Potential Therapeutic Effects of Exercise to the Brain

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Abstract: Exercise is a well-recognized facet of modern living; however, the threat of sedentary lifestyle is ever increasing with the arrival of the technological period. Although the beneficial effects of exercise to the health and function of the brain have been accepted by the scientific and medical community, much remains to be achieved to understand its mechanisms of action. With the advent of modern investigative tools, several more key molecular and cellular players have been implicated in the above process. Such include the family of neurotrophins (e.g. NGF and BDNF) and their receptors, some pro-inflammatory cytokines (L-1β, IL-6, TNF-α, IFN-γ), microglia and astrocytes, and the cholinergic neuronal cells in the forebrain. While experiments based on the voluntary exercise paradigm has been the preferred approach to studying the brain, less is known about the forced paradigm. We will discuss in this review how molecular players may feature differently in the context of exercise and more importantly how their actions converged to impact the structure, and function (learning and memory) of the CNS.

Keywords: Exercise, neurotrophins, p75 ^{NTR}, cytokines, learning, memory.

INTRODUCTION

Historical Perspective

As early as the 19th century, Franz Joseph Gall and Johann Gaspar Spurzheim proposed that the structure of the nervous system was amenable and further suggested that increased usage of the brain would increase its size. By the turn of the 20th century, this idea was further substantiated when Ramón y Cajal proposed that increased usage of the brain would also improve the connectivity of the nervous system. Subsequently, Wolfgang Kohler theorized that increased stimulation of the nervous system would affect its chemical composition.

With the benefit of hindsight and the advent of experimental technology, it is now generally accepted that the brain is capable of changes in response to both intrinsic and extrinsic influences. It was suggested that a complex living environment could somewhat induce changes in the brain weight and metabolism [1]. Specifically, environmental enrichment could up-regulate neurotrophins (NT), its receptors, and therefore possibly influence cognition [2,3]. More importantly to this review, exercise in the form of voluntary running is known to facilitate neuroplasticity or to improve neurogenesis in mice [4,5]. Further, it was characterized that running exceeded enriched environment in influencing neurogenesis and learning. However, the molecular bases for how exercise affects the structure and function of the brain are largely unknown.

Exercise and the Brain

Mechanistically, exercise was reported to have profound effects on the brain's neurochemistry and plasticity. Via molecular techniques, it was systematically shown that exercise could up-regulate NT such as nerve growth factor (NGF) and brain derived nerve factor (BDNF) endogenously [6,7]. Such NT had been reported to facilitate recovery from brain injury such as stroke [8]. The role of pre-conditioning exercise in reducing mortality and brain damage was also proposed [9]. It therefore appears that exercise could be useful in preventing neuronal demise, behavioral impairment and neurodegeneration. In light of this, sedentarism should therefore be avoided, and regular exercise advocated as a form of neuroprotection. In a recent study using an animal model for Parkinsonism, it was documented that forced exercise could protect the brain *via* the up-regulation and activation of certain trophic factors and signaling cascade such as extracellularly regulated kinases [10]. In another study using brain-imaging technology, it was shown that skill training while enhancing brain function could also result in anatomical changes [11]. In addition, there are now known psychological benefits associated with running, and such include positive mood changes and decreased levels of anxiety [12]. To date, the mechanisms for the above observations are still unclear, but as reviewed earlier, there are good reasons to implicate neurotrophic factors such as NGF and BDNF.

Voluntary Exercise Versus Forced Exercise

Interestingly, most of the studies reporting a beneficial action of exercise on the brain have been based on the voluntary paradigm [4,5,7,13,14]. The advantage of these studies is that their results can apply to human condition in which the individual chooses how much to run. Because of the same reasoning, the effects of voluntary exercise would not be easily translated to interpret the effects of treadmill exercise that is currently used on rehabilitative therapies in individual whose voluntary locomotion is impaired. In general terms, treadmill exercise is a type of forced exercise and may involve a different level of involvement of suprasegmental centers (telencephalic and diencephalic) and muscle work as compared to voluntary exercise. Forced exercise has the advantage to be applied to human conditions of impaired locomotion such as those associated with spinal cord injury. Studies in animals indicate that the forced exercise regime is advantageous in terms of outcome measurement, such as manipulation of exercise speed, frequency, duration and intensity. However, it was reported that voluntary exercise was more beneficial than treadmill exercise in enhancing survival and reducing bodily fat of aging rats compared to sedentary controls [15]. It is possible that declining stamina in association with age would no longer favor the rats in the treadmill group to reap the benefits of exercise (lacking the will to exercise).

To date, some investigators have started using the forced paradigm to elucidate the effects of exercise in the brain [16,17,18], however, specific mechanisms explaining adaptations associated with voluntary versus forced exercise are not yet known. It is likely that metabolic and neurochemical pathways among skeletal muscle, the spinal cord, and the brain offer plausible, testable mechanisms to account for the effects of physical activity on the central nervous system [19].

In the following Table **1**, a summary is provided for a list of experiments done to elucidate the effects of exercise to the brain, and profiling the key players involved, and type of paradigm employed.

THE MOLECULAR AND CELLULAR PLAYERS

Neurotrophins (NT)

NGF was the first described member of the NT family discovered by Rita Levi-Montacini five decade ago. NGF was originally

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Table 1. Review of Selected Literature from a PubMed Search Using the Following Key Words – "Exercise" & "Brain" Over the Last 10 Years

Authors & Year	Type of work	Implicated biochemicals	Exercise paradigm
Pham *et al.* [2,3]	Animal	BDNF, NGF	Voluntary
Smith & Zigmond [10]	Animal	GDNF	Forced
Shen *et al.* [20]	Animal	CREB, MAPK	Voluntary
Ang *et al.* [16]	Animal	Neurotrophins, p75 ^{NTR}	Forced
Radak *et al.* [21]	Animal	DT-diaphorase [anti-tumor agent]	Forced
Berchtold *et al.* [22]	Animal	BDNF	Voluntary
Colbert *et al.* [23]	Animal	TNF-alpha, IL-1 beta, IL-6	Forced
Ehninger *et al.* [24]	Animal	Microglia	Voluntary
O'callaghan *et al.* [25]	Animal	BDNF	Forced
Ding *et al.* [26]	Animal	TNF-alpha receptor	Forced
Nybo *et al.* [27]	Human	IL-6	Voluntary
Winter *et al.* [28]	Human	BDNF, catecholamines	Voluntary
Jolitha *et al.* [29]	Animal	Vitamin E, Hydrogen peroxide, Superoxide dismutase	Forced

discovered in the adult mouse submandibular salivary gland, and in 1983, the human homolog, beta-NGF, was fully sequenced [30]. Since then, at least another five members have been characterized; they are BDNF, NT-3, NT-4, NT-5 and NT-6 [31]. In essence, they functioned to support the growth, survival and differentiation of certain neuronal cells in the nervous system. While NT is known to be chemical communicators between these cells, much less is known about their roles as effectors molecules. For this review, emphasis would be on NGF and BDNF since considerably less data is available for the other members in the family.

NGF and BDNF

Four decades after NGF discovery, its analogous BDNF was painstakingly isolated from the pig's brain by Yves-Alain Barde and Hans Thoenen. NGF and BDNF are known to share some structurally and biochemical similarities, and such include a predicted molecular mass of approximately 13 kDa, a high isoelectric point (pI > 9), a 50% amino acid sequence homology, and the formation of disulfide bridges between the 6 cysteine residues [32]. In terms of function, it has been suggested that BDNF could increase the rate of turnover for neurotransmitters such as acetylcholine and dopamine *in-vitro* [33-35]. More recently, it is known to play a role in synaptic plasticity [36]. On the other hand, the role of NGF was thought to be restricted to the PNS [37], and this coupled with the fact that it was first isolated in the salivary gland, could give an impression of lesser importance for brain function**.** As a matter of fact, the use of exogenous NGF has been reported to prevent neuronal death after brain injury [38]. There is also evidence to suggest that NGF while serving its neurotrophic functions also acts as an immuno-regulatory cytokine [39]. It was reported that NGF could provide neuroprotection, by guarding neurons against hypoglycemia and excitotoxicity *via* stabilizing intracellular calcium [40,41]. NGF has also been reported to help reverse spatial memory losses associated with aging [42,43]. NGF and BDNF are capable of reversing spatial memory loss associated with aging. BDNF has been shown to facilitate long-term potentiation (LTP) [44], an electrophysiological correlate of learning and memory. NGF increased hippocampal choline uptake in aged rats with [45]. Further, NGF and BDNF can increase the activities of free-radical scavengers [46], and hence protect the neurons against free-radical damages. This was further substantiated by *in-vivo* studies showing the rescuing effects of such NT on the cholinergic neuronal population [47]. It has been shown that the level of such endogenous NT was altered under varying pathological states [48-50]. In view of the above, investigators have started using exogenous NGF and BDNF on animal models in an attempt to find solutions to symptoms associated with diseases such as Alzheimer and stroke [51,52].

It is proposed that these NT together with some anti-inflammatory cytokines could mediate potential immunological effects of physical exercise on the brain. Indeed, it was suggested that the interaction of NT with their low affinity receptor p75 ^{NTR} could serve to inhibit major histocompatibility complex (MHC) class II expression in microglia and acts as co-stimulatory molecule implicated in antigen presentation [53,54]. All these highlighted the potential that NT (endogenous and exogenous) may one day be useful in ameliorating the effects of neurodegenerative diseases and to facilitate neuroplasticity.

Activity-Dependent Regulation of Neurotrophins

Initial discoveries regarding the role of neurotrophins motivated the perception that they acted as primary factors in the regulation of neuronal survival and differentiation in the developmental organism [55]. In the last decade, however, their role has greatly expanded with findings that neurotrophins can mediate activity-dependent functional and structural plasticity in both the embryonic and mature CNS [56,57,58,59]. The function of BDNF provides insight into how activity-dependent regulation of neurotrophic factors and related factors can alter neuronal connectivity and modulate the functional complexity of neuronal circuits in the hippocampus. Indeed, abundant evidence indicates that BDNF participates in the regulation of axonal and dendritic branching and remodeling [60-63], augments the efficacy of synaptic transmission [64-67], and participates to modulate the functional maturation of excitatory and inhibitory synapses [68-70].

Activity-dependent regulation is a fundamental property of neurotrophins such as BDNF. Neuronal activity enhances the expression, secretion, and/or actions of BDNF at the synapse to result in the modification of synaptic transmission and connectivity. The literature shows that multiple experimental paradigms, structured around the concept of increasing neuronal activity, effectively augment neurotrophin expression. Early studies demonstrated that seizures dramatically increase the expression of BDNF mRNA [71,72] as well as the mRNA expression of another member of the neurotrophin family, NGF, in the hippocampus [73]. In a similar line of thought, it was discovered that sensory stimulation regulates BDNF

with visual input in the visual cortex [74], and whisker stimulation in the barrel cortex [75]. Additionally, physiological activity such as exercise [7,76], learning [77] and sleep and circadian rhythm [78,79] increase BDNF. There is evidence to suggest that BDNF may be more sensitive to regulation by activity than other members of its family. A particular study demonstrated that when the mRNAs for the precursor proteins pro-BDNF and pro-NGF were over-expressed in cultured hippocampal neurons, that secretion by activity was specifically a property of BDNF and not NGF, i.e., the application off a depolarizing stimulus was selective to triggering BDNF release [80].

Several experiments paradigms have demonstrated that, at least in the hippocampus, BDNF is sorted into the activity-regulated pathway whereas other neurotrophins are mainly sorted into the constitutive pathway [80, 81]. The use of BDNF-GFP (green fluorescent protein) fusion constructs has enabled the actual visualization of BDNF in hippocampal and cortical neurons. Accordingly, these studies have revealed that BDNF is packaged in secretory vesicles [82,83]. Co-localization of BDNF with specific markers, the presynaptic secretory protein synapsin I, and the postsynaptic scaffolding protein PSD95, revealed that the BDNF-GFP fluorescence was found to be concentrated at synaptic junctions [82,83]. The BDNF-GFP fluorescence spots were found to quickly disappear when depolarization or high frequency stimulation was applied, hence suggesting that BDNF was secreted from these synaptically localized secretory vesicles [84,83]. Thus BDNF, coupled with its prominence in the hippocampus, seems to exhibit a property that makes its particularly capable of mediating the behavioral implications of exercise and diet on neuronal and cognitive plasticity.

An interesting finding regarding the role of activity-dependent BDNF gene regulation comes from a study conducted by Chen and colleagues in 2003 [85]. Using a chromatin immunoprecipitation technique, they found that the transcriptional repressor Mecp2 is bound to the rat BDNF promoter III [homologous to mouse BDNF IV promoter] in cortical neurons. However, upon the application of activity, i.e., membrane depolarization and subsequent calcium influx, BDNF transcription occurs concurrent with the dissociation of Mecp2 repression from the BDNF promoter. In conclusion, the fact that the expression, release, and function of BDNF are regulated by activity [86,87], provide strong basis for a major role of BDNF mediating the beneficial effects of exercise and other aspects of lifestyle on cognitive function.

Studies involving rats and mice reported better cognitive performance as a result of increased physical activity [13,14,18]. With human subjects, it was reported that physically fit individuals have better cognitive and memory performance when benchmarked against sedentary peers [88-90]. To reiterate, the regulation of neurotrophins by activity could be accountable for the enhanced cognitive function as a result of exercise [91,21,92,93].

NT Receptors – The Role of the p75 ^{NTR}

NT exercise their influences through two classes of receptors. These are the high affinity tyrosine kinase (Trk) receptors and the low affinity p75 ^{NTR} respectively [31]. While the p75 ^{NTR} binds all members of the NT family, the Trk family of receptors composed by Trk A, Trk B and Trk C are highly specific in their binding. Trk A receptor has special binding affinity for NGF and NT-3, while Trk B and Trk C have larger affinity for BDNF/NT-3 and NT-4/5, respectively [94]. It has been suggested that p75 ^{NTR} helps modulate neurotrophic response by facilitating the activation of the Trk A receptor [95]. Further, the p75 ^{NTR} is also constitutively expressed on cholinergic neurons, which are implicated in the pathophysiology of Alzheimer's disease (AD) [96].

While there is a substantial evidence indicating that p75 ^{NTR} may be associated with neuronal death [97] as it contains a cytoplasmic "death domain" involved in apoptosis, the issue is still contentious [98]. Indeed, there may be a principal neuroprotective role for p75 ^{NTR} as pointed out by several other authors [99-101], or it may have a dual role for both neuronal death and survival depending on the circumstances [102]. Other interesting roles that the p75 ^{NTR} may have include its interaction with the NOGO receptor in controlling axonal elongation [103].

In the context of exercise, we have shown that p75 ^{NTR} was up regulated after forced exercise [16]. Assuming that p75 ^{NTR} could be neuroprotective suggested that exercise could benefit the brain.

Neuronal Cytokines

In the brain, there are low levels of constitutively expressed pro-inflammatory and anti-inflammatory cytokines [104]. Briefly, cytokines are low molecular-weight glycoprotein that act as intercellular messengers, such include pro-inflammatory interleukins (IL) such as IL-1β, IL-6, interferon gamma (IFN-γ), and TNF-α, which are known to be produced by activated endothelial, microglial or astrocytic cells in the brain [105]. These cytokines on binding to their receptors would then further activate yet to be identified second messengers system and subsequently, protein kinases and phosphatases. These proteins would ultimately affect gene regulation through the activity of transcription factors [106]. It is also apparent that cytokines levels in the circulatory system are constantly changing in response to exercise [107,108]. Additionally, it was also reported that tissue level cytokine expression might not necessarily correlate with plasma cytokine [23]. It is therefore imperative that any such quantification should be done on the CNS tissue proper to avoid any possible confounding effects. It is also clear that given the complexity of cellular and cytokine interactions within the brain, it is not inconceivable that no single cytokine could work in isolation but probably more in concert with others.

IL-1β

IL-1β, a 17.5 kilo Dalton (kDa) protein, shares the same function with its isoform, IL-1α, although they share only 30% sequence homology [106]. It has been reported that plasma IL-1β remains relatively unchanged after exercise or exhibits relatively small, delayed increments [108]. However, it has been shown that IL-1β was down-regulated with forced exercise [109]. While less is known about the role of IL-1α in brain pathologies, there is considerable data to show that the up-regulation of IL-1β played a harmful role in spontaneous hypertensive rats following cerebral ischemia [110,111]. By blocking the mechanism of IL-1 *via* a receptor antagonist, one could derive neuroprotective effects in the rats by reducing brain edema, the number of neutrophils in ischemic areas, and neutrophils-endothelial cells interaction [112-114]. Other deleterious roles of IL-1 include the up-regulation of endothelial cell adhesion molecules, the promotion of neutrophils tissue infiltration [106], and the eventual cortical cell death or acute degeneration [115,116].

IL-6

This pleiotropic cytokine of molecular weight of approximately 21 to 28 kDa, also known as 26 KD protein and hepatocyte-stimulating factor, is implicated in acute and chronic inflammatory activities [117,118]. However, it is not entirely clear at this stage whether it exerts anti-inflammatory or pro-inflammatory effects or both [117]. Further, its anti-inflammatory effect depends on the inhibition of IL-1 and TNF-α production, and stimulation of the production of their circulating antagonists [119]. More importantly, it was reported that plasma IL-6 could be elevated by as much as a 100 times after a marathon race [120], however, the opposite occurred in the CNS [109,27].

TNF-α

Tumor necrosis factor (TNF)-α has a molecular weight of approximately 17 kDa. Different cell types including activated astrocytes and microglia are capable of producing TNF-α in the brain [121,122]. The actions of TNF-α are mediated by two specific receptors, known as p75 (TNF-R2) and p55 (TNF-R1) [123]. The downstream events following the binding of the cytokine to the receptor include the activation protein kinase C, tyrosine kinase, mitogen-activated protein kinase, phospholipase A2, and phosphatidylcholine-specific phospholipase C [124]. This is followed by the activation of transcription factors such as nuclear factor-κB (NF-κB) which would translocates into the nucleus, where it activates the promoter of the genes for adhesion molecules and other cytokines [125]. Interestingly, there is down regulation of TNF-α after exercise but with no known biological significance. However, in the context of stroke, the inhibition of TNF-α is known to have a neuroprotective function [126-128].

IFN-γ

Interferon (IFN)-γ, a cytokine known for its antiviral activity is produced by activated CD4+, CD8+ T cells and, natural killer (NK) cells. In terms of its activity, there is often direct or indirect down regulation of IFN-γ by other cytokines such as IL-1 [129]. Since the CNS is considered an immunological privileged site [130], it is widely believed the resident cells are unable to produce IFN-γ [131,132]. More importantly, the detrimental effects of IFN-γ is well demonstrated its role in the pathogenesis of demyelinating disorders such as multiple sclerosis [133]. There are also controversial reports that suggest that glial cells such as astrocytes, and the microvessels in the CNS are capable of producing IFN-γ and its receptors [134-136]. IFN-γ is also known to induce the expression of various cytokines by stimulating p38 kinase [137] and of MHC class II expression. Other biochemical actions of IFN-γ include inducing the expression of various genes and the production of polypeptides responsible for anti-viral, anti-tumor, and anti-microbial activities. More importantly, it is capable of modulating the B and T lymphocytes, and the NK cells [129]. In response to exercise, plasma IFN-γ level is not known to change [108] while in the brain, this was found to be down-regulated [109].

Microglia and Astrocytes (Non-Neuronal Cells)

Glial cells such as microglia and astrocytes were once thought to serve only as supporting entities to the neurons in the CNS. It is now widely believed that both microglia and astrocytes have important protective roles in the nervous system against various pathologies. More importantly, both microglia and astrocytes are also known to maintain important immune function in the CNS *via* the release of cytokines [138,139]. In addition, NT signaling through the p75 ^{NTR} reportedly regulates their activities with involvement from some anti-inflammatory cytokines [53,54]. These non-neuronal cells react very quickly to challenges to preserve optimum working environment for the neurons [140,141]. However, overreaction of these glial cells and the accompanying release of cytokines have also been known to harm the surrounding neurons [142].

Specifically, the microglia appears to be having a double role, that of neurotoxic and neuroprotective effects. Activated microglia may exert a cytotoxic effect by releasing proteinases, cytokines (e.g. IL-1), reactive oxygen intermediates, and reactive nitrogen intermediates [143]. Activated microglia also served as phagocytes and is capable of destroying invading microorganisms, and removing potentially deleterious debris [144]. In up-regulating the expression of major histocompatibility complex class I and II antigens, and complement receptor, these non-neuronal cells have also been proposed to play the roles of inflammatory, antigen presenting, and immunoregulatory cells. Taken together, it appears that microglial cells play an important role in the area of neuroimmunology [145].

Astrocytes typically serve to maintain and support the normal function of the CNS. Like microglia, activated astrocytes have both beneficial and detrimental effects on the surrounding cells. It might participate in the healing process by actively monitoring and controlling the molecular and ionic contents of the extracellular space [146]. On the other hand, it would at times inhibit the regeneration response of the neurons [147]. The functional roles of astrocytes are further complicated by the latest literature that suggests that these cells may play a role in neurogenesis [148] and synaptogenesis [149].

Exercise has long been known to affect the immune system [150] and regulate the levels of endogenous cytokines [151,24]. Since cytokine is one of the key activating factors for microglia [142], it can therefore be argued that exercise may have an effect on microglia, although the latter produces cytokines on its own. While there was report that indicated that voluntary running could increase the number of 5-bromo -2'-deoxyuridine (BrdU) labeled microglial cells in several cortical regions [24], the opposite was found to be the case for these microglial cells in the horizontal diagonal band of Broca (HDB) after forced exercise [109]. Both reactive astrocytes and exercise are known to affect the level of endogenous cytokines [152]. Further, it was suggested that voluntary running could increase the number of BrdU labeled astrocytes in the hippocampus [153] while forced exercise resulted in reduced number of astrocytes in the HDB [109].

Cholinergic Neuronal System

The characterization and distribution of these cholinergic neurons in the basal forebrain have previously been studied and reviewed [154]. Importantly, these neurons are nourished by retrogradely transported NGF from the hippocampus [155]. It was also reported that NGF could reverse some of the experimentally induced cholinergic neurodegenerations in primate brains. [156]. The link between NGF, cholinergic neurons and spatial memory was further consolidated when aged rats with impairments in learning and memory, showed improvement after treatment using exogenous NGF [158-160]. In another study, it was reported that NGF from *ex vivo* transduced immortalized neural progenitor cells to the septum can prevent the development of age-associated neuronal atrophy and behavioral impairments in rats [161]. Taken together, there is now extensive evidence to support the view that the cholinergic neuronal system is intricately linked to learning and memory [162]. Cholinergic neurons are also implicated in Alzheimer-type dementia in man [157]. Indeed, impairments in spatial memory are closely correlated to decline in forebrain cholinergic neurotransmission [163].

Interestingly, it was reported that running could induce hippocampal release of acetylcholine in rats [164]. Furthermore, daily treadmill running could improve hippocampal protein kinase C activity, thereby enhancing spatial learning performance in mice [165]. We have also shown that forced exercise could increase the number of cholinergic neurons in the HDB [16]. Therefore, these results suggest a positive relationship between cholinergic function and physical training.

DISCUSSION AND PERSPECTIVE

NGF and BDNF

It is now reasonably clear that exercise, whether voluntary or forced is capable of altering the level of endogenous neurotrophins and their receptor mRNA in the brain [6,7,166,16]. Further, the uses of exogenous NGF and BDNF to help reverse various pathologies in different animal models have also been systemically explored [42,43,156,167] thus highlighting the possibility that NGF and BDNF may one day, be of therapeutic use in the clinics. However, more studies on mechanisms, doses, time of application, and toxi-

cology should be conducted before such a conclusion can be drawn. It seems that exercise has some advantages to exogenous supply of neurotrophins, as exercise, in addition to elevating specific NT, it has an action on the pharmacology that is intrinsic to the system. This implies that exercise may have an action on signaling mechanisms associated with the action of neurotrophins or other molecular systems. Indeed, it has been reported that exercise could improve neurogenesis, synaptogenesis, cognition, and functional recovery after CNS injury [3,4,168]. By performing blocking studies, there is evidence that exercise uses specific neurotrophins to affect select brain functions such as cognitive abilities [169].

In a pathological scenario like stroke, we have been able to demonstrate that exercise induced NGF and its p75 ^{NTR} was capable of reducing the infarct size in the middle cerebral artery occlusion rodent model [16]. This implied that exercise alone could mimic the effects of an exogenous source in providing neuroprotection [52,170,171]. This has immediate significance since recombinant neurotrophins often could not cross the BBB [172] without artificial conjugation.

Since forced exercise could in fact alter the number of cholinergic neurons in the HDB [16], we propose that this may be how exercise could indirectly enhance cognitive and memory functions by ameliorating cholinergic neuron atrophy *via* support from neurotrophins [173].

Cytokines and Glial Cells

It is now known that an over-expression of pro-inflammatory cytokines in the brain results in the pathogenesis of neuro-toxic and neurodegenerative disorders [104] and therefore impact the normal functioning brain [174]. In particular, IL-1β bears a deleterious consequence on cognitive processes [175]. In that context, if exercise could reduce the levels of these cytokines in the brain, this would reduce the likelihood of neuro-toxication or neuro-degeneration. We have shown that by up-regulating NGF/p75 ^{NTR}, the levels of endogenous cytokines are reduced, and we believed that this might be how exercise could indirectly improve learning and memory. However, the roles of the cytokines in relation to the inflammatory process are complex and should not be considered in isolation, but instead regarded as part of a network of interacting mediators.

To date, the effects of exercise on glial cell such as microglia and astrocytes are still controversial. We have shown that their activities and numbers are reduced after exercise [109] while others have reported otherwise. There is no simple explanation for this observation and hence need further research. However, at this juncture, we would like to suggest that exercise induced up-regulation of NGF, and the concomitant suppression of endogenous pro-inflammatory cytokines such as TNF-α and IL-1β could be the reason for the reduction of glial cell activities and numbers.

Exercise, Learning and Memory

Studies in humans [176,177] and in rodents [4,18] have demonstrated the beneficial effects of exercise on cognitive function. These studies have shown that exercise has the capacity to enhance learning and memory [4,177,178] under a variety of conditions, from counteracting the mental decline associated with aging [176] to facilitating functional recovery in patients suffering from brain injury or disease [179,180]. An analysis of 18 longitudinal fitness-training studies revealed that cardiovascular fitness training improves overall cognitive function regardless of task type [181]. The finding that voluntary exercise increases BDNF levels in the hippocampus, an area vital for learning and memory formation, has provided insight about the molecular mechanisms responsible for the effects of exercise on cognition [7,76,182]. Blocking BDNF action using specific immuno adhesive chimeres abolished the ability of exercise to augment learning and memory in the rat [169], in conjunction with abolishing the capacity of exercise to elevate BDNF-mediated synaptic plasticity.

Recently we have shown that forced running like voluntary running, could also significantly improve spatial learning and memory [173]. Evidently, superior escape latencies, more time spent in the correct zone, and reduced swim distance by the runners over the nonrunners confirmed this hypothesis. However, this improvement is inconsistent with data shown by another group exercising aged F-344 rats over a 10 weeks period [183]. Apart from the length of training, such differing outcome might be accounted for by strains differences and age of the animals used since these are all known to affect the results [184]. In addition, the different behavioral tests administered to the rats could also play a role. The circular platform spatial memory task used in the Barnes *et al*. study [183] is technically different from the MWM test employed in this study.

It should be appreciated that the forced exercise paradigm is stressful to the animals [185]. While acute stress has been reported to enhance the memory of events that are potentially threatening to the animals. Chronic stress, on the other hand, results in adaptive plasticity in the brain, in which local neurotransmitters as well as systemic hormones interact to produce structural as well as functional changes [186]. This includes the suppression of ongoing neurogenesis in the dentate gyrus [186-188]. There is a recent report suggesting that spatial learning functions independently of neurogenesis [189].

It is widely known that emotionally arousing experiences (stress) often facilitate the formation of memory readily. Such observations could be attributed to the release of adrenal stress hormones, epinephrine and cortisol (corticosterone in the rat), as a result of emotional arousal [188,190]. The elevated stress hormones associated with forced running could be the underlying reason why there is an increase in memory and learning abilities. It would therefore be important to study hormonal changes in the circulatory system. Accordingly, psychosocial stress level can be determined by screening the saliva for cortisol or alpha-amylase [191].

While voluntary exercise is known to benefit spatial learning and memory, the effects of forced exercise are still highly controversial. It is therefore necessary to conduct further research into the molecular and cellular-mechanisms of how exercise may indeed influence the CNS and its circuitry. While it was shown that exercise could promote LTP [4] and this could be due to the result of increased endogenous neurotrophic factors. The previous use of exogenous neurotrophic factors to help improve spatial reference and recent memory [158,160] lends weight to this possibility. More significantly, LTP has been reported to induce dendritic spine formation [192]. Further, it appears that the reduced production of pro-inflammatory cytokines such as TNF-α and IL-1β by the glial cells in the HDB of the septum could also somewhat contribute to the improved spatial memory and learning in the runners. TNF-α and IL-1β are known to inhibit LTP [193,194]. Collectively taken, there are strong reasons to believe that exercise may indeed help to improve spatial learning and memory probably *via* endogenous neurotrophic factors and some cytokines.

Having stated that exercise may help learning and memory, one should also be aware of the pitfall of overexerting as it is well known that overtraining can also lead to symptoms such as fatigue and mood disturbances [195,196]. Moreover, runners deprived of running experienced withdrawal symptoms such as depression and anxiety [197,198].

Future Work with Animal Models

With the availability of suitable animal models for the various neurological conditions (Alzheimer's and Parkinson's disease), it

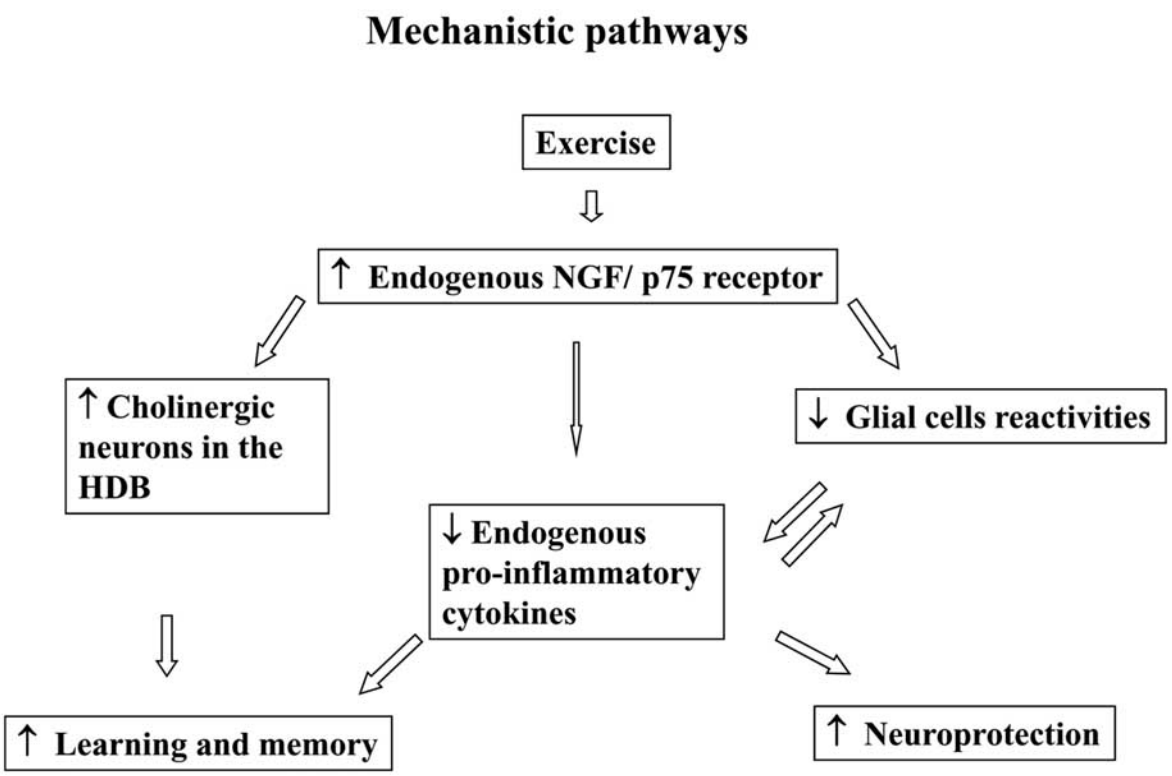

Fig. (1). Mechanistic path on how forced exercise, cholinergic neurons, glial cells, endogenous NGF/ p75 ^{NTR} and cytokines could interplay to help enhance the process of learning/ memory and neuroprotection in rats.

would be interesting to see if the key players listed in this review would be affected by exercise. More importantly, understanding how these biomarkers interplay in these animal models will certainly bring us one step closer to preventing the loss of valuable cognitive abilities associated with these diseases.

CONCLUDING REMARKS

In summary, the effects of voluntary exercises are clearly beneficial to the brain in normal and pathological conditions. This was the direct consequence of the interplay by elevated endogenous NGF and its p75 ^{NTR}, in an altered microenvironment that was not conducive for glial associated pro-inflammatory cytokines to act. Further, the increase in proliferation and numbers of the cholinergic neurons in the HDB may have contributed to the observed improvement in spatial memory (see Fig. **1**). However, the readers should be aware that the benefits arising from exercise extend beyond what is accounted for in this review.

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LIST OF ABBREVIATIONS

BBB	=	Blood brain barrier
BDNF	=	Brain derived neurotrophic factor
BrdU	=	5-Bromo -2'-deoxyuridine
cDNA	=	Cloned copies of otherwise fragile mRNA
CNS	=	Central nervous system
HDB	=	Horizontal diagonal band of Broca
IFN-γ	=	Interferon gamma
IL	=	Interleukin
IL-1β	=	Interleukin–1 beta
IL-6	=	Interleukin–6
kDa	=	Kilodalton
LTP	=	Long term potentiation
MWM	=	Morris water maze
NGF	=	Nerve growth factor
NK	=	Natural killer
NT	=	Neurotrophins
RT-PCR	=	Reverse transcription polymerase chain reaction
TNF-α	=	Tumor necrosis factor- alpha

REFERENCES

[1] Cummins, R. A.; Walsh, R. N.; Budtz-Olsen, O. E.; Konstantinos, T.; Horsfall, C. R. *Nature,* **1973**, *243*, 516.
[2] Pham, T. M.; Ickes, B.; Albeck, D.; Soderstrom, S.; Granholm, A. C.; Mohammed, A. H. *Neuroscience,* **1999**, *94*, 279.
[3] Pham, T. M.; Soderstrom, S.; Winblad, B.; Mohammed, A. H. *Behav. Brain Res.,* **1999**, *103*, 63.
[4] van Praag, H.; Christie, B. R.; Sejnowski, T. J.; Gage, F. H. *Proc. Natl. Acad. Sci. USA,* **1999**, *96*, 13427.
[5] van Praag, H.; Kempermann, G.; Gage, F. H. *Nat. Neurosci.,* **1999**, *2*, 266.
[6] Neeper, S. A.; Gomez-Pinilla, F.; Choi, J.; Cotman, C. *Nature,* **1995**, *373*, 109.
[7] Neeper, S. A.; Gomez-Pinilla, F.; Choi, J.; Cotman, C. W. *Brain Res.,* **1996**, *726*, 49.
[8] Johansson, B. B.; Ohlsson, A. L. *Exp. Neurol.,* **1996**, *139*, 322-7.
[9] Stummer, W.; Weber, K.; Tranmer, B.; Baethmann, A.; Kempski, O. *Stroke,* **1994**, *25*, 1862.
[10] Smith, A. D.; Zigmond, M. J. *Exp. Neurol.,* **2003**, *184*, 31-9.

[11] Draganski, B.; Gaser, C.; Busch, V.; Schuierer, G.; Bogdahn, U.; May, A. *Nature,* **2004**, *427*, 311.
[12] Peluso, M. A.; Guerra de Andrade, L. H. *Clinics,* **2005**, *60*, 61.
[13] Samorajski, T.; Delaney, C.; Durham, L.; Ordy, J. M.; Johnson, J. A.; Dunlap, W. P. *Neurobiol. Aging,* **1985**, *6*, 17.
[14] Anderson, B. J.; Rapp, D. N.; Baek, D. H.; McCloskey, D. P.; Coburn-Litvak, P. S.; Robinson, J. K. *Physiol. Behav.,* **2000**, *70*, 425.
[15] Narath, E.; Skalicky, M.; Viidik, A. *Exp. Gerontol.,* **2001**, *36*, 1699.
[16] Ang, E. T.; Wong, P. T.; Moochhala, S.; Ng, Y. K. *Neuroscience,* **2003**, *118*, 335.
[17] Fordyce, D. E.; Farrar, R. P. *Brain Res.,* **1991**, *541*, 57.
[18] Fordyce, D. E.; Farrar, R. P. *Behav. Brain Res.,* **1991**, *46*, 123.
[19] Dishman, R. K.; Berthoud, H. R.; Booth, F. W.; Cotman, C. W.; Edgerton, V. R.; Fleshner, M. R.; Gandevia, S. C.; Gomez-Pinilla, F.; Greenwood, B. N.; Hillman, C. H.; Kramer, A. F.; Levin, B. E.; Moran, T. H.; Russo-Neustadt, A. A.; Salamone, J. D.; Van Hoomissen, J. D.; Wade, C. E.; York, D. A.; Zigmond, M. J. *Obesity [Silver Spring],* **2006**, *14*, 345.
[20] Shen, H.; Tong, L.; Balazs, R.; Cotman, C. W. *Neuroscience,* **2001**, *107*, 219.
[21] Radak, Z.; Kaneko, T.; Tahara, S.; Nakamoto, H.; Pucsok, J.; Sasvari, M.; Nyakas, C.; Goto, S. *Neurochem. Int.,* **2001**, *38*, 17.
[22] Berchtold, N. C.; Chinn, G.; Chou, M.; Kesslak, J. P.; Cotman, C. W. *Neuroscience,* **2005**, *133*, 853.
[23] Colbert, L. H.; Davis, J. M.; Essig, D. A.; Ghaffar, A.; Mayer, E. P. *Int. J. Sports Med.,* **2001**, *22*, 261.
[24] Ehninger, D.; Kempermann, G. *Cereb. Cortex,* **2003**, *13*, 845.
[25] O'Callaghan, R. M.; Ohle, R.; Kelly, A. M. *Behav. Brain Res*., **2007**, *176*, 362.
[26] Ding, Y. H.; Mrizek, M.; Lai, Q.; Wu, Y.; Reyes, R., Jr.; Li, J.; Davis, W. W.; Ding, Y. *Curr. Neurovasc. Res.,* **2006**, *3*, 263.
[27] Nybo, L.; Nielsen, B.; Pedersen, B. K.; Moller, K.; Secher, N. H. *J. Physiol*., **2002**, *542*, 991.
[28] Winter, B.; Breitenstein, C.; Mooren, F. C.; Voelker, K.; Fobker, M.; Lechtermann, A.; Krueger, K.; Fromme, A.; Korsukewitz, C.; Floel, A.; Knecht, S. *Neurobiol. Learn Mem.,* **2007**, *87*, 597.
[29] Jolitha, A. B.; Subramanyam, M. V.; Asha Devi, S. *Exp. Gerontol.,* **2006**, *41*, 753.
[30] Ullrich, A.; Gray, A.; Berman, C.; Dull, T. J. *Nature,* **1983**, *303*, 821.
[31] Lewin, G. R.; Barde, Y. A. *Annu. Rev. Neurosci.,* **1996**, *19*, 289.
[32] Leibrock, J.; Lottspeich, F.; Hohn, A.; Hofer, M.; Hengerer, B.; Masiakowski, P.; Thoenen, H.; Barde, Y. A. *Nature,* **1989**, *341*, 149.
[33] Alderson, R. F.; Alterman, A. L.; Barde, Y. A.; Lindsay, R. M. *Neuron,* **1990**, *5*, 297.
[34] Nonomura, T.; Hatanaka, H. *Neurosci. Res*., **1992**, *14*, 226.
[35] Sauer, H.; Fischer, W.; Nikkhah, G.; Wiegand, S. J.; Brundin, P.; Lindsay, R. M.; Bjorklund, A. *Brain Res.,* **1993**, *626*, 37.
[36] Bramham, C. R.; Messaoudi, E. *Prog. Neurobiol.,* **2005**, *76*, 99.
[37] Korsching, S. *J. Neurosci.,* **1993**, *13*, 2739.
[38] Kromer, L. F. *Science,* **1987**, *235*, 214.
[39] Otten, U.; Ehrhard, P.; Peck, R. *Proc. Natl. Acad. Sci. USA,* **1989**, *86*, 10059.
[40] Cheng, B.; Mattson, M. P. *Neuron,* **1991**, *7*, 1031.
[41] Cheng, B.; Mattson, M. P. *Exp. Neurol.,* **1992**, *117*, 114.
[42] Fischer, W.; Bjorklund, A.; Chen, K.; Gage, F. H. *J. Neurosci.,* **1991**, *11*, 1889.
[43] Fischer, W. *Neurochem. Int.,* **1994**, *25*, 47.
[44] Fischer, W.; Sirevaag, A.; Wiegand, S. J.; Lindsay, R. M.; Bjorklund, A. *Proc. Natl. Acad. Sci. USA,* **1994**, *91*, 8607.
[45] Pelleymounter, M. A.; Cullen, M. J.; Baker, M. B.; Gollub, M.; Wellman, C. *Mol. Chem. Neuropathol.,* **1996**, *29*, 211.
[46] Nistico, G.; Ciriolo, M. R.; Fiskin, K.; Iannone, M.; De Martino, A.; Rotilio, G. *Free Radic. Biol. Med.,* **1992**, *12*, 177.
[47] Backman, C.; Rose, G. M.; Hoffer, B. J.; Henry, M. A.; Bartus, R. T.; Friden, P.; Granholm, A. C. *J. Neurosci.,* **1996**, *16*, 5437.
[48] Conner, J. M.; Hoener, M. C.; Varon, S. *Neuroscience,* **1998**, *83*, 1003.
[49] Hicks, R. R.; Martin, V. B.; Zhang, L.; Seroogy, K. B. *Exp. Neurol.,* **1999**, *160*, 469.
[50] Lee, T. H.; Kato, H.; Chen, S. T.; Kogure, K.; Itoyama, Y. *Stroke,* **1998**, *29*, 1687-96; discussion 1697.
[51] Scott, S. A.; Crutcher, K. A. *Rev. Neurosci.,* **1994**, *5*, 179.
[52] Schabitz, W. R.; Schwab, S.; Spranger, M.; Hacke, W. *J. Cereb. Blood Flow Metab.,* **1997**, *17*, 500.
[53] Neumann, H.; Misgeld, T.; Matsumuro, K.; Wekerle, H. *Proc. Natl. Acad. Sci. USA*, **1998**, *95*, 5779.
[54] Wei, R.; Jonakait, G. M. *J. Neuroimmunol.,* **1999**, *95*, 8.
[55] Barde, Y. A. *Prog. Clin. Biol. Res.,* **1994**, *390*, 45.
[56] Poo, M. M. *Nat. Rev. Neurosci*., **2001**, *2*, 24.
[57] Snider, W. D.; Wright, D. E. *Neuron,* **1996**, *16*, 229.
[58] McAllister, A. K.; Katz, L. C.; Lo, D. C. *Annu. Rev. Neurosci.,* **1999**, *22*, 295.
[59] Prakash, N.; Cohen-Cory, S.; Frostig, R. D. *Nature,* **1996**, *381*, 702.
[60] Lom, B.; Cohen-Cory, S. *J. Neurosci.,* **1999**, *19*, 9928.
[61] McAllister, A. K.; Katz, L. C.; Lo, D. C. *Neuron,* **1996**, *17*, 1057.
[62] Shimada, A.; Mason, C. A.; Morrison, M. E. *J. Neurosci.,* **1998**, *18*, 8559.
[63] Yacoubian, T. A.; Lo, D. C. *Nat. Neurosci.,* **2000**, *3*, 342.
[64] Boulanger, L.; Poo, M. M. *Nat. Neurosci.,* **1999**, *2*, 346.
[65] Kafitz, K. W.; Rose, C. R.; Thoenen, H.; Konnerth, A. *Nature,* **1999**, *401*, 918.
[66] Kang, H.; Schuman, E. M. *Science,* **1996**, *273*, 1402.
[67] Lohof, A. M.; Ip, N. Y.; Poo, M. M. *Nature,* **1993**, *363*, 350.
[68] Rutherford, L. C.; Nelson, S. B.; Turrigiano, G. G. *Neuron,* **1998**, *21*, 521.
[69] Seil, F. J.; Drake-Baumann, R. *J. Neurosci*., **2000**, *20*, 5367.
[70] Vicario-Abejon, C.; Collin, C.; McKay, R. D.; Segal, M. *J. Neurosci*., **1998**, *18*, 7256.
[71] Ernfors, P.; Bengzon, J.; Kokaia, Z.; Persson, H.; Lindvall, O. *Neuron,* **1991**, *7*, 165.
[72] Zafra, F.; Hengerer, B.; Leibrock, J.; Thoenen, H.; Lindholm, D. *EMBO J.,* **1990**, *9*, 3545.
[73] Gall, C. M.; Isackson, P. J. *Science,* **1989**, *245*, 758.
[74] Castren, E.; Zafra, F.; Thoenen, H.; Lindholm, D. *Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 9444.
[75] Rocamora, N.; Welker, E.; Pascual, M.; Soriano, E. *J. Neurosci.,* **1996**, *16*, 4411.
[76] Vaynman, S.; Ying, Z.; Gomez-Pinilla, F. *Neuroscience,* **2003**, *122*, 647.
[77] Kesslak, J. P.; So, V.; Choi, J.; Cotman, C. W.; Gomez-Pinilla, F. *Behav. Neurosci.,* **1998**, *112*, 1012.
[78] Bova, R.; Micheli, M. R.; Qualadrucci, P.; Zucconi, G. G. *Brain Res. Mol. Brain Res.,* **1998**, *57*, 321.
[79] Liang, F. Q.; Walline, R.; Earnest, D. J. *Neurosci. Lett.,* **1998**, *242*, 89.
[80] Mowla, S. J.; Pareek, S.; Farhadi, H. F.; Petrecca, K.; Fawcett, J. P.; Seidah, N. G.; Morris, S. J.; Sossin, W. S.; Murphy, R. A. *J. Neurosci.,* **1999**, *19*, 2069.
[81] Farhadi, H. F.; Mowla, S. J.; Petrecca, K.; Morris, S. J.; Seidah, N. G.; Murphy, R. A. *J. Neurosci* ., **2000**, *20*, 4059.
[82] Haubensak, W.; Narz, F.; Heumann, R.; Lessmann, V. *J. Cell Sci.,* **1998**, *111*(Pt 11), 1483.
[83] Kojima, M.; Takei, N.; Numakawa, T.; Ishikawa, Y.; Suzuki, S.; Matsumoto, T.; Katoh-Semba, R.; Nawa, H.; Hatanaka, H. *J. Neurosci. Res.,* **2001**, *64*, 1.
[84] Hartmann, M.; Heumann, R.; Lessmann, V. *EMBO J.,* **2001**, *20*, 5887.
[85] Chen, W. G.; Chang, Q.; Lin, Y.; Meissner, A.; West, A. E.; Griffith, E. C.; Jaenisch, R.; Greenberg, M. E. *Science,* **2003**, *302*, 885.
[86] Lu, B.; Chow, A. *J. Neurosci. Res.,* **1999**, *58*, 76.
[87] Schinder, A. F.; Berninger, B.; Poo, M. *Neuron,* **2000**, *25*, 151.
[88] Diesfeldt, H. F.; Diesfeldt-Groenendijk, H. *Age. Ageing,* **1977**, *6*, 58.
[89] Emery, C. F.; Huppert, F. A.; Schein, R. L. *Gerontologist,* **1995**, *35*, 378.
[90] Young, R. J. *Br. J. Sports Med.,* **1979**, *13*, 110.
[91] Blomquist, K. B.; Danner, F. *Percept. Mot. Skills,* **1987**, *65*, 175.
[92] Vaynman, S.; Gomez-Pinilla, F. *Neurorehabil. Neural. Repair.,* **2005**, *19*, 283.
[93] Vaynman, S. S.; Ying, Z.; Yin, D.; Gomez-Pinilla, F. *Brain Res.,* **2006**, *1070*, 124.
[94] Ebendal, T. *J. Neurosci. Res.,* **1992**, *32*, 461.
[95] Verdi, J. M.; Birren, S. J.; Ibanez, C. F.; Persson, H.; Kaplan, D. R.; Benedetti, M.; Chao, M. V.; Anderson, D. J. *Neuron,* **1994**, *12*, 733.
[96] Mufson, E. J.; Ginsberg, S. D.; Ikonomovic, M. D.; DeKosky, S. T. *J. Chem. Neuroanat.,* **2003**, *26*, 233.
[97] Troy, C. M.; Friedman, J. E.; Friedman, W. J. *J. Biol. Chem.,* **2002**, *277*, 34295.
[98] Friedman, W. J.; Greene, L. A. *Exp. Cell Res.,* **1999**, *253*, 131.
[99] DeFreitas, M. F.; McQuillen, P. S.; Shatz, C. J. *J. Neurosci.,* **2001**, *21*, 5121.
[100] Gentry, J. J.; Casaccia-Bonnefil, P.; Carter, B. D. *J. Biol. Chem.,* **2000**, *275*, 7558.
[101] Hamanoue, M.; Middleton, G.; Wyatt, S.; Jaffray, E.; Hay, R. T.; Davies, A. M. *Mol. Cell Neurosci.,* **1999**, *14*, 28.
[102] Roux, P. P.; Barker, P. A. *Prog. Neurobiol.,* **2002**, *67*, 203.
[103] Dechant, G.; Barde, Y. A. *Nat. Neurosci.,* **2002**, *5*, 1131.
[104] Szelenyi, J. *Brain Res. Bull.,* **2001**, *54*, 329.
[105] Trajkovic, V.; Vuckovic, O.; Stosic-Grujicic, S.; Miljkovic, D.; Popadic, D.; Markovic, M.; Bumbasirevic, V.; Backovic, A.; Cvetkovic, I.; Harhaji, L.; Ramic, Z.; Mostarica Stojkovic, M. *Glia,* **2004**, *47*, 168.
[106] Pantoni, L.; Sarti, C.; Inzitari, D. *Arterioscler. Thromb. Vasc. Biol.,* **1998**, *18*, 503.
[107] Pedersen, B. K.; Steensberg, A.; Fischer, C.; Keller, C.; Ostrowski, K.; Schjerling, P. *Exerc. Immunol. Rev.,* **2001**, *7*, 18.
[108] Suzuki, K.; Nakaji, S.; Yamada, M.; Totsuka, M.; Sato, K.; Sugawara, K. *Exerc. Immunol. Rev*., **2002**, *8*, 6.
[109] Ang, E. T.; Wong, P. T.; Moochhala, S.; Ng, Y. K. *Neuroscience,* **2004**, *129*, 337.
[110] Buttini, M.; Sauter, A.; Boddeke, H. W. *Brain Res. Mol. Brain Res.,* **1994**, *23*, 126.
[111] Liu, T.; McDonnell, P. C.; Young, P. R.; White, R. F.; Siren, A. L.; Hallenbeck, J. M.; Barone, F. C.; Feurestein, G. Z. *Stroke,* **1993**, *24*, 1746-50; discussion 1750.
[112] Loddick, S. A.; Rothwell, N. J. *J. Cereb. Blood Flow Metab.,* **1996**, *16*, 932.
[113] Relton, J. K.; Martin, D.; Thompson, R. C.; Russell, D. A. *Exp. Neurol*., **1996**, *138*, 206.
[114] Yamasaki, Y.; Matsuura, N.; Shozuhara, H.; Onodera, H.; Itoyama, Y.; Kogure, K. *Stroke,* **1995**, *26*, 676-80; discussion 681.
[115] Allan, S. M.; Parker, L. C.; Collins, B.; Davies, R.; Luheshi, G. N.; Rothwell, N. J. *Proc. Natl. Acad. Sci. USA,* **2000**, *97*, 5580.
[116] Patel, H. C.; Boutin, H.; Allan, S. M. *Ann. NY Acad. Sci.,* **2003**, *992*, 39-47.

[117] Akira, S.; Taga, T.; Kishimoto, T. *Adv. Immunol*., **1993**, *54*, 1.
[118] Hirano, T. *Chem. Immunol*., **1992**, *51*, 153.
[119] Tilg, H.; Trehu, E.; Atkins, M. B.; Dinarello, C. A.; Mier, J. W. *Blood,* **1994**, *83*, 113.
[120] Pedersen, B. K.; Steensberg, A.; Schjerling, P. *Curr. Opin. Hematol.,* **2001**, *8*, 137.
[121] Chung, I. Y.; Benveniste, E. N. *J. Immunol.,* **1990**, *144*, 2999.
[122] Ganter, S.; Northoff, H.; Mannel, D.; Gebicke-Harter, P. J. *J. Neurosci. Res.,* **1992**, *33*, 218.
[123] Smith, C. A.; Farrah, T.; Goodwin, R. G. *Cell,* **1994**, *76*, 959.
[124] Kolesnick, R.; Golde, D. W. *Cell,* **1994**, *77*, 325.
[125] Heller, R. A.; Kronke, M. *J. Cell Biol.,* **1994**, *126*, 5.
[126] Barone, F. C.; Arvin, B.; White, R. F.; Miller, A.; Webb, C. L.; Willette, R. N.; Lysko, P. G.; Feuerstein, G. Z. *Stroke,* **1997**, *28*, 1233.
[127] Feuerstein, G. Z.; Liu, T.; Barone, F. C. *Cerebrovasc. Brain Metab. Rev.,* **1994**, *6*, 341.
[128] Nawashiro, H.; Martin, D.; Hallenbeck, J. M. *J. Cereb. Blood Flow Metab.,* **1997**, *17*, 229.
[129] Ijzermans, J. N.; Marquet, R. L. *Immunobiology,* **1989**, *179*, 456.
[130] Pachter, J. S.; de Vries, H. E.; Fabry, Z. *J. Neuropathol. Exp. Neurol.,* **2003**, *62*, 593.
[131] Owens, T.; Babcock, A. *Front. Biosci.,* **2002**, *7*, d427.
[132] Sredni-Kenigsbuch, D. *Int. J. Neurosci*.,**2002**, *112*, 665.
[133] LaFerla, F. M.; Sugarman, M. C.; Lane, T. E.; Leissring, M. A. *J. Mol. Neurosci.,* **2000**, *15*, 45.
[134] Farrar, M. A.; Schreiber, R. D. *Annu. Rev. Immunol.,* **1993**, *11*, 571.
[135] Popko, B.; Corbin, J. G.; Baerwald, K. D.; Dupree, J.; Garcia, A. M. *Mol. Neurobiol.,* **1997**, *14*, 19.
[136] Wei, Y. P.; Kita, M.; Shinmura, K.; Yan, X. Q.; Fukuyama, R.; Fushiki, S.; Imanishi, J. *J. Interferon Cytokine Res.,* **2000**, *20*, 403.
[137] Rose, D. M.; Winston, B. W.; Chan, E. D.; Riches, D. W.; Henson, P. M. *Biochem. Biophys. Res. Commun.,* **1997**, *238*, 256.
[138] Eddleston, M.; Mucke, L. *Neuroscience,* **1993**, *54*, 15.
[139] Giulian, D. *J. Neurosci. Res.,* **1987**, *18*, 155-71, 132.
[140] Aloisi, F. *Glia,* **2001**, *36*, 165.
[141] Dong, Y.; Benveniste, E. N. *Glia,* **2001**, *36*, 180.
[142] Hanisch, U. K. *Glia,* **2002**, *40*, 140.
[143] Banati, R. B.; Gehrmann, J.; Schubert, P.; Kreutzberg, G. W. *Glia,* **1993**, *7*, 111.
[144] Streit, W. J.; Graeber, M. B.; Kreutzberg, G. W. *Glia,* **1988**, *1*, 301.
[145] Ling, E. A.; Ng, Y. K.; Wu, C. H.; Kaur, C. *Prog. Brain Res.,* **2001**, *132*, 61.
[146] Eng, L. F.; Yu, A. C.; Lee, Y. L. *Prog. Brain Res*., **1992**, *94*, 353.
[147] Eng, L. F.; Reier, P. J.; Houle, J. D. *Prog. Brain Res.,* **1987**, *71*, 439.
[148] Horner, P. J.; Palmer, T. D. *Trends Neurosci.,* **2003**, *26*, 597.
[149] Slezak, M.; Pfrieger, F. W. *Trends Neurosci.,* **2003**, *26*, 531.
[150] Pedersen, B. K.; Toft, A. D. *Br. J. Sports Med.,* **2000**, *34*, 246.
[151] Gleeson, M. *J. Physiol.,* **2000**, *529*(Pt 1), 1.
[152] Pedersen, B. K. *Immunol. Cell Biol.,* **2000**, *78*, 532.
[153] Steiner, B.; Kronenberg, G.; Jessberger, S.; Brandt, M. D.; Reuter, K.; Kempermann, G. *Glia,* **2004**, *46*, 41.
[154] Mesulam, M. M.; Mufson, E. J.; Wainer, B. H.; Levey, A. I. *Neuroscience,* **1983**, *10*, 1185.
[155] Korsching, S.; Auburger, G.; Heumann, R.; Scott, J.; Thoenen, H. *EMBO J*., **1985**, *4*, 1389.
[156] Tuszynski, M. H.; U, H. S.; Amaral, D. G.; Gage, F. H. *J. Neurosci.,* **1990**, *10*, 3604.
[157] Fischer, W.; Wictorin, K.; Bjorklund, A.; Williams, L. R.; Varon, S.; Gage, F. H. *Nature,* **1987**, *329*, 65.
[158] Frick, K. M.; Price, D. L.; Koliatsos, V. E.; Markowska, A. L. *J. Neurosci.,* **1997**, *17*, 2543.
[159] Hellweg, R.; Fischer, W.; Hock, C.; Gage, F. H.; Bjorklund, A.; Thoenen, H. *Brain Res.,* **1990**, *537*, 123.
[160] Markowska, A. L.; Price, D.; Koliatsos, V. E. *J. Neurosci.,* **1996**, *16*, 3541.
[161] Martinez-Serrano, A.; Bjorklund, A. *Proc. Natl. Acad. Sci. USA*, **1998**, *95*, 1858.
[162] Gold, P. E. *Neurobiol. Learn Mem*., **2003**, *80*, 194.
[163] Mandel, R. J.; Chen, A. D.; Connor, D. J.; Thal, L. J. *J. Pharmacol. Exp. Ther*., **1989**, *251*, 612.
[164] Dudar, J. D.; Whishaw, I. Q.; Szerb, J. C. *Neuropharmacology,* **1979**, *18*, 673.
[165] Fordyce, D. E.; Wehner, J. M. *Brain Res.,* **1993**, *619*, 111.
[166] Tong, L.; Shen, H.; Perreau, V. M.; Balazs, R.; Cotman, C. W. *Neurobiol. Dis.,* **2001**, *8*, 1046.
[167] Sinson, G.; Voddi, M.; McIntosh, T. K. *J. Neurochem.,* **1995**, *65*, 2209.
[168] Chen, Y. C.; Lei, J. L.; Chen, Q. S.; Wang, S. L. *Mech. Ageing Dev.,* **1998**, *102*, 81.
[169] Vaynman, S.; Ying, Z.; Gomez-Pinilla, F. *Eur. J. Neurosci.,* **2004**, *20*, 2580.
[170] Schabitz, W. R.; Sommer, C.; Zoder, W.; Kiessling, M.; Schwaninger, M.; Schwab, S. *Stroke,* **2000**, *31*, 2212.
[171] Yamashita, K.; Wiessner, C.; Lindholm, D.; Thoenen, H.; Hossmann, K. A. *Metab. Brain Dis*., **1997**, *12*, 271.
[172] Poduslo, J. F.; Curran, G. L. *Brain Res. Mol. Brain Res*., **1996**, *36*, 280.
[173] Ang, E. T.; Dawe, G. S.; Wong, P. T.; Moochhala, S.; Ng, Y. K. *Brain Res*., **2006**, *1113*, 186.
[174] Shytle, R. D.; Mori, T.; Townsend, K.; Vendrame, M.; Sun, N.; Zeng, J.; Ehrhart, J.; Silver, A. A.; Sanberg, P. R.; Tan, J. *J. Neurochem*., **2004**, *89*, 337.
[175] Palin, K.; Bluthe, R. M.; Verrier, D.; Tridon, V.; Dantzer, R.; Lestage, J. *Brain Behav. Immun.,* **2004**, *18*, 223.
[176] Kramer, A. F.; Hahn, S.; Cohen, N. J.; Banich, M. T.; McAuley, E.; Harrison, C. R.; Chason, J.; Vakil, E.; Bardell, L.; Boileau, R. A.; Colcombe, A. *Nature,* **1999**, *400*, 418.
[177] Suominen-Troyer, S.; Davis, K. J.; Ismail, A. H.; Salvendy, G. *Percept. Mot. Skills*., **1986**, *62*, 71.
[178] Rogers, R. L.; Meyer, J. S.; Mortel, K. F. *J. Am. Geriatr. Soc.,* **1990**, *38*, 123.
[179] Bohannon, R. W. *Curr. Opin. Neurol*., **1993**, *6*, 765.
[180] Grealy, M. A.; Johnson, D. A.; Rushton, S. K. *Arch. Phys. Med. Rehabil.,* **1999**, *80*, 661.
[181] Colcombe, S.; Kramer, A. F. *Psychol. Sci.,* **2003**, *14*, 125.
[182] Gomez-Pinilla, F.; Ying, Z.; Roy, R. R.; Molteni, R.; Edgerton, V. R. *J. Neurophysiol.,* **2002**, *88*, 2187.
[183] Barnes, C. A.; Forster, M. J.; Fleshner, M.; Ahanotu, E. N.; Laudenslager, M. L.; Mazzeo, R. S.; Maier, S. F.; Lal, H. *Neurobiol. Aging,* **1991**, *12*, 47.
[184] Wyss, J. M.; Chambless, B. D.; Kadish, I.; van Groen, T. *Neurobiol. Aging.,* **2000**, *21*, 671.
[185] Arida, R. M.; Scorza, C. A.; da Silva, A. V.; Scorza, F. A.; Cavalheiro, E. A. *Neurosci. Lett.,* **2004**, *364*, 135.
[186] McEwen, B. S. *Brain Res.,* **2000**, *886*, 172.
[187] Gould, E.; McEwen, B. S.; Tanapat, P.; Galea, L. A.; Fuchs, E. *J. Neurosci.,* **1997**, *17*, 2492.
[188] McEwen, B. S. *Biol. Psychiatry*, **2000**, *48*, 721.
[189] Rhodes, J. S.; van Praag, H.; Jeffrey, S.; Girard, I.; Mitchell, G. S.; Garland, T., Jr.; Gage, F. H. *Behav. Neurosci.,* **2003**, *117*, 1006.
[190] McGaugh, J. L. *Science,* **2000**, *287*, 248.
[191] Nater, U. M.; Rohleder, N.; Gaab, J.; Berger, S.; Jud, A.; Kirschbaum, C.; Ehlert, U. *Int. J. Psychophysiol.,* **2005**, *55*, 333.
[192] Toni, N.; Buchs, P. A.; Nikonenko, I.; Bron, C. R.; Muller, D. *Nature,* **1999**, *402*, 421.
[193] Butler, M. P.; O'Connor, J. J.; Moynagh, P. N. *Neuroscience,* **2004**, *124*, 319.
[194] Cunningham, A. J.; Murray, C. A.; O'Neill, L. A.; Lynch, M. A.; O'Connor, J. J. *Neurosci. Lett.,* **1996**, *203*, 17.
[195] McKenzie, D. C. *Can. J. Appl. Physiol.,* **1999**, *24*, 66.
[196] Morgan, W. P.; Brown, D. R.; Raglin, J. S.; O'Connor, P. J.; Ellickson, K. A. *Br. J. Sports Med.,* **1987**, *21*, 107.
[197] Chan, C. S.; Grossman, H. Y. *Percept. Mot. Skills,* **1988**, *66*, 875.
[198] Morris, M.; Steinberg, H.; Sykes, E. A.; Salmon, P. *J. Psychosom. Res.,* **1990**, *34*, 493.

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