v. 4, n. 12, 2024

International Journal of Health Science

ANTIHYPERTENSIVE MEDICATIONS AND BRAIN FUNCTION: MECHANISMS UNDERLYING BENEFICIAL AND HARMFUL THERAPEUTIC NEUROPSYCHIATRIC EFFECTS

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Abstract: Goal: To evaluate and synthesize the scientific evidence available in current literature on the effects of antihypertensive medications on brain function, focusing on the mechanisms underlying beneficial and harmful therapy. **Methods**: Narrative bibliographic review carried out through the PubMed database by applying the search strategy "hypertension", "antihypertensive", "Brain function", "neurological", "symptons", in association with the Boolean operators "OR" and "AND", resulting in 1,471 initial articles. After applying the inclusion and exclusion criteria, only 19 studies became official sources of the work. **Discussion**: The blood pressure control caused by the use of antihypertensive drugs leads to an improvement in microvascular function with a consequent impact on reducing inflammation in brain cells, which appears to be promising for preventing possible cognitive decline in patients with mild impairment. **Final considerations:** In elderly patients with dementia, the concrete effect of using antihypertensives is controversial. In this aspect, it is noteworthy that there are still gaps in the literature regarding the effectiveness, effects and management of antihypertensive drugs in alleviating neuropsychiatric disorders.
Keywords: Brain Function, Anti-Hypertensive Medications, Therapeutics.

INTRODUCTION

Systemic arterial hypertension (SAH) is a chronic condition widely prevalent in adults globally, with a robust association with adverse cardiovascular outcomes. However, recent investigations have elucidated a bidirectional relationship between hypertension and changes in brain function, encompassing mental and cognitive aspects (CARNOVALE C. et al, 2023). The prevalence of hypertension in individuals over 50 years of age is

estimated at around 50%, and a significant proportion of this population coexists with dementia. Furthermore, both hypertension and hypotension have been correlated with cognitive decline, highlighting the complexity of blood pressure (BP) management in this cohort (CHEON E.J., 2022; BEISHAN L. et al, 2022).

Variability in BP, arterial remodeling and changes in cerebral autoregulation are factors implicated in the reduction of cerebrovascular reactivity, contributing to cognitive decline and central brain lesions (SIBLE I.J. et al., 2023). Despite emerging evidence, there is still a gap in the literature regarding the effectiveness of antihypertensive management in mitigating associated neuropsychiatric disorders.

Given the intricate relationship between hypertension and brain function, it is imperative to explore the therapeutic potential of antihypertensive agents in the cognitive and neuropsychiatric domains. Understanding the mechanisms by which these medications influence brain function may elucidate more effective management strategies, addressing not only BP modulation but also preservation of cognitive function and prevention of brain injury.

The objective of this review was to evaluate and synthesize current scientific evidence concerning the effects of antihypertensive medications on brain function. Focus will be placed on the underlying mechanisms that mediate beneficial and detrimental therapeutic effects, as well as the ability of these agents to overcome central physiological barriers such as the Blood-Brain Barrier (BBB) and the cerebrospinal fluid blood barrier, with a particular interest in lipid solubility and properties. pharmacokinetics that facilitate or obstruct the action of these drugs in the Central Nervous System (CNS) (CARNOVALE C. et al, 2023).

METHODOLOGY

This is a narrative bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "What are the effects of antihypertensive medications on brain function?". The searches were carried out by searching the PubMed Central (PMC) database. The search terms were used in combination with the Boolean terms "AND" or "OR": ((hypertension) OR (antihypertensive)) AND ((Brain Function) OR (((Neuropsychiatric) OR (Neurological)) AND (symptoms). From this search, 1,471 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles in the English language published in the period from 2022 to 2023 and that addressed the themes proposed for this research, studies of the type review, meta-analysis, randomized clinical trial, cohort, available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. A total of 19 articles were selected to compose the present study.

DISCUSSION

Hypertension affects approximately one billion individuals globally and represents a significant risk factor for diseases that compromise the cerebral vasculature. The mechanisms involved include dysregulation of cerebral perfusion, lesions in white and gray matter, impairment of the blood-brain barrier, neuroinflammation and accumulation of beta-amyloid. According to Acosta, J. N. et al. (2023), high blood pressure is a key factor in the risk of neurovascular diseases. Research indicates that maintaining normotensive blood pressure levels can delay

the development of dementia and cognitive deficits. These factors contribute to structural changes in the brain, therefore, controlling blood pressure has implications that go beyond the prevention of cardiovascular risks, including the maintenance of cognitive and neural integrity (CHEN X. et al., 2022).

According to Carnovale C. et al. (2023), there is a significant bidirectional relationship between hypertension and mental disorders. Hypertensive patients are more prone to mental disorders, which, in turn, can worsen the hypertensive condition. This bidirectional relationship involves dysfunction of the hypothalamic-pituitary-adrenal axis and continuous activation of the sympathetic nervous system, leading to increased blood pressure and, consequently, hypertension. The list of associated psychiatric disorders includes depression (unipolar or bipolar), anxiety, post-traumatic stress disorder (PTSD), psychosis, schizophrenia, mania and cognitive decline (CARNOVALE C. et al., 2023).

Regarding antihypertensive agents, Barroso W. K. S. et al. (2021) highlight three main classes: Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin II AT1 Receptor Blockers (ARB), which act on the Renin-Angiotensin-Aldosterone System (RAAS); Thiazide diuretics, which decrease blood volume; and Calcium Channel Blockers (CCB), which reduce peripheral vascular resistance. Each class has its specific mechanism of action in reducing blood pressure. Other classes of antihypertensives include beta-blockers, which act primarily by reducing cardiac output and renin secretion; centrally acting sympatholytics, which decrease sympathetic activity; and alpha-blockers, which act as antagonists of postsynaptic alpha-1 receptors, reducing peripheral vascular resistance without changing cardiac output (BARROSO W. K. S. et al., 2021).

Given the complexity of the pharmacological treatment of hypertension in patients with pre-existing neuropsychiatric comorbidities, the choice of therapy must be judicious. In patients with mild cognitive impairment, often due to Alzheimer's disease or vascular cognitive impairment, microvascular health is a potential therapeutic target. Medications such as Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs), including candesartan, may offer cognitive benefits by improving cerebrovascular reactivity (HENLEY B. et al., 2023).

According to a study by Kerkhofs D. et al. (2022), amlodipine treatment in elderly hypertensive mice demonstrated a mitigation of microglial inflammatory responses and memory impairment. Kopczak A. et al. (2023) corroborate these findings, indicating that amlodipine stands out compared to losartan and atenolol in improving microvascular function. Furthermore, Telmisartan, an ARB, exhibits multifactorial effects, acting on neurons, microglia, astrocytes and blood vessels.

This pharmacological approach shows promise for conditions characterized by chronic neuroinflammation, such as aging and neurodegenerative diseases (QUAN W. et al., 2023).

Carnovale C. et al. (2023) note that ACEIs and ARBs such as captopril, lisinopril, valsartan, telmisartan, and irbesartan have the potential to improve depressive behaviors in animal models. Furthermore, losartan, captopril and candesartan have shown efficacy in reducing anxiety. Within the scope of beta-blockers, propranolol has been the most investigated for neuropsychiatric uses, showing benefits in reducing aggression and improving problem solving, social communication and working memory in various neurological conditions (CARNOVALE C. et al., 2023). Naessens, D. et

al. (2023) report that prolonged use of atenolol in hypertensive rats showed no impact on the resistance of the cerebral vasculature, but restored the contractile function of cerebral arteries, without affecting cerebral atrophy and axonal damage.

Other classes of antihypertensives, such as alpha-blockers and alpha-2-agonists, also have beneficial effects in neuropsychiatric conditions such as Post-Traumatic Stress Disorder (PTSD) and Attention Deficit Hyperactivity Disorder (ADHD), respectively (CARNOVALE C. et al., 2023). Regarding calcium channel blockers, they do not appear to affect brain function when used in antihypertensive therapeutic doses. However, high doses of verapamil and diltiazem were associated with depressive effects, while nifedipine showed antidepressant properties (CARNOVALE C. et al., 2023). Finally, diuretics have been shown to be effective in reducing blood pressure and may have applicability in central symptoms of Autism Spectrum Disorder (ASD), especially through bumetanide. However, the results are inconsistent and require further investigation (CARNOVALE C. et al., 2023).

According to Zheng, Z. et al. (2022), carvedilol is widely used in the treatment and reduction of risks associated with various comorbidities, such as systemic arterial hypertension and risk of stroke, among others. The study in question highlighted the role of carvedilol in inhibiting cell apoptosis, which was beneficial to reduce the expression of Bax and cleaved caspase-3, and to increase the expression of Bcl-2 in OGD/R-PC12 cells. However, the authors highlight that the underlying regulatory mechanisms still require further investigation. The study concludes that carvedilol, a beta-adrenergic blocker, attenuates cellular apoptosis by modulating the expression of ATF3, suggesting a potential therapeutic role in the treatment of ischemic stroke.

Other research has also explored the effects of beta-blockers. The study by Zhou, J. et al. (2022) sought to consolidate the evidence on the use of propranolol in reducing physiological and pathological tremors. Using healthy mouse models with symptoms of tremor and cerebellar ataxia, the study demonstrated that propranolol can alter the activity of the cerebellar circuit and, consequently, reduce tremors. Furthermore, the study corroborated previous hypotheses about the depressant effects of propranolol on the central nervous system.

Kim's study. J. et al. (2022) examined the class of calcium channel blockers, identifying neuroinflammation as a common element in several neurological pathologies, proposing that its reduction may be beneficial to treat cognitive dysfunctions. The study demonstrated that felodipine, an L-type calcium channel blocker, was able to modulate microglial activity and reduce the levels of pro-inflammatory cytokines, resulting in an improvement in spatial memory.

Although the systematization of the clinical and neuropsychiatric effects of antihypertensive drugs is not yet complete, there is robust evidence about their benefits and harms. Alpha-1 blockers, for example, have shown potential in reducing trauma-related memories and improving cognition, even under stress. Alpha-2 agonists promote cognitive functions and relieve anxiety, but intensify the side effects of antidepressants. Beta-blockers improve memory and communication, but can induce sleep disorders and depressive symptoms (CARNOVALE C. et al., 2023).

Among the most solid data, we highlight the fact that noradrenergic lipophilic antihypertensives cause depressive symptoms and Bumetanide shows promising results for autism and epilepsy in specific cases. Therefore,

although there is not yet sufficient systematic information to prove the effectiveness of these drugs in treating psychiatric illnesses, different therapeutic approaches can be considered according to the patients' personal and family history (CARNOVALE C. et al., 2023).

In the neuroclinical context, previous studies have demonstrated that ACE inhibitors (ACEIs) have the potential to reduce microglial activation and neuronal damage in mice with Alzheimer's disease, as well as improve cognitive function and memory in observational studies and clinical trials with patients. of the same disease. A study by Nagy, A. et al. (2022), for example, investigated the relationship between the concentration of ACEIs and cognition, showing a significant correlation with negative effects on motor skills, attention and learning related to Lisinopril. This effect was attributed to the concentration of the drug, which did not significantly impact the decrease in blood pressure, but increased white matter abnormalities (NAGY, A. et al., 2022).

The picture is even more complex when it comes to dementia, a condition often associated with hypertension. According to Beishan, L. et al. (2022), blood pressure targets in dementia are still uncertain, and both high and low blood pressure levels have been associated with cognitive worsening. There is a pressing need for further investigation, especially in relation to different pressure targets in already established dementia and vascular physiological effects (BEISHAN, L. et al., 2022).

For elderly patients with dementia, the actual effect of antihypertensive medications is controversial. A meta-analysis conducted by Lennon, M.J. et al. (2023) revealed that hypertensive patients without treatment have a 42% and 26% higher risk of developing dementia when compared to controls and hypertensive patients undergoing treatment, respectively. Furthermore, other factors such as age, sex and racial group did not show significance in modulating the development of dementia in hypertensive patients (LENNON, M.J. et al., 2023).

FINAL CONSIDERATIONS

This review highlighted the high prevalence of hypertension in the global population and its role as a critical risk factor for diseases affecting the cerebral vasculature. A significant relationship was identified between hypertension and the incidence of dementia, attributing this to changes in arterial remodeling, variations in blood pressure (BP) and changes in cerebral autoregulation, which contribute to the decrease in cerebrovascular reactivity, cognitive decline and potential brain injuries.

Proper maintenance of blood pressure levels is essential not only to reduce cardiovascular risks, but also to delay the development of neurocognitive disorders. Furthermore, this review revealed a bidirectional relationship between hypertension and mental disorders, where disorders such as depression, anxiety, and Post-Traumatic Stress Disorder (PTSD) can exacerbate hypertension. Antihypertensive medications, especially the beta-blocker carvedilol, have demonstrated efficacy in reducing neuropsychiatric symptoms and improving cognitive function, although their influence on cerebral vascular resistance still requires further studies. However, the optimal therapeutic targets for blood pressure in patients with dementia remain unclear, requiring additional research. In elderly people with dementia, the effect of antihypertensives is still controversial, and there are gaps in the literature regarding the efficacy, effects and management of these medications in the treatment of neuropsychiatric disorders.

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