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Neurophysiological Effects of Exercise

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Abstract

Convincing findings from animal and clinical studies have shown that exercise improves mood and cognition in addition to cardiovascular and metabolic benefits. Exercise, with the greatest effects on the hippocampus, which has a central role in learning and memory, increases neurogenesis and synaptic plasticity. Although the exact molecular mechanisms responsible for the exercise-induced neuroplasticity need to be clarified, some neurotrophic and angiogenic factors (e.g. BDNF, IGF-1, bFGF2 and VEGF) and different neurotransmitter systems (glutamate, GABA, endocannabinoids and monoamines) may have critical contributions in these processes. Exercise-induced changes in the brain morphology, chemistry and functions seem to be responsible for the beneficial effects of exercise, like improved learning and memory, anti-depressant-like and anxiolytic effects, reduced cognitive decline related to ageing and improvements in symptoms of neurodegenerative diseases. In this chapter, after discussing basic neurophysiological information regarding the brain, cognition, neurotransmitter systems, neural plasticity, learning, memory and behaviour tasks, the focus is on the exercise-induced changes in neuroplasticity, cognitive functions and mood and the factors mediating the effects of exercise, and finally, the effect of exercise on ageing and neurodegenerative diseases is discussed.

Keywords: exercise, cognition, learning, memory, depression, ageing, neurodegenerative diseases

1. Introduction

The brain is highly dynamic, constantly reorganizing organ that undergoes both acute and chronic changes throughout the lifespan. There is a remarkable linkage between structural and functional brain modulations and exercise, as several recent papers have comprehensively described the neuromolecular events resulting from regular exercise (will be further discussed

in the text). Though physical activity and exercise are commonly used in place of the other, there are two terms with different meanings. Physical activity is defined as body movements by skeletal muscles resulting in energy consumption, while exercise is defined as a planned, structured and repeated type of physical activity. The cardiovascular and metabolic benefits of regular exercise are well known, and it causes a reduction in risk for many diseases such as obesity, type 2 diabetes, heart diseases, cancer and other diseases and chronic conditions [1, 2]. Studies have shown that exercise is not just effective on peripheral tissue, at the same time, it affects the central nervous system (CNS). For example, regular exercise improves cognition, reduces age-related memory loss, delays and alleviates the symptoms of neurodegenerative diseases, increases the speed of neuronal healing after injury and is even known to improve depression. However, the underlying mechanisms responsible for the beneficial effect of exercise are still unclear, a variety of cellular and molecular systems important for maintaining neuronal network and synaptic function such as neurotransmitters, angiogenic and neurotrophic factors may be instrumental for positive effects of exercise on brain [3–7]. Nevertheless, growing evidence suggests that an increase in hippocampal neurogenesis may mediate, at least in part, the exercise-induced improvement in cognitive function and mood.

2. Basic neurophysiology

The brain is one of the most important and magnificent organs of an organism that can be categorized under the CNS. The human brain contains nearly 98% of the body's neural tissue [8]. It is made up of more than 100 billion nerves that correspond with one another by means of long protoplasmic fibres called axons, which carry signal pulses—action potentials—to distant parts of the brain or body targeting specific recipient cells [9]. Physiologically, the function of the brain is to exercise centralized control over the other organs of the body. It controls and coordinates most sensory systems, muscle movements, social behaviour and homeostatic body functions such as heart and respiratory rate, blood pressure, fluid balance and body temperature. The brain is the source of cognition, mood, emotion, memory, motor and other forms of learning.

2.1. The structure and functional organization of the brain

The adult brain is dominated in size by the cerebrum. The cerebrum is the seat of most higher mental functions such as conscious thoughts, sensations, intelligence, memory and complex movements. It can be divided into two main parts: the right and left cerebral hemispheres. The surfaces of the cerebral hemispheres are highly folded and covered by neural cortex, a superficial layer of grey matter, with an inner layer of white matter [8]. Grey matter consists mainly of neuronal cell bodies, dendrites, glial cells (astroglia and oligodendrocytes), synapses and capillaries, while white matter consists primarily of axons that connect various areas of the brain [10, 11]. Each hemisphere provides a different set of activities, behaviours and controls. The right hemisphere is often called the creative side of the brain, while the left hemisphere is the rational or analytical side of the brain. The two hemispheres communicate through a large bundle of nerve fibres referred to as *corpus callosum* and through several smaller

nerve pathways [10]. Therefore, even though there are some functions that seem to be dominant in one hemisphere, both hemispheres play a part in overall brain activity.

The second largest part of the brain is cerebellum, which is partially hidden by the cerebral hemispheres [8]. As the cerebral cortex, the cerebellum consists of white matter and a thin, outer layer of densely folded grey matter. The cerebellum processes information from the brain and peripheral nervous system. It is involved in several functions such as fine movement coordination, balance and equilibrium, muscle tone and sense of body position.

Generally, there are four recognized sections in the brain, known as lobes (frontal, occipital, parietal and temporal). While any complex ability depends on the coordinated process of neural networks across lobes, each lobe can be roughly linked with particular functions [10]. The frontal lobe lies beneath the forehead, and it is responsible for cognitive and reasoning functions, social behaviour and motor skills. The parietal lobe is posterior to the frontal lobe and has several functions including sensation, perception and spatial reasoning. This lobe is responsible for interpreting sensory information from various parts of the body. The smallest lobe of the four lobes, the occipital lobe, is located at the back of the brain, and it is the primary visual-spatial processing centre. Lastly, the temporal lobe is located on both sides of the brain, which is involved in the processing of auditory input (sound) and the olfactory sense (smell). Each lobe is further subdivided into interlinking networks of neurons specialized for very precise information processing. These four regions of the brain work in harmony in order to maintain the homoeostatic balance of the human body.

2.2. Brain development

Brain development results from the common work of genes and environment, where genes have the function of leading the initial steps of development and the generation of neural connections and networks [12]. The very first step of brain development stage begins with the recruitment of progenitor cells (precursors of neurons and glial cells) into a specialized structure called the neural plate. The neural plate then folds to form the neural tube, an early embryonic structure. As the foetus develops, the grooves and plicae in the neural tube intensify, producing particular layers of the brain. From the anterior part of the neural tube generates the telencephalon, which enlarges rapidly due to cell division and proliferation, and eventually gives rise to the brain. Some of the cells differentiate into neuronal and glial cells, which are the major cellular constituents of the brain. The newly produced neurons migrate to different areas of the developing brain to self-organize into main brain structures. When the neurons reach their regional positions, they extend axons and dendrites, which provide them communication with other neurons via synapses. Synaptic intercommunication leads to the establishment of specific neural lines that mediate sensory and motor processing and underlie behaviour. The first areas of the brain to fully develop are the brainstem and midbrain, responsible for the autonomic functions necessary for life. At birth, these lower segments of the nervous system are effectively developed, whereas the higher regions like the limbic system and the cerebral cortex are still rather primitive. Brain regions involved in complicated neuronal functions such regulating emotions, cognition and language grow rapidly in the first

3 years, and then, the brain proceeds its development gradually within the first 20 years of life [10, 11].

Studies using high-resolution imaging techniques demonstrate that the brain still continues to grow and develop undergoing notable changes into adulthood, as white matter volume has been shown to increase in adults [13, 14]. The process of adult neurodevelopment includes several mechanisms such as formation of new brain cells, synapses and cellular components, changes in cerebral blood flow and neuronal activity, as well as myelination of axons. Neurodevelopment takes place both in the central and peripheral nervous system, although there are some differences in terms of speed and extent.

2.3. Introduction to main neurotransmitters

Neurotransmitters are endogenous chemicals, which modulate signals and provide efficient communication among large numbers of brain cells. They are synthesized by neurons and packaged into synaptic vesicles that cluster beneath the presynaptic membrane of a synapse and are released into the synaptic cleft, where they bind to specialized receptors in the postsynaptic membrane of the synapse, changing its activity [15]. The major neurotransmitters of the brain are summarized below.

2.3.1. Glutamate

Glutamate is the most common neurotransmitter in the brain. It always has an excitatory role. Most glutamate is produced in neurons from glutamine, which is mainly formed in astrocytes and transported into neurons [16]. There are several types of glutamate receptors:

2.3.1.1. AMPA receptors

These are ionotropic receptors (ligand-gated ion channels). Their opening allows the influx of calcium and sodium and the efflux of potassium.

2.3.1.2. N-methyl-D-aspartate (NMDA) receptors

These are also ionotropic receptors increasing the permeability for calcium, sodium and potassium. The opening of NMDA receptors needs a conformational change for the removal of a magnesium ion, which closes the pore. If the membrane is sufficiently depolarized via AMPA receptors, magnesium leaves the channel. NMDA receptors allow a calcium influx adequate for the function of calcium-dependent enzymes, which can then regulate properties of the synapse, thereby forming the synaptic plasticity. The receptors are densely centralized in the hippocampus, basal ganglia and amygdala.

2.3.1.3. Kainate receptors

Kainate receptors are also ionotropic and functionally similar to AMPA receptors.

2.3.1.4. Metabotropic receptors

Eight well-known types of metabotropic receptors are identified as mGluR1-8. They are mostly found on presynaptic neurons, where they increase the turnover of phosphatidylinositol.

2.3.2. GABA (γ -aminobutyric acid)

Occurring in 30–40% of all synapses of the brain GABA is the main inhibitory neurotransmitter. It is synthesized from glutamate by glutamic acid decarboxylase [15]. GABAergic receptors are as follows:

2.3.2.1. GABA-A

An ionotropic receptor allows the influx of chloride into the cytoplasm, thereby leading to a lowering of the membrane potential. The receptor has a supramolecular complex design, which in addition to GABA binds benzodiazepines, barbiturates, corticosteroids and alcohol.

2.3.2.2. GABA-B

This is a metabotropic receptor inhibiting adenylate cyclase via $G_{\text{inhibitory}}$ protein. Thus, decrease in cAMP levels mediates membrane protein phosphorylation status, which induces a hyperpolarization and a decreased activity of calcium channels.

2.3.2.3. GABA-C (GABA-A- ρ receptor)

An ionotropic receptor activation leads to an influx of chloride ions into the cytoplasm. In contrast to GABA-A receptors, they open more slowly and remain open for a longer period of time.

2.3.3. Dopamine

Dopamine in the CNS plays an important role in the regulation of motor functions, initiation of behavioural patterns and modulation of visceral functions. Five dopamine receptors have been identified, which are all associated with a G-protein regulating adenylate cyclase activity. They can be divided into two groups depending on whether they activate adenylate cyclase via a $G_{\text{stimulatory}}$ protein (D1, D5) or inhibit it via a $G_{\text{inhibitory}}$ protein (D2–D4). The concentration of receptor subtypes varies in different areas of the CNS; for instance, cortical motor areas are rich in D2, while the limbic system mainly expresses D3 and D4 receptors. Dopaminergic neurons are widely distributed in the hypothalamus and mesencephalon [15].

2.3.4. Noradrenaline

Noradrenaline in the CNS mainly regulates the activity of other neurotransmitters. Generally, noradrenergic pathways modulate both the excitatory function of glutamate and the inhibitory function of GABA. Noradrenergic neurons are found in the brainstem, particularly in the locus coeruleus, tegmentum and the reticular formation of the medulla and pons [15].

2.3.5. Serotonin

Serotonin is an indolamine which plays a similar role in the CNS as the noradrenaline. It regulates a range of activities and mediates the function of other projection circuits. Seven models of serotonin receptors have been identified to date, 5-HT_{1-7R}, some of which are excitatory and some inhibitory. The effect of serotonin depends on their localization and the types of receptors presented [15]. Serotonergic neurons can be mainly found in raphe nuclei of the reticular formation.

2.3.6. Acetylcholine (ACh)

ACh is a neurotransmitter used in neuromuscular junctions of all vertebrates, all preganglionic neurons of the autonomous nervous system and all postganglionic parasympathetic neurons. In the CNS, it regulates several cortical activities such as arousal, sleep and memory consolidation. ACh is synthesized by transferring the acetyl group from acetyl-CoA to choline by choline acetyltransferase. The cholinergic signal is terminated by the serine hydrolase acetylcholine esterase, bound to the postsynaptic membrane. The hydrolysis produces choline, which is taken up by the presynaptic neuron and recycled, and acetate [15].

2.4. Cognition

Cognition is the number of abilities that is related to knowledge, understanding, thinking and awareness. The Latin root of cognition is *cognoscere*, which translates into “to conceptualize”, “to recognize” and “to know”. Cognitive abilities cover processes such as attention, memory, judgement and evaluation, logic and reasoning, problem solving and decision-making, comprehension, production of language and the application of acquired knowledge. It is important to realize that these processes are overlapping in nature and often work together in complex ways to formulate any conclusions about the external and internal world. In healthy individuals, the brain is capable of learning new skills in each of these areas [17].

The cognitive ability of humans is the most advanced in the entire animal kingdom. Such advancement is believed to be conferred by an expanded cerebral cortex and a highly developed prefrontal cortex, both of which are brain regions important for cognition. Cognition changes throughout the lifespan matching the development, maturation and ageing of the brain. While cognitive activity gains its peak during middle adulthood, there is a normal degradation in cognitive ability and brain atrophy with age [18, 19]. The revelation that physical changes in the brain can occur across the lifespan provides a biological basis supporting the importance of neuromodulators, cognitive trainings and the efficacy of physical activity [20].

2.5. Neural plasticity

Neural plasticity can be generally defined as the ability of the nervous system to embrace a new functional or structural condition in response to various extrinsic and intrinsic determinants [21]. The term “neuronal plasticity” date back to Santiago Ramon y Cajal (1852–1934) who described non-pathological changes in the structure of adult brains [22]. In a wider sense,

plasticity of the brain can be regarded as “the ability to make adaptive changes related to the structure and role of the nervous system at the cellular, molecular, and system levels” [22, 23]. Neuronal plasticity can refer not only for morphological changes in certain brain areas, for alterations in neuronal networks including changes in neuronal connectivity, as well as the formation of new neurons (*neurogenesis*), but also for neurobiochemical changes (*synaptic or non-synaptic plasticity*) [22]. Neuroscientists distinguish synaptic plasticity, which points to alterations in how neurons link up to each other, from non-synaptic plasticity, which refers to changes in the neurons themselves. Neuroplastic modulation can occur at small ranges, such as physical changes to individual neurons, or at whole-brain scales, such as cortical remapping in feedback to injury.

Neuronal plasticity in the brain is greatly enhanced during critical periods early in life and was long believed to be limited thereafter. Studies from a number of laboratories investigating the reorganizations in somatosensory, primary visual, primary auditory cortices and in thalamus have unwrapped a considerable degree of plasticity in the mature brain, too [24]. It is now accepted that the brain has an incredible potential to modify its morphological and functional organization throughout the lifespan, in response to changes in environmental inputs. This brain plasticity underlies normal development and maturation, skill learning and memory, healing from injury, as well as the outcomes of sensory deprivation or environmental enrichment [25]. Usually, plasticity in the adult neocortex lies silent, but can be reactivated by modifications of sensory input or sensory-motor interferences, which alter the level and pattern of activity in cortical circuits [26]. Such treatments, potentially in combination with drugs targeting molecular brakes on plasticity present in the mature brain, might help recovery of activity in the injured or diseased brain [26].

The molecular mechanisms of brain plasticity are under intensive scrutinizations. Calcium ions and channels, glutamate and NMDA receptors, free radicals, lipid peroxides and growth factors (neurotrophins) play a crucial role in these processes. A form of functional neuronal plasticity is long-term potentiation (LTP) that is the long-lasting enhancement in signal transmission between two neurons after synchronous stimulation [22, 27].

2.5.1. Neurogenesis

The most appealing phenomenon of neuroplasticity appears to be adult neurogenesis. Adult neurogenesis occurs in the certain brain areas. So far it appears that in most mammals, the formation of new neurons in adult brains occurs in two parts, the subventricular zone and the dentate gyrus (DG) of hippocampus (hippocampal neurogenesis), and the number of newly generated neurons is fewer compared to the total number of brain cells [22]. However, there are also reports from studies in mice that new neurons can be gradually generated in the adult substantia nigra (SN) [22, 28]. The existence of neurogenesis in mature brains rises hope that even injured brain regions can be functionally repaired and reactivated. Damage to the adult brain such as ischaemic insults causes the proliferation of subventricular zone cells and thus the generation of neuronal precursor cells. These precursors migrate along blood vessels to the wounded region [22, 29]. Nevertheless, only a small percentage can survive, because inflammatory effects that occur in the ischaemic brain area inhibit neurogenesis and the proper

integration of new cells into a functional neuronal network [22, 30]. Anti-inflammatory drugs can strengthen neurogenesis, as observed in rodent studies of peripheral inflammation [22, 31].

2.5.2. Synaptic plasticity

Synaptic plasticity is an essential organizational characteristic of mammalian brain function, and it refers to the condition where existing connections among neurons are reinforced or weakened and new synapses are formed or existing ones removed. The potential for synaptic plasticity and therefore for learning and memory is not steady throughout life, as it often reaches a peak soon after birth and then gradually declines with increasing age [26]. Besides, synaptic plasticity in the adult brain is widely distributed and is a key feature of various brain regions, like the hippocampus, the striatum or the cerebellum. Mechanisms of synaptic plasticity are a modification of excitation and inhibition process; a change in LTP or long-term depression (LTD); a modulation of neuronal excitability; and the anatomical changes, which require a longer period of time.

2.6. Neural base of learning and memory

Learning and memory are two intimately linked cognitive processes that derive from interactions with the environment. Learning is defined as the act of acquiring new knowledge or skills; it also may involve a change in attitude or behaviour through experience, instruction or study, whereas memory is a cognitive process of the brain enabling past experiences and information to be remembered and recalled. Memory is built on learning and is subject to the same factors influencing learning. This is why memorization of an event or of information can be improved by a strong emotional situation, a special state, high motivation or elevated attention [10]. Learning and memory undergo significant change over the lifespan in both males and females. The ability to learn and remember begins early during the developmental period, is moulded by environmental and hormonal influences during puberty, reaches its apex during adulthood and finally declines with advanced age [32].

The nature of the cellular basis of learning and memory remains obscure despite being one of the most densely examined nervous system mechanisms. A popular model for the physiological processes underlying learning and memory involves that memories are collected by alterations in the strength of synaptic connections within the appropriate neural circuitry. Thus, synaptic plasticity is considered a fundamental working mechanism of memory and learning in biological neural networks. Several lines of evidence have converged to indicate that learning and memory setting requires plasticity of dendritic spines in the medial prefrontal cortex and the hippocampus [32]. Major characteristic of the hippocampus is the ability of hippocampal neurons to undergo LTP, a persistent increase in synaptic intensity emerging from long-lasting electrical stimulation.

2.6.1. Hippocampus

The hippocampus is the region in the brain most closely associated with learning. Located inside the medial temporal lobe, beneath the cortical surface of the brain, it belongs to the

limbic system and plays important activity in learning, memory and spatial navigation. Thus, damage to the hippocampus can produce profound memory impairments, specifically in the ability to create long-term memories. The names of the main histological divisions of the hippocampus are DG, CA1, CA2 and CA3 regions [33]. The entorhinal cortex, the greatest source of hippocampal input and target of hippocampal output, is powerfully and reciprocally associated with many other parts of the cerebral cortex and therefore acts as the major link between the hippocampus and other parts of the brain. Within the hippocampus, the flow of signals and information is generally unidirectional, first to the DG, then to the CA3 part, then to the CA1 part, then to the subiculum and then out of the hippocampus to the entorhinal cortex [33, 34].

2.6.2. Long-term potentiation

LTP is a physiological model to explain the formation of definite forms of learning and memory, and it refers to changes in a cell that cause it to respond more efficiently to stimulation [35]. It was first described in detail by Bliss and Lomo in 1973, reporting that repetitious activation of excitatory synapses in the hippocampus induced an increment in synaptic strength that generally last for hours or even days [36]. Since then, LTP has been studied intensively over the years, and a great deal has been learned about it. The best-studied form of LTP occurs at synapses that come to an end on dendritic spines and use the transmitter glutamate. The synaptic changes depend on special type of glutamate receptor, the ionotropic NMDA receptor, which possesses the special characteristic of permitting calcium ions to get into the postsynaptic spine only when presynaptic activation and postsynaptic depolarization occur at the same time [37]. LTP experiments have focused especially on the three main pathways in the hippocampal network: the perforant pathway between the entorhinal cortex and DG granule cells, the mossy fibre pathway between DG granule cells and CA3 pyramidal cells, and the Schaffer collateral pathway between CA3 and CA1 pyramidal cells. NMDA receptor is the trigger for the induction of LTP at synapses made between pyramidal neurons in CA3 and CA1 layers of the hippocampus [38]. Drugs that interfere with NMDA receptors prevent LTP formation and also have negative effects on some types of memory, especially spatial memory. Although NMDA receptors display a significant role in synaptic plasticity, thus in learning and memory, sustained NMDA receptor activation can lead to various pathological conditions [39–41]. Therefore, too much activation of the NMDA receptor is detrimental.

2.7. Experimental behaviour tasks

Spatial learning and memory are neurobiological activities that allow us to remember important details related to our surroundings. Researches evaluate this phenomenon in rodents using different types of behavioural tasks. By investigating spatial memory in experimental tasks, neurobehavioral scientists can gain valuable understanding of how these processes are vary after brain injury in humans or how the functions of particular genes on learning are affected. The tests most widely used and for which the most data exist are briefly described here.

2.7.1. *T mazes*

T mazes are the first labyrinths that can be used to measure spatial working memory. There are many test procedures; however, the easiest to evaluate spatial learning and memory is to prize rodents for rotating in one direction across a series of experiments. The T-maze is shaped like a T. The test animal begins from the base of the T labyrinth. A reward may be placed at one of the arms of the maze or different rewards may be placed at each arm. The rat/mouse walks forward and chooses the left or right arm of the maze. On the test trial, to try out if the animals learn a position habit such as always turning right, the maze is rotated 180°, and if it is a habitual behaviour, the animal will turn right regardless of where that arm is within the room, but if it is a learned behaviour, the rodent will turn left so as to end up in the same place in relation to distal cues [42].

2.7.2. *Morris water maze*

The Morris water maze is consisting of a round tank filled with opaque water with two small hidden platforms located 1–2 cm under the surface of the water [43]. As soon as the rodent is placed on a start platform, it begins to swim around until it finds the other platform to stand on. The platform is not visible, so the animals must depend on their spatial memory and use extra-maze visual cues to locate the platform. The animal is usually introduced into the water at different locations around the tank. The researcher measures how long it takes for a rodent to find hidden platform. Data collection in the water maze can be simply optimized and automated, and it does not need food-restriction. In addition to this, the water maze task does require complex and coordinated movements [44].

2.7.3. *Radial arm maze*

Among behavioural tests, one of the most suitable devices for measuring spatial learning and memory is the radial arm maze [45, 46]. Briefly, radial arm maze consists of eight horizontal arms placed radially around a central platform above the floor. Typically, a cup at the end of several of the arms contains some small nutrient reward for the experimental subject. The rodents are usually food deprived to motivate the foraging behaviour, and they will try to find the food in the most effective way. The optimal strategy is to visit each arm once before returning to any formerly visited branch. Therefore, to complete the experiment successfully, animals must remember where it has been and where food has been and/or remains available [47].

3. Exercise-induced changes in the brain

3.1. Exercise and neuroplasticity

Neuroplasticity or brain plasticity refers to modification of the nervous system in response to differing needs or environmental conditions. Currently, scientific information indicates that

neuroplasticity extends beyond the developmental period into the adult period and plays a significant role in processes such as learning and gaining new skills, consolidation and recall of memories as well as healing after injury. Neuroplasticity is mediated by different mechanisms causing both functional and morphological changes in the CNS-like neurogenesis, apoptosis, increase and/or decrease in synaptic activity and reorganization of the neuronal network [3–6]. Of these, though neurogenesis is a mechanism only accepted since the 1960s, currently it is well known that newborn neurons can be formed in the olfactory bulb and DG of the adult mammalian brains [3–6].

As mentioned before, the hippocampus has a unique role in learning and memory formation, with high capacity for neuroplasticity. There are many studies showing exercise strongly stimulates neuroplasticity in the hippocampus [1–5]. Rearrangement of DG morphology, especially, in response to exercise is noteworthy, with increases in total length and complexity of granular cells, spine density in dendrites and neurogenesis. These effects of exercise are not limited to the DG, but include entorhinal cortex and CA1 pyramidal cells [3, 5, 48]. However, it should be noted that exercise-induced neurogenesis occurs specifically in DG subfield of hippocampus [4–6]. Borght et al. showed that 1–10 days of wheel-running exercise induces a gradually increment in the hippocampal cell proliferation [49]. Although proliferation had returned to baseline level 1 day after cessation of running, the number of immature neurons remained in the high level for at least 6 days. In rats, a single bout of resistance exercise increases synapsin I, synaptophysin and PSD-95 (a protein related to synapses) levels in the hippocampus and improves contextual memory [50]. In addition to the increase in neuron numbers with exercise, importantly, enhanced maturation of newborn neurons has been also reported [48]. Therefore, these findings suggest that the hippocampus, especially DG, has a considerable capacity for neuroplasticity and rapidly responds to alterations in physical activity.

The increased hippocampal plasticity with exercise is accompanied by an enhancement in synaptic activity of neurons. It is known that the physiologic model of learning and memory of LTP is affected by exercise. Running induces an increase in LTP amplitude in the DG region, but did not cause a change in CA1 region of the hippocampus [3–5, 51]. The increased LTP in the DG, where neurogenesis occurs, indicates the newborn neurons may have a functional role in this process. Though the rate of neurogenesis induced by exercise is low, the LTP threshold in young cells is lower and LTP lasts longer [52]. In contrast to increased LTP observed in the running rodents, LTD seems unaffected by exercising [3]. These results suggest that newborn cells have an important role in brain plasticity and their contribution can be enhanced with exercise.

Studies on rodents have shown that performance involving different spatial memory tests (Morris water maze, Y-maze, T-maze and radial arm maze) was better in exercising subjects [3]. Human studies have obtained similar results and suggested an enhancement in cognitive functions with exercise. Pereira and colleagues showed that aerobic exercise training of healthy individuals for 12 weeks significantly increased cerebral blood volume in the DG as well as cognitive functions [53]. Together, the evidences from different studies suggest that both

aerobic and resistance exercise improve learning and spatial memory and reduce the cognitive loss related to ageing or neurodegenerative diseases [53–55].

3.1.1. Mediators of exercise-induced neuroplasticity

Though the exact mechanisms responsible for the increased neuroplasticity with exercise are not clear, various neurotrophic and angiogenic factors as well as neurotransmitter systems may be involved in these processes.

3.1.1.1. Trophic factors

During development of the brain and spinal cord, proliferation and differentiation of stem cells and progenitor cells are regulated by a variety of growth factors. It has been reported that growth factors are still effective in the adult period and play a significant role in synaptic plasticity, neurogenesis and cognitive functions. The increased neuroplasticity with exercise has been shown to have a contribution from growth factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), nerve growth factor (NGF) and basic fibroblast growth factor-2 (bFGF-2).

BDNF is the most important modulator of brain plasticity, showing effect through tropomyosin receptor kinase B (TrkB) receptor, inducing neuronal differentiation, proliferation and survival pathways. It is reported that BDNF as a neurotrophic factor has beneficial effects on the cognitive functions via its ability to improve synaptic plasticity, neurogenesis and LTP [3–7]. Studies of rodents showed 2–7 days of voluntary (running wheel) exercise causes a BDNF increase in different regions of the brain including the hippocampus [56]. Especially in the DG area of the hippocampus, increased BDNF levels remain high as long as exercise continues and for 2 weeks after exercise is stopped [57]. Remodelling of the hippocampus induced by exercise seems to have a critical contribution from BDNF, because the positive effect of exercise on neuroplasticity is prevented by genetic ablation or pharmacological blocking of the BDNF receptor TrkB [58, 59]. In consistent with results from animal studies, the clinical research in healthy subjects revealed an increase in the brain levels of BDNF, as detected in blood samples from the internal jugular vein following 3 months of endurance training [60]. In humans though specific changes in hippocampal BDNF levels are not well known, increased circulatory BDNF level has been reported following the exercise. Indeed, exercise-induced elevation in serum BDNF levels seems to return to baseline within 10–60 min after exercise and then decrease to a level lower than baseline [61]. In agreement with this result, a significant decrease in resting serum levels of BDNF is reported in trained subjects [62].

IGF-1 is primarily produced by the liver with the stimulation of growth hormone and modulates growth, differentiation and survival pathways of cells [3, 5, 7]. IGF-1 is accepted as a neurotrophic factor in the CNS due to its contribution to the processes of neurogenesis, differentiation, proliferation, synaptic plasticity of neurons. IGF-1 and its receptor expression have been shown in the hippocampus. Exercise increases IGF-1 level in the hippocampus in addition to plasma. Indeed, elevated IGF-1 level in the circulation is reflected in the brain, as IGF-1 can cross the blood–brain barrier via carrier proteins [63]. In sedentary individuals,

injection of peripheral IGF-1 imitates the effects of exercise including increased neurogenesis and improves reduced neurogenesis related to age [64, 65]. There is a positive correlation between circulating IGF-1 levels and improved cognitive functions in healthy elderly [66]. As IGF-1-induced changes in the hippocampus are correlated with BDNF levels, it is proposed that the positive effects of IGF-1 on neuroplasticity may be mediated by BDNF [67]. Therefore, IGF-1 may have a direct and indirect contribution through increasing BDNF levels to spatial learning and memory processes.

It has been reported that adult hippocampal neurogenesis occurs near the local microvasculature and exercise stimulates endothelial cell proliferation and angiogenesis in this area of the brain. On the 3rd day of running, angiogenic processes start in addition to neurogenesis, while after a 50-day exercise period, the capillary intensity in the DG area appears to increase [49, 68]. Pereira and colleagues have shown that aerobic exercise increases blood flow in the hippocampus and improves cognitive functions in both mice and human [53]. This effect of exercise on the vascular system is reported to be mediated by IGF-1 and VEGF [3, 5, 7]. VEGF is a factor induced by hypoxia, stimulating angiogenesis mediated by tyrosine kinase receptors in endothelial cells. In addition to angiogenic effects, VEGF shows neurotrophic effect and induces growth and proliferation of progenitor cells [69]. Similar to the increase in the circulating IGF-1 levels, an increase in VEGF concentration is also reported during exercise, while peripheral IGF-1 and VEGF blocking inhibit neurogenesis induced by running [63, 69].

Other trophic factors that have been shown to be regulated by exercise and influence adult neurogenesis include bFGF-2 and NGF. However, as the increase in these factors is small and temporary, especially when compared with BDNF, they are slightly less important for the neuroplasticity induced by exercise [3].

3.1.1.2. Neurotransmitters

In addition to neurotrophic and angiogenic factors, it is known that some neurotransmitter systems are included in the regulation of neuroplasticity. For example, the most important excitatory neurotransmitter, with a key role in learning and memory processes of glutamate, stimulates neural progenitor cells and increases neurogenesis [3, 6, 7]. The expression of NR2A and NR2B subunits of the NMDA receptor increases after running exercise, and this elevation contributes to neuroplasticity induced by exercise [51, 70]. Another main neurotransmitter of the CNS with inhibitory effects, GABA, is known to affect neuroplasticity. Indeed, both inhibitor and activator effects of GABAergic system on the proliferation of progenitor cell have been reported in the hippocampus [71, 72]. During exercise, genes related to the GABAergic system (GABA_A receptor, glutamate decarboxylase GAD65) are down-regulated, a system which may modify hippocampal neuroplasticity [73].

Another neurotransmitter system activated by exercise is the endocannabinoid (eCB) system. eCBs are produced by both central and peripheral tissues and during exercise circulating concentrations increase. A single bout of endurance exercise (70–80% maximal heart rate) provided optimal increase in eCB [74]. Cannabinoid receptor type 1 (CB1R) is found in different regions of the brain including frontal cortex, amygdala, hippocampus and hypothalamus [75]. Voluntary wheel-running exercise increases the agonist binding region

for CB1R in the hippocampus and the levels of the endocannabinoid anandamide [76]. These alterations seem to be necessary for exercise-induced neuroplasticity in the hippocampus and are suggested to be mediators of the anti-depressant and anxiolytic effects of exercise [77].

Serotonin, dopamine and norepinephrine are the central neurotransmitters known as monoamines. Studies demonstrated that monoamines can regulate synaptic plasticity, neuronal survival and mood. It is suggested that monoamines may have a role in the exercise-induced positive effects on brain. Long-term exercise induces significant elevation of norepinephrine and serotonin levels in different brain areas, compared to the sedentary controls [78]. Klempin et al. studied tryptophan hydroxylase-2-deficient mice and investigated the neurogenic effects of serotonin deficiency [79]. The researchers found that basal neurogenesis in the hippocampus of these animals was normal; however, they showed exercise-induced neurogenesis to be reduced. These results indicate that the serotonergic system plays an important role in the effect of exercise on neuroplasticity.

3.2. Exercise and mood

Though chronic and uncontrolled stress has a negative effect on mood, it is understood that differences in the type of stress may change results [80]. For example, voluntary exercise is a stress factor (physical stress) due to activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis [81]. However, exercise also causes release of growth hormone and various neurotrophic factors different to other stress factors such as psychological stress. Additionally, in those who exercise the transformation of the stress hormone cortisol to the inactive form of cortisone is higher and this situation is not observed with psychological stress. Finally, as exercise can be ceased whenever the person desires, it is different to other types of stress and causes different results [7].

Clinical studies of patient with mild-to-moderate levels of depression have shown that exercise reduces depressive symptoms [82]. Additionally, animal studies showed that wheel-running activity had anti-depressant-like effects on learned helplessness, forced swim test and tail suspension tests [83]. Though the underlying mechanism responsible for the anti-depressant-like effects of exercise is not fully known, neurotrophic factors and neurotransmitter systems may provide significant contribution. For example, BDNF, IGF-1 and VEGF are thought to regulate anti-depressant-like effects of exercise [77]. Of these, BDNF may be more important than the others, because depression is related to BDNF deficiency of both the circulation and CNS. In depressive patients, peripheral BDNF levels are at lower levels compared to control [84]. Moreover, postmortem studies have shown low levels of BDNF in the cortical and hippocampal areas of the brain [85]. Studies using a variety of behaviour models have confirmed the effect of BDNF on mood by showing anti-depressant and anxiolytic effect of recombinant BDNF administration into the brain [86]. More importantly, reduced BDNF levels and depressive behaviour associated with acute and chronic stress are successfully prevented by exercise [77].

The reduction in hippocampal VEGF expression during chronic stress in rodents has shown that VEGF may be related to depression [77]. Peripheral blocking of VEGF exerts prevention

of exercise-induced antidepressant-like effects, neurogenesis, as well as angiogenesis in the hippocampus [69, 87]. Additionally, VEGF polymorphism (VEGF2578C/A) causing low serum VEGF levels in humans may induce the development of treatment-resistant depression [88]. When VEGF and IGF-1 are injected into the brain, they show anti-depressant effects [89, 90]. Peripheral IGF-1 blocking prevents exercise-induced anti-depressant effects and hippocampal neurogenesis showing the importance of IGF-1 [63, 89].

As acute and chronic exercise causes an increase in plasma endorphin levels, it is proposed that endorphins may play a role in the anti-depressant effects of exercise [7]. Though endorphins are related to positive mood and well-being, the role of endorphins in exercise is still controversial as there are studies showing increased peripheral endorphins do not affect the brain [7, 91]. Monoamines are neurotransmitters with anti-depressant effects, and it is thought they may mediate the effects of exercise [92]. It has been reported that exercise increases monoamine levels in different brain area. In rodents, altered serotonin levels and serotonin metabolism has been reported in different brain area such as striatum, hippocampus, hypothalamus, cerebral cortex and brain stem following acute and chronic exercise [93]. In clinical practice, serotonergic medications are used as anti-depressants and actually exercise may be as effective as these medications for mild and moderate depression [94]. As mentioned before, eCB system may contribute to exercise-induced antidepressant-like effects [95]. Indeed, exercise-induced increase in peripheral and central concentrations of eCBs and monoamines are thought to mediate the anti-depressant and anxiolytic effects of exercise.

3.3. Exercise and ageing

Regular exercise activates neurogenesis, angiogenesis, synaptogenesis and synaptic functions in the brain via a variety of neurobiological modulators, ensuring cognitive healing. As a result, it is thought that regular exercise may prevent or improve cognitive loss in both healthy elderly people and those with risk of dementia.

In the normal ageing process, the neural plasticity of the brain reduces and this is accompanied by cognitive declines [2, 4]. The positive effects of exercise on the brain continue in elderly individuals though not as strongly as for young individuals. It has been shown that exercise exerts protective effects against cognitive decline and brain atrophy related to ageing. Kronenberg and colleagues reported that 3–9 months of exercise partially restored the reduced cell proliferation related to ageing and increased the number of mature cells [96].

Regular exercise reversed the age-related LTP decrease and it was accompanied by improved memory, increased hippocampal neurogenesis and increased BDNF levels in middle-aged rodents [97, 98]. Reduced BDNF and TrkB expression in the DG region was restored by 5 weeks [99] and 8 months [97] of forced treadmill exercise and by voluntary exercise [98] in middle-aged rats. This effect was in parallel with increased neurogenesis and improved cognitive functions [97–99]. Similarly, 8 weeks of treadmill exercise restored reduced NGF levels in the hippocampus of elderly rats [100]. Tsai et al. showed that 1 year

of regular resistance exercise increased IGF-1 levels and improved cognitive functions in the elderly [55].

Human studies have identified a positive correlation between the incidence, duration and distance of daily walking activity by the elderly and the size of the hippocampus [101]. A similar study investigated the correlation between cardiovascular fitness and hippocampus volume in the elderly and showed a positive correlation between aerobic fitness (VO₂ peak) and right and left hippocampus size [102]. Elderly individuals participating in a 6-month aerobic exercise programme (60–70% of maximal heart rate, 3 times per week, 1 h) were observed to have increased grey matter and white matter volumes in the brain [103]. Cognition studies have found that cognitive functions in elderly individuals completing 3 h or more of aerobic exercise per week for at least the last 2 years were better than in sedentary individuals [104]. Another study observed that sedentary elderly individuals who participated in a 24-week aerobic exercise programme had improved cognitive functions [105]. Taken together, these results suggest that exercise is a good strategy to improve age-related brain atrophy and cognitive decline.

3.4. Exercise and neurodegenerative diseases

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), show general properties of progressive loss of neurons. Indeed, neuronal degeneration predominantly affects different neuron groups and it is well documented that dopaminergic neurons in PD, striatal GABAergic neurons in HD and cortical and hippocampal cholinergic neurons in AD are progressively degenerated during diseases. Certain degrees of learning and memory loss are associated with progressive structural and functional deterioration of neurons in all neurodegenerative diseases [4, 6]. As the exercise stimulates neurogenesis and improves cognition in both young and old individuals, it is reasonable to think that it may have protective effect against neurodegenerative diseases.

3.4.1. Alzheimer's Disease

Pathologically, AD is characterized by acetylcholine depletion, amyloid (or senile) plaque formation, neuronal apoptosis in the cortex and hippocampus as well as brain atrophy. Additionally, decreased cognitive functions, memory loss, behavioural changes and dementia are the other characteristics of the disease [106]. In a number of AD mice models, running was observed to improve neurogenesis and cognitive functions. For example, short-term running improved cognitive functions of elderly Tg2576 mice [107], and 5-month long-term voluntary running not only prevented plaque formation in the frontal cortex and hippocampus, but also improved spatial learning in TgCRND8 D mice [108]. Similar results were obtained from APP/PS1 double transgenic AD mouse model with treadmill exercise improving learning, memory and LTP and providing amelioration of neuropathological characteristics of the disease [109]. In humans with high risk of AD, increased physical activity has been shown to reduce hippocampal atrophy [110, 111].

3.4.2. *Parkinson's disease*

PD develops as a result of degeneration of dopaminergic neurons with projection from the SN pars compacta to the striatum and causes severe motor symptoms such as weakened motor activity control, akinesia, tremor and rigidity. Additionally, non-motor symptoms such as cognitive reduction, olfactory dysfunction, anxiety and depression may be observed in these patients [4, 6]. In a variety of rodent PD models, it has been shown that exercise may be beneficial in improving some neuropathological and behavioural defects [4, 6]. It has been reported that 4 weeks of exercise increases the trophic factor levels and cell proliferation rate in the striatum and additionally exerts a protective effect on tyrosine hydroxylase positive neurons in the striatum and SN [112]. Clinical studies of PD patients have shown that physical activity ensured improvements in postural stability, balance and cognitive functions [113, 114]. Even more, exercise provided attenuation of depression frequently observed in both AD and PD patients [115].

3.4.3. *Huntington's Disease*

HD is a progressive neurodegenerative disease caused by a genetic mutation of HD gene and characterized by neuron death in the striatum mainly, but also in some regions of the cortex and hippocampus. The most significant symptoms of HD are loss of coordination of voluntary movement, bradykinesia and rigidity. Reduced cognitive capacity observed in these patients causes progressive severe dementia over time [4, 6]. Studies on different transgenic mice models such as R6/1 HD, R6/2 HD and N171-82Q HD have shown that running wheel activity does not increase BDNF level or stimulate neurogenesis in the hippocampus [116, 117]. Nevertheless, exercise delays HD symptoms and improves cognition in similar study models [118]. The cognitive improvement caused by running in HD transgenic mice does not appear to be due to increased neurogenesis, but rather is due to structural remodelling of existing neurons in the hippocampus. Human studies have provided contradictory results. For example, Altschuler reported there was no recovery of the initiation or progression of HD symptoms in a semi-professional marathon runner [119]. On the contrary, in another study of HD patients undergoing 9 months of multidisciplinary rehabilitation, including exercise, an increase in grey matter volume in the right caudate region and bilateral dorsolateral prefrontal cortex is reported in addition to significantly improved word learning and memory performance [120]. Contradictory findings suggest that more detailed investigation into the effects of exercise in HD patients is needed.

3.5. **Effective type, duration and intensity of exercise**

Aerobic exercise basically has positive effects on cardiovascular and metabolic functions, while resistance exercise is very beneficial for muscle strength and bone density. As mentioned above, there is much scientific proof of the positive effects of exercise on neurologic functions. Studies have shown that both exercise types have similar positive effects on neuroplasticity. Cassilhas and colleagues in a study comparing the effects of aerobic and resistance exercise found that both types of exercise produced similar improvements in learning and spatial memory after an 8-week training period. However, as aerobic exercise causes an increase in IGF-1, BDNF,

TrkB and β -CaMKII (calcium/calmodulin-dependent kinase II) in the hippocampus, resistance exercise caused an increase in peripheral and hippocampal IGF-1, IGF-1R and AKT. According to the results of this study, aerobic and resistance exercise produces similar positive effects on learning and spatial memory by using different molecular mechanisms [121].

Molteni and colleagues investigated the time-dependent changes of the gene expression in the hippocampus induced by acute and chronic (3, 7 and 28 days) voluntary running wheel activity [73]. The researchers found that BDNF expression increased with all exercise durations and reported that BDNF played a central role in exercise-induced brain plasticity. Similarly, the CaM-K signal system increased with both acute exercise and chronic exercise; however, they reported that the MAP-K/ERK system was activated by long-term exercise.

When the effect of exercise types with different intensities is examined, mild-moderate intensity exercise seems to be more beneficial to the brain, while exhaustive exercise appears to be destructive. For example, Soya and colleagues investigated the effects of acute exercise (30 min, treadmill) at different intensities on the BDNF expression in the hippocampus in rats and showed that mild running (15 m/min) increased BDNF mRNA and protein levels [122]. Running at faster speeds (20 m/min) increases serum corticosterone levels along with only BDNF mRNA levels in the hippocampus, while causing a reduction in protein levels. The researchers stated that low-intensity exercise with minimum stress levels was more beneficial to the hippocampus. Another study investigated the effect of mild and intense treadmill exercise on cognitive function after traumatic brain injury in rats, and showed that 2 weeks of mild exercise increased hippocampal BDNF expression and improved cognitive functions [123]. In another study, Li and colleagues investigated the effects of exhaustive exercise and showed that different intensities of acute exhaustive exercise cause neuronal cell apoptosis in rats. From these results, it is understood that exhaustive exercise is not beneficial to the hippocampus and may in fact have a destructive effect [124].

4. Conclusion

The beneficial effects of exercise are most likely the result of a combination of increased number and maturation of newborn cells, modifications in synaptic plasticity and spine density and enhanced angiogenesis in the hippocampus. The most pronounced changes induced by exercise are observed in the DG subfield within the hippocampus. Exercise-induced increase in hippocampal neuroplasticity appears to be mediated by a variety of neurotrophic and angiogenic factors and neurotransmitter systems. Changes in hippocampus morphology and chemistry may mediate beneficial effects of exercise, such as improved learning and memory, anti-depressant-like and anxiolytic effects, reduced cognitive decline related to ageing and delay/reduction in symptoms of neurodegenerative disease.

Although further research is needed to understand the cellular mechanism responsible for the effects of exercise on the brain, it is clear that exercise could be used to maintain and improve cognitive function throughout the lifespan. It should be also noted that exercise is the most

effective, low-cost and low-tech method for successful ageing, and therefore, it has a great potential to prevent or reduce age-related cognitive decline. Neurologically to ensure the optimum benefit from exercise, regular, mild-moderate intensity of the aerobic or resistance exercise appears to be appropriate, while it is recommended to avoid exhaustive type of exercise.

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