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Review Article

The Functional Analysis of Intracellular MAPK Pathways in Major Depressive Disorder

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Abstract

The review of scientific evidence strongly links the Mitogen-Activated Protein Kinase (MAPK) pathway with Major Depressive Disorder (MDD). The MAPK pathway has been shown in several marine, porcine and human studies to regulate transcription factors, thus expression of messenger RNA, in multiple neuronal cell types. Specifically, MAPK cascade signaling associations have been demonstrated with cells of the prefrontal cortex and hippocampus, Alzheimer neuronal cells, and raphe nuclei of the brainstem. These findings strongly suggest that continued research of the MAPK pathway will promote novel techniques to treat MDD.

Keywords: Major depressive disorder; MAPK pathway; Signal transduction

Background

Major Depressive Disorder (MDD) is a highly prevalent psychiatric disorder which is becoming an increasingly serious public health concern [1,2]. The symptoms of MDD include (1) feelings of sadness, hopelessness, and overall depressed mood; (2) loss of interest in activities that were previously enjoyable; (3) increased or decreased weight or appetite; (4) change in activity level; (5) difficulty sleeping or excessive sleeping; (6) feeling tired; (7) feelings of guilt; (8) difficulty concentrating; and (9) thoughts of suicide. To be diagnosed with depression a person must exhibit 5 or more symptoms for 2 or more weeks. The primary clinical treatments for MDD include medications and collaborative care which is designed to treat the symptoms of major depressive disorder [3]. Because of the wide range of symptoms of MDD, multiple drug therapies must be utilized.

MDD has been shown to be associated with several different cellular actions (cell growth, apoptosis, differentiation, etc.) and genetic pathways. There have been numerous studies investigating MDD, including the role of the Mitogen-Activated Protein Kinase (MAPK) pathway in MDD and possible treatment modalities that could help alleviate some of the symptoms and presentations of depression. Studies have examined not only the MAPK pathway, but also the genes that play a role in regulation of the MAPK pathways. Topics of research include the role of the immune system [4], epigenetic associated with gene pathways that affect depression [5], effects of genes on astrocytes in people with MDD [6], and drug treatments which could generate neurite growth [7]. Results of these studies have demonstrated that the MAPK pathway plays a key role in the development of MDD.

The MAPK pathway plays a key role in regulating cell proliferation, signal transduction, cell differentiation, and cell death. The MAPK pathways have been grouped into three main families including (1) extracellular signal-regulated (ERK) MAPK, (2) p38 MAPK, and (3) Jun amino (N)-terminal Kinase (JNK) MAPK pathways [8]. After a stimulus moves through different pathways, the MAPK pathway ultimately determines the biological response to the stimulus. When a stressor is introduced to a mammal, the genes in the MAPK pathway play certain roles in inflaming, causing apoptosis, or growing and developing cells. When stress is introduced, the genes in the MAPK pathway that are first affected are inositol 1,4,5-triphosphate (IP_3), Protein Kinase C (PKC), and MAPK phosphatase (MKP). Stress results in an up-regulation of these genes. The up-regulation of IP_3 and PKC result in the up-regulation of P38 pathway which results in inflammation of cells and apoptosis. The up-regulation of MKP results in the down-regulation of JNK and ERK pathways which results in cell growth, development, and differentiation [2] (Figure 1).

Currently, many interdisciplinary studies have confirmed that MDD involves in multi-genomic changes and specific target gene dysfunctions. For the purpose to develop effective antidepressant drugs, the researchers looked at the sequencing data of genes to find variants that could be targets for antidepressant drugs. A study looked specifically at Brain-Derived Neurotrophic Factor gene (BDNF). The researchers identified 6 Single-Nucleotide Polymorphisms (SNPs) that were associated with MDD: rs12273539, rs11030103, rs6265, rs28722151, rs41282918, and rs11030101. These SNPs were hypothesized to be targets for antidepressants to fight against MDD [9]. Another study used whole-exome genotyping to test the effectiveness of fluoxetine and desipramine. The aim of this study focused primarily on the Mexican American population. The researchers found that one single-nucleotide polymorphism occurred on chromosome 6. The drugs that were tested in this study were predominantly aimed to interact at brain methylation sites. Ultimately, the researchers found that fluoxetine was more successful in treating these sites than desipramine [10]. A third study performed Genome-Wide Association Studies (GWAS) on a Mexican-American cohort and a European-ancestry cohort. They found 44 variants associated with MDD in the Mexican-American cohort and that the primary gene variation that was linked with major depressive symptoms was variations in the PHF21B gene. Researchers found that this gene was one of the main agonists in stress-response [11]. Another study used Whole-Genome Sequencing (WGS) to detect mutations that could contribute to the development of MDD. More

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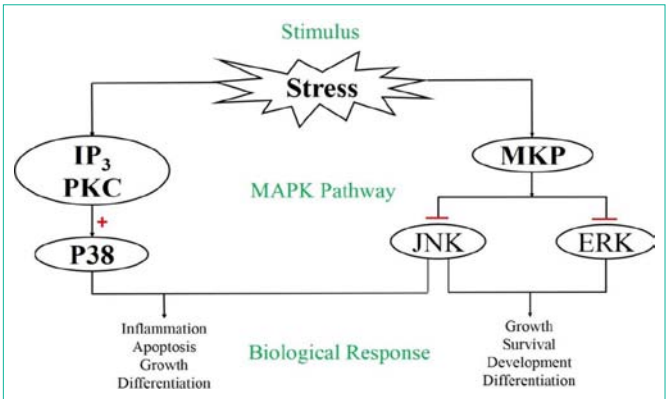

Figure 1: MAPK pathways in response to stress stimulation. (+: up-regulation; -: down-regulation).

specifically, researchers looked at whole-genome Single Nucleotide Variants (SNVs) on 12 different genomic regions. They found that based on the whole-genome SNV distribution, the regions could be related to MDD [12]. Finally, a study used Single-Nucleotide Variant Proportion (SNVP) to look at MDD Whole-Genome Sequencing (WGS) data. They found that SNVP could be used as a biomarker associated with major depression. This study lends credibility to using SNVP to study DNA sequencing in MDD [13]. Ultimately, these studies support the idea that DNA sequencing can aide in the development of treatment of MDD, like antidepressants.

Current Studies of Signal Transduction Pathways Related to MDD

One study performed on mice and humans to determine which genes and pathways are associated with MDD, found, in addition to the MAPK pathway, other pathways such as DNA-Damage-Inducible Transcript 4 proteins (DDIT4), Phosphodiesterase 4D Interacting Protein (PDE4DIP), and AXL receptor tyrosine kinase (AXL) play a role in MDD. Further, the researchers investigated how changes in the messenger RNA (mRNA) at the molecular level affect the prefrontal cortex, which is associated with MDD. MAPKs are known to provide cascade signals to other molecules, including transcription factors. Once a pathway is signaled, many targeted genes and transcription factors can alter the expression of the mRNA. One of the main theories of the pathophysiology of MDD asserts that the exposure to chronic stress alters transcriptional regulation of growth factors and hormones leading to impaired neurogenesis and neuroplasticity [14,15].

In another study based on older adults between the ages of 55 and 90 with normal cognitive function, mildly impaired function, or had been diagnosed with Alzheimer's disease, other associated genes and pathways such as Glutamate Metabotropic Receptor 7 (GRM-7), angiopoietin 4 (ANGPT4), leucine rich repeat and fibronectin type III domain containing 5 (LRFN5), and ERK/MAPK, were also identified. Glutamate receptor, metabotropic 7-antisense RNA 3 (GRM7-AS3) is a RNA gene which is complementary to a functional RNA. GRM7 is one of the Group III glutamate metabotropic receptors. Chang et al. recently identified GRM7 as among the important proteins involved in neuronal signaling and cellular structure in major depressive disorder [16]. Yet again, the MAPK pathway is mentioned to play a role in MDD [17].

As previously mentioned, stress is a key factor that can alter different signals pathways and responses from certain genes. Oxidative stress and neuroinflammation is one stimulus-response mechanism that is thought to cause symptoms of MDD. Oxygen is needed for neuronal function and therefore brain function. However, in certain situations, oxygen can also behave as a neurotoxin. Reactive Oxygen Species (ROS) are highly reactive molecules derived from oxygen possessing unpaired electrons that are known readily oxidize and modify the functions of RNA, DNA, proteins, and lipids, with inevitable damage inflicted to neurons [18]. The result of this damage promotes an inflammatory response, causing the up-regulation and down-regulation of certain genes which are thought to cause MDD [4]. A related study further identifies stress as causative to changes in the regulation of the MAPK pathway, including the long-term changes to neuronal cells. The findings of the study were the production of the dual histone mark histone 3 serine 10 phosphorylation lysine 14 acetylation (H3S10p-K14ac), driven by concomitant activation of the Glucocorticoid Receptor (GR) and N-Methyl-D-Aspartate Receptor (NMDAR)/Extracellular Signal-Regulated Kinases 1 and 2 (ERK1/2)/ mitogen and stress response kinase-1 E-26-like protein 1 (MSK1-Elk-1) pathways, which plays a significant role in initiating gene transcription, required for long-term changes in neuron function [5]. These results show possible mechanisms and pathways for the progression of MDD in a person.

Possible Mechanisms of MAPK on MDD Development

Some theories for mechanisms of pathways involved with MDD have also been proposed, particularly mechanisms for the MAPK pathways. One study investigated the role of Src homology phosphatase 2 (Shp2) genes in suppressed ERK1/2 activation after exposure to glucocorticoids. Shp2 benefits MAPK by maintaining the kinase state of activation. The researchers found that Dexamethasone (DEX) suppressed activation of ERK1/2 possibly through inhibiting the interaction of Shp2 with Tropomyosin receptor kinase B (TrkB). The duration of MAPK activation and combination with other signaling cascades are important for cellular functions including synaptic plasticity [19]. Ultimately, the study found that glucocorticoids played a negative role in neuronal function, which is thought to be related to major depressive disorder [20]. Another mechanism that has been studied in the MAPK pathway is the MKP-1 of the MAPK cascade. The results of the experiment indicated that induction of MKP-1 is not only a direct consequence of stress but is also an important negative regulator of MAPK that contributes to the expression of depressive symptoms [21-23]. The results of this experiment lead the evaluators to believe MKP-1 would be a good target for antidepressant drugs [24].

The raphe nuclei are a group of nuclei in the brainstem responsible for regulating serotonin levels in the brain. A study concluded that an alteration in p38α MAPK affects the raphe nuclei, causing a low presence of serotonin, which has shown to lead to a depressive state. More specifically, deleting p38α and the lack of compensation of p38β caused behavioral effects in models of stress-induced depression and addiction, inferring p38α is a key regulator of the dorsal raphe nuclei [25]. Therefore, when stress is present, p38α is altered affecting serotonin production in the raphe nuclei. The change in serotonin levels is thought to be a factor in leading to a depressive state in

the body. Another study showed p38α was a mechanism for the dysregulation of the dorsal raphe nuclei, while also looking at the physiological effects of stress exposure. Per the study, prior stress experience promotes passive coping/behavioral inactivation to subsequent stress exposures caused by an enhanced stress-induced release of 5-HT (5-hydroxytryptamine) into the forebrain [26]. This result in an enhanced stress-response in a mild stress state, meaning the chemical response to stress is overly expressed, altering p38α. The alteration leads to a change in serotonin production, causing a depressive state. An additional study looked at the sex differences in anxiety, depressive, and drug addictive states in guinea pigs. This study also looked at the role the raphe nuclei and the MAPK pathway played in causing these circumstances. Ultimately, they found p44/42 MAPK activity was altered in guinea pigs, which is thought to lead to some of the depressive symptoms in the guinea pigs [27]. One final study related to the raphe nuclei also found that p38α played a role in causing a depressive state. They found stress-induced potentiation of Cocaine-conditioned Place Preference (CPP) and increases in sodium-dependent serotonin transporters (SERT) surface expression in the nerve terminals of the serotonergic neurons are also G protein-coupled Receptor Kinase 3 (GRK3) and p38α MAPK dependent [28].

MAPK Involved in Antidepressant Development

The treatment of major depressive disorder has also been studied extensively. One way thought to help treat MDD is to help stimulate glial and astrocyte cell growth. This is a response to the loss of these types of cells as a result of MDD. One idea was to target Connexin-43 (Cx43) which is located in cell gap junctions and play a role in glial and astrocyte health. Amitriptyline was used to stimulate Cx43. The findings of this study were the amitriptyline can help to upregulate these genes and pathways which can thereby help treat the symptoms of depression. Meaning, in theory, antidepressants which are utilizing in this treatment should be effective in treating major depressive disorder [6]. Another possible treatment modality tested was in an attempt to produce more neurite outgrowth. The drug aripiprazole was tested to see its effects on neurite outgrowth to help treat MDD. It was found that it increased levels of heat shock protein Hsp90α, which helps to induce neurite outgrowth. It also acted on the IP3receptors, a key factor that is involved in the regulation of P38 MAPK pathway, which is involved in cell apoptosis and differentiation. Therefore, it is thought that aripiprazole would help treat MDD [7]. Another study sought to see how the organization of dendritic spines could help treat depression. This treatment was looked at because depression has shown to alter spine morphology. The evidence presented in this study demonstrated that depression and chronic stress are characterized by atrophy of limbic brain regions and decreased complexity and number of axo-spinous synapses and dendrites in the hippocampus and prefrontal cortex. Using antidepressants, the organization of dendritic spines can be treated [29].

Summary

MDD is a disease that many people struggle with and it is something that can deteriorate a person's health. There are many things that contribute to MDD, but the MAPK pathway is thought to play a major role in the development of this disease. There are many different findings and mechanisms of the MAPK pathway that are being researched to try and narrow down some of the causes of MDD. Several treatments have also been proposed to try and help the people who struggle with MDD on a daily basis. MDD research is ongoing with the development of improved treatments as the mechanisms of the disease are better understood. Our findings strongly link MDD to the MAPK pathway and suggest that continued research in this area will probably lead to novel techniques to target the alternations of the pathway and ultimately treat MDD.

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