine uptake into the brain, and their subsequent conversion into tryptophan metabolites (kynurenine pathway and indolamines) and catecholamines, respectively. Physical hyperactivity will lower BCAA and raise tryptophan and tyrosine uptake [21,22]. Conversely, raising blood BCAA levels, which can occur in response to BCAA administration or with the onset of certain metabolic diseases (e.g. uncontrolled diabetes), lowers tryptophan and tyrosine uptake. In either case, tryptophan metabolism and catecholamine synthesis in the brain parallels the variable ratio of tryptophan and tyrosine to BCAA.

Here, I propose a unified theory for schizophrenia, mania, and depression using the interaction between tryptophan and tyrosine.

Theory

The BBB and coenzyme BH4 exhibit double competitive relationships linked to neurotransmitters.

First, there is a competitive relationship between BCAA and tryptophan and tyrosine.

Second, L-3,4-dihydroxyphenylalanine (L-DOPA) and 5-HTP, the precursor amino acids for catecholamines and indoleamines respectively, mutually affect neuronal activity of each other through inhibition of the respective rate-limiting enzymes, which is highly dependent on BH4 allocation [23–25].

Using these competitive relationships, chaos theory is employed to unify the state between schizophrenia, mania, and depression.

The two main components of chaos theory are that non-linear systems (e.g. turbulence, weather, the stock market, and our brain states) rely upon an underlying order, no matter how complex they are; and that very simple or small systems and events can cause very complex behaviours or events. This latter idea is known as sensitive dependence on initial conditions, a phenomena described by Edward Lorenz in the early 1960s [26].

Deduction

In the context of chaos theory, physical activity is considered the initial, circular, or incidental condition, and not a consequence of disease, and hence is closely related to the competitive relationship between BCAA and tryptophan and tyrosine (Fig. 4).

According to the competitive relationship between L-DOPA and 5-HTP, coenzyme BH4 is linked to the functional state of TPH1 in 5-HTP cells in the intestine (Fig. 3).