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The effects of physical exercise on neurodegeneration and cognitive decline

Which molecular pathways are involved?

Written by: Priscilla Slagter (s1817299)
Supervisor: Prof. Dr. E.A. van der Zee

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Abstract

It is well known that physical exercise reduces the risk of cardiovascular disease, metabolic syndrome and obesity. Several studies have now shown that physical exercise also has a beneficial effect on cognitive impairment and dementia due to ageing and neurodegenerative diseases. However, exercise is a very broad term and most research that has been done focuses on different aspects of exercise. Since it is impossible to cover all these aspects in this thesis, I will focus on the effect of physical exercise in improving cognition and neuroprotection in elderly and in particular which molecular pathways are affected. Animal and human research show that by regulating the expression of several growth factors, including IGF-1, BDNF, VEGF and NGF, neurotransmitters and anti-inflammatory cytokines, exercise is capable of improving cognitive functions. However, the effect of exercise depends on duration, the sort of exercise that is performed and age. Also, not all cognitive processes improve to the same extent. Since most elderly are not capable of performing physical exercise, recent research has shifted towards the effects of whole body vibration on improving cognition as an alternative for physical exercise.

Key words: physical exercise, synaptic plasticity, cognitive impairment, growth factors, neurotransmitters, anti-inflammatory cytokines.

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1. Introduction

Exercise is a very broad term and most research that has been done focuses on different aspects of exercise. For example, exercise can be divided into mental and physical exercise, which both have positive effects on cognition (Evers, et al., 2011). Within these two types of exercise there are different exercise programs, that differ in intensity and duration, that the researchers can choose from. Another thing that differs between the studies is the age of the subjects and whether or not they have pre-existing mental impairments. There are also differences in the use of animal models or human subjects. Since it is impossible to cover all these aspects of exercise in this thesis, I will focus on the effect of physical exercise in improving cognition and neuroprotection in elderly and in particular which molecular pathways are affected.

It is well known that physical exercise reduces the risk of cardiovascular disease, metabolic syndrome and obesity. Several studies have now shown that physical exercise also has a beneficial effect on neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, Multiple Sclerosis, Huntington's disease, ischemic stroke, depression and cancer (Cotman et al., 2007; Hillman et al., 2008; Ferreiraa et al., 2011). It is also known that in elderly people who don't suffer from neurodegenerative diseases, physical exercise has a protective effect against cognitive impairment and dementia due to ageing. Ageing is also a major risk factor for most neurodegenerative diseases and since nowadays people get older, the number of people suffering from cognitive decline due to neurodegenerative diseases or ageing will only increase. Physical exercise seems to be a relative easy, inexpensive and non-invasive way to improve cognitive function.

In this thesis I will explain the effects of synaptic plasticity, anti-inflammatory cytokines, several growth factors and neurotransmitters that are activated or inhibited by physical exercise. Since rodents are an easy model for uncovering the molecular mechanisms behind the effects of exercise, most information is obtained by animal research. However, when available I will also include whether or not research on human subjects found the same results.

2. Effects of exercise on synaptic plasticity

Synaptic plasticity refers to the modification and regulation of synapses and synaptic networks (Rostas et al., 1991). New synapses can be made in response to injury or as part of a continues renewal cycle. The number of synapses in a region is also regulated by pre- and postsynaptic mechanisms, by increasing the number of synapses the signal becomes stronger and this will make it easier for example to retrieve memories.

Synaptic plasticity in de dentate gyrus, a region of the hippocampus, is probably due to enhanced neurogenesis in this region (Vivar et al., 2012). Neurogenesis in adults produces three types of neurons, new granule cells in the dentate gyrus of the hippocampus and two other types of neurons that are relocated to the olfactory bulb (Fabel and Kempermann, 2008; Kiuchi et al., 2012). Compared to mature granule cells, the new granule cells in the hippocampus have a lower threshold for long-term potentiation (LTP) induction and enhanced LTP. LTP is an enhanced postsynaptic potential after high frequency stimulation and it is very important for learning and memory (Lee et al., 2012). In contrast, exercise seems to have no effect on long-term depression (LTD), another form of synaptic plasticity which reduces the number and efficacy of synapses due to prolonged low frequency stimulation (Ménard and Quirion, 2012). Therefore LTD is thought to be involved in weakening already formed memory traces.

Increasing age is naturally accompanied by a reduction of neurogenesis (Vivar et al., 2012). Physical exercise stimulates neurogenesis in the hippocampus, though not in the olfactory bulb. Due to neurogenesis there is need for more nutrients. This need is met by a higher metabolism and by increased brain vascularization (Smiley-Oyen et al., 2008). Neurogenesis, increased metabolism and brain vascularization are mediated through the activation of several growth factors, anti-inflammatory cytokines and neurotransmitters which will be discussed in the following chapters.

3. Effects of exercise-induced growth factors

The most well-known growth factors mediating the effects of exercise on the brain are insulin like growth factor 1 (IGF-1), brain-derived neurotrophic factor (BDNF), vascular endothelial-derived growth factor (VEGF) and nerve growth factor (NGF) (Cotman et al. 2007). The effects of exercise on learning are mostly controlled by IGF-1 and BDNF, while the effects on angiogenesis and hippocampal neurogenesis are mostly controlled by IGF-1 and VEGF. In addition, IGF-1 and BDNF also influence the activity of some neurotransmitters.

Besides influencing different processes, these growth factors are secreted in response to different types of exercise. Recently, Cassilhas and colleagues (2012) compared two types of exercise, aerobic versus resistance exercise, in rats. They found that both forms of exercise increased learning and spatial memory, but they achieved this through different molecular pathways. Resistance exercise activated the IGF-1 pathway, while aerobic exercise activated the BDNF pathway.

3.1 Insulin like growth factor 1

During development IGF-1 is expressed by all cell types in the mammalian and rodent brain and it aids in cell proliferation, differentiation and survival (Fernandez and Torres-Alemán, 2012). In the adult brain IGF-1 levels are also present, although at much lower rates. Besides being produced in the brain, IGF-1 is produced by almost every other organ.

Within ten to twenty minutes after the onset of exercise plasma levels of growth hormone start to rise (Frystyk, 2010). The exact mechanism by which exercise exerts this increase is not yet fully understood, although it is believed that at least growth hormone releasing hormone and somatostatin are involved. After secretion, growth hormone stimulates the production of IGF-1. In addition, IGF-1 brain levels also increase due to transport of peripheral IGF-1 over the blood-brain barrier (Vivar et al., 2012). The increased amount of IGF-1 levels in the brain lead to neurogenesis and reverses the reduction of neuronal production seen in ageing (Lichtenwalner et al., 2001).

IGF-1 exerts its neuroprotective effects and promotes neurogenesis through activation of the PI3K-Akt/SGK pathway (Frystyk, 2010). When IGF-1 activates its receptor on the cell membrane, PI3K is recruited to the receptor where it binds to PDK1 (Brunet et al., 2001) (**FIG. 1**). This complex subsequently activates SGK and Akt which both prevent the cell from going into apoptosis by inhibiting the activation of FOXO and p53. Akt is also indirectly responsible for the activation of NF-κB, which activates genes necessary for cell survival. One of those genes is IAP, which inhibits the activation of caspase 9 and by doing so indirectly inhibits the activation of caspase 3 as well. In addition, Akt phosphorylates the protein BAD thereby preventing it from executing its pro-apoptotic functions.

The PI3K-Akt pathway is involved in learning, as well (van der Heide et al., 2006). However, for this simultaneous activation of the NMDA receptor is required. When both pathways are activated they promote LTD of the hippocampal neurons (van der Heide et al., 2005).

While high levels of IGF-1 seem to be beneficial for neurogenesis and improve memory in mammals, it has been shown in nematode and *Drosophila* models that low levels of IGF-1 increase lifespan (Bishop et al., 2010). This contradiction can be explained by the fact that mammals have many IGF-1 receptors located throughout their body (Rincon et al., 2004). However, the receptors in- and outside the brain react in different ways upon activation by IGF-1. Model organisms like *C. elegans* and *D. melanogaster* have IGF-1 receptors that are mainly located in the central nervous system. The different localization of the IGF-1 receptors arose during evolution when mammals obtained a more complex metabolic pathway. This also led to different receptors for insulin and IGF-1 that activate specific downstream pathways, whereas *C. elegans* and *D. melanogaster* only have one receptor for IGF-1 and insulin.

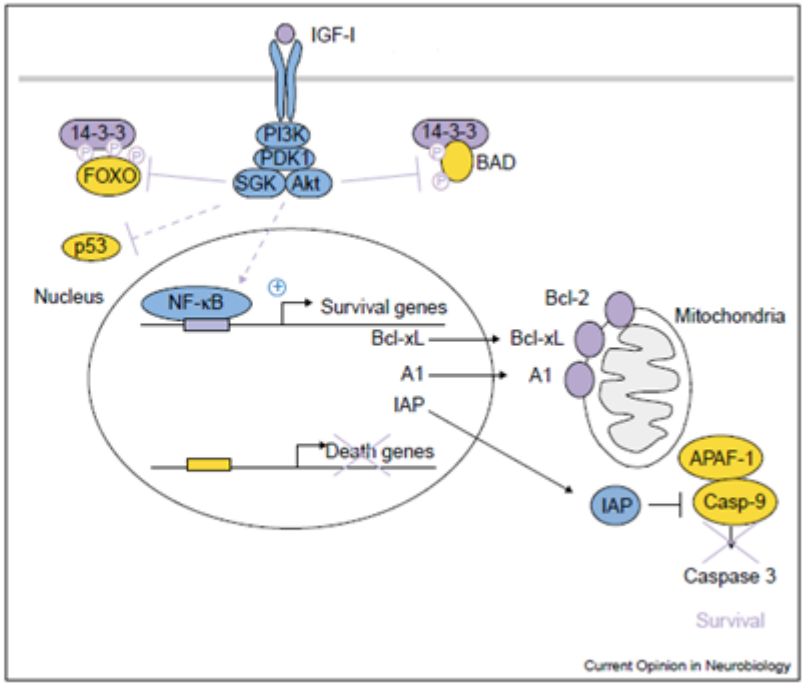

Figure 1. *When IGF-1 activates the PI3K-Akt/SGK signaling pathway, Akt and SGK inhibit the activation of FOXO and p53 which both promote apoptosis. Akt also indirectly activates NF-κB which results in the transcription of survival genes like Bcl-xL, A1 and IAP. By inhibiting caspase 9, IAP prevents the activation of caspase 3 and promotes cell survival. In addition, Akt inhibits the pro-apoptotic effects of BAD by phosphorylation. By Brunet et al., 2001.*

3.2 Brain-derived neurotrophic factor

BDNF is a protein that belongs to the family of neurotrophins and it is predominantly found in the hippocampus, although it is present in other brain areas and the plasma as well (Coelho et al., 2012). There are two forms of BDNF, namely precursor BDNF (preBDNF) which binds to the p75NTR receptor and stimulates cell death and mature BDNF (mBDNF) which stimulates the plasticity of the brain by promoting cell survival, differentiation and neuronal growth and it influences brain functions such as learning and memory (Wu, 2011). The serine protease tPa, who's levels are increased by exercising, activates plasmin which in turn cleaves proBDNF into mBDNF. Like the above mentioned IGF-1, BDNF is capable of crossing the blood-brain barrier and its levels decrease with age which is associated with age-related neuronal loss. A reduction in BDNF levels is also seen in elderly that suffer from neurodegenerative diseases (Knaepen et al., 2010).

Knaepen and colleagues (2010) compared the results of 24 studies on physical exercise conducted in humans. They found that strength training did not influence the levels of BDNF, while during aerobic training as well as a single aerobic exercise levels of BDNF increased.

The data on a single strength exercise were contradicting, since some studies showed an increase of BDNF levels while others found no change. This may be due to the fact that there is a lot of difference between the exercise programs of the different studies. It is possible that the intensity of the exercise program of the study that showed no change was not high enough to elicit a response.

Both human and animal research give reason to believe that higher levels of BDNF are a downstream effect of increased levels of the neurotransmitters serotonin and noradrenalin (Ma, 2008). Since BDNF levels also increase after exercise, it is hypothesized that this is also due to activation of these neurotransmitters. Indeed, research has shown that especially activation of noradrenalin by the β-adrenergic receptors leads to activation of BDNF. BDNF in turn activates the TrkB receptors on the cell membrane which leads to the activation of the PI3K-Akt pathway that has been described above (Wu et al., 2011) (**FIG. 2**). In addition, it also leads to activation of Ras (Lallemend, 2005). Ras then activates several other proteins and finally ERK is activated. Like the PI3K-Akt pathway, ERK also promotes cell survival and neuronal growth by gene transcription.

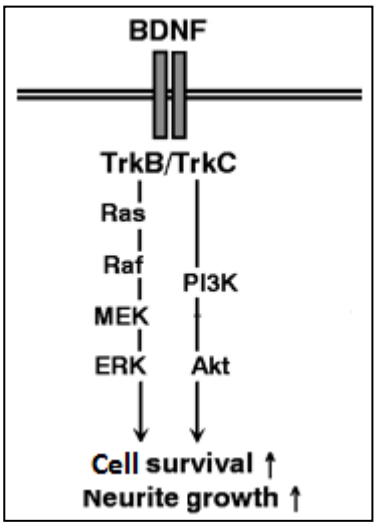

Figure 2. *Upon activation of the Trk receptors by BDNF, both the ERK and the PI3K-Akt pathways are activated resulting in cell survival, differentiation and neuronal growth. By Lallemend, 2005.*

3.3 Vascular endothelial-derived growth factor

VEGF belongs to a subfamily of the growth factors. Other members in this family are involved in placental and lymphatic angiogenesis, while VEGF is known to stimulate angiogenesis in adults (Ferrara et al., 2003). Kiuchi and colleagues (2012) found that mice that were subjected to exercise had higher levels of VEGF. As a consequence the mice had improved capillary density and a higher rate of survival of newly generated neurons in the hippocampus.

During exercise, VEGF is released in the periphery and crosses the blood-brain barrier (Cotman et al., 2007). There it can bind to two different receptors, vascular endothelial-derived growth factor receptor 1 (VEGFR-1) and vascular endothelial-derived growth factor receptor 2 (VEGFR-2) (Cross et al., 2003). VEGFR-1 is expressed by endothelial cells and astrocytes and it inhibits VEGFR-2 function (Warner-Schmidt and Duman, 2008). This may aid in controlling the activity of VEGF, since overexpression of VEGF may lead to the development of cancer. VEGFR-2 is expressed in the hippocampus by endothelial cells, mature neurons and progenitors of neuronal cells. When VEGFR-2 is activated by VEGF it activates the PI3K-Akt and Erk pathways that have been described above. In addition, it also activates the MAPK pathway that starts migration of neuronal progenitors (**FIG. 3**).

Since angiogenesis by VEGF and neurogenesis are both located in the hippocampus it is thought that increasing levels of VEGF due to exercise might lower depressive-like behavior and increase learning and memory (Warner-Schmidt and Duman, 2008).

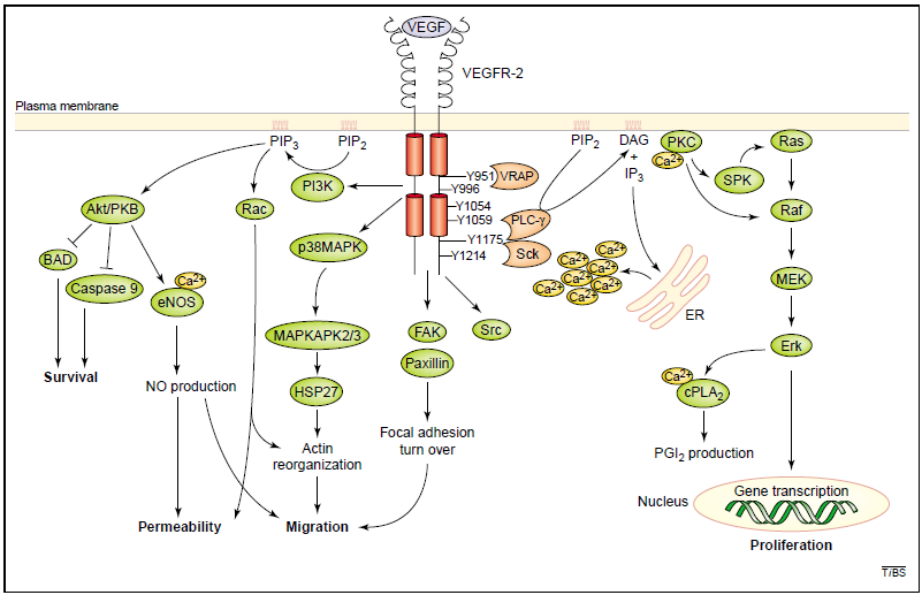

Figure 3. *Activation of VEGFR-2 by VEGF leads to activation of the PI3K-Akt pathway that promotes survival of neurons and by activating eNOS it also stimulates the permeability of the blood vessels. In addition, VEGFR-2 activates PKC which leads to activation of Ras and Raf, two components upstream of Erk. After activation Erk starts with the transcription of genes that are important for cell proliferation. MAPK is also activated by VEGFR-2 and this pathway leads to migration of new neuronal progenitors. VEGFR-2 function is inhibited by VEGFR-1 to prevent overexpression. By Cross et al, 2003.*

3.4 Nerve growth factor

NGF, like BDNF, belongs to the family of neurotrophins and it plays an important role in the growth, differentiation and maintenance of the peripheral and central nervous system (Chung, 2010). During ageing and conditions that impair cognitive function NGF levels drop, however human and animal studies have now shown that exercise increases the amount of NGF and its receptors in the hippocampus.

NGF binds to either p75 receptors with a low affinity or to TrkA receptors with a high affinity. p75 belongs to the tumor necrosis superfamily and in it is thought that, in the absence of TrkA, activation of this receptor induces apoptosis (Casaccia-Bonnefil et al., 1998). When NGF binds to the TrkA receptor, PI3K and Shc can bind to its docking sites (**FIG. 4**). Like described above activated PI3K activates Akt and PDK, which itself is also capable of activating Akt. Akt then phosphorylates the proteins BAD, FOXO and caspase 9 which results in the inhibition of pro-apoptotic signals. In addition, Akt phosphorylates IKK and CREB which results in the transcription of genes necessary for survival. Sch activates the MAPK pathway by activation of Ras and Raf. Phosphorylation of MAPK leads to activation of Rsk, which also stimulates the activity of CREB and inhibits the activation of BAD (Yuan and Yankner, 2000; Chae and Kim, 2009).

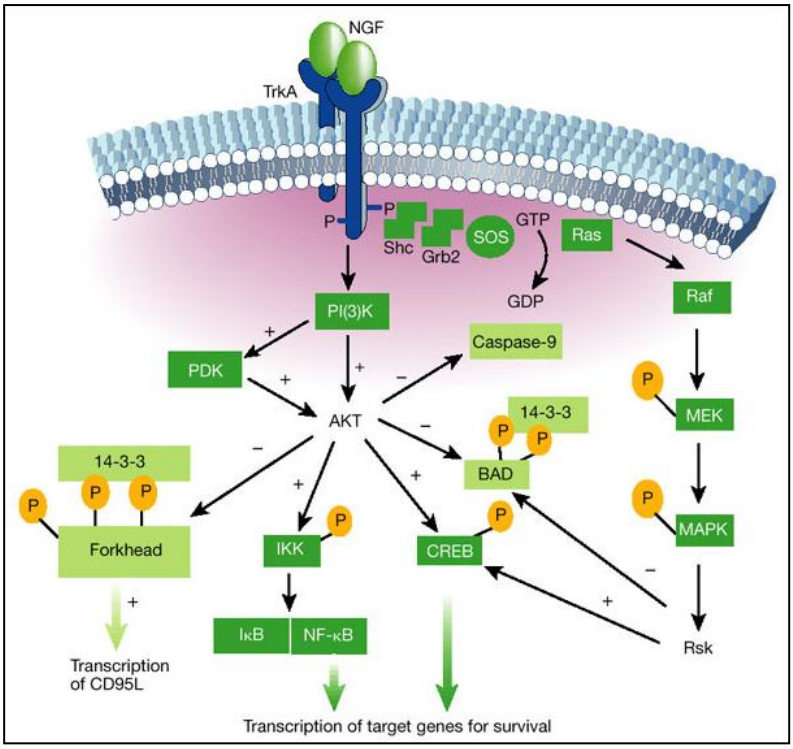

Figure 4. *When NGF binds to the TrkA receptor, PI3K and Shc can bind to its docking sites. Activated PI3K in turn activates Akt and PDK, which itself is also capable of activating Akt. Akt then phosphorylates IKK and CREB, which results in the transcription of genes necessary for survival. Phosphorylation of BAD, FOXO and caspase 9 results in the inhibition of pro-apoptotic signals. Sch activates the MAPK by activation of Ras and Raf. Phosphorylation of MAPK leads to activation of Rsk, which also stimulates the activity of CREB and inhibits the activity of BAD. By Yuan and Yankner, 2000.*

3.5 Neurotransmitters

Animal research has shown that activation of glutamatergic transmission of the synapses in the hippocampus depends upon the earlier described BDNF and IGF-1 signaling (Lessmann, 1998; Aleman and Torres-Alemán, 2009). Glutamate, the main excitatory neurotransmitter, can bind to two different receptors namely the NMDA receptor and the AMPA receptor (Gassmann and Bettler, 2012). While both receptors induce synaptic plasticity leading to LTP, BDNF and IGF-1 only activate the NMDA receptor and not the AMPA receptor (Levine et al., 1998; Ménard and Quirion, 2012) (**FIG. 5**). When the NMDA receptor is activated it in turn activates calcium/calmodulin-dependent protein kinase II. This stimulates the activity of the MAPK/ERK pathway that eventually leads to the activation of CREB and the transcription of genes involved in learning and memory (van Praag, 2009). In contrast, it has also been shown that long term stimulation of the NMDA receptor with a low frequency reduces the density of this receptor, leading to LTD.

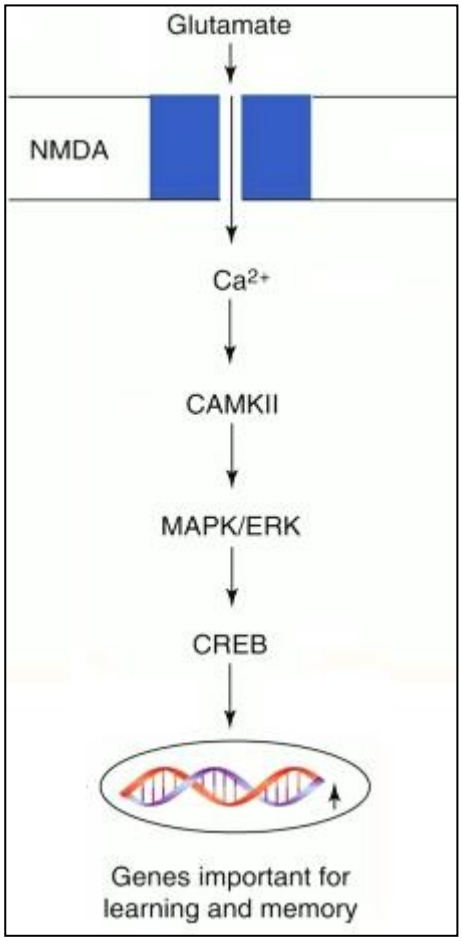

Figure 5. *Glutamate binds to the NMDA receptors, after which a signaling cascade is activated that eventually leads to the transcription of genes involved in learning and memory. Modified from van Praag, 2009.*

Besides their effects on glutamatergic transmission, growth factors also influence the effects of other neurotransmitters. For example, high levels of IGF-1 result in inhibition of acetylcholine release (Seto et al., 2002). Since acetylcholine is thought to activate BDNF in the hippocampus, IGF-1 indirectly regulates the amount of BDNF. However, acetylcholine is also involved in learning and memory tasks (Micheau and Marighetto, 2011). Inhibition of this neurotransmitter by high levels of IGF-1 may lead to impairments in cognition. In addition, the elevated levels of IGF-1 inhibit the release of GABA. GABA is the main inhibitory neurotransmitter in the brain and is involved in filtering and integrating incoming signals (Gassmann and Bettler, 2012).

4. Effect of exercise-induced anti-inflammatory cytokines

Systemic inflammation is a common feature of many risk factors contributing to cognitive decline, while it worsens the inflammation process in the brain (Cotman et al., 2007). Several studies done in humans and rodents found that levels of interleukin 6 (IL-6) were increased after exercise, however the appearance of IL-6 depends on exercise intensity, duration and what form of exercise is being practiced (Petersen and Pedersen, 2005; Brandt and Pedersen, 2010). IL-6 is released into the bloodstream due to muscle contractions which leads to high levels of calcium in the cytosol (**FIG. 6**). During moderate contractions this leads to the activation of the calcineurin-NFAT/AP1 pathway which results in the activation of IL-6. More intense contractions lead to activation of NF-κB and JNK which also activate IL-6. During longer periods of exercise the MAPK pathway becomes active, as well. This pathway can directly activate IL-6 or it can activate IL-6 by activation of NF-κB.

IL-6 activates other anti-inflammatory cytokines, such as interleukin 10 (IL-10) and interleukin 1 receptor antagonist (IL-1ra) (Petersen and Pedersen, 2005; Brandt and Pedersen, 2010). IL-10 prevents the activation of many proinflammatory cytokines, including IL-1α, IL-1β, IL-8 and TNF-α. IL-1ra inhibits the activation of the IL-1 receptor and thereby inhibits the signaling pathway of the IL-1 receptor. In addition, IL-6 can also directly inhibit the production of TNF-α. Reducing the amount of pro-inflammatory cytokines is necessary because they inhibit the signaling pathways of growth factors such as IGF-1 and BDNF in neurons (Cotman et al., 2007).

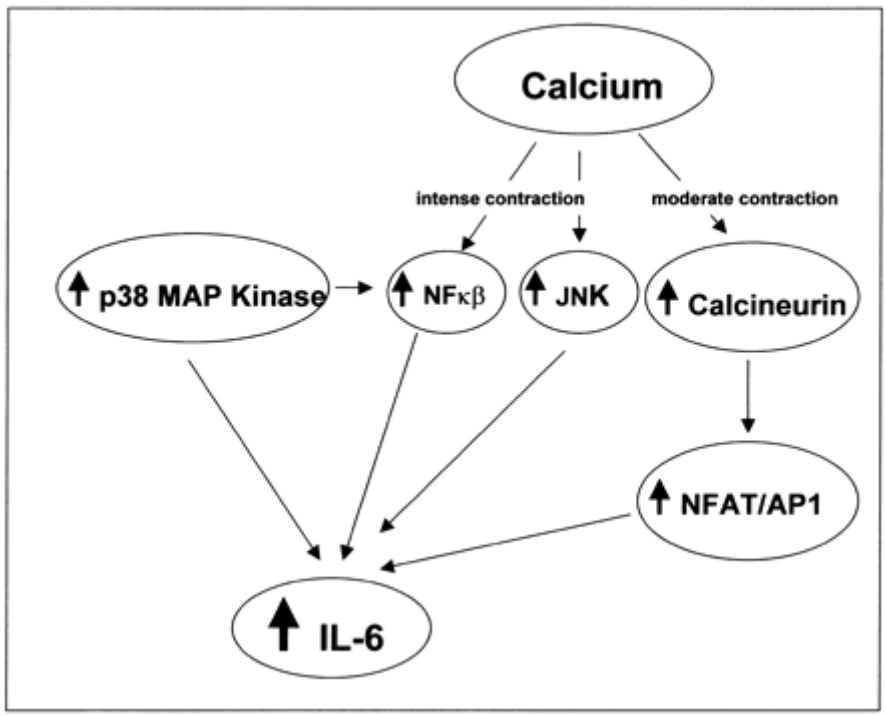

Figure 6. *During exercise **c**ontracting muscles secrete high levels of calcium in the cytosol. There it activates different pathways that are involved in activating IL-6. By Petersen and Pedersen, 2005.*

5. Conclusion & Discussion

Ageing is an important risk factor for neurodegenerative diseases and even in healthy elderly it can cause mild forms dementia and cognitive impairment. Physical exercise may improve cognitive decline and slow down neurodegeneration and therefore the aim of this thesis was to examine what molecular pathways are involved by exercise.

We can conclude that physical exercise prevents neurodegeneration and cognitive decline in healthy elderly and elderly suffering from neurodegenerative diseases by regulating the expression of several growth factors, including IGF-1, BDNF, VEGF and NGF, neurotransmitters and anti-inflammatory cytokines (Petersen and Pedersen, 2005; Cotman et al. 2007; Hillman et al., 2008). However, the effect of exercise depends on duration, the sort of exercise that is performed and age. Also, not all cognitive processes improve to the same extent. As seen in **figure 7**, especially executive tasks which include scheduling, planning and multi-tasking is improved after physical exercise.

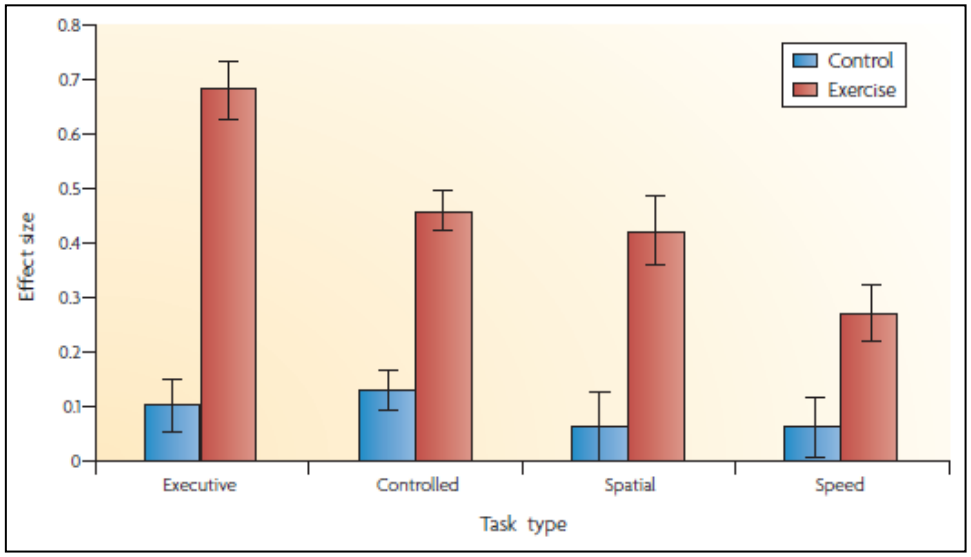

Figure 7. *Elderly in the aerobic exercise group show a larger improvement in all different categories of cognitive processes, compared to the controls. The most improvement was seen in the executive control tasks. By Hillman et al., 2008.*

All growth factors that I mentioned activate the PI3K-Akt pathway which is responsible for activation of NF-κB, a protein that increases the transcription of genes involved in survival, and the inhibition of pro-apoptotic proteins like FOXO, p53 and BAD (**FIG. 8**). The Erk pathway, involved in promoting cell survival and neuronal growth by gene transcription, is activated by BDNF and VEGF. In addition, the MAPK pathway is activated by VEGF and NGF. This pathway inhibits the protein BAD, thereby preventing the cell from going into apoptosis. It also activates the protein CREB which starts the transcription of genes necessary for survival.

In addition to activating proteins that protect against apoptosis and promote the transcription of genes that are necessary for cell survival, the growth factors and neurotransmitters also aid in neurogenesis, brain vascularization and enhanced metabolism

in the hippocampus. These processes are important for hippocampal synaptic plasticity, and thus learning and memory.

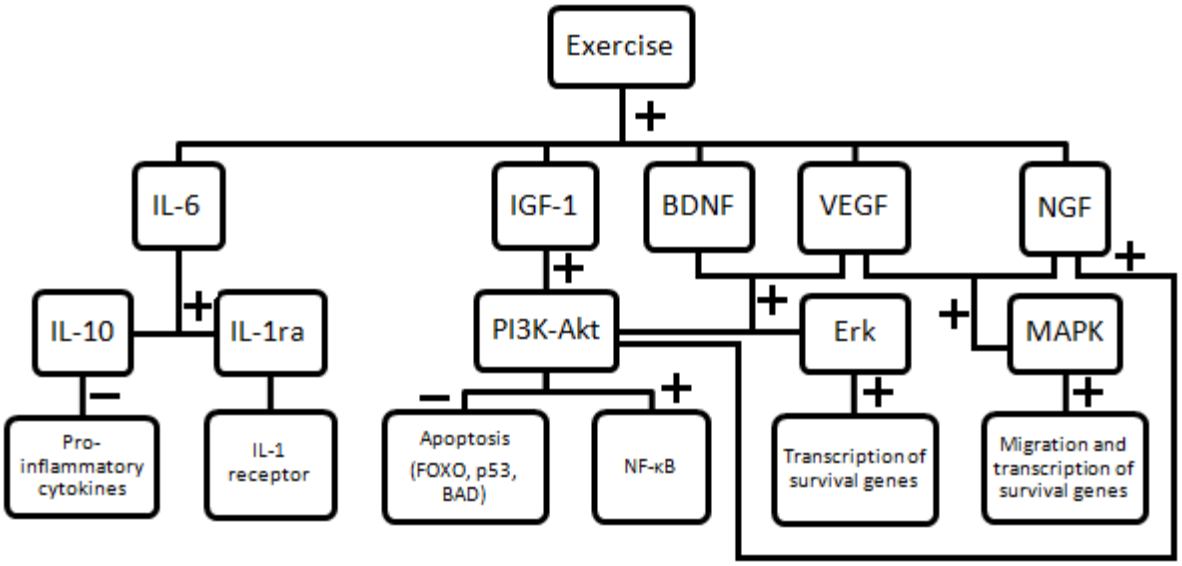

Figure 8. *Exercise activates the anti-inflammatory cytokine IL-6, which leads to the activation of other anti-inflammatory cytokines and the activation of IL-1ra. Exercise also activates the growth factors IGF-1, BDNF, VEGF and NGF. All growth factors activate the PI3K-Akt pathway, the Erk pathway is activated by BDNF and VEGF and the MAPK pathway is activated by VEGF and NGF. All pathways promote survival and inhibit apoptotic signals.*

Besides the positive effects of exercise on neurodegeneration and learning and memory, there are also some negative effects of exercise. Exercise is a form of physical stress and as such, it results in high levels of corticosteroids (Wosiski-Kuhn and Stranahan, 2012). Prolonged exposure to both high and low levels of corticosteroids are harmful for hippocampal neurons. Animal research has shown that glucocorticoids, a subclass of corticosteroids, induces atrophy and reduces density of dendritic spines. However, in animals that were subjected to exercise there was more branching of the dendrites and the density of the dendritic spines in the hippocampus increased. These effects were especially visible in the dentate gyrus. A possible explanation for this is the fact that exercise reduces the affinity of the hippocampal mineralocorticoid receptors, another subclass of corticosteroids, and it reduces the number of hippocampal glucocorticoid receptors as well.

Another part of exercise that could have adverse side effects is the increase in VEGF levels, since high levels of VEGF result in the growth of blood vessels which may aid in the development of cancers. However, research has shown that exercise is actually beneficial in cancer patients (Courneya, 2003). An explanation for this may come from the fact that VEGF can bind to two receptors VEGFR-1 and VEGFR-2. It is thought that VEGF activity is regulated by VEGFR-1 which inhibits VEGFR-2 function, thereby preventing overexpression of VEFG and thus increased growth of blood vessels (Cross et al., 2003; Warner-Schmidt and Duman, 2008).

Since there are mechanisms to oppose the negative side effects of exercise, I think that exercise is an easy and non-invasive way to improve neurodegeneration and memory

functions. However, most elderly are not capable of physical exercise due to physical impairments and immobility. Thus for this age category another form of exercise might prove to be beneficial to improve cognitive function. Recent research has focused on whole body vibration as an alternative to physical exercise for improving learning and memory functions. However, data on this is scarce and it has only been examined in animals. Thus, while whole body vibration instead of physical exercise might prove to be a good alternative for the elderly, more research on animals as well as in humans is needed.

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