SRIWIJAYA JOURNAL OF MEDICINE

Genetic Factors Affecting Neuroplasticity

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Abstract

Neuroplasticity pertains to the brain's ability to adjust functions or structure in response to events and is an important factor for skill-learning development as well as functional recovery from a neurological disorder. Numerous factors could influence neuroplasticity processes. This literature review aims to discuss the roles of genetic factors in neuroplasticity. The literature search was conducted using the keywords “neuroplasticity”, genetics”, “genes”, and polymorphism” in search engines like google scholar and PubMed, covering original articles, reviews, and text book both in Bahasa Indonesia and English for the last ten years. Genetic variation including gene polymorphism was responsible for the impact of BDNF, ApoE, and dopamine on the functional neural repair of the brain. Certain processes might directly influence neuroplasticity; others might interfere indirectly through the process. A deeper insight into genetic influence regarding neuroplasticity could lead to a better understanding and potential improvement of treatment.

Keywords: neuroplasticity, genetic, polymorphism, genes

1. Introduction

Aging is a complex process that is determined by genetic and epigenetic factors. These factors lead to a decrease in physiological functions, including the endocrine, immune system and cognitive functions. The majority of aging individuals showed a gradual decline in their cognitive abilities, which was linked to changes in the hippocampus and cortex, both of which are brain regions used for learning and memory.[1] Age-related memory changes could vary from individual to individual, and not all memory types are equally affected. Generally, cognitive function is related to neuronal plasticity. Neuroplasticity is the ability of neurons or glial cells to repair or increase the effectiveness of synapses through dynamically evolving biochemical or morphological changes.[1,2] Neuroplasticity can be manipulated in both healthy and sick individuals by pharmacological and non-pharmacological approaches.[2]

Genetic factors might have direct and indirect influences on neuroplasticity. Neuroplasticity is influenced by genes and their changes through various mechanisms. This influence is related to non-genetic factors such as age, mood, experience, physical activity, and exercise intensity, social factors, menstrual cycle, and disease factors (features of central nervous system injury, severity of behavioral deficits, treatment effects) which have been previously known to influence brain plasticity.[2,3,4] Genetic variation allowed the identification of markers that could predict an individual's brain plasticity. Single nucleotide polymorphisms (SNPs) of the

human brain-derived neurotrophic factor (BDNF), apolipoprotein-E (ApoE), and dopamine gene were known to affect brain plasticity.[3,5]

The effects of any polymorphism were at the cellular/molecular level of the nervous system, where these variants can influence brain plasticity through the interaction of environmental genes with impacts on recovery and learning. The effect of gene polymorphisms could be seen by observing the interaction of individuals with their surroundings, which in the context of physical therapy and medical rehabilitation could be viewed as a behavior intervention or a therapeutic approach involving cellular pathways that were influenced by gene polymorphisms. Genetic variation might influence therapeutic interventions if the mechanism of action involves neurogenic pathways.[5] This literature review will provide a brief explanation of how genetic factors affect neuroplasticity, where better comprehension of this will subsequently lead to the discovery of better management of the condition.

2. Results and Discussion

2.1. Neuroplasticity

Neural plasticity of the central nervous system (CNS) could be described as the changes in the total strength of synapses, it could be manifested at a neural network level as the reorganization of representational maps. Neuroplasticity could form in the presence of increased dendritic spine formation, pruning and remodeling, regulations of calcium channels, and some receptor alterations. Long-term potentiation (LTP) is the most commonly studied plasticity. This involves a long-term increase in synaptic strength between two neurons as a result of high-frequency stimulation of presynaptic excitation pathways.[3]

Neural plasticity in the human brain, especially cortical map plasticity, could be explored in a number of methods, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and transcranial magnetic stimulations (TMS). The TMS or transcranial direct current stimulations (tDCS) techniques had been used to obtain cortical excitability, intracortical facilitation (ICF), paired associative stimulations (PAS), short interval cortical inhibition (SICI), and movement directional targets.[6,7] Serial measurements of SICI or ICF were also used to evaluate physiological plasticity.[3]

A study on stroke patients has shown that viable tissue in distant areas such as the peri-infarct and nodules may develop functional reorganization in disperse networks and homologous regions in the hemisphere opposite the lesion. This relationship suggested that individuals with higher capacity for synaptic plasticity, protein and RNA synthesis, synaptogenesis, and post-disease physiological changes were more likely to experience behavioral improvements. As certain genes are involved in neuronal plasticity, genetic mutations in humans may affect the development of neuronal plasticity and reduce disability after disease.[3] Neuroplasticity presented as a proposed mechanism for intervention ideas on neurological rehabilitation, especially the ones that involved progressive goal-oriented practices with challenge and repetitions that relied on neuroplastic changes to produce favorable improvement of the diseases. SNP that contributed to neuroplasticity may be relevant to the development of neurological rehabilitation.[5]

2.2. Genetic factors affecting neuroplasticity

Genetic factors might determine the variations of neuroplasticity both directly and indirectly. Genetic variations such as human

genome polymorphism enabled the recognition of markers that could predict human brain plasticity and recovery after CNS injury. This awareness thus led to more studies on the biological benefits and drawbacks of proteins via polymorphism, the development of potential treatments inspired by the way gene variant does endogenously, and predict the prognosis of interventions according to the presence and absence of gene polymorphisms.[3]

2.3. Brain-derived neurotrophic factors (bdnf)

BDNF is one of the neurotrophins most actively found in the brain and is considered crucial for neural protection and neural plasticity processes.[3,5] High levels of BDNF were detected in the hippocampus, cerebellum, amygdala, and cerebral cortex, with BDNF most abundantly found in hippocampal neurons. Other body organs such as the heart, lungs, and liver also displayed low levels of BDNF.[8] It played a key role in enhancing synaptic transmission, facilitating long-term potentiation of learning processes, and was responsible for the survival and differentiation of developing neuronal populations.[5,8] The expression of BDNF was coordinated in transcription, translation, and post-translational modification, where the transcription process was controlled by numerous promoters that would determine the specific tissue and activity-dependent expressions.[8] The production of BDNF is dependent on activities and increased release of BDNF was presented in a period of skill learning as well as aerobic exercise.[5]

BDNF is essential in many forms of plasticity, especially in neurological condition refinement. Both BDNF and its receptor (TrkB) had been used as markers of motor neurons and neuroplasticity.[3] BDNF's role in regulating neuroplasticity in the adult brain includes regulation of trafficking, phosphorylation, and increased synaptic strength. Because BDNF contributes to LTP, it was hypothesized to be a fundamental part of the cellular mechanisms that support memory formation and maintenance through the development of synaptic integration. Furthermore, BDNF increased neurogenesis through alterations in cell survival and proliferation. Changes in the connections between synapses were also predicted to support memory storage.[8] BDNF is involved directly in brain plasticity by short-term and long-term influences.[3] BDNF rapidly depolarizes postsynaptic neurons immediately after release, producing short-lived postsynaptic effects on ion channels and NMDA receptors, thereby stimulating excitatory synaptic transmission by promoting presynaptic neurotransmitter release. may increase.[3,8] On the other hand, BDNF could provoke a long-term change in synaptic plasticity, neurotransmitter, and neuropeptide production as well as excitability. BDNF played an important role in neural development in conjunction with modulating neuronal function in terms of synaptic transmission, use-dependent plasticity, and long-term potentiation in adulthood.[8]

The release of BDNF could incline with experience and surrounding stimuli. A previous study in rats presented that contextual fear spatial and scene conditioning both raised BDNF mRNA and protein levels in the hippocampus. BDNF mRNA also increases in the amygdala due to amygdala-dependent fear conditioning. The studies supported the idea of a stimuli-specific increase of BDNF in the CNS.[3]

Reduction of the BDNF release in the brain was identical to functional deficits as the formation or modification of new synapses between excitatory and inhibitory synapses in the somatosensory cortex fail to achieve balance compared to individuals with normal BDNF levels. Changes in genes controlling

BDNF production impaired spatial learning and memory, and blockage of BDNF in the hippocampus minimizes the positive cognitive effects of exercise. Interfering BDNF receptors in the motor cortex could result in the inhibition of BDNF functions, affecting motor performance disorders and disrupting cortical reorganization. [3,8]

2.4. BDNF polymorphism

The most common SNP found for BDNF was due to guanine to adenine substitution on nucleotide 196 which altered the substitution of amino acid at codon 66 from valine to methionine. This event was known as val^{66}met polymorphism.[3,5,8] The polymorphism occurred on the 5' prodomain of the BDNF gene which was the zone encoding the pro-BDNF precursor peptide that would form a mature BDNF protein.[3,8] Then, BDNF would be released as a combination of pro-BDNF and mature BDNF. Pro-BDNF would bind with the p75 NTR receptor as it facilitates LTD and induced apoptosis, while mature BDNF would bind with tyrosine kinase receptors (TrkB) and improve cell survival.[8] Since the polymorphism did not alter the function of the mature BDNF protein but altered the intracellular activity of pro-BDNF, the polymorphism affects activity-dependent BDNF release. Approximately 30–50% of the population had the heterozygous (Val/Met) or homozygous (Met/Met) form of the BDNF-Val^{66}met polymorphism.[3,8] Individuals with this type of polymorphism in one or two copies of the Met allele were considered to have the BDNF-val^{66}met polymorphism and showed reduced levels of activity-dependent release of BDNF.[5]

BDNF polymorphisms can affect both behavior and neurology in individuals. Stroke patients with BDNF polymorphisms behaviorally presented an overall reduction in motor skill learning and slower learning rates compared to individuals without BDNF polymorphism.[5] BDNF polymorphisms most likely influence responses to exercise practice related to neurogenic processes to enhance motor skill learning or relearning. Different reactions were observed in a period of repetitive finger task practice on individuals with BDNF polymorphism and nondisabled individuals. The observations showed that individuals with polymorphism had a lower neural plasticity response, although effects could also be seen in older subjects.[5] The polymorphism had also been associated with brain structure and function changes such as synaptic plasticity and performance of the memory. Brain structures that may undergo alterations include the hippocampus, parahippocampal gyrus, prefrontal cortex, and amygdala. Individuals with the Met allele are predicted to have poor memory performance on verbal tasks and deficits in the task and spatial memory tasks.[8]

A study of gait adaptation when walking on a split-belt treadmill in chronic stroke patients showed differences in adaptation speed between those with and without the polymorphism. Individuals with no polymorphism showed significant changes in her first 30 trials of adaptation, whereas individuals with met allelic polymorphisms achieved similar levels of overall adaptation. required longer practice. This study showed that post-stroke patients who exhibited polymorphism may require additional practice to achieve the same behavioral outcomes compared to patients without polymorphism.[5,9]

Other protocols conducted to observe and compare changes in neuroplasticity such as non-invasive brain stimulation protocols including transcranial direct current stimulation, transcranial magnetic stimulation, and paired associative stimulation, were associated with the Met allele. It was shown to differ based on the presence of one or more copies.[5] BDNF polymorphisms have also been suggested as

one of the possible factors proposed to explain the relatively high variability of brain responses to stimuli. [5,10]

On the other hand, some studies had reported no significant relationships between the BDNF val[66]met polymorphism and certain phenotypes such as executive function, visual ability, cognitive ability, general cognitive ability, and memory. The studies suggested the possible cause of discrepancy was due to uncontrolled variables such as gender, physical exercise, and stress. Moreover, individuals with heterozygous type polymorphism were able to compensate with low BDNF levels and increased activity of the medial temporal lobe during an episodic memory assignment.[8] Besides, another study reported that aerobic exercise had shown cognitive improvements in both young and old age groups. Hence, increasing level of BDNF proves the proposed mechanism that lifestyle adaptation through physical exercise could trigger cognitive-enhancement. [11]

2.5. Apolipoprotein E

Apolipoprotein E, known as ApoE, is a lipoprotein that is responsible for neuronal processes associated with repair and recovery in the brain.[5,12] It is produced by astrocytes in the peripheral and central nervous systems of the liver. ApoE is located on chromosome 19q13.2 and encodes three common alleles (ε2, ε3, ε4).[12] ApoE took part in the regulatory role to distribute and transport fat-soluble vitamins, lipoproteins and cholesterol to the nerve tissues in order to maintain neuroplasticity along with optimal mitochondrial functions and immune response of the neurons.[11,13] Three isoforms of apolipoprotein E, namely ApoE ε2, ApoE ε3, and ApoE ε4, had 2 important roles including the N-terminal domain with receptor binding sites and the C-terminal domain that binds to β-Amyloid 14.[12] The gene variants produce proteins with different associations with different physiological properties and health risks.[11]

Previous studies also suggested that BDNF level expression could be influenced by the variants of the ApoE genotype related to exercise activities.[11] A significant relationship had been suggested between ApoE ε4 status and serum BDNF level as individuals who did not carry the ε4 allele presented a significant increase of BDNF levels in 6 months of experimental treatment of aerobic exercise, while individuals with ε4 allele did not. This experiment demonstrated the possible ε4 allele and BDNF interaction to physiologic transformation which would have gained benefit for neuroprotection from physical activity.[14]

2.6. Apolipoprotein E Polymorphism

There were three genotypes of the ApoE gene that could affect the structures and functions of ApoE, namely ApoE ε2, ApoE ε3, and ApoE ε4. The presence of the ApoE genotype could be found in varying numbers in the populations.[5,12] ApoE e3 had a neuroprotective function against neurodegenerations and cognitive decrease, whereas ApoE e4 had the opposite effect. Thus, the presence of ApoE ε4 (both homozygous and heterozygous carrier) could cause a negative influence on neuroplastic processes and is considered a risk gene for Alzheimer's disease up to 12 folds.[5,11,12] Further research also suggested that the ε4 allele was associated with the risk of developing atherosclerosis and cardiovascular disease.[11] ApoE e4 also had poorer outcomes after traumatic brain injury and stroke.[5,12] In addition, individuals with ApoE ε4 exhibit diminished neurogenesis processes as neurite outgrowth in human cell cultures was augmented after inducing nerve growth factors and ApoE ε3, but not in the ε4 allele carrier. Individuals with ApoE ε4 also featured a decrease in hippocampal volume, activity-related activation, and reduced cognitive

function compared to normal individuals.[15] Moreover, previous studies on neuroimaging and neuropathology had shown that carriers of ApoE ε4 had β-Amyloid deposition more abundant and rapidly compared to non-carriers. [16]

2.7. Dopamine

Dopamine is one of the major neurotransmitters that has played an important role in central nervous system processes such as movement, mood, impulse control, memory, emotional behavior, and learning.[5,17,18] Dopamine-regulated variants feature neural functions, including excitability, synaptic plasticity, synaptic transmission, gene transcription, and protein trafficking.[19] Dopamine also regulated numerous functions in the peripheral such as cardiovascular functions, catecholamine release, vascular tone, hormone secretion, and renal functions.[17] This neurotransmitter was actively found in the cerebral cortex and basal ganglia of the brain where dopaminergic terminals in the motor cortex contributed to cortical plasticity and were crucial for motor skill learning.[5,19] As dopamine played an important role in movement and learning, any changes or interruptions in the dopamine and dopamine receptors connections in the primary motor cortex could lead to the weakening of motor skills learning.[5,18]

Dopamine utilized its performance by binding to and activating some specific G protein-coupled receptors (GPCR) which could diversify or amplify their effect by forming homo- and hetero-dimers.[17,20] These dopamine receptors were known to have 5 subtypes (D1R, D2R, D3R, D4R, and D5R) and were classified according to their characteristics of the structure, pharmacological effect, and signaling properties.[5,17] The D1R and D5R were in the D1R-like family, whereas the D2R-like family consisted of D2R, D3R, and D4R. The dysfunctions of dopamine transmission and receptor signaling had been associated with neuropsychiatric disorders such as schizophrenia, attention deficit hyperactivity disorder (ADHD), psychosis, Tourette Syndrome, depression, and addiction.[17,21] Additionally, impaired function of dopamine-dopamine receptor activity had been implicated with neurodegenerative diseases such as Parkinson's disease, Huntington's disease, and multiple sclerosis.[17]

2.8. Dopamine polymorphism

Certain genetic polymorphism including the genes of dopamine transporter protein (DAT), dopamine receptors (D1R, D2R, and D3R), as well as catechol-o-methyltransferase (COMT), might affect the neurotransmission process of dopamine by either increasing or decreasing the action. Most people with one of the dopamine polymorphisms had relatively low levels of dopamine activity, associated with hypodopaminergic conditions such as working memory impairment and attention deficit hyperactivity disorder.[5,22] There was also evidence that polymorphism in the BDNF gene might interact with polymorphisms in dopamine-related genes and may contribute to plasticity processes.[23]

A polymorphism that reduced dopamine transmission was associated with the poorer daily function of an individual.[22] The existence of polymorphisms in the dopamine system (D3R) might affect the working memory and executive functions of Parkinson's patients. The apoptosis of dopaminergic neurons in the substantia nigra of the brain caused dopamine deficiency in Parkinson's disease patients. Further research on dopamine polymorphisms found dopamine replacement therapy as an acceptable pharmacological intervention with therapeutic efficacy for motor symptoms.[5] Drugs that aimed to raise dopaminergic transmission could aid in improving learning and plasticity in a healthy individual.[18,19] Considering the physiologic inverted U-

shaped relationship of dopamine dose and its effect on behavioral output, the outcome of patients to dopamine modulating treatments could diverge according to their position in the curve due to their genes.[24] Dopaminergic drugs would have a potential benefit to measure genetic variability and help predict intersubject differences in response to treatment.[6,18]

A previous study linking COMT gene mutations to different exercise capacities suggested that baseline dopaminergic tone was a factor in recovery in stroke patients treated regularly with physical therapy. A single nucleotide polymorphism in the COMT gene rs4680, caused by a substitution of the G allele (Val) for the A allele (Met) at amino acid 158, known as Val[158]Met, caused the individual to express lower motor learning capability under L-DOPA treatment as the Met carrier of COMT had improved baseline performance and worse drug-influence performance on pre-frontal cortex-based activity.[19,24] This occurred because COMT levels are higher in the prefrontal cortex and lower in the striatum. Since motor learning requires activity in the striatum and motor cortex, COMT carriers of Met alleles with high dopamine levels in the prefrontal cortex increase inhibition of striatal dopamine and enhance motor learning-based tasks. may decrease.[24]

On the other hand, individuals with DAT polymorphism presented a strong effect of methylphenidate treatment both behaviorally and neurophysiologically. Other research reported the beneficial effect of motor learning, impulse control, and working memories in patients with low dopaminergic tone risk genes after taking drugs that raised dopamine level.[24]

3. Conclusion

The literature findings above suggested that genetic factors were influential towards neural plasticity and rehabilitation from various neurological disorders. Genetic factors could contribute to affecting neuroplasticity either directly or indirectly through alterations of processes that might consequently impact neural plasticity. Genetic studies exhibited greater perspectives in exploring and extending the knowledge of neuroplasticity and its potential treatment development specific to individual gene characteristics.

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