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Exploring the Role of P53 in Synaptic Plasticity in the Hippocampus: A Narrative Review of its Implications for Memory and Learning

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The hippocampus is essential for learning and memory, with the p53 protein serving as a critical regulator of these cognitive processes. While p53 is predominantly recognized for its role in apoptosis, it also plays a vital role in modulating synaptic plasticity and preserving hippocampal health. This review explores the influence of p53 on synaptic function and long-term potentiation (LTP) in CA1 neurons, emphasizing its neuroprotective properties within the central nervous system. A comprehensive literature search was conducted across databases such as PubMed and ScienceDirect, employing systematic inclusion and exclusion criteria. We limited our analysis to experimental studies published in English between 2001 and 2022, specifically including articles that were not systematic reviews or literature articles, and excluding animal studies, simplified abstracts, and book chapters. A total of six articles were deliberately chosen for review, examining varied patterns of p53 and synaptic function in diverse contextual settings. The findings reveal that p53 gene regulation is integral to neuronal transcription and is influenced by synaptic activity, with LTP induction correlating with increased p53 transcription levels. Furthermore, miR-34c enhances synaptic function by promoting the expression of synaptotagmin 1. Under apoptotic conditions, p53 is localized at synaptic terminals, contributing to mitochondrial dysfunction and oxidative stress, which leads to synaptic mitochondrial depolarization. The activation of p53 in the CA1 region highlights its dual role in facilitating apoptosis while also providing neuroprotection. These findings suggest that targeting p53 pathways may offer novel therapeutic strategies for enhancing synaptic function and protecting against neurodegenerative diseases, emphasizing the need for a balanced approach to modulate its activity for optimal neuronal health.

Keywords: Hippocampus; Long-Term Potentiation (LTP); Neuroprotection; P53; Synaptic Plasticity.

p53, known as the "Genome Guardian,"[1] is a tumor-suppressor gene that plays an important role in regulating the cell cycle[2] and apoptosis.[3] This gene monitors DNA damage[4] and can induce cell cycle termination or apoptosis if damage is detected, thus preventing the development of cancer.[5] Mutations in the p53 gene,[6] prevalent in a variety of cancers, including breast, colon, and lung

cancers, which cause an impaired cellular response to DNA damage.[7,8] Therapeutic strategies targeting p53 include restoring its function in mutant form and utilizing nanoparticle-based delivery systems for p53-encoding DNA or RNA.[9] In addition, the role of p53 in oncology,[10] affects processes in the central nervous system,[7] where the dysfunction is related to diseases such as Alzheimer's[11,12] and Parkinson's.[12] Despite its function for p53-targeted therapy, challenges remain in achieving effective and safe treatments, especially in cancers with p53 inactivation.[7]

Some studies have shown that p53 as a tumor suppressor gene plays a role in maintaining genetic stability and regulating the cell cycle. This protein serves as a transcription factor[13] involved in various cellular processes, such as apoptosis,[14] DNA repair,[4] dan respons terhadap stres seluler.[8] In the brain, p53 has a multifunctional role that includes brain development,[5] regulation of neural stem cells, and pathology of brain diseases. Wild and mutant type p53 has become a major target in the development of therapeutics to improve the efficacy of cancer treatment,[7] especially brain cancers such as glioblastoma.[5] Research shows that p53 plays an important role in the differentiation and maintenance of neural stem cells, as well as the organization of brain structures during development. p53 dysfunction, such as mutation or loss of function,[6] often causes significant genomic instability, which can affect the normal development of the brain and lead to neurodegenerative disorders.[15] Studies using human brain organoids have shown that loss of p53 function can result in neurodevelopment irregular,[5] which reinforces its important role in maintaining healthy brain function.[1,16] In addition, p53 mutations are often associated with the development of brain tumors, especially glioblastoma, which is one of the most aggressive forms of brain cancer. The mutation in p53 eliminates its tumor-suppressing function, thus allowing for uncontrolled cell proliferation and tumor formation. Therefore, p53 is an important focus in brain cancer therapy research. Efforts to restore lost p53 function or target p53 mutations are expected to improve treatment strategies for glioblastoma and other brain tumors.[17]

Early research suggests that p53 may have a broader function in the brain than as a regulator of the cell cycle. For example, some studies have shown that p53 is involved in the regulation of neuronal apoptosis, which can affect synaptic structure and function.[18,19] However, the literature on p53's involvement in synaptic plasticity mechanisms, such as long-term potentiation (LTP) and long-term depression (LTD), is still very limited and early. A significant domain gap in the literature is the lack of understanding of how p53 plays a role in synaptic regulation at the molecular and functional levels. Most research on p53 has focused on its role in cancer, but the role of p53 in neuronal tissue and how it affects synaptic plasticity has not been sufficiently explored. This is important given the growing body of evidence suggesting that the p53 protein can affect synaptic transmission through the modulation of cellular signals related to oxidative stress and apoptosis.[20] Therefore, further research is needed to deeply understand the molecular mechanisms involved in p53 in synaptic plasticity. This understanding is important because it could open up new opportunities in the development of therapies for neurological disorders such as Alzheimer's disease or depression, where disorders of synaptic plasticity play an important role. For example, further research may explore whether manipulation of p53 in neurons can improve or worsen synaptic plasticity, which may have implications for the development of new therapies for neurodegenerative disorders. The purpose of this review is to understand the role of p53 protein in synaptic plasticity mechanisms, which include long-term potentiation (LTP) and long-term depression (LTD). This review aims to answer the gap domain that exists in the literature, namely the limited understanding of how p53 contributes to synaptic processes in the brain.

MATERIALS AND METHODS

We conducted extensive searches using databases: PubMed, ScienceDirect, and Springer. All papers are published in English. The primary author searched article titles and abstracts with the keywords "p53" and "brain." Review articles were also used as an additional study. Quotations are inputted into an Excel spreadsheet. The author extracts data and synthesizes it. The author extracts data between 2003 and 2023. We limited our analysis to experimental studies. Articles in English published between 2001 and 2022, were included.

Animal studies, did not include systematic reviews or literature articles, and simplified and expanded abstracts were published in the proceedings and book chapters. A total of 6 articles were deliberately chosen to be reviewed. These articles examined P53 and synaptic varied patterns and described studies done in varied contextual settings.

RESULTS

Research results from various studies show a significant role of p53 in synaptic plasticity, both through specific molecular pathways and gene regulation related to synaptic function. (Table 1). Research results from Zhongli Shi,[21] showed that p53 is involved in increased synaptic plasticity through the ROS-JNK-p53 pathway mediated by miR-34c and synaptotagmin 1 (SYT1), which serves to enhance synapses. The study involved 71 mice and identified a key role of p53 in the regulation of synaptic activity through specific molecular pathways. Study Vladimir O. Pustylnyak,[22] reported that p53, along with p73 and egr1, increased at LTP (Long-Term Potentiation) in the CA1 hippocampus in mice, with the result that p53 played an important role in the increase in LTP associated with learning and memory. Study Haixia Kuang,[23] It was found that p53 could regulate synaptic plasticity by reducing neural stimulation, which led to increased synaptic plasticity in mice. Study David Lau,[24] showed that p53 expression was influenced by synaptic activity in newborn black mice. Charles P. Gilman,[25] dan Pavel D,[26] both found that p53 is expressed at the synaptic terminal after apoptotic stimulation, as well as plays a role in the regulation of gene transcription involved in synaptic function. Overall, this table illustrates that p53 plays an important role in improving synaptic plasticity, both through molecular regulation of the apoptosis pathway and through direct control of genes related to synaptic function. These findings underscore the potential role of p53 in the development of therapies for diseases involving synaptic dysfunction.

DISCUSSION

Data from the studies listed in the table show that most of the results support the hypothesis of the role of p53 in synaptic plasticity. However, some of the findings that emerged did not fully meet expectations, especially in the context of p53-specific mechanisms. A study by Zhongli Shi,[21] found that p53 plays a role in increasing synaptic plasticity through the ROS-JNK pathway mediated by miR-34c and synaptotagmin 1 (SYT1). These results reveal a broader function of p53 than just the control of apoptosis, which has traditionally been associated with p53. The discovery that p53 can affect synapses through this molecular pathway is quite surprising, given the previous focus on p53 was more on regulating cellular responses to stress.[21] Study Vladimir O. Pustylnyak,[22] also reported that p53, along with p73 and egr1, experienced an increase in the hippocampus of CA1 related to LTP. These results suggest that p53 may have additional functions in modulating learning and memory, which were not previously associated with this protein. In addition, research by Haixia Kuang,[23] It found that p53 may reduce neural exciability, which in turn increases synaptic plasticity. These findings are not entirely in line with the conventional view that p53 plays more of a regulatory role in apoptosis or the cell cycle, rather than a controller of neural execitability.

The results of the study related to the role of p53 in synaptic plasticity, which is a transcription factor influenced by cellular stress, has an important role in synaptic plasticity in the hippocampus, a vital brain area for learning and memory. In addition to being involved in apoptosis[15] These proteins also regulate neuronal survival and synaptic changes.[27] P53 functions significantly in the long-term potentiation process (LTP)[28], where synapses strengthen in response to repeated stimulation. Activation of p53 during LTP increases the expression of neuroprotection-related genes, such as S100B, which contribute to the maintenance of synaptic integrity.[26]

P53 serves as the main regulator in the initial phase of the synaptic plasticity process. This protein is involved in protein synthesis and gene regulation which has an impact on the strengthening and weakening of synapses.[29] Some studies suggest that p53 may affect the expression of genes related to nerve growth factors, as well as proteins that play a role in synapse strengthening, as occurs in the process of Long-Term Potentiation (LTP).[30] This confirms that p53 plays an important role in the modulation (upstream) of synaptic

Table 1. p53 on Synaptic Plasticity

Author	Year	Participant n=	Marker	Result	Discussion	Ref
Zhongli Shi	2018	Mice, n=71	MiR-34c, ROS-JNK-p53, synaptotagmin 1 (SYT1)	synaptic enhancement	Synaptotagmin 1 enhances synapses with the help of miR-34c via the ROS-JNK-p53 pathway and the miR-34c/SYT1 pathway	21
Vladimir O. Pustylnyak	2015	Rat, n=4	p53, p73, egr1	LTP enhancement	p53 is increased in hippocampal LTP CA1, and other genes p73, and EGR 1	22
Haixia kuang	2022	Rat, n=38	p53	synaptic enhancement	p53 regulates synaptic plasticity by reducing neural excitability and the amount of excitability of S1BF	23
David Lau	2009	Newborn black mice n= 4	p53	synaptic enhancement	The expression of the p53 gene is regulated by synaptic activity.	24
Charles P. Gilman	2003	Mice, young adult. n= 12	p53	synaptic enhancement	p53 expression at synaptic terminals after the apoptotic stimulus.	25
Pavel D	2014	Mouse, n= 10	p53	synaptic enhancement	p53 controls the transcription of genes involved in synaptic function	26

Note: long-term potentiation (LTP), long-term depression (LTD), pyramidal neurons in the primary somatosensory cortex barrel field (S1BF), negatively regulated synaptotagmin 1 (SYT1), Early growth response (Egr)-1,

plasticity, which impacts learning and memory mechanisms through long-term changes in synaptic power. Thus, p53 can be thought of as a regulatory element that plays a role in the early phases and influences the way neurons adapt and interact with each other.[31]

The molecular mechanism of p53 occurs in the early phase of LTP with increased expression of the p53 gene in the CA1 hippocampus which serves as a transcription factor regulating gene expression.[22] These genes include BDNF (Brain-Derived Neurotrophic Factor) and IEGs (Immediate Early Genes), which play an important role in synapse formation and synaptic strengthening through the process of Long-Term Potentiation (LTP).[13,31,32] In addition, P53 can interact with a variety of other proteins involved in synaptic regulation. For example, its interaction with proteins involved in signaling pathways such as PI3K-Akt and MAPK, which contribute to the strengthening of synapses and regulation of neuronal growth.[21]

However, several other studies provide strong indications that p53 plays a role in maintaining the viability of hippocampus neurons, especially in the CA1 region during the aging process.[33] Another study found the presence of p53-containing neurons in the hippocampus of old mice, which are potentially involved in synaptic changes and neuronal viability during aging and neurodegeneration.[1] These findings reinforce the hypothesis that p53 not only plays a role in apoptosis but also in the maintenance of synaptic function during neurodegenerative processes. In contrast, Wilson et al.'s,[34] this study suggests that p73, rather than p53, may have a more dominant role in Alzheimer's pathology in the hippocampus, despite low p53 expression. The study of abate et al.,[11] proposed that p53 may interfere with synaptic plasticity in Alzheimer's disease by decreasing the expression of the GAP-43 protein, which is essential for synaptic growth.

Some studies, such as the engel at al.,[35] showed that p53 deficiency did not significantly affect synaptic reorganization in the hippocampus, although it affected the duration of seizures. This suggests that the p53 effect may be specific to the type of synapse and its context.[36] Another study explains on the role of p53 in pyramidal neurons of the somatosensory cortex or brain organoid development, without examining the specific relationship with the hippocampu.[37,38] Overall, this study suggests that the role of p53 in hippocampal synapses is still an area that has not been fully explored and requires further research to understand its impact in the context of neurodegeneration and broader synaptic function.

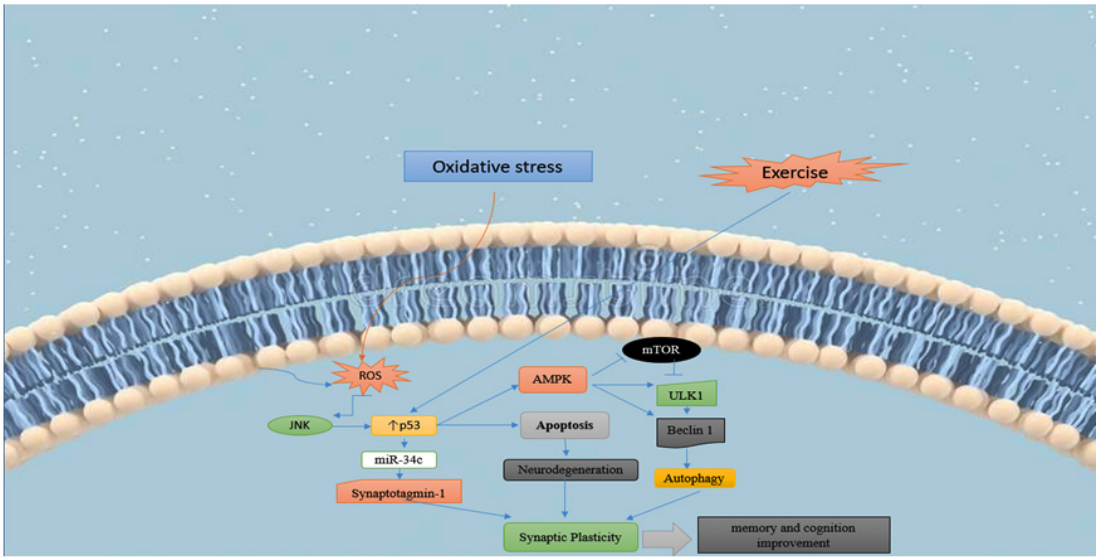

Fig. 1. Oxidative stress will cause an increase in ROS, then ROS through the JNK pathway, increased p53, and mediated by mir34c will increase synaptotagmin so that synaptic nerve plasticity increases

A major limitation of this review is its narrow focus on literature that directly explores the relationship between p53 and synaptic plasticity in the hippocampus. Most of the research reviewed in this review does not explicitly address the role of p53 in hippocampal synaptic plasticity, but rather highlights its function in processes such as proliferation,[39] Neural stem cell differentiation,[32] apoptosis,[40] or response to cellular stressx,[40] such as radiation[42] and seizures[35,43]. This creates a gap in understanding the specific mechanisms of how p53 affects synaptic function in the hippocampus, particularly in relation to learning and memory[28] which is related to long-term potentiation (LTP).[26] In addition, many studies emphasize the role of p53 in apoptosis[14] or neuronal degeneration[25] In general, it provides a less in-depth understanding of the role of p53 in the specific regulation of synaptic plasticity. Some of the research in this review is also not directly relevant to the context,[25] hippocampus[44] or synaptic plasticity,[45] because the focus is on other areas of the brain such as the somatosensory cortex, or on other processes such as organoid development.[1]

Thus, the scope of research that actually targets the role of p53 in the hippocampus is still limited. Another limitation of this review is the reliance on animal models, especially mice, which may not fully reflect the processes that occur in the human brain. Although many molecular mechanisms can be translated from animal to human models, species differences may affect the validity of applying these findings to humans. In addition, the lack of longitudinal studies assessing the long-term effects of p53 on synaptic plasticity, especially in the context of aging or neurodegeneration, is another limitation. Many of the studies discussed focused on short-term or acute effects, while the role of p53 in progressively developing synaptic changes, such as that in Alzheimer's disease, still needs more research. Thus, more studies are needed to understand the relationship of p53 with synaptic plasticity, especially in the hippocampus, and in the context of neurodegenerative diseases in humans.

CONCLUSION

p53, traditionally known for its role in cell cycle regulation and stress responses, is increasingly recognized for its significant involvement in synaptic plasticity within the hippocampus, a critical region for learning and memory. This review highlights p53's multifaceted roles in modulating synaptic strength through various molecular pathways, including gene transcription regulation. Given the implications of p53 in enhancing synaptic function, future research should focus on elucidating its specific mechanisms in synaptic plasticity and exploring its potential as a therapeutic target in neurodegenerative diseases. Understanding how p53 influences synaptic dynamics could pave the way for innovative strategies aimed at improving cognitive function and mitigating the effects of age-related decline and neurodegeneration.

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Ethics Statement

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Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

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This research does not involve any clinical trials

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Not applicable.

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