

# INFLUENCE OF INCREASED BLOOD FLOW ON COGNITIVE IMPROVEMENT: A NARRATIVE REVIEW

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## ABSTRACT

**Introduction:** Mild Cognitive Impairment (MCI) is a decline in cognitive functions such as memory, attention, and language. Effective treatment focuses on correctable causes, such as depression and metabolic diseases. Physical activity plays an important role in brain health, improving memory, cerebral blood perfusion, and promoting new synaptic connections, in addition to increasing cerebral blood flow (CBF) and the supply of oxygen and glucose to specific areas of the cortex. The objective of this literature review is to elucidate the influence of increased CBF on cognitive improvement. **Methodology:** This literature review was conducted between September 2023 and August 2024, using the MEDLINE/PubMed, Google Scholar, and SciELO databases. Results: CBF is determined by the relationship between blood pressure and cerebrovascular resistance, which is impacted by factors such as blood viscosity and the caliber of cerebral vessels. Nitric oxide (NO), released by endothelial cells in response to increased CO<sub>2</sub>, plays a crucial role in regulating CBF by promoting vasodilation. The klotho protein regulates its production and is associated with preventing neurodegeneration by protecting endothelial tissue against senescence and apoptosis. Furthermore, platelet factor 4 (PF4) is related to the improvement of the inflammatory response and cognitive function. Physical activity increases the release of neurotransmitters and brain-derived neurotrophic factor (BDNF), promoting angiogenesis and synaptogenesis. Conclusion: Increased CBF has a positive impact on cognition, providing more nutrients to the brain and protecting brain areas involved in memory and learning.

**Keywords:** Cerebrovascular Circulation; Cognition; Platelet Factor 4; Klotho Protein

## INTRODUCTION

Mild Cognitive Impairment (MCI) is a decline in one or more cognitive functions, such as: memory, attention, language<sup>1</sup>, and constitutes one of the main causes of morbidity and mortality among the elderly, producing progressive impairments. Thus, risk factors for MCI include aging, immobility, and depression<sup>2</sup>.

For the correct treatment of MCI, it is necessary to identify patients who are in a pre-clinical stage of dementia, such as Alzheimer's disease (AD), and if possible, to identify treatable causes such as depression, metabolic disease, and inadequate use of medications that interfere with cognition and their corrections<sup>3</sup>. As a pharmacological alternative for the treatment of AD and Parkinson's disease (PD), there are acetylcholinesterase inhibitors/anticholinesterases associated with occupational therapeutic intervention<sup>4,5</sup>. In contrast, non-pharmacological therapies have been suggested as a means of intervention capable of halting the advances of neurodegeneration without incurring side effects. It has already been demonstrated that regular physical activity/exercise plays a key role in brain and cardiovascular health, improving memory, blood perfusion in the brain, and attention<sup>6</sup>, and in the emergence of new synaptic connections after regular aerobic training<sup>7</sup>.

Furthermore, it is known that motor activities increase arterial supply to areas of the cortex: premotor, supplementary motor, and sensorimotor, due to the activation and elevation of the metabolism of these regions, thereby bringing more oxygen and glucose to these areas<sup>8</sup>. Despite this preliminary understanding, there is still a need to better understand such mechanisms; therefore, the objective of this literature review is to elucidate the influence of increased blood flow on cognitive improvement.

## METHOD

This study is characterized as a narrative review on the topic of blood flow and cognitive performance. It was conducted between September 2023 and August 2024 and followed recommendations as outlined in the PRISMA checklist.

For the collection of studies, the electronic databases MEDLINE/PubMed, Google Scholar, and Scielo were accessed. The search strategy used the composition and combination of the following keywords: Cognition; Cerebrovascular Circulation; Platelet Factor; Klotho protein.

## RESULTS

According to Machado, CBF is given by the ratio of blood pressure to cerebrovascular resistance, which depends on various factors: intracranial pressure, condition of the vascular wall, blood viscosity, and caliber of cerebral vessels<sup>9</sup>. The latter is related to the partial pressure of carbon dioxide [ $\text{PaCO}_2$ ], since cellular metabolism releases carbon dioxide ( $\text{CO}_2$ ) and causes baroreceptors to release nitric oxide (NO)<sup>10</sup>. This reaction to hypercapnia is known to be less than that to hypocapnia, where if it occurs, there is vasoconstriction reducing CBF<sup>11</sup>.

Endothelial cells release NO through heme proteins called NO synthase (NOS). In the brain, there is specifically bNOS (*brain NO synthase*) or cNOS, as it is also called, and generally, in vessels, eNOS (*endothelial constitutive NO synthase*)<sup>12</sup>. Both isoforms are calcium-dependent, meaning that the higher the intracellular concentration of  $\text{Ca}^{2+}$ , the more active isoforms are formed, and if the concentration falls, they lose their function<sup>13</sup>.

One of the proteins responsible for regulating the production of NO, to which cells are always exposed, is *klotho*, also responsible for protecting endothelial tissue against senescence and apoptosis. Klotho also decreases the inflammatory response and formation of tumor necrosis. Deficiency of this protein is associated with reduced cell lifespan, cognitive deficiencies, and hippocampal neurodegeneration<sup>14</sup>.

NO plays a role in the adhesion of blood elements, such as platelets, to the endothelium, decreasing its permeability<sup>15</sup>. One of the chemokines released by platelets into the bloodstream is platelet factor 4 (PF4), involved in coagulation and with an immunomodulatory function. Comparing blood from young and elderly individuals, the concentration of PF4 is higher in the younger ones. In clinical trials with mice, it can be observed that supplementing elderly specimens with PF4 shows a significant improvement in the inflammatory response in hippocampal microglia by decreasing complement system factors and pro-aging immunological factors, leading

to changes such as: containment of cognitive decline, improvement of hippocampus-dependent learning, and long-term memory<sup>16</sup>.

It also plays an important role in the *Long Term Potentiation* mechanism, in which after the neuron releases  $Ca^{2+}$  into the synaptic cleft, it also releases NO, functioning as a retrograde messenger in the hippocampus, and this seems to be related to learning and the formation of late memories<sup>17</sup>.

One of the main stimuli for increasing CBF and the necessary supplies to the brain are induced by increased levels of physical activity/exercise. This is responsible for increasing the release of neurotransmitters such as norepinephrine, epinephrine, serotonin, in addition to increasing the expression of a key factor, called brain-derived neurotrophic factor (BDNF), which is related to memory and learning, as it leads to angiogenesis (formation of new vessels), synaptogenesis (formation of new synapses) throughout the brain<sup>18</sup>.

## CONCLUSION

Increased CBF has a positive impact on cognition, improving it or halting cognitive decline. This process is accompanied by the release of NO and related compounds, which are responsible for preventing cell senescence and promoting protection to the temporal areas, the hippocampal region, and the prefrontal region responsible for cognition. Physical exercise appears to be a key factor in inducing cognitive improvements.

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