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Review

Exercise, cognition and Alzheimer's disease: More is not necessarily better

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Abstract

Regional hypoperfusion, associated with a reduction in cerebral metabolism, is a hallmark of Alzheimer's disease (AD) and contributes to cognitive decline. Cerebral perfusion and hence cognition can be enhanced by exercise. The present review describes first how the effects of exercise on cerebral perfusion in AD are mediated by nitric oxide (NO) and tissue-type plasminogen activator, the release of which is regulated by NO. A conclusion of clinical relevance is that exercise may not be beneficial for the cognitive functioning of all people with dementia if cardiovascular risk factors are present.

The extent to which cardiovascular risk factors play a role in the selection of older people with dementia in clinical studies will be addressed in the second part of the review in which the effects of exercise on cognition are presented. Only eight relevant studies were found in the literature, emphasizing the paucity of studies in this field. Positive effects of exercise on cognition were reported in seven studies, including two that excluded and two that included patients with cardiovascular risk factors. These findings suggest that cardiovascular risk factors do not necessarily undo the beneficial effects of exercise on cognition in cognitively impaired people. Further research is called for, in view of the limitations of the clinical studies reviewed here.

Keywords: Physical activity; Exercise; Cognition; Alzheimer's disease; Cerebral perfusion; Nitric oxide

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In the elderly population, there is a strong relationship between the level of physical activity and cognition (Van Gelder et al., 2004; Fratiglioni et al., 2004). The key question whether this relationship is causal, however, remains to be answered (Fratiglioni et al., 2004). For example, a period of decreased physical activity that precedes the onset of dementia could be either the cause of the dementia or be the result of the prodromal cognitive impairment (Fratiglioni et al., 2004). One way to answer the question about the causality is to perform intervention studies.

In a recent meta-analysis of physical intervention studies, Colcombe and Kramer (2003) provide convincing evidence that aerobic fitness training in older persons improves cognitive functioning, especially executive-control processes. Although the magnitude of the effects varied, a beneficial impact of aerobic exercise training was found in general, independent of type, duration, or intensity of physical activity. Of the 18 intervention studies they considered, only two (Palleschi et al., 1996; Powell, 1974) examined the effects of such training on a group of older persons with cognitive impairment. In other words, persons with dementia receive little attention in physical exercise studies. Studies that do include older people with dementia tend to deal with the effects of exercise on functional mobility (MacRae et al., 1996; Teri et al., 1998) or sleep (Alessi et al., 1999; Namazi et al., 1995) rather than on cognition. This is the more remarkable since cognition is most vulnerable in older persons with dementia. One goal of the present article is, therefore, to review the few clinical studies that have examined the influence of exercise on cognition in this population.

Literature searches were performed in Pubmed, Web of Science, PsycINFO, and BioMed Central. In view of the small number of intervention studies concerning the effects of physical activity on cognition in people with dementia, *all* studies in this field were included irrespective of the aetiology of the cognitive impairment and year of publication. The key words used in the search included *physical activity*, *exercise*, *fitness training*, *aerobic*, *physical therapy* in combination with *cognition*, *cognitive function*, *cognitive functioning neuropsychological*, *memory*, *executive functioning*. These key words were combined with the following words *dementia*, *demented*, *Alzheimer's disease*, *nursing home residents*, *cognitive impairment*, *cognitively impaired*, *mild cognitive impairment*, *memory impairment*. The inclusion criteria were (1) studies that reported on participants having some degree of cognitive impairment or diagnosis of dementia (2) a programme focused exclusively on exercise, physical activity or fitness training; (3) cognition as the dependent variable. Studies were excluded if (1) they were not written in English; (2) no details were reported on the cognitive status of the participants; (3) when next to exercise, also another type of sensory stimulation was offered, e.g. music. The combination of two types of sensory stimulation may improve cognition in people with dementia (Van de Winckel et al., 2004), but it remains obscure which type of stimulation was (most) effective.

Clinical studies that provided sufficient data for calculating effect-sizes d (Cohen's d: 0.20 = small, 0.50 = moderate, and 0.80 = large) (Cohen, 1992) are labelled 'Clinical studies A' (see Table 1a). In case a control group was present, effect sizes were calculated *between* groups; if a control group was absent the effect size *within* the group is noted. Studies in which data to calculate effect sizes are lacking are labelled 'Clinical studies B' (see Table 1b).

Churchill and co-workers (2002) discussed in an excellent review the results of experimental animal studies in which responses to exercise, including synaptogenesis, neurogenesis, glial plasticity, and vascular plasticity in the *normal aging brain* were examined. In a transgenic mouse model of AD, mice with the opportunity to exercise voluntarily on a running wheel for five months showed a decrease in extracellular amyloid-ß (Aß) plaques in the frontal cortex and hippocampus (Adlard et al., 2005). In addition, the performance on the Morris water maze was found to be improved indicating an enhanced rate of learning (Adlard et al., 2005). In sum, in animal experimental studies with both healthy mice and mice with AD-like neuropathology, exercise has been found to generate positive responses in the brain.

The question arises whether these plastic reactions to exercise also occur in people with dementia. The second goal of the present paper is to try to provide an answer to this question by focusing on the relationship between exercise and vascular plasticity, i.e. cerebral perfusion, particularly patients with Alzheimer's disease (AD). The reason for focusing on the relationship between perfusion and exercise, particularly in AD, is threefold: (1) cerebral perfusion is a good measure for neural activity (Iadecola, 2004), (2) regional hypoperfusion, associated with a reduction in cerebral metabolism (Attwell and Iadecola, 2002; Wolf et al., 2001), is a hallmark of AD (Miklossy, 2003) and contributes to cognitive decline (Miklossy, 2003; Swaab, 1991, 2004), and (3) exercise has been shown to exert a positive influence on cerebral perfusion (Ide et al., 1999) and thus seems to be a good read out system for effects.

A comprehensive overview of cerebral perfusion in AD is beyond the scope of this paper. Since endothelium-derived factors play a pivotal role in the regulation of cerebral perfusion (Farkas and Luiten, 2001), a literature search was performed for studies that examined those factors with respect to AD. Subsequently, the factors resulting from that search had to be studied in relation to the following key words cerebral perfusion/cerebral blood flow/cerebral hypoperfusion and exercise/physical activity/aerobic activity. Only nitric oxide (NO), a potent vasodilator (Huang et al., 1995), met those criteria and will thus be discussed.

Table 1a
Clinical studies A

Study	Sample (men/women)	*N*	Age	Design	Type of intervention	Dependent variables	Results
Diesfeldt and Diesfeldt-Groenen-wijk, 1977	Psychogeriatric patients with mental and physical handicaps (6/34)	40	$M=82$	Experimental group/control group; repeated measures	15 min bending/stretching, 25 min playing a game consisting of throwing and kicking a ball and knocking down skittles	Free recall task (immediate free recall and total-recall score); posting-box task; recognition task	Significant increase in total recall score ($d=0.23$) in the experimental group, other measures did not change significantly
Friedman and Tappen, 1991	Nursing home residents with probable AD (NINCDS-ADRDA criteria and MMSE scores <19) (17/13)	30	>60	Experimental group/control group; repeated measures	30-min walk three times a week for 10 weeks	Communication scale for the cognitively impaired[a]; communication observation scale for the cognitively impaired (COS)	Improvement on the COS ($d=1.06$) in the experimental group. Conversation only did not result in a significant improvement
Palleschi et al., 1996	Males diagnosed with possible AD (NINCDS-ADRDA criteria, GDS phase 4 or 5, MMSE[b] score 18–21) (0/15)	15	$M=74.0$ SD $=1.5$	Single group; repeated measures	Exercise on a cycloergometer (heart rate at $+/-70\%$ of max pulse rate) 20 min exercise 3 days a week, for 3 months	Test of attentional matrix; verbal span test; supraverbal span test[c]; MMSE	Significant improvement on all tasks ($d=1.52$, $d=1.73$, $d=2.71$, $d=1.94$, respectively)
Powell, 1974	Geriatric mental patients (13/17)	20	$M=69.3$ (59–89)	Two treatment groups/ one control group; repeated measures	Mild exercise: brisk walking, callisthenics, rhythmical movements social therapy group: social interaction and music both treatment groups 1 h a day, 5 days a week, for 12 weeks	Wechsler memory scale (WMS)[d] Raven's progressive matrices (PMT)[e] memory for designs test[f]; nurses observation scale for inpatient evaluation[g]; geriatric assessment scale[h]	Significant improvement in the exercise group on the WMS ($d=0.14$) and PMT ($d=0.59$). No changes in the social therapy group
Scherder et al., 2004	Older persons with mild cognitive impairment (MMSE score 7–12) (38/5)	43	Gr. I: $M=84$ SD $=6.4$ Gr. II: $M=89$ SD $=2.4$ Gr. III: $M=86$ SD $=5.1$	Two treatment groups/ one control group; repeated measures	Walking group: self-paced slow walking with an aid hand and face exercises group: performing hand movements and producing facial expressions) control group: continued receiving social visits or continuance of normal social activities intervention took place for 30 min a day, three times a week, for 6 weeks	Category naming; trailmaking (TMT) A and B[i]; digit span and visual memory span from the Wechsler memory scale-revised[j]; verbal learning and memory test[k]; face recognition and picture recognition from the rivermead behavioural memory test[l]	Improvement in tasks appealing to executive functioning, i.e. verbal fluency and TMT in the walking group ($d=0.42$ and $d=0.46$, resp) and the hand and face group ($d=0.59$ and $d=0.13$, resp) compared to the control group

Characteristics of studies examining the effects of physical activity on cognition in cognitively impaired elderly. AD, Alzheimer's disease; ADRDA, Alzheimer's disease and related disorders association; GDS, global deterioration scale; h, hour; *M*, mean; min, minutes; MMSE, mini mental state examination; NINCDS, national institute of neurological and communicative disorders and stroke; resp, respectively; SD, standard deviation.

[a] Tappen, 1988.
[b] Folstein et al., 1975.
[c] Spinler and Tognoni, 1987.
[d] Wechsler, 1945.
[e] Raven, 1965.
[f] Graham and Kendall, 1960.
[g] Hönigfeld et al., 1966.
[h] Plutchik et al., 1970.
[i] Reitan and Wolfson, 1985.
[j] Wechsler, 1984.
[k] Mulder et al., 1995.
[l] Wilson et al., 1987.

Table 1b
Clinical studies B

Study	Sample (men/women)	*N*	Age	Design	Type of intervention	Dependent variables	Results
Lindenmuth and Moose, 1990	People with Alzheimer's disease (27/16)	43	*M* = 82.8 (65–98)	Experimental group/control group; repeated measures	Experimental group: somatic and isotonic-relaxation exercises for 8 weeks Control group: no intervention	Cognitive abilities screening test	Experimental group showed significant change
Rolland et al., 2000	People with probable AD (NINCDS-ADRDA criteria) (13/10)	23	*M* = 78 (71–92)	Single group	Endurance exercise: walking, exercise bicycle for 5–12 weeks (*M* = 7) for 35 min (10–80 min)	Activities of daily living scale[a]; instrumental activities of daily living scale[b]; MMSE; neuropsychiatric inventory[c]; zarit scale[d]; mini-nutritional assessment[e]; tinetti test[f]	Improved nutritional status, improved cognitive function, improvement in behavioural problems
Sobel, 2001	People with a clinical AD diagnosis (MMSE[g] scores 8–25) (22/28)	50	*M* = 82 (62–99)	Two separate days two treatment groups design Ass 1, followed directly Ass 2 en then 4–9 days later Ass 3	Cognitive: 20 min of Bingo Physical: 20 min of walking or arm and leg extensions	Boston naming test and word list recognition test from the CERAD[h]	Cognitive stimulation enhanced performance on both tasks, whereas physical intervention did not reach statistical significance

Characteristics of studies examining the effects of physical activity on cognition in cognitively impaired elderly. AD, Alzheimer's disease; ADRDA, Alzheimer's disease and related disorders association; Ass, assessment; *M*, mean; min, minutes; MMSE, mini mental state examination; NINCDS, national institute of neurological and communicative disorders and stroke; SD, standard deviation.

[a] Katz, 1983.
[b] Lawton and Brody, 1969.
[c] Cumming et al., 1994.
[d] Zarit et al., 1982.
[e] Guigoz et al., 1994.
[f] Tinetti et al., 1988.
[g] Folstein et al., 1975, 1983.
[h] The Consortium to Establish a Registry for Alzheimer's disease, 1987.

1. Outline of this review

First of all, studies on the relationship between hypoperfusion, nitric oxide, cognition, and exercise in AD are described. These studies lead to the important but rather unexpected conclusion of *clinical relevance* that exercise may not be beneficial for the cognitive functioning of all people with dementia but may depend on the presence of cardiovascular risk factors. These studies will be described first. The extent to which cardiovascular risk factors play a role in the selection of older people with dementia in clinical studies will be addressed in the second part of the review in which the effects of exercise on cognition are presented.

2. Hypoperfusion, nitric oxide, cognition and exercise in Alzheimer's disease

First, the focus will be on cerebral (hypo) perfusion, in relation to neural activity, exercise, hypometabolism and cognition. Subsequently, nitric oxide (NO) and tissue-type plasminogen activator, the release of which is regulated by NO will be discussed with respect to hypoperfusion and exercise in AD.

3. Cerebral (hypo) perfusion in relation to neural activity, exercise, hypometabolism, and cognition

3.1. Cerebral perfusion and neural activity

During neuronal activity, an increase of oxygen usage is followed within a few seconds by an increase in cerebral blood flow (CBF) (Attwell and Iadecola, 2002). An increase in oxygen and glucose uptake is indicative for enhanced cerebral metabolism (Ide and Secher, 2000). As alterations in regional cerebral metabolism can be inferred from measurements of regional cerebral perfusion (Wolf et al., 2001), cerebral perfusion is frequently used as a global measure for neural activity in brain imaging studies (Wolf et al., 2001; Iadecola, 2004). Fluctuations in cerebral perfusion are maintained by cerebral autoregulation, an important protective mechanism that ensures near-constant CBF (Baumbach and Heistad, 1983). In autoregulation, the arterial-arteriolar bed actively adjusts the caliber of its

vessels in response to changes in cerebral perfusion pressure (CPP) by dilating when CPP decreases and constricting when CPP increases (Daley et al., 2004).

3.2. Cerebral perfusion and exercise

Changes in peripheral cardiovascular activity reflected in increased heart rate (HR) and mean arterial blood pressure (MAP) cause an increase in CBF in various cortical and subcortical brain areas in healthy volunteers (Critchley et al., 2000). During isometric exercise, an increase in CBF was observed in the right anterior cingulate cortex (ACC), cerebellar vermis and brain stem. CBF appeared to be dependent on the extent of HR and MAP increase: for example, a higher MAP was associated with a greater CBF in the ACC and insula, whereas a lower MAP enhanced the CBF in e.g. the hippocampus and medial temporal gyrus. Similarly, CBF showed a specific positive relation with HR with respect to the pons and a specific negative correlation concerning middle frontal gyrus, cingulate, orbitofrontal cortex, and amygdala (Critchley et al., 2000).

In addition to isometric exercise, CBF velocity is increased in healthy participants by dynamic activities such as rowing (Pott et al., 1997) and cycling (Hellström et al., 1996). Even by submaximal cycling CBF (Jørgensen et al., 1992) and metabolism (Ide et al., 1999) increased. In the primary motor cortex of rats, growth of capillaries as well as enhanced cerebral perfusion was observed as a result of prolonged exercise (Swain et al., 2003).

3.3. Cerebral hypoperfusion and hypometabolism in AD

A reduction in cerebral metabolism is accompanied by a decrease in CBF (Prunell et al., 2004). Of note is that there is no agreement on the question whether reduced cerebral metabolism in AD precedes hypoperfusion or vice-versa. It is suggested that a decrease of cerebral perfusion leads to hypometabolism (De la Torre, 2002), whereas others claim that a reduced metabolism is the cause of hypoperfusion (Meyer et al., 2000).

Decreases in the cerebral metabolic rate for glucose and hypoperfusion have consistently been observed in the temporoparietal cortex in AD (Warkentin et al., 2004) whereas different levels of hypoperfusion have been found in the frontal and occipital cortex of different AD patients (Warkentin et al., 2004). More specifically, participants who developed AD late showed decreased perfusion in the hippocampal-amygdaloïd complex, the anterior and posterior cingulate and the anterior thalamus (Johnson et al., 1998; Matsuda, 2001). Of note is that glucose hypometabolism has been observed even in the preclinical stage of dementia for example in the temporal lobe, posterior cingulate gyrus and precuneus (Reiman et al., 1965; Matsuda, 2001; Swaab et al., 2002). Hypoperfusion is also considered to be evidence for cerebromicrovascular pathology underlying AD (De la Torre, 2002) Cerebral hypoperfusion tends to lead to leuko-araiosis and cortical watershed infarcts, which may exacerbate cognitive decline (Miklossy, 2003).

A protein which plays a major role in cerebral perfusion and metabolism and is a known risk factor for sporadic AD, is apolipoprotein E4 (ApoE4) (Corder et al., 1993). ApoE4 genotype appears not only to be involved in a decreased metabolism in AD (Salehi et al., 1998), but also in a decreased metabolism in ApoE4 carrying control subjects (Dubelaar et al., 2004). In AD, ApoE4 genotype is accompanied by a decrease in brain blood flow velocity (Lehtovirta et al., 1998) and enhances cerebrovascular amyloidogenesis (Martel et al., 1997), i.e. extracellular accumulation of Aβ (Parihar and Hemnani, 2004). Cerebrovascular amyloidogenesis is directly related to cerebral amyloid angiopathy (CAA) (Suzuki et al., 1994), i.e. the deposition of e.g. Aβ in the vessel walls of the cerebral vasculature (Weller and Nicoll, 2003). In other words, ApoE4 increases the risk for CAA (Weller and Nicoll, 2003) and an etiological relationship between CAA and vascular lesions, in particular intracerebral hemorrhage, has been observed in AD (Weller and Nicoll, 2003). ApoE4 has been associated with a reduction in CBF in the parietal, temporal and occipital areas in AD (Lehtovirta et al., 1998; Matsuda, 2001), together with a reduction in regional cerebral metabolic rate for glucose in the posterior cingulate, and the parietal, temporal, and prefrontal regions (Van Dyck, 2004).

3.4. Cerebral hypoperfusion and cognition in AD

Several studies indicate that a significant correlation between hypoperfusion and cognitive dysfunction in AD. Hypoperfusion and the scores on the Cambridge Cognitive Examination (CAMCOG) (Roth et al., 1986) were significantly correlated (Tsolaki et al., 2001). In a study using multiple regression analysis, left posterior temporal regional CBF (rCBF) was a predictor of performance on the clock drawing test (Ueda et al., 2002). In addition, correlations were found between the MMSE scores and hypoperfusion in frontal, parietal en temporal cortex (Jagust et al., 1997; Tsolaki et al., 2001; Ushijima et al., 2002). More specifically, only items appealing to attention/calculation showed a decline in CBF in the frontal cortex; all other items covering e.g. orientation and recall were associated with a decreased CBF in the posterior brain regions (Ushijima et al., 2002). In another study, rCBF in the right posterodorsal anterior and superior prefrontal cortex and the inferior parietal cortex was lower in a group of AD patients in whom the condition was progressing rapidly (Nagahama et al., 2003). Lower perfusion rates correlated with poorer performance on the MMSE.

4. Nitric oxide in relation to hypoperfusion and exercise in Alzheimer's disease

4.1. Nitric oxide and hypoperfusion

A key factor associated with cerebral hypoperfusion in AD is a dysfunction of nitric oxide (NO) metabolism (Selley, 2003; Churchill et al., 2002). NO, derived from vascular endothelial nitric oxide synthase (eNOS), plays a pivotal role in cerebral perfusion by its influence on vascular tone, blood pressure, and

vascular homeostasis (Huang et al., 1995; Kubes and Granger, 1992). Cerebral autoregulation is mediated by NO (White et al., 2000). Moreover, NO reduces the risk for atherosclerosis and thrombosis and improves blood flow by lowering stress on the blood vessel wall, thus protecting endothelial cell function (Maxwell, 2002).

It is suggested that AD-related hypoperfusion disturbs basal NO levels, causing alterations in the endothelium and inducing vascular injury (Cooke and Dzau, 1997). More specifically, it is presumed that when the cerebral perfusion decreases below a certain critical level, eNOS tries to maintain vascular homeostasis by upregulating NO (De la Torre, 2002). In failing to do so, NO becomes deregulated, damages the endothelial cells and impairs glucose transport to the brain (Chen et al., 1999). This vicious circle is presented in Fig. 1 (left side).

Subsequently, as a result of deterioration in NO homeostasis, oxidative alterations may contribute to cell death (Fernández-Vizarra et al., 2004). Not only the surpassing of a critical level of brain perfusion disturbs NO production and contributes to AD neuropathology. Selley (2003) observed that inhibition of NO production also results from increased levels of homocysteine in the blood of AD patients. A high level of homocysteine is a risk factor for cardiovascular disease (Herrmann, 2001).

NO shows a close relationship to several neurotransmitter systems. For example, the relationship between NO and the nicotinic cholinergic system is reflected in the glutamate/nitric oxide synthase (NOS)/soluble guanylyl cyclase (sGC) pathway. More specifically, data suggest that the NOS/sGC pathway is activated by a presynaptic action of nicotine, resulting in among others hippocampal excitation (Fedele and Raiteri, 1999). Activation of nicotinic acetylcholine receptors—with consequent neural vasodilatation—contributes to an increase in CBF and NO production in the hippocampus of conscious rats (Nakajima et al., 2003). The entire cortical mantle including the hippocampus is densely innervated by a very fine NOS positive fibre network that finds its origin in scattered NOS interneurons. From the findings of Nakajima and co-workers (2003) it can be concluded that basal forebrain and medial septal cholinergic neurons have direct projections onto the NOS positive interneurons and this way have a well developed access to vasodilation mechanisms via release of NO. Such a neuronal organization of cerebrovascular innervation was also concluded from studies by Moro and colleagues (1995) who demonstrated co localization of NOS and muscarinic receptors in interneurons in neocortical regions projecting onto cerebral microvessels (Hamel, 2004). Taken together these experimental studies point to a potent basal forebrain cholinergic influence on cortical blood flow regulation mediated by NO production through NOS interneurons provided with both nicotinic and muscarinic postsynaptic receptorsystems (Harkany et al., 2000). It is noteworthy that a cholinergic denervation of NOS expressing interneurons and cortical microvessels has been found in AD patients (Tong and Hamel, 1999; Hamel, 2004), particularly in the temporal cortex (Tong and Hamel, 1999). There are other

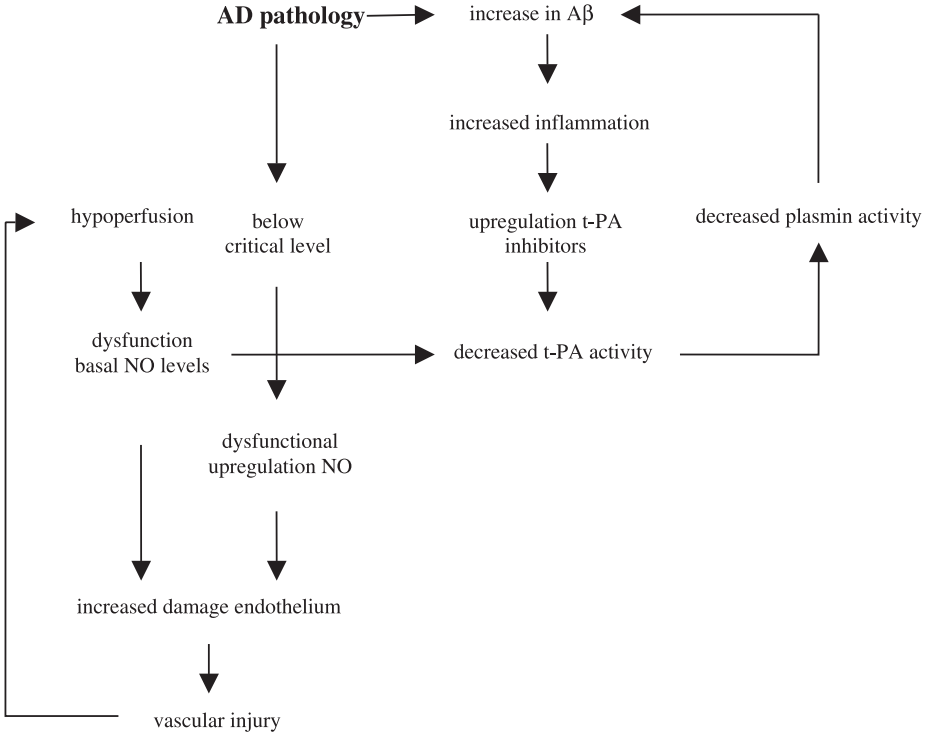

Fig. 1. NO and t-PA in AD. Alzheimer's disease (AD)—related hypoperfusion disturbs basal nitric oxide (NO) levels, and hypoperfusion below a critical level leads to dysfunctional upregulation of NO (De la Torre, 2002). Both processes increase the damage to the endothelial cells, resulting in vascular injury and initiating a vicious circle (Cooke and Dzau, 1997). Since the release of tissue-type plasminogen activator (t-PA) is regulated by NO, NO dysfunction could also result in a decreased t-PA activity (Schini-Kerth, 1999). Reduced t-PA causes reduced plasmin activity which aggravates accumulation of amyloid β peptide (Aβ) in AD. Increase of Aβ can enhance inflammation and upregulation of t-PA inhibitors, leading to a vicious circle (Tucker et al., 2002).

neural systems related to NO, for example the nitrergic sytem (Tong and Hamel, 2000). However, since a close relationship between the nitrergic system and NO in AD is lacking, this system will not be discussed here.

In sum, cerebral perfusion is highly dependent of NO and NO metabolism is severely affected in AD.

4.1.1. Tissue-type plasminogen activator and hypoperfusion

In endothelial cells, NO regulates the release of tissue-type plasminogen activator (t-PA) (Schini-Kerth, 1999), an enzyme that plays a crucial role in preventing thrombosis (Muldowney and Vaughan, 2002). The main function of t-PA is to convert plasminogen—an inactive proenzyme (Lijnen and Collen, 1997)—into plasmin (Melchor et al., 2003), which in turn degrades fibrin clots in the circulation (Lijnen and Collen, 1997; Muldowney and Vaughan, 2002). Plasmin formation in the pericellular environment takes place by another plasminogen activator: the urokinase-type plasminogen activator (u-PA) (Lijnen and Collen, 1997). Fibrinolytic activity induced by vascular endothelial growth factor (VEGF), a pivotal angiogenic growth factor (Carmeliet, 2000), is dependent on u-PA (Prager et al., 2004).

Amyloid β (Aβ) peptide, a product of Aβ precursor protein, causes in normal aging an upregulation of t-PA in combination with u-PA in rat. This results in an increase in plasmin activity which, in turn, degrades Aβ (Tucker et al., 2000, 2002). An increase in Aβ, a neuropathological hallmark of AD (Koistinaho and Koistinaho, 2005), is associated with an upregulation of t-PA *inhibitors* and consequently with a decrease in t-PA activity, particularly in areas that are most vulnerable to AD, i.e. the hippocampus and amygdala (Melchor et al., 2003). Tucker and co-workers (2002) further propose a vicious circle, implying that by inflammation in AD, inhibitors of t-PA and u-PA are increased. The increase in t-PA and u-PA inhibitors would reduce plasmin activity, which causes an increase in Aβ levels and a further augmentation of inflammation. This vicious circle is presented in Fig. 1 (right side). Furthermore, the suggestion that t-PA and related plasmin might also be able to *enhance* Aβ activity and, hence, neurotoxicity could not be confirmed in rat (Tucker et al., 2000). In addition, in the human AD hippocampus, there was no evidence for a local inhibitory effect of the amyloid containing plaques on neuronal metabolism (Salehi et al., 1998).

Plasmin, generated by t-PA activity, degrades other proteins like laminin (Chen and Strickland, 1997). Laminin—a protein produced by Schwann cells—plays a crucial role in the development of the peripheral and central nervous system, among others by promoting neurite outgrowth (Matsuda et al., 2002), Schwann cell migration (Anton et al., 1994) and the formation of myelin (Eldridge et al., 1989). Laminin is expressed in the hippocampus, more specifically in CA1–CA3 and the dentate gyrus (Chen and Strickland, 1997). In AD, laminin interacts with Aβ peptide, attenuating the aggregation of Aβ possibly by inhibition of Aβ fibril formation (Monji et al., 2000) and, hence, decreasing its presumed neurotoxicity (Morgan and Inestrosa, 2001). However, in ischaemic lesions, that are also a neuropathological hallmark of AD (Koistinaho and Koistinaho, 2005), plasmin degrades laminin and causes neuronal damage in mice (Wang et al., 1998; Nagai et al., 1999) (see Fig. 2). One mechanism underlying the increase in plasmin is that ischaemic lesions overstimulate glutamate receptors which mediate the enhancement of the synthesis of t-PA (Chen and Strickland, 1997). In other words, degradation of laminin, which will occur by an increase in t-PA in patients with ischaemic lesions after stroke and particularly after relatively small infarcts (Wang et al., 1998) might lead to further neuronal loss (Chen and Strickland, 1997). In contrast to a high level of t-PA which enhances cell death in patients with cerebral ischaemia, a low level of plasminogen in mice causes an increase in intravascular deposition of fibrin that increases infarct size (Nagai et al., 1999). The resulting high concentrations of laminin might also have a neurotoxic effect (Liesi et al., 1989).

Taken together, activity of t-PA and u-PA enhances the production of plasmin which, in turn, is able to degrade Aβ. However, plasmin may also cause a decline of laminin, a protein that decreases neurotoxicity in AD. Not only a too low level of laminin, but also a high laminin concentration could enhance neuronal damage.

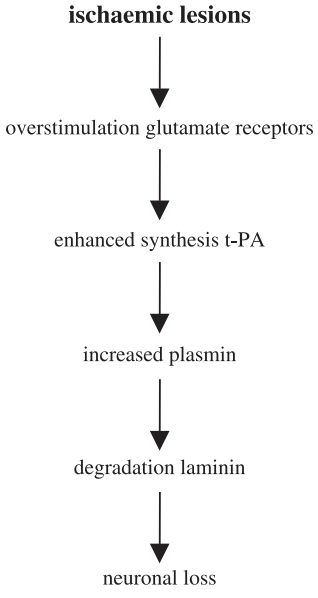

Fig. 2. Role of t-PA, plasmin and laminin in ischaemic lesions. Ischaemic lesions, part of the neuropathology of AD (Koistinaho and Koistinaho, 2005), overstimulate glutamate receptors, resulting in (1) enhanced synthesis of t-PA, (2) an increase in plasmin, (3) degradation of laminin (Wang et al., 1998) and (4) neuronal loss (Chen and Strickland, 1997). Exercise leads to an upregulation of NO (Endres et al., 2003) and increases cerebral perfusion which could attenuate endothelial dysfunction in AD. Exercise enhances t-PA (Smith et al., 2003) and consequently plasmin activity, stimulating degradation of Aβ and hence reducing neuronal damage. On the other hand, in the presence of ischaemic lesions, the increased plasmin activity may degrade laminin, increasing neuronal damage (Chen and Strickland, 1997).

4.2. Nitric oxide and exercise

Animal experimental studies show a positive relationship between exercise, nitric oxide, and cardio- and cerebrovascular functioning (Endres et al., 2003). Mice with cerebral ischaemia due to occlusion of the middle cerebral artery that participated in a running group showed an upregulation of eNOS accompanied by vasodilatation and a significant reduction in the size of the lesion, brain swelling, and sensory-motor deficits. These effects were not observed in non-running mice. Of note here is that irrespective of the nature of running, i.e. voluntary or trained, the rCBF increased significantly in the posterior brain regions, with high values in the hippocampus (Endres et al., 2003). Enhancing the release of NO might also contribute to anti-inflammatory processes, as NO-releasing ferutic acid derivative was effective in the reduction of microglia activation in the temporal lobes of rats (Wenk et al., 2004). An important point that needs further examination is that serotoninergic dysfunction resulting in a hyposerotoninergic condition—characteristic for AD (Meltzer et al., 1998)—causes a supersensitivity to NO (Srikiatkhachorn et al., 2000), implying that even mild physical activity could result in beneficial effects in AD.

Some support for a relationship between exercise and the cholinergic system emerges from animal experimental studies, in which walking significantly increased release of acetylcholine in conscious rats (Kurosawa et al., 1993). Interestingly, the higher the walking speed, the higher the cholinergic-induced increase in CBF in the hippocampus (Nakajima et al., 2003).

Finally, exercise may attenuate the endothelial dysfunction caused by high levels of homocysteine (Hayward et al., 2003), although it may be dependent on the duration and intensity of exercise. Strenuous exercise may even lead to a homocysteine increase in recreational endurance athletes (Herrmann et al., 2003).

In short, physical activity leads to enhanced NO release which may generate improved cerebrovascular function, may enhance anti-inflammatory activity, and may lead to increased acetylcholine release.

4.2.1. Tissue-type plasminogen activator and exercise

Smith and co-workers (2003) observed that the endothelium of the forearm is less able to release t-PA antigen in older persons with a low level of physical activity. Interestingly, the capacity of the endothelium to release t-PA can be restored after a period of aerobic exercise, particularly walking (Smith et al., 2003). These authors suggest that the increase in t-PA might restore endothelial fibrinolytic function which is diminished in aging. The increase in t-PA might be due to an increased arterial pressure and pulsatile flow during physical activity. Although Smith and colleagues (2003) made their observations on the forearm, we hypothesize that their findings could be generalized to the cardiovascular condition, and hence the perfusion of the brain.

In sum, an increase of t-PA by means of exercise may restore endothelial fibrinolytic function and improve cerebral perfusion.

5. Exercise and cognition in older persons with dementia: clinical studies A and B

5.1. Clinical studies A

In one of the earliest reports on this topic, a group of 20 psychogeriatric patients underwent an acute bout of exercise for 40 min and showed a significant improvement in memory performance (greater retrieval capacity) compared with a control group (Cohen's $d=0.23$) (Diesfeldt and Diesfeldt--Groenendijk, 1977). Cardiovascular risk factors were not controlled for. A few studies have been described in which persons with dementia were given exercise for a longer period. In a randomised controlled study, 20 geriatric mental patients were divided into two treatment groups, one group being given conventional social therapy and one exercise therapy, and one control group (Powell, 1974). Patients with cardiovascular risk factors such as hypertension were excluded from the study. After 12 weeks of treatment the exercise group showed improved performance on the Progressive Matrices Test (Raven, 1965) (Cohen's $d=0.59$) and the Wechsler Memory Scale (Wechsler, 1945) (Cohen's $d=0.14$) compared with the control group. The higher scores on both tests implied that global intellectual functioning and memory improved. The results of another memory test and two behavioural assessments did not show significant improvement. In another study, 15 males diagnosed with possible AD exercised on a cycle ergometer (Palleschi et al., 1996). No information was provided about the patients' cardiovascular condition. Their performance on the test of the attentional matrix (Spinler and Tognoni, 1987) (Cohen's $d=1.52$), the verbal span test (Spinler and Tognoni, 1987) (Cohen's $d=1.73$), the supraverbal span test (Spinler and Tognoni, 1987) (Cohen's $d=2.71$) and the Mini Mental State Examination (MMSE) (Folstein et al., 1975) (Cohen's $d=1.94$) were found to have improved after the intervention period. These treatment effects suggest an improvement in attention en global cognitive functioning. It should be noted however that a control group was lacking in this study. Friedman and Tappen (1991) reported on 30 moderate to severe AD patients who took part in either a walking programme or a conversation programme for 10 weeks (Friedman and Tappen, 1991). Patients with cardiovascular risk factors such as diabetes mellitus and hypertension as well as those with congestive heart failure were among the participants. After the treatment period performance on the Communication Observation Scale (Hoffman et al., 1985) (Cohen's $d=1.06$) improved only in the walking group. In other words, patients who went walking showed an improvement in verbal and non-verbal communication. In a recent pilot study by Scherder and colleagues (2005) 43 advanced older individuals with mild cognitive impairment—a transitional stage to AD (Petersen et al.,

1999)—participated. Persons were randomly divided into three treatment groups: a walking group ($n=15$), a group carrying out hand and face exercises ($n=13$) and a control group ($n=15$) that received social visits. Patients with cardiovascular risk factors were not excluded from the study. Performance on tasks that measure executive functioning, verbal fluency and the Trailmaking Test (Reitan and Wolfson, 1985), improved in both the walking group (Cohen's $d=0.42$ and $d=0.46$, respectively) and the hand/face exercise group (Cohen's $d=0.59$ and $d=0.13$, respectively). However, considering the small sample size firm conclusions could not be drawn.

In sum, the results of the five studies reviewed above suggest that exercise has a positive effect on cognition, in particular attention, memory, communication, executive functions, and global mental functioning in older persons with cognitive impairment. However, most studies included only a small number of people and showed serious methodological flaws. Two studies did not control for the presence of cardiovascular risk factors, only one study excluded those who were familiar with these factors.

5.2. Clinical studies B

One 20-min session of physical activity (walking or arm and leg extensions) was not found to lead to statistical differences on a test of language ability and word retrieval or a verbal recognition task in a group of 25 AD patients. A 20-min session of Bingo, however, did induce a significant improvement on the tasks (Sobel, 2001). No information was provided about the presence of cardiovascular risk factors.

A group of 23 moderate to severe AD patients participated in a programme of endurance exercise that consisted of walking and riding an exercise bicycle (Rolland et al., 2000). Patients with cardiac disease were excluded. The AD patients significantly improved in the performance on the MMSE, implying that global cognitive functioning improved. Unfortunately, a control group was not included. In another intervention study, 43 older AD patients participated in a programme consisting of somatic and isotonic-relaxation exercises (Lindenmuth and Moose, 1990). Information about the cardiovascular condition of these patients was not provided. The cognitive abilities of the experimental group were stated to have improved after 8 weeks of training. However, the nature of the cognitive abilities that improved was not further specified. Moreover, the participants were allowed to choose whether they preferred to be in the experimental group or control group, participation in the exercise group was irregular, and the control group did not take part in any alternative activity.

Taken together, two out of three studies report an improvement in global cognitive functioning, by exercise. The methodological shortcomings of these studies are similar to those of the clinical studies A. Only one study controlled for the presence of cardiovascular risk factors and excluded those who were familiar with them.

6. Discussion

Hypoperfusion, nitric oxide, cognition and exercise in Alzheimer's disease.

Cerebral hypoperfusion, characteristic for AD (Miklossy, 2003) and related to a decrease in cerebral metabolism (Attwell and Iadecola, 2002; Wolf et al., 2001) reduces the level of cognitive functioning (Miklossy, 2003; Swaab, 1991; 2004). If cerebral hypoperfusion can be restored and kept at an appropriate level by exercise, one may hypothesize that collapsed cortical capillaries can participate again in the circulation. This sequence of events reflects the preservation of the hemodynamic integrity at a capillary level (Miklossy, 2003). In addition, exercise may lower increased blood pressure (Whelton et al., 2002) and may improve the cardiovascular condition, i.e. heart rate variability (Pober et al., 2004), factors that also contribute to the positive effects of exercise on cerebral perfusion (Critchley et al., 2000; Keller and Lemberg, 2002).

A theoretical model of the relationship between exercise and cerebral perfusion is presented in Fig. 3. This model could serve as a guide for future studies, since it indicates that exercise is not necessarily beneficial for *all* people with dementia, particularly in the presence of ischaemic lesions. The positive effects of exercise on cerebral perfusion appear to depend on the patient's cardiac condition. Koike and co-workers (2004) observed that in patients with valvular heart disease, and hence with reduced cardiac output, the cerebral oxyhemoglobin level declined during increasing physical effort on a cycle ergometer. These authors suggest that the blood supply to these patient's muscle cells during exercise occurs at the expense of the blood supply to other organs such as the cerebrum. Others confirm that a limited cardiac output during exercise with a large muscle mass affects the regional increase in cerebral perfusion (Ide et al., 1998). There is ample evidence that cardiovascular disorders like hypertension increase the risk of AD (Skoog and Gustafson, 2003; De la Torre, 2002). More specifically, it has been observed that high systolic blood pressure increases the risk for hippocampal atrophy and consequently the risk for AD (Launer et al., 2000). Kivipelto and colleagues (2002) describe the important role of hypertension and hypercholesterolemia in the development and expression of AD and suggest proper, early interventions aimed at reducing these cardiovascular risk factors to alter the incidence of AD. Indeed, ischaemic lesions have been observed in AD (Koistinaho and Koistinaho, 2005). When ischaemic lesions are present, (high-intensity) physical activity might lead to laminin depletion and hence to neuronal damage (Chen and Strickland, 1997; Nagai et al., 1999). It, therefore, seems vital to maintain the laminin concentration at physiologically normal levels. The question arises to what extent this important information is incorporated into clinical studies examining the effects of exercise on cognition of older people with cognitive impairment.

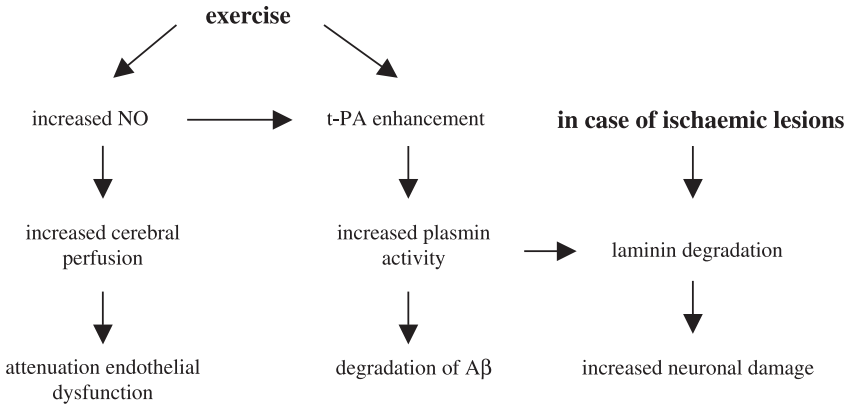

Fig. 3. Role of NO, t-PA, plasmin and laminin in effects of exercise in AD. Exercise leads to an upregulation of NO (Endres et al., 2003) and increases cerebral perfusion which could attenuate endothelial dysfunction in AD. Exercise enhances t-PA (Smith et al., 2003) and consequently plasmin activity, stimulating degradation of Aβ and hence reducing neuronal damage. On the other hand, in the presence of ischaemic lesions, the increased plasmin activity may degrade laminin, increasing neuronal damage (Chen and Strickland, 1997).

6.1. Clinical studies A and B

Seven of the eight clinical studies reviewed here show positive effects of physical activity on cognition, in particular attention, memory, communication, executive functions and global mental functioning, in older people with dementia. Of those studies, only two excluded participants who suffered from hypertension and/or had a history of cardiac problems (Powell, 1974; Rolland et al., 2000) while four did not control for cardiovascular risk factors (Diesfeldt and Diesfeldt-Groenendijk, 1977; Palleschi et al., 1996; Sobel, 2001; Lindenmuth and Moose, 1990). It may be noted that three of the last-mentioned four studies reported a beneficial influence of exercise on cognition (Diesfeldt and Diesfeldt-Groenendijk, 1977; Palleschi et al., 1996; Lindenmuth and Moose, 1990). Since we have no evidence that only cognitively impaired older people without cardiovascular risk factors participated in these studies, it may be argued that the absence of cardiovascular risk factors is not a prerequisite for effective treatment. Support for this argument emerges from two studies reviewed here, which specifically included people with cardiovascular risk factors and where cognitive improvement was still observed (Friedman and Tappen, 1991; Scherder et al., 2005). The findings of the present review do however suggest that the presence of cardiovascular risk factors might explain those cases where treatment failed to have a beneficial effect. For example, in one study where subjects were required to undertake periods of exercise (walking) combined with conversation adapted to appeal to patients' residual verbal capacities this form of treatment was not found to improve patients' overall communication (Cott et al., 2002). (This study was excluded from the present review, because we did not consider interventions involving the combination of two types of sensory stimulation.) The authors mentioned differences in pre-treatment scores between the experimental group and the control group as one of the possible reasons for their negative results. Cardiovascular risk factors (which they did not control for) might have been an alternative explanation. All in all, it seems appropriate to suggest that further research into the effects of physical activity on the cognition of older people with cognitive impairment should control for cardiovascular risk factors. On the one hand, this might explain why exercise is not effective in improving cognition in certain patients, while on the other it would permit testing of the hypothesis that greater cognitive improvement is found in patients without cardiovascular risk factors than in those with this risk.

The fact that only studies of the direct effects of physical activity on cognition in older people with dementia were selected might be considered a limitation of the present review. This restriction was in fact imposed in order to highlight the paucity of studies of this type. Some authors have suggested that the strikingly low number of studies in this field might be due to poor patient compliance with the treatment (Tappen et al., 2000) or patients' inability to understand the programme description (Naso et al., 1990). Others found however that frail persons with dementia are quite capable of following an exercise programme (Lazowski et al., 1999). It is worth noting that exercise can also improve cognition indirectly, for example by reducing depression. Since it is known that depression can reduce cognitive functioning (Bierman et al., 2005), a reduction in depression brought about by exercise (Palmer, 2005) might enhance cognitive functioning. It would be worthwhile discussing the results of studies of the indirect effect of exercise on cognition in persons with AD and other forms of dementia in a subsequent review.

A further limitation of the clinical studies reviewed here is the relatively small number of patients included, which is due to the high drop-out rate. The small sample size reduces the predictive power of the results. However, all studies considered here gave a positive outcome, though the most informative effect sizes (Cohen's d), i.e. those calculated from studies including both an experimental and a control group, showed an extremely wide range from $d=0.13$ (corresponding to a very small effect) to $d=1.06$ (very large effect).

In conclusion, we recommend that people with AD should undergo careful physical examination, specifically aimed at cardiovascular risk factors, before entering a physical training programme in future studies. The presence of cardiovascular

risk factors might attenuate or even undo positive effects of exercise on cognition. It follows that participation in exercise programmes next to one's usual physical activities is not necessarily beneficial for all patients. A good motto for those advising persons with dementia on possible exercise regimens might thus be 'more is not always better'.

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