The molecular fundamentals of neurorehabilitation and their modulation by thyroid hormones

Abstract. Neurological disorders affect a large population, often leading to different levels of disability and resulting in a decreased quality of life. Neurorehabilitation is the process of restoring the functions of the nervous system after injuries, diseases, or other impairments. The molecular basis of neurorehabilitation includes various aspects such as changes in gene expression, regulation of synaptic connections, nerve cell growth, and repair, among others. Typical objectives in rehabilitating the patient with neurologic disease are to minimize pain, reestablish normal neural pathways, prevent secondary complications, and ultimately improve quality of life. It is also essential not to worsen neurologic function or pain in patients with spinal instability. A decreased free triiodothyronine and thyroid stimulating hormone levels upon admission may predict an unfavorable outcome at the end of early rehabilitative treatment. Thus, thyroid hormone levels are not only important during acute treatment but also in prolonged critical illness. Thyroid hormones, specifically thyroxine and triiodothyronine, can influence these molecular processes through their receptors in nervous tissue. Thyroid hormones are essential for the normal functioning of the nervous system, including neurogenesis (the formation of new neurons) and synaptic plasticity (changes in the strength and structure of connections between neurons). Research has shown that thyroid hormones can affect the expression of genes related to the growth and survival of neurons, as well as synaptic plasticity processes, which may be relevant for rehabilitation after nervous system injuries. A deficiency of thyroid hormones such as in hypothyroidism can lead to disturbances in the development and functioning of the nervous system, which, in turn, can complicate the neurorehabilitation process. Thus, understanding the molecular basis of neurorehabilitation and the influence of thyroid hormones can help improve approaches to the rehabilitation of patients with various nervous system impairments.

Keywords: neurorehabilitation; nervous system; thyroid hormones; physical therapy

The molecular foundation of neurorehabilitation encompasses complex biological processes and molecular mechanisms underlying the restoration of nervous system functions following injuries, diseases, or other impairments. Neurorehabilitation promotes the stimulation of neurogenesis, the formation of new neurons. This process occurs in major neurogenic zones such as the hippocampus and subventricular zone and can be enhanced through physical exercises and specialized training. The neurogenic zones in the brain include regions where the formation of new neurons, the deposition of neuroglial cells, and their subsequent differentiation occur [1, 2]. These neurogenic zones are crucial for regulating brain functions in adults such as learning, memory, and mood regulation.

Thyroid hormones play a vital role in both brain development and optimal brain function, contributing to various bodily functions throughout life. Beginning with prenatal development, they support the growth and specialization of the nervous system [3]. In adulthood, they are instrumental in sustaining concentration, memory, metabolic rate, ther-
mogenesis, cardiovascular health, and nutritional processes [4]. Moreover, thyroid hormones participate in intricate mechanisms like gene regulation, memory consolidation, and learning processes.

Recent advancements in medical and molecular research have significantly enhanced our comprehension of the pivotal role and intricate mechanisms of thyroid hormones. Studies have revealed their involvement in pivotal processes including neurogenesis, neuronal and glial cell differentiation, myelination, and synaptogenesis [5].

Thyroid hormones within the brain are known to regulate multiple pathways that contribute to structural aspects during development, including neurogenesis, cell migration, myelination, and the differentiation of neurons and glial cells. These hormones also impact adult neurogenesis, primarily occurring in two brain regions: the subventricular zone of the lateral ventricles and the dentate gyrus [6]. This neurogenesis is often linked with cognitive deficits, psychiatric disorders, and depression. Administration of thyroid hormones stimulates neurogenesis in these brain regions, while hypothyroidism suppresses it. It’s well-documented that thyroid disorders can lead to cognitive dysfunction and psychological deficits, such as anxiety and depression [7–9]. The correlation between thyroid hormone deficiency and anxiety and depression has been extensively researched [10, 11].

Experimental studies on rats have revealed that hypothyroidism leads to a reduction in the activity of choline acetyltransferase and a decrease in the levels of this enzyme, which is involved in the synthesis of acetylcholine. Acetylcholine is a crucial neurotransmitter that plays a key role in the regulation of memory, cognitive functions, and learning ability [12]. Disruptions in acetylcholine synthesis due to a decreased choline acetyltransferase activity may result in memory dysfunction and cognitive impairments in patients with hypothyroidism [10]. These findings suggest a comprehensive impact of hypothyroidism on neurotransmitter systems and brain structures, particularly in the context of the hippocampus, providing insight into the association between hypothyroidism and cognitive deficits.

Studies indicate a decline in cognitive function during hypothyroidism due to diminished synaptic plasticity in the hippocampus. Notably, research highlights the critical role of thyroid hormone receptor α1 in regulating the survival of adult hippocampal progenitors, emphasizing its importance in governing the maturation processes of neuronal precursors [13].

Autoimmune disorders of the thyroid gland impact the transcriptional activity of genes that regulate neurogenesis and neurotrophins. This influence can potentially lead to depression and neurological complications.

Our research has revealed that the transcriptional activity of genes regulating nerve impulse transmission, including BDNF, CBLN1, and MEF2C, is likely lower in patients with hypothyroidism, by 2.8–41.8 times (p ≤ 0.003–0.001) compared to the control group, while that of GDNF is increased by 5–10.7 times (p ≤ 0.005). Conversely, in patients with autoimmune thyroiditis, there is higher expression of BDNF, CBLN1, and PNOC by 3.4–4.6 times (p ≤ 0.03), with a decreased expression of GDNF and NTSR1 by 3.6–21.0 times (p ≤ 0.005), respectively. No changes in the transcriptional activity of genes CNTF, CRH, GALR1, GALR2, HCRT, NPFF, and NPY were found in all observation groups [14].

We also discovered that the expression of certain neurogenesis-regulating genes is reduced in all patients, regardless of thyroid gland pathology: NGFR, NRG1, and NTF3 by 4.43–17.4 times (p ≤ 0.015), while genes ARTN, PSPN, TFG, MT3, NELL1 showed no change in their transcriptional activity (p > 0.05). Additionally, lower expression was found in primary hypothyroidism for the FGF2 gene by 20.1–20.8 times (p < 0.001), and in patients with autoimmune thyroiditis without hypothyroidism, for GFRA3, NTRK1, and NTRK2 genes by 6.4–10.5 times (p ≤ 0.002) [15, 16].

Restoring connections between neurons (synapses) is a crucial step in neurorehabilitation. Physical activity and specialized tasks can facilitate the formation of new synapses and improve communication between neurons.

Neurorehabilitation, including physical exercises and cognitive training, can support brain plasticity, which is crucial for recovery after injuries. Physical activity promotes the production of neurotrophic factors such as BDNF. These molecules play a key role in the survival and growth of neurons. Physical rehabilitation can influence molecular mechanisms aimed at reducing inflammation and stress responses in nervous tissue. Muscles produce myokines (biologically active substances) during physical activity, which can influence molecular processes in the nervous system, contributing to recovery. Understanding these molecular aspects allows for the development of more effective neurorehabilitation strategies targeting specific molecular mechanisms to enhance nervous system recovery. The molecular foundations of neurorehabilitation involve understanding the intricate processes underlying neural plasticity, repair, and regeneration in the nervous system following injury or disease. Neuroplasticity refers to the inherent ability of the brain to modify and adjust in response to various experiences. This concept encompasses the brain’s capacity to undergo changes, reorganization, or growth in neural networks. These changes can manifest as functional adaptations following brain damage, where the brain redistributes functions from affected areas to undamaged regions, or as structural modifications resulting from learning, leading to alterations in the brain’s physical configuration [17–19]. Recent research has provided evidence that the brain continues to generate new neural pathways and modify existing ones to accommodate novel experiences, acquire new knowledge, and form fresh memories [18–20].

Neurorehabilitation relies heavily on the concept of neuroplasticity, which refers to the brain’s ability to reorganize its structure and function in response to experience, learning, and injury. Molecular processes underlying neuroplasticity include changes in synaptic strength, dendritic branching, axonal sprouting, and neurogenesis.

The brain can reorganize and form new neural connections in response to learning or experience. Neurorehabilitation aims to harness neuroplasticity to promote recovery and functional improvement after neurological injury or disease. Neuroplasticity is the ability of the nervous system, particularly the brain, to reorganize and change in response to
Strategies aimed at promoting synaptogenesis are integral to processes, and contributing to neuroprotection and repair. Synaptogenesis is also involved in neuroprotection and repair. By promoting synaptogenesis, neurorehabilitation aims to harness these mechanisms to promote recovery, improve functional outcomes, and enhance the quality of life for individuals with neurological conditions or brain injuries.

Inflammation is a double-edged sword in neurorehabilitation. While acute inflammation helps clear debris and initiate repair processes, chronic inflammation can exacerbate tissue damage and impair recovery. Molecular signaling pathways involved in the inflammatory response such as cytokines and chemokines need to be carefully regulated to promote healing without causing further harm.

Neurotransmitters such as dopamine, serotonin, glutamate, and gamma-aminobutyric acid play essential roles in modulating neural activity and synaptic transmission. Imbalances in neurotransmitter levels are associated with various neurological disorders [28]. Neurorehabilitation strategies may target these neurotransmitter systems to restore normal function and promote recovery.

Molecular processes regulating gene expression and epigenetic modifications play crucial roles in neurorehabilitation. Changes in gene expression patterns can influence neuronal survival, synaptic plasticity, and axonal regeneration. Epigenetic modifications such as DNA methylation and histone acetylation regulate gene expression without altering the underlying DNA sequence and are implicated in neuroplasticity and recovery processes. Understanding these molecular mechanisms provides insights into the development of novel neurorehabilitation strategies aimed at enhancing functional recovery and improving outcomes for individuals with neurological injuries or diseases. By targeting specific molecular pathways, researchers and clinicians can design interventions to promote neural repair, rewiring, and regeneration, ultimately restoring lost function and improving quality of life.

Neurogenesis is the process of generating new neurons (nerve cells) in the brain. While it was previously believed that neurogenesis primarily occurs during early development and decreases with age, emerging research suggests that it can occur throughout life, particularly in certain brain regions such as the hippocampus. The role of neurogenesis in neurorehabilitation lies in the fact that stimulating the formation of new neurons may promote the recovery of functions after brain injuries or neurological disorders. New neurons may contribute to improving memory, learning, and other cognitive functions, which is particularly important for patients with memory disorders or other cognitive deficits. Neurogenesis may also impact emotional state and mental health, helping reduce depression and stress often observed in patients with neurological disorders. New neurons can integrate into motor pathways in the brain, helping restore motor skills after brain injuries or damage to motor areas. Stimulating neurogenesis can help the brain adapt to new conditions such as recovery after injuries or changes in the environment [29, 30].

Overall, neurogenesis plays a crucial role in neurorehabilitation, and stimulating it can be beneficial for improving brain functions and enhancing the quality of life for patients with neurological disorders or after brain injuries. By adhering to these basic principles, neurorehabilitation aims to promote recovery, improve functional outcomes, and enhance the overall well-being of individuals with neurological conditions or injuries.

In summary, synaptogenesis plays a crucial role in neurorehabilitation by facilitating the restoration of neural connectivity, enhancing neural communication, promoting neural plasticity and adaptation, supporting learning and memory processes, and contributing to neuroprotection and repair. Strategies aimed at promoting synaptogenesis are integral to the rehabilitation process and can lead to improvements in functional outcomes and quality of life for individuals with neurological conditions or brain injuries.

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Neurotrophic factors are molecules that support the growth, survival, and differentiation of neurons. BDNF, NGF, and GDNF are examples of neurotrophic factors involved in neurorehabilitation. They promote neuronal survival, axonal growth, and synaptic plasticity, facilitating recovery after injury. Additionally, we also observed a decrease in the level of neurotrophic factors in patients with thyroid pathology [31, 32].

Neurotrophic factors promote the survival of neurons and stimulate the growth of new neurites, which are essential for the regeneration of damaged neural pathways. By providing trophic support to neurons, these factors can enhance the recovery of neural function following injury or disease. Neurotrophic factors play a vital role in synaptic plasticity, the ability of synapses to strengthen or weaken over time in response to activity and experience [33]. They promote the formation of new synapses and modulate synaptic strength, which is essential for learning, memory, and functional recovery, have neuroprotective effects, helping mitigate damage and prevent cell death in the nervous system. Also, they can stimulate repair mechanisms such as axonal sprouting and remyelination, which contribute to the restoration of neural function after injury. Neurotrophic factors promote neuroplasticity, the brain’s ability to reorganize and adapt in response to changes in the environment or internal factors. They facilitate the structural and functional changes necessary for neural adaptation and recovery of function during rehabilitation. By supporting neuronal survival, regeneration, synaptic plasticity, and neuroprotection, neurotrophic factors contribute to the overall process of functional recovery during neurorehabilitation. Neurotrophic factors help restore neural circuits, improve synaptic connectivity, and enhance the recovery of motor, sensory, and cognitive functions.

The main neurotrophic factors and their role in neurorehabilitation include BDNF, which is crucial for promoting neuron survival, growth, and synaptic plasticity. In neurorehabilitation, it can aid in the regeneration and strengthening of neural connections, enhancing cognitive and motor functions. NGF supports the survival and growth of sensory and sympathetic neurons, contributing to the development of neural networks. It may play a role in improving perception and motor skills during neurorehabilitation. GDNF is essential for the survival and growth of dopaminergic neurons, which are important for motor coordination and control. In neurorehabilitation, GDNF may help restore functions in patients with movement disorders like Parkinson’s disease. The role of these neurotrophic factors in neurorehabilitation is to promote neuron survival, growth, and regeneration, support synaptic plasticity, and facilitate functional recovery following injuries or neurological disorders. Utilizing strategies that stimulate the production and activity of these factors can improve the effectiveness of neurorehabilitation programs and aid in the recovery process [34, 35].

BDNF is a protein known to stimulate neurogenesis, promote neuron and microglia survival, enhance neuroplasticity, and contribute to cell differentiation in the hippocampus. BDNF is also released from skeletal muscles during exercise, facilitating communication between the nervous and muscular systems [36].

Both short-term and prolonged exercise regimens have been shown to result in elevated levels of BDNF both peripherally and in the brain. This is supported by numerous studies [37, 38], as well as a comprehensive review [39].

Irisin, often referred to as the exercise hormone, is another protein released from skeletal muscles during physical activity and is involved in metabolic processes within the body. This is particularly relevant in the context of preventative and therapeutic interventions for age-related conditions such as senile dementia, obesity, and type 2 diabetes [40].

Irisin originates from a transmembrane precursor protein known as FNDC5. In addition to its predominant expression in muscle tissue, FNDC5 is also highly expressed in the brain. The processed form of FNDC5 has been identified in the cerebrospinal fluid and various brain regions. Several studies have indicated that irisin plays a crucial role in regulating brain metabolism and inflammation. Given the significant impact of metabolism and inflammation on stroke outcomes, our published study demonstrated that low-frequency vibration therapy administered after middle cerebral artery occlusion led to a notable reduction in innate immune response, improvement in motor function, and reduction in infarct volume in reproductively senescent female rats [41].

Irisin, an exercise-induced myokine, is released following cleavage of the membrane-bound precursor protein FNDC5, which is also expressed in the hippocampus. Our research reveals reduced levels of FNDC5/irisin in the hippocampi and cerebrospinal fluid of individuals with Alzheimer’s disease (AD), as well as in experimental AD models. Knockdown of brain FNDC5/irisin in mice impaired long-term potentiation and novel object recognition memory. Conversely, increasing brain levels of FNDC5/irisin restored synaptic plasticity and memory in AD mouse models. Peripheral overexpression of FNDC5/irisin improved memory deficits, while inhibition of either peripheral or brain FNDC5/irisin weakened the neuroprotective effects of physical exercise on synaptic plasticity and memory in AD mice. By demonstrating that FNDC5/irisin plays a crucial role in mediating the beneficial effects of exercise in AD models, our findings highlight FNDC5/irisin as a novel agent capable of counteracting synaptic dysfunction and memory impairment in AD [42].

Physical exercises impact the production of irisin through various physiological mechanisms. When engaging in physical activity, especially aerobic exercises such as running, swimming, or cycling, muscle contractions stimulate the release of irisin from skeletal muscles. This process is particularly prominent during moderate to high-intensity exercise sessions. Irisin is primarily produced and secreted by skeletal muscle cells in response to exercise-induced stress. The signaling pathways involved in irisin release include the activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha, a key regulator of mitochondrial biogenesis and energy metabolism. Its activation triggers the expression of FNDC5, which is then cleaved to produce irisin. Additionally, factors such as oxidative stress, and hormonal changes during exercise contribute to the regulation of irisin secretion. For exam-
ple, irisin release may be influenced by the activation of the sympathetic nervous system and the secretion of catecholamines like epinephrine and norepinephrine [43]. Once released into the bloodstream, irisin can exert various metabolic effects on different tissues, including the browning of white adipose tissue, modulation of glucose metabolism, and enhancement of energy expenditure. These metabolic effects are thought to contribute to the overall health benefits associated with regular physical activity, including improved insulin sensitivity, weight management, and cardiovascular health.

While research on the use of irisin in neurorehabilitation is still relatively new, the prospects of its application look promising. Considering its potential beneficial properties for the brain and nervous system, irisin could become an interesting subject for further research and development of neurorehabilitation approaches [43].

The effect of physical exercises on the expression of neurotrophic factors involves a complex interplay of biological mechanisms. During physical exercise, increased blood flow and oxygen delivery to the brain stimulate neuronal activity, leading to the release of neurotransmitters and activation of intracellular signaling pathways. These pathways, in turn, regulate the expression of neurotrophic factor genes, promoting their synthesis and release. BDNF, for example, has been implicated in synaptic plasticity, neurogenesis, and neuronal survival, all of which contribute to improved cognitive function and mood regulation. Furthermore, physical exercise can modulate the expression of neurotrophic factors in specific brain regions involved in motor control, learning, and memory. For instance, aerobic exercise has been shown to increase BDNF levels in the hippocampus, a brain region critical for learning and memory formation. Similarly, resistance training has been associated with elevated levels of NGF and GDNF in the motor cortex and basal ganglia, enhancing motor skill acquisition and movement coordination [44–46].

Overall, the upregulation of neurotrophic factors through physical exercise represents a key mechanism by which regular physical activity promotes brain health and function. Understanding the molecular pathways involved in this process may offer insights into the development of targeted interventions for neurological disorders and cognitive decline. Therefore, comprehending the molecular underpinnings of neurorehabilitation and the impact of thyroid hormones can enhance strategies for rehabilitating patients with diverse nervous system impairments.

References


Молекулярні основи нейрореабілітації та їх модуляція тиреоїдними гормонами

Резюме. Неврологічні розлади вражають велику частину населення, часто призводячи до інвалідності та істотного погіршення якості життя. Нейрореабілітація — це процес відновлення функцій нервової системи після травм, хвороб або інших уражень. Молекулярні основи нейрореабілітації включають у себе різні аспекти, такі як зміни в експресії генів, регуляція синаптичних зв’язків, нейрогенез тощо. Основними завданнями реабілітації пацієнта з неврологічним захворюванням є мінімізація больового синдрому, відновлення функціонального стану нервових шляхів, запобігання вторинним ускладненням і зрештою поліпшення якості життя. Зниження рівнів вільного трийодтироніну та тиреотропного гормону при госпіталізації може запобігти несприятливим результатам на прикінці раннього реабілітаційного лікування. Таким чином, рівень гормонів щитоподібної залози важливий не тільки під час лікування гострих станів, але й протягом тривалого періоду реабілітації. Гормони щитоподібної залози можуть впливати на процеси нейрогенезу (утворення нових нейронів) і синаптичної пластичності (зміни в силі та структурі зв’язків між нейронами). Дослідження показали, що гормони щитоподібної залози можуть впливати на експресію генів, пов’язаних із ростом та виживанням нейронів, а також на процеси синаптичної пластичності, що має значення для реабілітації після уражень нервової системи. Дефіцит гормонів щитоподібної залози при гіпотиреозі може призвести до порушень у розвитку та функціонуванні нервової системи, що, в свою чергу, ускладнює процес нейрореабілітації. Таким чином, розуміння молекулярних основ нейрореабілітації і впливу гормонів щитоподібної залози може допомогти вдосконаленні підходів до реабілітації пацієнтів із різними ураженнями нервової системи.

Ключові слова: нейрореабілітація; нервова система; тиреоїдні гормони; лікувальна фізкультура