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Review Article

Neuroregeneration: From Molecular Mechanisms to Clinical Applications and Natural Stimulating Agents

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Abstract
Neuroregeneration (NR) is a process through which the neurons are repaired and recovered. The process can be triggered and modulated physiologically or pharmacologically. Based on the evidence, neuroregenerative pathways are activated in many neurological conditions, such as Alzheimer's disease (AD) and Parkinson's disease (PD). Therefore, targeting these pathways has become an interesting subject for researchers active in this field. In addition, in recent decades, natural remedies have become of interest to researchers, on the one hand, and consumers, on the other hand. Hence, this review aimed to collect the existing evidence about NR, the underlying molecular mechanisms, clinical applications, and the natural stimulating agents. Accordingly, scrutinizing the available literature revealed that many natural agents have the required ability to potentiate NR, each of which can be an interesting topic for further studies.
Keywords: Neuroregeneration, Neurodegeneration, Herbs, Natural products

Introduction

Neuroregeneration (NR) is defined as the growing back or repair of degenerated nervous tissues and nerve cells involved in the production of new neuronal cells, the synapses, myelin, glia, and axons.[1] The functional mechanism of NR varies between the central nervous system (CNS) and the peripheral nervous system. The CNS is incapable of self-repair and regeneration, while the peripheral nervous system has this intrinsic capability.[2,3]

The recovery time of the damaged nerves varies from case to case and can be affected by numerous factors.[4] The reported data have shown that the regeneration rate for neurons is significantly slow, and many approaches for accelerating this process have failed to reach important achievements.[5] Nonetheless, some supporting therapies have been shown to be capable of neuronal survival, axonal regeneration, and reinnervation of peripheral targets. In this context, plant-derived products have gained particular attention so that several recent studies have confirmed their therapeutic benefits. Tragically, the cost of surgical treatments is excessive, and their application has been restricted due to various disadvantages such as tumorigenicity, immunosuppression, and chromosomal aberrations. Therefore, non-surgical therapies, such as medications and electrical nerve stimulation, would be preferred in this regard.[4] Surprisingly, plants and plant-derived compounds have provided a bright light to scientists due to their pharmacological properties, including anti-inflammatory,[6] anti-oxidative,[7] neuroprotective,[8] and analgesic effects.[4,9] Here, it would be proposed that natural compounds have the potential to stimulate NR and subsequently alleviate many related conditions, the idea of which will be reviewed in the following section.

Possible Contributing Mechanisms

Figure 1 shows a simple schematic theme for NR. Reviewing the literature demonstrated that neural germinal cells found in the subventricular and subgranular regions of the hippocampal dentate gyrus in the CNS of adult mammals[10] would differentiate into neuroblasts and migrate to the damaged area for producing new neural cells following a brain injury.[11]

Oxidative stress (OS) is a pathological characteristic of regenerative failure resulting from an oxidative imbalance between cellular oxidant and antioxidant defense in the nervous system.[12] Depletion of the antioxidant resources would accelerate the progression of many illnesses because it causes nearly all cell components, including lipid membranes, proteins, and DNA, to break down.[13] The accumulation of reactive oxygen species would lead to neuronal death and functional impairments in case of overcoming the antioxidant capacity.[14] A growing number of studies indicate a significant connection between OS and neurological diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD).[8,15] In addition, OS contributes to the pathogeneses of secondary damage after traumatic injuries to the spinal cord and brain.[16]

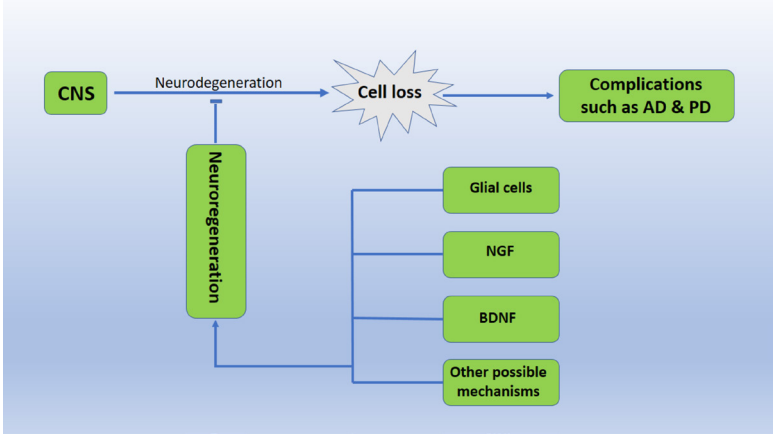

Figure 1. A Schematic Theme on the Role of Neuroregeneration Against Complications Such as AD and PD. *Note*. AD: Alzheimer's disease; PD: Parkinson's disease; CNS: Central nervous system; NGF: Nerve growth factor; BDNF: Brain-derived neurotrophic factor

Therefore, the regulation of OS has been suggested for resolving neurological diseases.[7,17]

Clinical Applications

Table 1 presents some important clinical applications for NR. Based on the available literature, the pathogenesis of AD is based on the extracellular aggregation of amyloid beta plaques and intracellular aggregation of hyperphosphorylated tau.[18] Studies have shown that the neurotrophic factor small-molecule mimetic-based NR and synaptic repair can offer a highly promising therapeutic strategy for AD and may result in the development of an efficient medication to reverse cognitive impairment.[19]

PD is the second most prevalent neurodegenerative disease globally, where the degeneration of nigrostriatal dopamine neuronal cells causes motor diagnostic symptoms. There is no cure for PD, and current therapy is limited to supportive care, alleviating the signs and symptoms of the disease to some extent. Considering that the symptoms are consequences of dopaminergic progressive degeneration, medications restoring the relevant neurons may help in better treating the disease.[20]

A condition known as Huntington's disease leads to the gradual degeneration of the neurons. This condition is triggered by a mutation in the *HTT* gene, which significantly impacts human functions and typically leads to psychiatric, cognitive, and motor impairments. Ablative surgery and fetal tissue cell transplantation, which are still at the experimental stage, indicate an inadequate recovery rate in patients with Huntington's disease. Considering that it is improbable that brain damage caused by mutated huntingtin protein can be treated completely through pharmacotherapies, stem cell-based treatments are essential for rebuilding damaged brain regions.[21]

Treatments that slow, prevent, or reverse the progress of multiple sclerosis are the major remaining needs regarding this neurodegenerative disease. One of the most practical approaches is elevating endogenous remyelination to a clinically significant extent that can save nerve conductivity and slow neurodegeneration. Therefore, this is a pressing clinical demand to find remyelinating treatments that have the ability to restore function and stop axon degeneration.[22]

Given that protecting against degeneration and stimulating the regeneration of neuronal cells are essential for promoting neurological rehabilitation following stroke, reprogramming reactive astrocytes in damaged regions of the brain can be a suitable replacement therapy for re-establishing functional connections between neurons and subsequently alleviating the complications.[23]

Natural Stimulating Agents

Many natural agents (Table 2) have the potential to stimulate NR; some of the most popular ones are introduced below:

Curcumin

One of the most researched phytochemical agents found in the spice turmeric is curcumin, which displays sophisticated and varied activities.[24] Interestingly, the agent has been reported to accelerate myelination and improve peripheral nerve injury in rats.[25] Furthermore, the proliferation, differentiation, and maturation of neural stem cells were enhanced in some areas of the hippocampus following cerebral ischemia.[26] Further, curcumin can be utilized to lower Schwann cell apoptosis and stimulate injury-related cell autophagy, remyelination, and axon regeneration.[27] Notably, based on a report, curcumin can effectively repair the entire sciatic nerve lesion, probably through the proliferation of Schwann cells.[28] It has been found that in injured rats, curcumin displays a protective effect on the sciatic nerve structure and dorsal root ganglion.[29] Numerous naturally occurring bioactive molecules such as curcumin have been shown as potential antioxidant and anti-inflammatory agents.[30] Overall, this study showed the advantageous effects of curcumin and melatonin on nerve regeneration following peripheral nerve crush injury.[25]

Resveratrol

Resveratrol, the polyphenol found in chocolate, grapes,

Table 1. Popular Conditions Alleviated by Neuroregeneration

Diseases	The Reported Counter-Neuroregenerations	References
Alzheimer's disease	The role of neurotrophic factor small-molecule mimetic-based neuroregeneration and synaptic repair in alleviating cognitive impairments	19
Parkinson's disease	Regeneration of dopaminergic neurons	20
Huntington	The role of stem cell-based therapies in regenerating damaged brain areas	21
Multiple sclerosis	Therapeutic enhancement of endogenous myelination	22
Stroke	Reprogramming of activated astrocytes in damaged brain areas into neurons and subsequent re-establishment of functional connections between neurons	23

Table 2. Some Natural Agents Stimulating Neuroregeneration

Compound	Activity	References
Curcumin	Promoting myelination, proliferation, differentiation, and maturation of neural stem cells in the dentate gyrus area of the hippocampus following cerebral ischemia	24-30
Resveratrol	Functioning in antioxidant-associated NR and modulating hydroxyl, superoxide, and other radicals	31-37
Ginkgo biloba	Antagonizing oxygen free radicals, stabilizing cell membranes, promoting neurogenesis and synaptogenesis, increasing BDNF levels, and differentiating stem cells into nerve cells	38
Bacopa monnieri	Functioning as a nerve tonic antioxidant that is able to alleviate anxiety, depression, and seizures	39-41
Withania somnifera (Ashwagandha)	Recovering neuritic atrophy and synaptic loss and increasing axonal and dendritic regeneration, along with synaptic regeneration of the impaired neurons	42, 43
Ginseng	Having restorative, antioxidant, anti-aging, anticancer, anti-fatigue, anti-stress, and anti-depressive effects	44
Vitamin B	Contributing to neurotransmitter synthesis and remyelination, preserving myelin sheaths, and reducing neurotoxic glutamate	45-51
Vitamin E	Functioning as a chain-breaking antioxidant and preventing free-radical reactions and lipid peroxidation	52-56
Lycopene	Having anti-inflammatory and antioxidant effects, protecting against lipid peroxidation, and promoting antioxidant enzyme activity	57, 58
Flavonoids	Improving memory impairments and promoting NR, particularly against AD pathogenesis	59, 60
Alpha-lipoic acid	Functioning as an antioxidant, a cofactor for many mitochondrial reactions, increasing the levels of antioxidants, decreasing NR, and improving the recovery of nerve functions	52, 61-63

Note. BDNF: Brain-derived neurotrophic factor; AD: Alzheimer's disease; OS: Oxidative stress; NR: Neuroregeneration.

red wine, and many plants (e.g., knotweeds and pine trees),[31] has been known for many pharmacological potentials, including the inhibition of platelet aggregation and improvement of microcirculation, as well as anti-inflammatory, antioxidative, and anti-inflammatory effects.[32,33] Resveratrol demonstrates its neuroprotective abilities by managing autophagy and apoptosis after neuronal injury,[34] probably through leveling the content of hydroxyl, superoxide, and other radicals, which seems to be associated with its antioxidant ability.[35] Overall, it seems to protect the cell membranes against lipid peroxidation and, subsequently, DNA damage.[36,37]

Ginkgo biloba

EGb761, which is extracted from the leaves of the *Ginkgo biloba* tree, has been reported to antagonize oxygen free radicals, stabilize cell membranes, stimulate neurogenesis and synaptogenesis, elevate the level of brain-derived neurotrophic factors, and imitate the conditions necessary for stem cells during differentiation into nerve cells.[38]

Bacopa monnieri

Bacopa monnieri, which grows in marshy or damp areas, has the potential to be used in conditions such as epilepsy, depression, anxiety, and hypertension.[39] Several secondary metabolites, such as bacosides A and B, facilitate refurbishing damaged neurons and subsequently stimulate NR.[40,41]

Withania somnifera (Ashwagandha)

Ashwagandha, which is famous in Ayurvedic medicine, is traditionally and commonly known as a nootropic tonic agent.[42] A methanol extract of the plant was linked with neurite extension and, specifically, that of dendrites.[43] The available data show the ability of the plant to recover both neuritic atrophy and synaptic loss, as well as the considerable improvement of dendritic and axonal regeneration and synaptic reconstruction.[42]

Ginseng

For centuries, ginseng has been utilized as a traditional herbal medicine, and it is famous for exerting antianxiety, antidepressant, and cognition-enhancing characteristics. Components derived from ginseng root have exhibited restorative, adaptogenic, vasodilatory, immunomodulatory, anti-inflammatory, anti-aging, antioxidant, anti-fatigue, anticancer, anxiolytic, and anti-depressive consequences in the experimental models.[44]

Vitamins B and E

While vitamin B6 is essential for neurotransmitter synthesis and prevention of the release of neurotoxic glutamate, vitamin B1 essentially contributes to the energy production needed for the process and functions as a site-directed antioxidant.[45,46] Conversely, vitamin B12 is strongly and directly involved in remyelination and the preservation of myelin sheaths and significantly increases

neuron survival.[47-51]

Moreover, vitamin E, which is an essential lipid-soluble vitamin with known antioxidant effects,[52,53] has a positive impact on the prevention and alleviation of neurodegenerative diseases and the protection of neurons from oxidative damage.[54] Vitamin E functions as a chain-breaking antioxidant, preventing lipid peroxidation and free-radical reactions.[55] The administration of vitamin E has been shown to decrease degenerations, muscle atrophy, nerve gliosis, biochemical markers for OS, and other injury-related factors, such as improved sciatic nerve function, increased number of functional motor neurons, suppressed cold, and mechanical allodynia.[56] Furthermore, it could elevate superoxide dismutase and brain-derived neurotrophic factor levels in animal models and decrease tau-protein hyperphosphorylation, suggesting that vitamin E may be used to prevent and delay neurodegeneration in the CNS. Thus, vitamin E can lower oxidative events and suppress the brain inflammation whose mechanisms are present in several neurodegenerative diseases, according to the encouraging results of the in vivo research.[54]

Lycopene

Lycopene (a carotenoid), which is widely available in the structure of many plants and fruits, including tomatoes, papaya, watermelon, and pink guava,[57] has become popular for its high antioxidant capacity. These characteristics protect against several types of cancers, cardiovascular conditions, diabetes, and skin disorders.[58] As an antioxidant, it protects cell membranes from lipid peroxidation via the stimulation of antioxidant enzyme activity. The carotenoid seems to be able to alleviate peripheral nerve damage. However, it is recommended that further studies be conducted to ascertain the underlying mechanisms through which lycopene activates peripheral nerve regeneration.[57]

Flavonoids

Many herbs, such as *Scutellaria baicalensis* Georgi, the traditional Chinese herbal medicine, contain flavonoids that have antioxidant, anti-inflammatory, and immune-stimulating properties.[59] It has been claimed that flavonoid-rich herbs have the potential to increase the expression of the Brdu protein, improve memory deficits, and stimulate NR in patients suffering from AD.[60]

Alpha-Lipoic Acid

The powerful antioxidant and cofactor for numerous mitochondrial reactions, alpha-lipoic acid (ALA),[52] has been found to regenerate other antioxidants, including vitamins C and E, and therefore, increase free radical scavenging.[61] Several animal studies have confirmed the role of ALA following perineural invasions.[62,63] At perineural invasion occurrence, ALA has been shown to elevate levels of antioxidants, reduce OS, enhance function recovery and conduction velocity of the nerves, and regenerate myelin and axons.

Future Perspectives

Although there is still a lack of knowledge about the exact mechanisms leading to NR, the process seems to play an important role in better treating neurological conditions in the upcoming years. On the other hand, the approach to natural treatments is expanding very rapidly. Therefore, these agents are very likely to play a major role in the treatment protocol of neurological disorders, particularly those with neurodegenerative pathologies. Overall, it seems that focusing on NR, the natural stimulating agents, the underlying mechanisms, and the possible side effects can become a research priority in the coming years.

Conclusion

Reviewing the literature confirmed NR as an important defense mechanism against various neurological conditions. The activation of this mechanism may decelerate the progression of many CNS pathologies. This activation can be triggered and modulated by many pharmacological agents, among which natural remedies have been extensively introduced in recent years. However, details in this regard are still unclear and can be elucidated by further preclinical and clinical studies in the near future.

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Methodology: Kiarash Fekri.
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Visualization: Hadiseh Abdollahi, Ali Monadi Tabari, and Kiarash Fekri.
Writing–original draft: Hadiseh Abdollahi and Kiarash Fekri.
Writing–review and editing: Kiarash Fekri and Ali Monadi Tabari.

Competing Interests

None to declare.

Ethical Approval

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