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Neurobiological Alterations Induced by Exercise and Their Impact on Depressive Disorders

Ingo Helmich[1,*], Alexandra Latini[2], Andre Sigwalt[2], Mauro Giovanni Carta[3], Sergio Machado[4], Bruna Velasques[4], Pedro Ribeiro[4] and Henning Budde[5]

[1]*Department of Neurology, Psychosomatic Medicine, and Psychiatry, Institute of Health Promotion and Clinical Movement Science, German Sports University Cologne, Germany*

[2]*Departamento de Bioquímica, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil*

[3]*Centro per la Ricerca e la Terapia in Salute Mentale, Department of Public Health, University of Cagliari, Italy*

[4]*Brain Mapping and Sensory Motor Integration, Institute of Psychiatry, Rio de Janeiro, (IPUB/UFRJ), 69 apto. 104, Profesor Sabóia Ribeiro Street – Leblon – Rio de Janeiro, Brazil*

[5]*Department of Training and Movement Sciences, Institute of Sportscience, Humboldt University Berlin, Germany*

Abstract: *Background:* The impact of physical activity on brain metabolic functions has been investigated in different studies and there is growing evidence that exercise can be used as a preventive and rehabilitative intervention in the treatment of depressive disorders. However, the exact neuronal mechanisms underlying the latter phenomenon have not been clearly elucidated. The present article summarises key results derived from studies that focussed on the neurobiological impact of exercise on brain metabolic functions associated with depressive disorders. Since major depressive disorder (MDD) is a life threatening disease it is of great significance to find reliable strategies to prevent or to cure this illness. Therefore, the aim of this paper is to review (1) the physiological relationship between physical activity and depressive disorders and (2) the potential neurobiological alterations induced by exercise that might lead to the relief of mental disorders like depression.

Methods: We searched electronic databases for literature concerning the relationship between exercise and depression from 1963 until 2009.

Results: The data suggests an association between physical inactivity and higher levels of depressive symptoms. Properly designed studies could show that exercise training can be as effective as antidepressive medications.

Conclusion: The exact mechanisms how exercise affects the brain are not fully understood and the literature lacks of well designed studies concerning the effects of exercise training on depressive disorders. But the observed antidepressant actions of exercise are strong enough that it already can be used as an alternative to current medications in the treatment of depressive disorders.

Keywords: Depression, exercise, brain.

1. INTRODUCTION

The fact that exercise and physical activity have positive effects on health is well known. Most of the research on exercise-induced changes carried out during the past years has mainly focussed on its impact on cardiovascular and musculoskeletal diseases [1]. Only recently it has been noted, that exercise also leads to neural alterations that increase brain function and mental health [2]. Neurobiological functioning in the human brain seems to depend upon an active or non-active lifestyle. Neuronal alterations can be induced lifelong [3] but already in the fetal state movements of the unborn child and the mother can induce growth, development and networking of nerve cells [4]. Therefore physical activity seems to be an important stimulus for neural adaptations of the brain in all age groups. The main effects of exercise on brain function are found in an altered blood flow [5] (which might explain the lower risk of cerebrovascular diseases in an active population), reduced risk of neurodegenerative and age-related cognitive deficits [3, 6, 7] as well as improved learning and memory functions [2]. Many studies show benefits due to exercise such as reduced age-related neuronal loss [8] and an increase in cell proliferation and neurogenesis, the process by which new neurons are generated [9]. In

*Address correspondence to this author at the Department of Neurology, Psychosomatic Medicine, and Psychiatry, Institute of Health Promotion and Clinical Movement Science, German Sports University Cologne, Am Sportpark Müngersdorf, 50933 Köln, Germany; Tel: +49 [0]221 - 4982 - 7290; Fax: +49 [0]221 - 4982 - 726; E-mail: i.helmich@dshs.koeln.de

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addition, recent studies have shown that exercise produces antidepressant responses in rodent models [10] and moode-levating actions in humans [11, 12]. The antidepressants effects of exercise are of special interest, since major depressive disorder is a life threatening disease accompanied by a high risk of suicide and is a major cause of morbidity worldwide [13-15]. Therefore, the aim of this paper is to review the relationship between physical activity and depressive disorders and the potential neurobiological alterations induced by exercise that might lead to the relief of mental disorders like depression. To do so, we searched electronic databases for literature and reviewed articles concerning the latter phenomenon from 1963 until 2009.

1.1. Epidemological Data of Depression

Since MDD is a major health problem and the effectiveness of current medical antidepressants is only about 65% [16], the antidepressant actions of exercise are of immense interest. According to the Global Burden of Disease study [17] mild to moderate major depressive disorder (MDD) ranks now second behind ischemic heart disease for years of life lost due to early death or disability. MDD is the most prevalent of all psychiatric disorders, affecting up to 25% of women and 12% of men during their lifetimes [18]. According to Greden *et al.* 340 million people worldwide are affected by depression [19]. The pan-European study DEPRES [20] showed in 1997 that 13359 out of 78463 adults who participated in screening interviews across six countries in Europe suffered from depression. This represents a prevalence of 17% for Western Europe. The resulting economic burden is about $83.1 billion per year only in the USA [21].

The main symptoms of MDD are depressed mood, anhedonia (lost of interest or pleasure), increased tiredness, irritability, difficulties in concentrating, abnormalities in appetite and sleep and suicidal intentions [22]. Depressive symptoms are correlated with the presence of chronic disease [23], inability to work [24], increased mortality risk [25], increased use of medical services [26], decreased well being and lowered functioning [27]. Ten percent of those diagnosed with MDD commit suicide [28, 29], depressed patients tend to develop coronary artery disease and type 2 diabetes [30]. Today's treatments as mentioned above remain sub-optimal. Only 50% of all patients show complete remission, although up to 80% demonstrate partial responses [22]. Furthermore, the medications require long-term treatment for weeks to months before a therapeutic response is achieved [16]. Therefore, there is an enormous demand for more effective methods to treat depressive disorders.

Although the prevalence of depression and its impact is high, knowledge about the pathophysiology of MDD is still not completely understood. That is primarily due to difficulties in observing pathological changes within the human brain and that most depressions occur idiopathically [31]. The risk factors of depression are diverse like stressful life events, endocrine abnormalities (hypothyroidism and hypercortisolism), cancers and side effects of drugs [22, 32, 33]. The diagnosis of MDD bases on symptomatic criteria set forth in the Diagnostic and Statistical Manual [34]. It becomes clear from the criteria's that the diagnosis of depression is not based on objective diagnostic tests, but rather on a set of symptoms. Therefore depression cannot be seen as a single disease. It is a syndrome that consists of numerous diseases of different causes and pathophysiologies that makes the diagnosis of MDD subjective and is based on the documentation of certain symptoms over a time of at least two weeks [22]. The diagnostic criterias overlap with other conditions such as anxiety disorders, which have substantial co-morbidity with depression [35, 36].

1.2. Causes of Depression

Epidemiological studies show that 40%–50% of the risk to suffer from depression is genetic [37, 38]. This makes depression a highly hereditary disorder. Despite some promising leads, there are still no confirmed genetic findings for mood disorders [39].

Nongenetic factors are as diverse as stress and emotional trauma, viral infections, and even stochastic processes during brain development have been implicated in the etiology of depression [38, 40].

Depressive syndromes occur in the context of innumerable medical conditions like endocrine disturbances (hyper- or hypocortisolemia, hyper- or hypothyroidism), collagen vascular diseases, Parkinson's disease, traumatic head injuries, certain cancers, asthma, diabetes and stroke. Several brain regions and circuits that regulate emotion, reward and executive functions are implicated in this disease. Dysfunctional changes within the interconnected limbic region have been implicated in depression and also in antidepressant action [41]. A large body of post-mortem and neuroimaging studies of depressed patients have reported reductions in grey-matter volume, glial density in the prefrontal cortex and the hippocampus. These regions are thought to mediate the cognitive aspects of depression, such as feelings of worthlessness and guilt [33, 42, 43]. Patients with depression have shown to suffer from statistically significant smaller left hippocampal volume than non-depressive comparison subjects [44]. In this study Magnetic Resonance Imaging (MRI) was used to measure the volume of the hippocampi in 16 patients with major depression (10 men, 6 women) and 16 case-matched non-depressed controls. Patients with a history of Post-traumatic Stress Disorder or current medication use other than antidepressant were excluded from this investigation. The findings of this study showed that the right hemisphere suffered from a reduction of hippocampal volume by 12% but without statistical significance. The left hemisphere showed a significant reduction in volume of the hippocampus by 19% in the depressed patients compared to the matched controls. These results suggest that depression causes loss of brain volume observed in the hippocampi, especially in the left hemisphere.

1.3. Physical Activity and Depression

Data from epidemiological studies suggests an association between physical inactivity and higher levels of depressive symptoms [45, 46]. It has been shown that reduced physical activity leads to increased symptoms of depression in older adults [47] and that depressive symptoms decrease when physical activity is resumed [48]. Blumenthal *et al.* (1999) could show that the influence of a 16-week exercise training program as a therapeutic treatment of depressive patients is as effective as antidepressive medications. 156 men and women with diagnosed MDD (50 years) were

randomly assigned into three groups of interest: (1) aerobic exercise, (2) antidepressants (sertraline hydrochloride) and (3) combined exercise and medication group. The subjects attended three supervised exercise sessions per week for 16 consecutive weeks at an intensity of 70% to 85% of heart rate reserve that was calculated from the maximum heart rate. The maximum heart rate was achieved during a treadmill test every participant had to fulfil in advance. Each aerobic exercise session began with 10-minutes warm-up exercise, followed by 30 minutes of continuos walking or jogging at the described intensity. The end of the session was characterised by a 5 minutes cool-down. The heart rate was monitored and recorded 3 times per session by a trained exercise physiologist *via* radial pulses. The study could show that 16 weeks of treatment exercise was equally effective in reducing depression among patients with MDD as antidepressants [48]. Several meta-analyses [49-54] studied the impact of exercise on depression and all concluded that exercise had positive effects. Two studies concluded that more intense exercise led to larger improvements in mood [55, 56]. There is evidence that physical activity induces physiological changes in endorphine and monoamine levels, and also reduces the levels of the stress hormone cortisol [57]. Recent studies suggested that exercise stimulates the growth of new nerve cells [9] and induces the release of proteins and peptides, which are known to improve health and survival of nerve cells, such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1) and the gene VGF (nerve growth factor inducible) [58-62].

Even though the effectiveness of exercise in decreasing symptoms of depression has been well established, Mead *et al.* concluded in 2009, after reviewing articles concerning the influence of exercise on depressive symptoms, that the effect of exercise was not significant [63]. LePore infered that exercise may only be a diversion from negative thoughts [64] and social contacts might influence the positive outcome. Especially the determination regarding the optimum type, frequency and duration of exercise is questioned by Mead *et al.*, 2008. He points out that future research has to consider the design of exercise to determine more specifically what kind of exercise is of benefit and what not, e.g. whether exercise should be performed supervised or unsupervised, indoors or outdoors, or in a group or alone [63].

1.4. The Specific Role of Monoamines in Depression

The 'monoamine hypothesis' of depression, which postulates that depression is caused by decreased monoamine function, especially serotonin (5-hydroxytryptamine 5-HT) and norepinephrine (NE) in the brain, originated from early clinical observations [41, 65]. Today's antidepressant and anxiolytic drugs such as Tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs) and Selective serotonin reuptake inhibitors (SSRIs) are still designed to increase monoamine transmission acutely [66]. They primarily affect the serotonergic and/or the norepinephrine system, whether by inhibiting the reuptake of serotonin and/or norepinephrine into the presynapse or by inhibiting the activity of monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitters and thereby increasing the availability of serotonin and/or norepinephrine in the synaptic cleft [67, 68]. Although these monoamine-based agents are potent antidepressants [66], the cause of depression is far from being due to a simple deficiency of central monoamines. The problem is that the MAOIs and SSRIs produce immediate increases in monoamine transmission, whereas their mood-enhancing properties require weeks of treatment. Because of this delay in time it is thought that the acute increases in the amount of synaptic monoamines induced by antidepressants produce secondary neuroplastic changes that occur over a longer timescale and involve transcriptional and translational changes that mediate molecular and cellular plasticity [22, 65]. Nevertheless monoamine-based antidepressants remain the first line of therapy for depression, but their long therapeutic delays in time and low remission rates (about 30%) [66] have encouraged the search for more effective agents [41, 69].

One of the mechanisms through which exercise produces the antidepressant effects might be similar to that of the antidepressant drug treatment since exercise also affects the central serotonergic system. The synthesis of brain 5-HT depends on two main variables, the neuronal concentration of its precursor, tryptophan (Trp), and the activity of its rate-limiting enzyme, tryptophan hydroxylase (TPH; converts tryptophan into 5-hydroxytryptophan) [70]. Acute physical exercise increases blood free tryptophan and decreases albumin bound tryptophan both in animals [71-73] and humans [74-76] by increasing the rate of lipolysis. It was shown in humans that an increase in levels of the serotonin metabolite, 5-hydroxyindoleacetic acid follows physical exercise [77]. Since Trp is competing with other amino acids like valine, leucine and isoleucine to enter the brain, it has also been demonstrated that exercise decreases the levels of these amino acids leading to higher availability of the serotonin precursor Trp in the brain [78-80]. Therefore the higher concentrations of Trp in blood plasma and also in the cerebrospinal fluid following exercise enhance the serotonin neurotransmission in the brain.

Other experiments with animals have demonstrated an immediate increase in the activity of brain cells that produce norepinephrine after acute exercise [81-83]. Since Serotonin-norepinephrine reuptake inhibitors is a common choice of treatment that acts antidepressive by inhibiting the reuptake norepinephrine into the presynapse and thereby increasing the availability of norepinephrine in the synaptic cleft [67, 68], it is noteworthy that the same effects can be achieved by exercise. Increased levels of norepinephrine and its metabolites as well as the activation of tyrosine hydroxylase, an enzyme that is involved in the production of norepinephrine is also observed after acute [81-83] and chronic exercise in animals [84-86]. Therefore it can be presumed that excercise produces the same mood-elevating effects as antidepressants by altering the availability of norepinephrine.

Although not as consistent yet nevertheless notable is the effect of exercise on the levels of dopamine as an antidepressant factor. It has been demonstrated that dopamine activity is increased following exercise [77, 87]. Dopamine seems to play an important role in patients with Parkinson's disease but has also been described to correlate to motivational problems and anhedonia seen in patients affected by MDD [88]. The release of dopamine is observed as a consequence of activating the reward system [89]. A common feature of ad-

dictive drugs is that they alter the levels of dopamine in the nucleus accumbens. Exercise is a rewarding behaviour that shares many features with those of addictive drugs. It has been observed in rodents that running increases levels of dopamine in the nucleus accumbens and that those animals can be trained to lever press for access to running wheels to get their reward [90]. Similar behaviour can be observed in humans that train excessively which can result in fatigue and mood disturbances as been reported in overstrained humans [91]. Therefore dopamine seems to be of certain relevance why exercise can be addictive and reinforcing, and also why it has its antidepressant effect on humans.

However, as mentioned previously, the monoamine hypothesis of depression remains inadequate. As in the case of antidepressants exercise induces higher concentrations of serotonin and/or norepinephrine but this cannot explain the observed mood-elevating delay in time [66]. Therefore neuroplastic changes that involve transcriptional and translational changes would appear to play a critical role in the treatment of MDD (see chapter: "1.6 Neurotrophic Factors and Neurogenesis").

1.5. The Role of the Hypothalamic–Pituitary–Adrenal Axis in Depression

Depression is often described as a stress-related disorder, and there is evidence that episodes of depression occur in the context of some form of stress. Even though, stress per se is not sufficient to cause depression but early clinical studies identifying reproducible but small increases in serum glucocorticoid concentrations in depression [92, 93] led to a significant interest in the role of a dysfunctional hypothalamic–pituitary–adrenal axis (HPA) in the pathophysiology of depression. Physical [94] or psychological stress [95] increases serum glucocorticoid concentrations, and some depression-like symptoms can be produced in rodents by chronic administration of glucocorticoids [96]. High levels of glucocorticoids can reduce hippocampal subgranular zone (SGZ) proliferation rates and produce atrophic changes in hippocampal subregions [97]. This could contribute to the hippocampal volume reductions seen in depression [45]. Patients with Cushing's syndrome, who have extremely high concentrations of circulating cortisol, also show depressive features and atrophic changes in the hippocampus [22, 97]. Several metabolic abnormalities that are often associated with depression, such as insulin resistance and abdominal obesity, can be at least partly explained by an increase in glucocorticoids [32, 98]. Hypercortisolaemia in depression is manifested at several levels, including impaired glucocorticoid-receptor-mediated negative feedback [98], adrenal hyperresponsiveness to circulating adrenocorticotropic hormone (ACTH) [92] and hypersecretion of corticotrophin-releasing factor (CRF) [99], the hypothalamic activator of ACTH release from the pituitary [98].

Chronic antidepressant administration has shown to increase the concentration of corticosteroid receptors, which can restore HPA negative feedback and normalize cortisol levels and HPA function [100]. Therefore it appears that there is an interrelationship between stress, high glucocorticoid levels and depression. But not only antidepressants, also exercise can induce changes on the functioning of the HPA axis. Although acute high intensity physical activity leads to increased levels of stress hormones corticotropin and cortisol, long-term exercise (meaning that the body adapts to training stimuli) attenuates the human stress response [101-103]. Exercise can be a stressful stimulus itself depending on the intensity and duration of the activity [94] so that stressful stimulations like exercise need to be followed by adaptations of the organism. If the organism becomes adapted to exercise, then the subsequent response of catecholamine release to stressful intensities of exercise is less than that observed in nontrained subjects [104]. After a training program undertaken at moderate intensities for 4 weeks, the organism already reacts with lower concentrations of ACTH and cortisol to exercise [104, 105]. Furthermore, the effects of exercise in trained subjects indicate that after ending the exercise, the concentrations of cortisol reach their basic levels faster than in untrained subjects [106].

Whether these effects of lower reactivity to stressful exercise events can be related to stressful events in daily life remains unclear. A meta analysis of Crew and Landers [107] including 34 studies, 92 effect strengths (ES), N=1.449 demonstrated a correlation between the level of fitness and reactivity to stressful events (ES=.48). This study demonstrated that trained subjects do not react as strongly to stress as untrained subjects exposed to stress. The problem with the latter study was the measured outcome of stress e.g. cardiovascular parameters. In nearly all stress-exercise-related situations, untrained individuals react with higher heart frequencies but data regarding physiological parameters such as noradrenaline, adrenaline or ACTH levels are generally missing [104]. In many reviews and meta analyses [108-110] that have investigated the correlation between the level of fitness (by maximal and submaximal exercise tests) and stressors it was shown that trained subjects exhibit a higher reactivity to stress (ES=.08, $p<.001$) and recover faster from stress too (37 studies, 118 ES, N=1.092). Most effects were demonstrated in heart frequency, blood pressure, blood flow and vascular resistance. The resulting effects on adrenaline, noradrenaline, ACTH and cortisol were diverse. Animal studies have indicated that animals that exercised voluntarily show improved stress-coping abilities in physically demanding and psychological challenges. The latter improved stress-coping abilities appeared as adaptive responses of the HPA axis [110-112], improvements in sleep quality and increased stress resistance of sleep/EEG profiles [113], and also reduced anxiety-related behaviour in voluntary exercised mice and rats compared to sedentary control animals [114].

1.6. Neurotrophic Factors and Neurogenesis

Decreases in volume observed in the hippocampi and other regions of the forebrain in depressed patients have supported a hypothesis for depression involving decrements in neurotrophic factors [115, 116]. Most studies have focused on BDNF, which is expressed in limbic structures. Neurotrophic factors are known to regulate neural growth and differentiation during development and are also regulators of plasticity and survival of adult neurons and glia [22]. Support for the 'BDNF hypothesis of depression' has come from a large preclinical literature showing that stress can reduce BDNF-mediated signalling in the hippocampus, whereas chronic treatment with antidepressants increases BDNF-mediated signalling [115]. Similar changes have been observed in the post-mortem hippocampus [117], as well as in serum BDNF-

concentrations of humans with depression [115]. The second support for the theory that neurotrophic factors are of importance in treating depression is based upon the time delay of the mood-elevating effects of antidepressants, which is only seen after prolonged administration (several weeks to months). The cellular effect of antidepressants is the induction of hippocampal neurogenesis - the process by which neural progenitors of the SGZ divide mitotically to form new neurons that differentiate and integrate into the dentate gyrus [65, 118]. This process goes along with the mood-elevating time delay in patients. Blockade of hippocampal neurogenesis inhibits the therapeutic-like effects of most antidepressant treatments in rodent models [118]. Moreover, antidepressant treatment, possibly through the actions of transcription factor "cAMP response element binding protein" (CREB) or other transcriptional regulators [15, 65], increases the amounts of several growth factors in the hippocampus that influence neurogenesis. These include BDNF as well as VEGF and the recently discovered neuropeptide VGF, which themselves have antidepressant and pro-neurogenic properties in rodents [119-121]. Furthermore, both central and systemic administration of IGF-1 increases hippocampal cell proliferation and neurogenesis in the adult rat [122, 123]. The same effects are seen after administration of clinically effective antidepressant drugs. Central administration of IGF-1 has shown to produce antidepressant-like effects in the rat forced swim test [124]. This data supports the 'neurotrophic hypothesis of depression', which means that neuronal adaptations induced by antidepressant drugs are necessary to produce mood-elevation effects. This supports the theory that neurotrophic factors play a key role in the relief of depressive symptoms.

Like antidepressants, exercise can also increase the synthesis of new neurons in the adult brain and therefore induce mood-elevating effects. Van Praag *et al.* (1999) observed an increase in hippocampal neurogenesis in rats with regular access to a running wheel [9]. Recent studies demonstrated that adult neurogenesis can be influenced by stress [125], ageing [126], environmental enrichment [127, 128] and physical activity [9, 129].

Kempermann *et al.* in 1997 showed the positive effects of environmental enrichment on neurogenesis in mice [127]. These mice were also tested in a spatial memory task, the Morris water maze [62], in which the enriched animals learned faster than control animals suggesting the possibility that the new neurons cause enhanced cognition [127]. Experiments comparing animals undergoing exercise (wheel running) and animals raised in an enriched environment without exercise showed more Bromodeoxyuridine (BrdU; a synthetic nucleoside, used in the detection of proliferating cells)-positive cells in the runners group than in the group that was exposed to enriched environment without exercise [130]. Further investigations demonstrated that already 10 days of wheel running increases cell genesis in rodents [131-133]. The increase of hippocampal neurogenesis by running became strongly manifested [134-139] that is also associated with improved hippocampal synaptic plasticity [140].

The mechanisms by which exercise induces neurogenesis is based on the increase of following molecules: BDNF, VEGF, IGF-1, the neuropeptide VGF, 5-HT and -endorphins [119, 134, 141].

As already mentioned several days of voluntary wheel running enhance the levels of BDNF mRNA in the hippocampus as has been shown in several studies [141-147]. The changes in the mRNA were found in neurons of the dentate gyrus (DG), the hilus and the CA3 region of the hippocampus. In addition to the hippocampus, exercise also augmented levels of BDNF mRNA in the lumbar spinal cord [148], the cerebellum and the cortex [143]. Other growth factors like nerve growth factor (NGF) [143] and fibroblast growth factor 2 (FGF-2) were also altered by exercise [149].

It is well known that -endorphins are increased after exercise [150, 151]. It has been shown that the infusion of opiates induces an increase in cell proliferation and also that antagonists of the opiate receptor decrease cell proliferation in the dentate gyrus [152, 153].

Infusion of recombinant protein in mammals to elevate the levels of VEGF, a protein secreted from blood that acts on endothelial cells to stimulate the formation of bloodvessels, has been shown to increase cell proliferation in the adult hippocampus and ventricular zone [154]. It was demonstrated that the levels of VEGF are also elevated following exercise [61, 155]. Fabel *et al.* pointed out in 2003 that VEGF is necessary for the effects of running on adult hippocampal neurogenesis whereas peripheral blockade of VEGF neutralizes running-induced neurogenesis [135].

Another growth factor that is up-regulated in the brain [156] and in the periphery [60] after exercise is the insulin-like growth factor IGF-1. IGF-1, structurally related to pro-insulin, plays an important role in depressive disorders by contributing to neural development through neurogenesis and synaptogenesis, facilitating oligodendrocyte survival and stimulating myelination [157-159]. IGF-1 promotes cell proliferation and inhibits cell death during healthy but also during stressed or diseased states [160]. Peripheral administration of IGF-1 has been shown to induce up-regulation of BDNF mRNA levels in the brain [156]. Therefore it is suggested that IGF-1 initiates growth factor cascades in the brain that can alter mechanisms of plasticity [57]. Furthermore, Carro *et al.* could show in three experiments that exercise has neuroprotective effects by its increased passage of circulating IGF-1 into the brain [156] since after blocking the passage exercise no longer worked neuroprotective in simulated brain insults in rodents. Further evidence comes from Fernandez *et al.* who could show that systemic administration of IGF-1 to brain-damaged sedentary mice or rats is sufficient to elicit functional recovery after simulated brain insult in rodents [161]. Based on these findings circulating IGF-I has a physiological neuroprotective tonic effect on the brain that is depressed in sedentary subjects.

Hunsberger *et al.* used a microarray technique to show that exercise upregulates a primary signaling cascade for neurotrophic factors and a peptide precursor, VGF [119]. The VGF protein showed a robust antidepressant response in behavioural animal models [119]. Furthermore, it was demonstrated that VGF induces synaptic plasticity genes that are also altered after exercise (Nrn1 and Syn1) [162, 163]. It is remarkable that exercise regulates so many genes especially in the hippocampus and underscores that exercise can be a potent tool to influence brain metabolic functions.

1.7. The Relationship Between Depressive Disorders, Cytokines and Exercise

Recent research has shown that pro-inflammatory cytokines not only induce "sick symptoms", but also impinge on physically ill patients by leading to depressive disorders. In approximate 33% of patients who are treated by recombinant human cytokines interleukin-2 (IL-2) and interferon- (IFN-) major depressive disorder is observed [164]. It has been shown in animal models of inflammation that existing states of decreased reactivity to reward (anhedonia) and reduced social exploration can be reversed by antidepressant treatment [164].

Sickness is basically an adaptive response to infection. As in the case of depressive disorders, it is characterized by endocrine, autonomic and behavioral changes. But unlike depression, sickness is completely reversible once the disease-causing agent has been eliminated. Van den Biggelaar *et al.* studied 267 people at the age of 85 without any psychiatric history. In this study it was shown that increased inflammatory biomarkers appear before the onset of depression [165]. Certain mediators like pro-inflammatory cytokines are produced in an infection that contain interleukin-1 and (IL-1 , IL-1), tumor necrosis factor- (TNF-) and interleukin-6 (IL-6). These in the periphery produced cytokines also act on the brain causing behavioral symptoms postulated as "sickness behavior" [166, 167]. It has been repeatedly observed in patients suffering from major depression that the levels of pro-inflammatory cytokines, acute-phase proteins, chemokines and adhesion molecules are increased [168-175]. The most frequently observed alterations are increased levels of IL-6 in the plasma as in the serum and/or elevations of C-reactive protein [166, 168-171]. Further alterations were observed in elevated concentrations of IL- - and TNF- in peripheral blood and in the CNS of patients suffering from MDD [172, 175, 176].

Major depressive disorders caused by immunotherapy in cancer or hepatitis C patients who were receiving immunotherapy supported the theory of cytokine-induced depression first postulated by Smith [177] and later by Maes [178]. Behavioral data in animal studies have indicated a relationship between cytokines and depression. Systemic administration of lipopolysaccharide (LPS) induced the expression of IL-1 and other pro-inflammatory cytokine mRNAs and proteins in the brain in many studies [179-182] in addition showing that depressive-like behaviour remained after sickness behaviour had already retreated. Frenois *et al.* observed a decrease in the preference for a sucrose solution, a phenomenon that was still apparent when food intake and drinking had already normalized. If the animals received antidepressants before LPS-treatment the reduced intake of a sweetened solution was neutralized [183]. Another link in favour of relationship between cytokines and depression stems from the fact that immunotherapy reduces the plasma levels of tryptophan which determines the rate of serotonin synthesis in the brain [184]. This finding correlated in the same study with the patient's depression scores. A key role in the context of inflammation and depressive disorders seems to play IL-1- that inhibits the expression of BDNF in the hippocampus of rats after undergoing social isolation [185]. Stress-induced neuronal cell loss in animals is also associated with increased levels of TNF- and NF- B (nuclear factor 'kappa-light-chain-enhancer' of activated B-cells) [186]. Over-expression of TNF- is observed in decelerated brain growth and neural damage, which is associated with reduced IGF-1 activity, in this case especially in the cerebellum [187]. Dantzer *et al.* (1999) showed that IGF-1 can counteract the behavioral depressing effects of cytokines [188]. This finding is of great interest since IGF-1 can therefore act as an anti-inflammatory cytokine in the brain and can also be induced by exercise.

Exercise has been shown to influence the immune system and seems to play an important role in the relationship between the immune function and depressive disorders. During exercise, the cascade in cytokine response differs from the "classical" response to infections represented by the onset of circulating IL-6 during exercise [189]. Epidemiological data suggests a relationship between physical inactivity and low-grade inflammation in healthy subjects [190-192]. Starkie *et al.* could (2003) show that exercise in the form of 3 hours ergometer cycling can suppress endotoxin-induced TNF- production [193]. Exercise works as an anti-inflammatory agent by leading to higher levels of IL-6 which is followed by raising IL-1ra and IL-10 levels [194] and also by suppression of TNF- production as demonstrated in animals and *in vitro* studies [195]. Exercise gives rise to high levels of epinephrine that has also been shown after infusion to inhibit TNF- production in response to endotoxin *in vivo* [196]. Except for strenuous exercise which is mainly pro-inflammatory, the exact dose of exercise that has anti-inflammatory effects has not been clearly established. However, the data suggests that moderate aerobic exercise seems to induce the most promising effects considering the anti-inflammatory and antidepressive outcomes.

To summarize the relationship between depressive disorder, cytokines and exercise, epidemiological data shows the correlation between physical inactivity and low-grade inflammation [190-192]. Since immunotherapy reduces plasma levels of tryptophan, it is noteworthy that levels of tryptophan can be directly influenced by exercise. As already mentioned acute physical exercise increases blood free tryptophan and in animals [71-73] and humans [74-76]. And also IGF-1, which counteracts the behavioral depressing effects of cytokines [188], can be influenced by physical activity [60, 156].

2. CONCLUSION

Exercise induces physiological changes that make it a potentially powerful agent for use as a therapeutic method of intervention in many health disorders such as diabetes, stroke, certain cancers, coronary heart disease and or obesity. It seems that neurobiological health and functioning depends on the physical activity level of each person’s life. The observed behavioural and biological influence of exercise training on depressive disorders suggests that it induces the same neurobiological alterations as antidepressant drug treatment by elevating the levels of serotonine [79, 80, 197], increasing central norepinephrine neurotransmission [81-83], altering the hypothalamic adrenocortical system [110-112] and raising -endorphin concentrations [150, 151]. Furthermore, exercise stimulates the growth of new nerve cells [9] and the induction of the release of proteins and peptides that improve the health and survival of nerve cells like BDNF, VEGF,

IGF-1 and VGF [57, 59, 60, 119, 141]. Increased inflammatory biomarkers seem to appear before the onset of depression, but the cytokine-response to exercise and its effect on depressive disorders needs to be further investigated. There is no accurate published information concerning dosage, duration, frequency, intensity or type of exercise to be used as an antidepressive treatment. Therefore, future research has to concentrate on the effects of specific forms of exercise. Therefore it would be interesting to answer following questions in the near future: Do the behavioural results correlate with the molecular changes in neurotrophic factors or monoamine, cytokine or cortisol alterations? Can there be observed changes in the neuronal morphology, e.g. dendritic atrophy and spine reduction after the induction of "depression" and their possible modification after an exercise therapy? What specific role are cytokines playing in depression and are they related to and contribute to positive outcomes when exercise is used as an intervention in depressive disorders? How should the exercise be designed for it to be useful as an intervention in brain-related disorders like depression? Since MDD is a major health problem and the effectiveness of current antidepressants is limited, the antidepressant actions of exercise are of great interest and could represent more than just an alternative to current treatments. In all, these findings support the theory that brain health is activity dependent and that exercise training should be further promoted as a preventive and rehabilitative strategy to avoid or treat brain-related disorders.

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