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The Schizophrenia hypothesis: Tyrosine hydroxylase pathway

Şizofreni hipotezi: Tirozin hidroksilaz yolağı

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ABSTRACT

It has been previously reported that there was no significant difference in tyrosine hydroxylase activity between schizophrenia patients and controls. In that case, where does an excessive dopamine come from in the patients with psychosis. It should be come back here and this hypothesis must be rehandle and reconsider over and over. On the other hand, as expected, high tyrosine hydroxylase activity showed in basal ganglia, putamen, caudate nucleus and nucleus accumbens, in patient with schizophrenia compared to controls.

Keywords: Tyrosine hydroxylase pathway, dopamine, phosphorylation, schizophrenia, hypothesis

ÖZET

Daha önce şizofreni hastaları ve kontroller arasında tirozin hidroksilaz aktivitesinde önemli bir fark olmadığı bildirilmişti. O zaman psikoz hastalarında aşırı dopamin nereden geliyor? Buraya geri dönülmeli ve bu hipotez tekrar tekrar ele alınmalı ve yeniden düşünülmelidir. Öte yandan, beklendiği gibi, şizofreni hastalarında kontrollerle karşılaştırıldığında bazal ganglionlarda, putamende, kaudat çekirdekte ve çekirdek akumbenste yüksek tirozin hidroksilaz aktivitesi gösterildi.

Anahtar kelimeler: Tirozin hidroksilaz yolağı, dopamin, fosforilasyon, şizofreni, hipotez

Introduction

Schizophrenia is a chronic and frequently debilitating psychiatric illness affecting young adults[1]. The dopaminergic hyperactivity or over production of dopamine is one of the possible pathophysiological mechanisms underlying schizophrenia[2]. Dopamine antagonists alleviate the symptoms of schizophrenia and dopamine agonists exacerbate these symptoms[2,3]. Amphetamines stimulating the release of dopamine and noradrenaline can cause psychosis which resembles schizophrenia symptoms[3]. Schizophrenia results from an interaction between genetic and environmental factors[3,4].2.2,5 Early life events such as perinatal hypoxia and later life events including cannabis use may contribute to the development of schizophrenia[4]. Besides this neurodevelopmental perspective, schizophrenia is also a neurodegenerative disorder. Schizophrenia is characterized by progressive loss of gray and white matter and cognitive impairments[4].

Tyrosine hydroxylase is the first step and rate limiting, key enzyme of the catecholamine biosynthesis pathway[5,6]. This enzyme catalyses the hydroxylation of L-tyrosine to L-DOPA. Increased level of DOPA is associated with schizophrenia[6]. Elevated tyrosine hydroxylase activities have been demonstrated in the certain brain regions including locus coeruleus, ventral tegmental area, substantia nigra as well as the adrenal medulla and sympathetic nerves[5]. The regulation of tyrosine hydroxylase is a complex process that can be affected by glucocorticoids, growth factors, protein kinases, as well as stress, increased neuronal activity, pharmacologic agents and genetic mechanisms[5]. Dysregulation of dopamine, and norepinephrine production can lead to psychotic disorders[5,7]. Amphetamine psychosis mediated by release of both dopamine and noradrenaline closely resembles acute paranoid schizophrenia[7]. It has been suggested that the primary disturbance of catecholamine metabolism may play in the development of psychotic symptoms[5,7]. Deficits in the reward system that is responsible for social mobilization and affective motivation are related to dysfunction of the central dopaminergic[5,8]. These findings support the current hypothesis in schizophrenia.

Schizophrenia is a heterogeneous clinical syndrome involving cognitive, behavioral and emotional symptoms[8,9]. The psychotic symptoms often have an insidious onset during young adulthood. The course of the illness is characterised by cognitive impairment and exacerbations and remissions of acute symptoms[8,9]. The dopamine hypothesis of schizophrenia postulates dopaminergic imbalance in the target circuits and brain areas[8]. It has been identified as positive symptoms related to hyperdopaminergic state in the subcortical brain structures, mesolimbic pathway, and negative symptoms and cognitive deficits arising from hypodopaminergic activity in the prefrontal cortex, mesocortical pathway[8].

Apoptosis or programmed cell death resulting in neuronal atrophy and progressive glial cell loss may contribute to the pathophysiology of schizophrenia[1]. The apoptotic cascades are regulated by the intracellular signals pathways involving the phosphorylation mechanisms of protein kinases that are activated by physiological stimuli or by cellular injury[6,10]. Dysregulation of protein kinase activity has been demonstrated in patients with schizophrenia[2,11]. In addition, both typical and atypical antipsychotic drugs alter kinase activity in central nervous system[2,11].

In this study, tyrosine hydroxylase pathway includes dopa decarboxylase and dopamine hydroxylase which are dopamine synthesizing enzymes regulated by phosphorylation mechanisms reviewed in the pathogenesis of schizophrenia.

Dopamine β hydroxylase

Dopamine β hydroxylase catalyses the oxidative hydroxylation of dopamine to norepinephrine. The enzyme has been localized in brain noradrenergic neurons, peripheral sympathetic nerves, and adrenal medulla. It's activity is significantly regulated by genetic inheritance[12,13]. Low dopamine hydroxylase activity, in response to stress, could lead to an excess dopamine and acute psychotic symptoms[12]. The authors reported both increased and decreased as well as no differences in dopamine hydroxylase activity between schizophrenia patients and control subjects[12-15].

Dopa decarboxylase (Aromatic amino acid decarboxylase)

Dopa is converted to dopamine by Dopa decarboxylase existing in the central and peripheral nervous system as well as adrenal gland, kidney and liver[16,17]. Dopa decarboxylase also, much less efficiently, catalyses 5-hydroxytryptophan to serotonin[16]. There are large individual differences in the dopa decarboxylase activity[17]. Elevated dopa decarboxylase activities have been demonstrated in the brain of patients with psychosis[18,19]. Dopa decarboxylase may be involved in the pathogenesis of schizophrenia[19].

Role of aromatic amino acids in schizophrenia

Phenylalanine, tyrosine and tryptophan named as standard aromatic amino acids are precursor for the monoamine neurotransmitter serotonin and the catecholamines dopamine, norepinephrine and epinephrine[19-22]. Monoaminergic and catecholaminergic dysregulation has been argued in schizophrenia. There are evidences for an increase dopamine and serotonin in at least certain brain regions among patients with schizophrenia[3]. Also, it has been found a degeneration of the central noradrenergic reward pathway located on locus coeruleus[3].

Regulation of tyrosine hydroxylase activity

The production of dopamine is regulated by tyrosine hydroxylase which is the initial enzyme in the biosynthesis of catecholamines[6]. Changes in the amount and activity of tyrosine hydroxylase can markedly alter in the brain catecholamine levels[23]. Tyrosine hydroxylase activity can be modulated by both induction of the enzymatic phosphorylation and of gene transcription by cellular factors like cAMP[23,24]. The highest tyrosine hydroxylase enzyme activity may contribute to genetic susceptibility to schizophrenia[25].

Tyrosine hydroxylase levels are regulated by various conditions including growth factors, glucocoticoids, physical and psychological stress such as cold and immobilization, neuronal activity, memory, synaptic plasticity, metabolism, and behaviors in response to different stimuli in central nervous system[26-28]. The expression of tyrosine hydroxylase is declined in aging and neurodegenerative disorders such as Parkinson's disease, Huntington's disease, Alzheimer's disease which are similar to chronic schizophrenia[27,29].

Tyrosine hydroxylase phosphorylation

Tyrosine hydroxylase is phosphorylated by a variety of protein kinases leading to its activation[25]. The enzyme phosphorylation is a primary and fast control mechanism in the central nervous system and peripheral tissues[25]. Additional mechanism for the sort term regulation; acutely (minutes and days) includes the feedback inhibition by catecholamines. Long term regulation; chronically (days and weeks) can also be mediated by hormones (e.g. glucocorticoids), drugs (e.g. cocaine), or second messanger such as cAMP increase tyrosine hydroxylase transcription[26,29,30]. Nicotine both acutely and long term stimulites tyrosine hydroxylase phosphorylation increasing concentration of dopamine in the nerve terminal[30,31].

Stress activated protein kinases leading to phosphorylation can be stimulated by a various stresses[29,32]. Inflammatory cytokines and cellular injury including genotoxic stress which is DNA lesions such as single strand DNA or limiting nucleotide levels, as well as hyperosmolarity, heat shock, oxidative stress and hypoxia can activate protein kinase pathways mediating pathophysiological mechanisms in the central nervous system[29,31,32]. These processes may conclude multiple cell death causing neurodegenerative diseases and schizophrenia[25].

Phosphorylation and Schizophrenia

Stress activated protein kinase signaling pathways which are strongly influenced by genetic factors can induce the apoptotic cell death[32,33]. The increased cAMP-dependent protein kinase activity has been reported in schizophrenic patients[34]. Apoptotic mechanisms can influence normal synaptic pruning and thereby contribute to pathophysiology of schizophrenia in adolescence and early adulthood[35,36]. Lower levels of the anti-apoptotic proteins (Bcl-2, p53) protecting against pro-apoptotic stimuli such as ischemia and growth factor withdrawal were found in schizophrenia patients[36].

A various adverse events including obstetric complications such as hypoxia during pregnancy as well as environmetal stresses such as drug use have been implicated the risk of developing schizophrenia[36-38]. The possible role of apoptosis in the pruning hypothesis of schizophrenia can result from genetic and epigenetic factors that are directly associated with a complex molecular cyclic cascades of phosphorylation and dephosphorylation[36,38-41].

The Schizophrenia Hypothesis

According to this hypothesis, elevated tyrosine hydroxylase phosphorylation in the subcortical brain regions leads to increased dopamine synthesis and positive psychotic symptoms (see flowchart). Positive psychotic symptoms tend to diminish over the course of the illness, possibly due to the decline in dopamine activity with age[9] associated with the decrease in tyrosine hydroxylase activity[25].

Microstructural damage to the brain resulting from congenital or subsequent traumas progresses and leads to degeneration due to the disruption of the apoptosis cascade with the onset of physiological apoptosis in early adulthood[6]. This process gives rise to a domino effect that cannot be stopped. The most severe symptoms begin with negative symptoms. In this process, dopamine, the acute phase reactant and the main neurotransmitter of the brain, comes to the fore among neurotransmitters[16]. Antipsychotic treatments are secondary symptomatic treatments rather than primary treatments in that they provide relief and help the brain heal by reducing dopamine levels[8].

Considering that phosphorylation occurs more in the hypoxic brain than in the non-hypoxic brain[6,28], the pathway that triggers apoptosis may be stress-activated protein kinases[1,6]. While the greatest risk for schizophrenia is genetically encoded phosphorylation[9], minimal damage also poses a risk for schizophrenia[4]. The process of genetically disrupted throsine hydroxylase protein expression results in failure to manage the apoptotic stress process and ultimately causes schizophrenia[21,28]. In the event that overexpressed tyrosine hydroxylase gene expression, which is normally physiological, is genetically forced, dopamine levels increase excessively, leading to psychosis[18,20].

Cannabis and amphetamines trigger the release of dopamine and noradrenaline release[3,7]. In susceptible individuals, dopamine cannot bind to the catecholamine site of the tyrosine hydroxylase enzyme and the

negative feedback mechanism is disrupted. In the event that dopamine releease is triggered by such agents, dopamine does not remain in the cell and tyrosine hydroxylase activation reoccurs. Immunological trigger mechanisms also play a role in the process. Overload or drug abuse may cause excessive phosphorylation via immune induction.

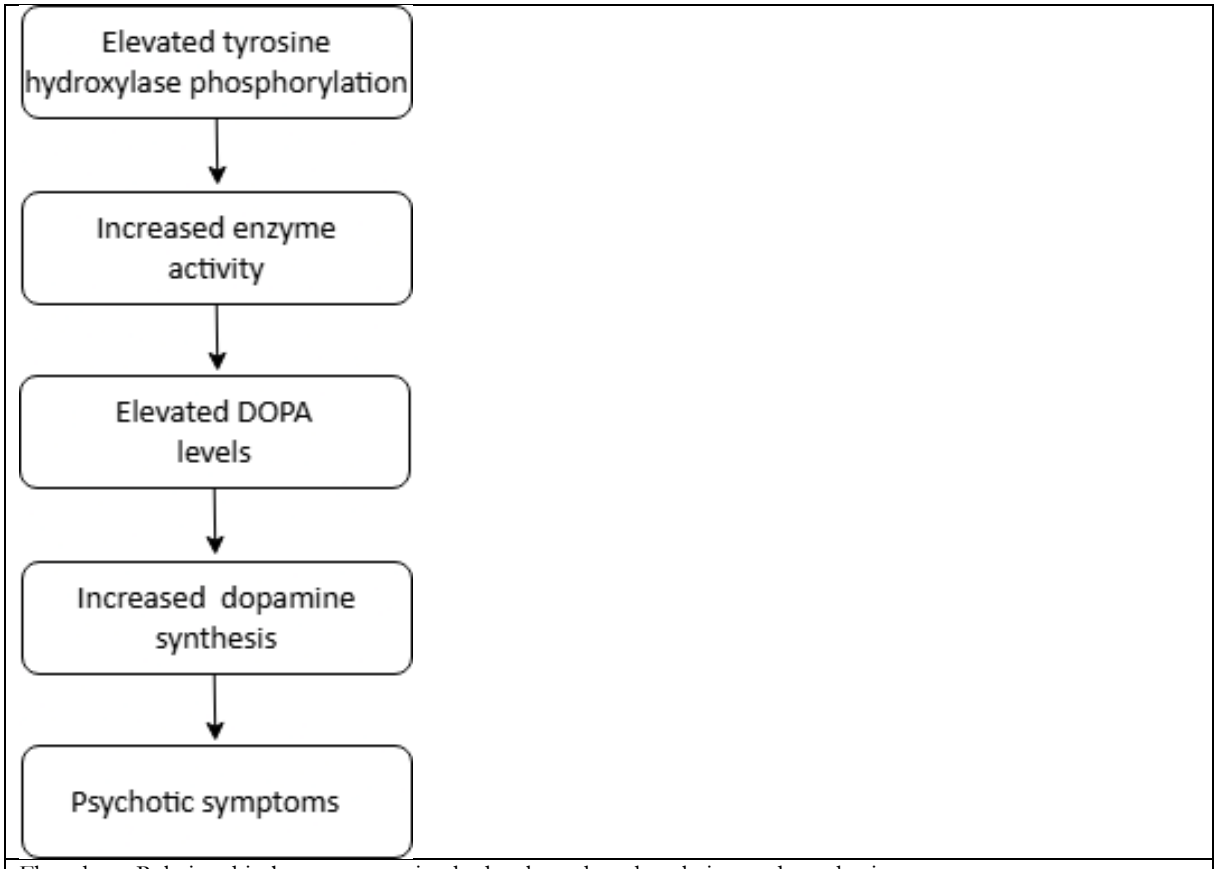
These mechanisms can occur at any age, but are particularly evident in early adulthood[9]. The phosphorylation activation hypothesis may explain late- and very late-onset degenerative diseases and post-stroke psychosis[8]. Activation of similar pathways in epileptic psychoses may also lead similar symptoms[18].

The fact that dopamine increases in some areas while decreasing in others and increases in the acute period while decreasing in the chronic period may explain the contradictory results reported in the literature.

In sum, it can be said that it is difficult to find another hypothesis that encompasses all the hypotheses put forward about schizophrenia and is compatible with all the research findings to date (see Table 1).

Conclusion

The tyrosine hydroxylase pathway phosphorylation can explain dopamine hypothesis, neurodevelopmental hypothesis, neurodegenerative symptoms, findings of research, and inheritance of schizophrenia.



Flowchart: Relationship between tyrosine hydroxlase phosphorylation and psychotic symptoms

Table 1. Related factors between Tyrosine Hydroxylase phosphorylation and Schziophrenia

Related factor	Tyrosine hydroxylase phosphorylation	Schizophrenia
Genetic	Major Control mechanism	Major etiology
Dopamine, norepinephrine	Product	Implicated in etiology
Cell injury	Increased	Risk factor
Hypoxia	Increased	Risk factor at Delivery
Short term	Regulation	Treatment response
Long term	Stabilitization	Bad prognos
Stress	Increased	Can be trigger
Inflammation	Induction	Play a role
Growth factors	Regulator	Initial age adulthood
Apoptosis	Play a role in cascade	Result in neurodegeneration
Positive symptoms	Increased activity	Subcortical area
Negative symptoms	Decreased activity	Cortical area
Neurodegeneration	Appropriate	Can be explain
Neurodevelopment	Appropriate	Can be explain

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