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Nonsteroidal anti-inflammatory drugs as a pharmacological alternative in Alzheimer's disease

Antiinflamatórios não esteroides como alternativa farmacológica na doença de Alzheimer

Antiinflamatorios no esteroides como alternativa farmacológica en la enfermedad de Alzheimer

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Abstract

Introduction: Inflammatory response in AD is characterized by the presence of activated microglia (the resident immunocompetent cells of the brain) in close association with neuritic plaques. Current evidence suggests that microglia are primarily involved in phagocytic activity and may be responsible for inducing additional neuronal damage by generating oxygen species and proteolytic enzymes. If anti-inflammatory drugs protect against the neurodegeneration seen in the brain of AD patients, then patients with a history of anti-inflammatory use should have a reduction in pathological changes in the brain and brain inflammation. Objective: to explain about the use of non-steroidal anti-inflammatory drugs as drug therapy for Alzheimer's disease. Results: Brain inflammation is believed to contribute to the pathological features of Alzheimer's disease (AD), and it has been postulated that anti-inflammatories protect against this tissue damage. However, one of the controversial factors regarding the use of non-steroidal anti-inflammatory drugs to reduce the risk of developing Alzheimer's disease is the toxicity associated with these drugs. Methodology: This is a systematic literature review with works searched in the following databases: National Library of Medicine (PubMed MEDLINE), Scientific Electronic Library Online (Scielo), Cochrane Database

of Systematic Reviews (CDSR), Google Scholar, Library Health Virtual (VHL) and EBSCO Information Services. Relevant sources inherent to the theme were analyzed, using as one of the main criteria the choice of current, original and international articles. A total of 12 scientific articles were available for review. Final considerations: Anti-inflammatory drugs have been suggested as a possible treatment for Alzheimer's disease (AD). The association of immune proteins and immunocompetent microglial cells with senile plaques (SP) in AD and normal aging suggests that these drugs may be able to modify the course of AD, either interfering with SP formation or suppressing inflammation.
Keywords: Alzheimer's disease; Neurodegenerative; Pharmacotherapy; INEs.

Resumo

Introdução: A resposta inflamatória na DA é caracterizada pela presença de microglia ativada (as células imunocompetentes residentes do cérebro) em estreita associação com placas neuríticas. Evidências atuais sugerem que a microglia está envolvida principalmente na atividade fagocítica e pode ser responsável por induzir danos neuronais adicionais através da geração de espécies de oxigênio e enzimas proteolíticas. Se os medicamentos anti-inflamatórios protegem contra a neurodegeneração observada no cérebro dos pacientes com DA, então os pacientes com histórico de uso de anti-inflamatórios devem ter uma redução nas alterações patológicas no cérebro e na inflamação cerebral. Objetivo: explanar sobre o uso de anti-inflamatórios não esteroides como terapia medicamentosa para a doença de Alzheimer. Resultados: Acredita-se que a inflamação cerebral contribui para as características patológicas da doença de Alzheimer (DA), e foi postulado que os antiinflamatórios protegem contra esse dano tecidual. Porém, um dos fatores controversos em relação ao uso de antiinflamatórios não esteroidais para reduzir o risco de desenvolver a doença de Alzheimer é a toxicidade associada a esses medicamentos. Metodologia: Trata-se de uma revisão sistemática da literatura com trabalhos pesquisados nas seguintes bases de dados: National Library of Medicine (PubMed MEDLINE), Scientific Electronic Library Online (Scielo), Cochrane Database of Systematic Reviews (CDSR), Google Scholar, Library Health Virtual (BVS) e Serviços de Informação EBSCO. Foram analisadas fontes relevantes inerentes ao tema, utilizando como um dos principais critérios a escolha de artigos atuais, originais e internacionais. Um total de 12 artigos científicos foram disponibilizados para revisão. Considerações finais: Os antiinflamatórios têm sido sugeridos como possível tratamento para a doença de Alzheimer (DA). A associação de proteínas imunes e células microgliais imunocompetentes com placas senis (SP) na DA e no envelhecimento normal sugere que essas drogas podem ser capazes de modificar o curso da DA, interferindo na formação de SP ou suprimindo a inflamação.
Palavras-chave: Doença de Alzheimer; Neurodegenerativo; Farmacoterapia; AINEs.

Resumen

Introducción: La respuesta inflamatoria en la EA se caracteriza por la presencia de microglía activada (las células inmunocompetentes residentes del cerebro) en estrecha asociación con placas neuríticas. La evidencia actual sugiere que la microglía participa principalmente en la actividad fagocítica y puede ser responsable de inducir daño neuronal adicional al generar especies de oxígeno y enzimas proteolíticas. Si los medicamentos antiinflamatorios protegen contra la neurodegeneración observada en el cerebro de los pacientes con EA, entonces los pacientes con antecedentes de uso de antiinflamatorios deberían tener una reducción de los cambios patológicos en el cerebro y de la inflamación cerebral. Objetivo: explicar sobre el uso de antiinflamatorios no esteroideos como terapia farmacológica para la enfermedad de Alzheimer. Resultados: Se cree que la inflamación cerebral contribuye a las características patológicas de la enfermedad de Alzheimer (EA), y se ha postulado que los antiinflamatorios protegen contra este daño tisular. Sin embargo, uno de los factores controvertidos respecto al uso de fármacos antiinflamatorios no esteroides para reducir el riesgo de desarrollar la enfermedad de Alzheimer es la toxicidad asociada a estos fármacos. Metodología: Se trata de una revisión sistemática de la literatura con trabajos buscados en las siguientes bases de datos: Biblioteca Nacional de Medicina (PubMed MEDLINE), Biblioteca Electrónica Científica en Línea (Scielo), Base de Datos Cochrane de Revisiones Sistemáticas (CDSR), Google Scholar, Biblioteca Virtual de Salud (VHL) y Servicios de Información de EBSCO. Se analizaron fuentes relevantes inherentes al tema, teniendo como uno de los principales criterios la elección de artículos actuales, originales e internacionales. Un total de 12 artículos científicos estuvieron disponibles para su revisión. Consideraciones finales: Se han sugerido fármacos antiinflamatorios como posible tratamiento para la enfermedad de Alzheimer (EA). La asociación de proteínas inmunes y células microgliales inmunocompetentes con placas seniles (SP) en la EA y el envejecimiento normal sugiere que estos fármacos pueden modificar el curso de la EA, ya sea interfiriendo con la formación de SP o suprimiendo la inflamación.
Palabras clave: Enfermedad de Alzheimer; Neurodegenerativo; Farmacoterapia; AINEs.

1. Introduction

Described for the first time in 1906, by the German doctor Alois Alzheimer, at a scientific conference where he presented the case of his patient Auguste Deter, Alzheimer's Disease (AD) was then defined as a disease characterized by notable clinical complexity, with the intertwining of psychiatric, behavioral, neurological, general clinical and biological

specific symptoms, with peculiar anatomical and histopathological changes. Currently, Alzheimer's dementia is receiving great attention from public authorities in the field of health, since the number of people with dementia has become increasingly greater, pointing to a true global epidemic (Gyengesi et al., 2020).

Alzheimer's disease is the most common neurodegenerative pathology associated with age, whose cognitive and neuropsychiatric manifestations result in progressive disability and incapacitation. The disease affects approximately 10% of individuals over the age of 65 and 40% over the age of 80. It is estimated that, by 2050, more than 25% of the world's population will be elderly, thus increasing the prevalence of the disease. The initial symptom of the disease is characterized by the progressive loss of recent memory. As the pathology progresses, other changes occur in memory and cognition, including deficiencies in language and visual -spatial functions. These symptoms are often accompanied by behavioral disturbances, including aggression, depression, and hallucinations (McGeer et al., 2006).

Brazil appears as the eighth country that contributes most to population growth in the world according to the United Nations , and according to the last census carried out in 2010 by the Brazilian Institute of Geography and Statistics (IBGE), around 14.5 million Brazilians aged 60 years or over, representing something around 8.6% of the total population, a very considerable number in relation to the 1991 census, which showed a total of 7.3% of elderly people living in the country at that time. The World Health Organization (WHO) highlights that worldwide by 2025, there will be 1.2 billion people over the age of 60, with very elderly individuals (aged 80 or over) making up the fastest growing group. Furthermore, recent estimates indicate that there is an increase of almost 35 million elderly people worldwide affected by Alzheimer's type dementia (Sereniki et al., 2008).

AD can be divided into three phases – mild, moderate or severe – characterized by their level of cognitive impairment and their degree of dependence. In the first phase, impairment of recent memory and disorientation of time and space are identified and lasts on average 2 to 3 years. In the intermediate phase, which lasts from 2 to 10 years, remote memory impairment, difficulties in solving problems and operational activities are noticed, affecting basic and instrumental activities of daily life. And in the final phase, lasting 8 to 12 years, there is total dependence, evidenced by the loss of the ability to perform basic and instrumental activities and immobility. The diagnosis of AD can only be established based on a clinical picture and exclusion of other cases of dementia through laboratory and neuropathological examinations. (Parihar et al., 2004).

As for treatment, AD still has no cure, however, there are pharmacological measures that aim to reduce cognitive and memory effects, which are based on the prescription of anticholinesterases (rivastigmine, donepezil and galantamine) and memantine (antiglutamatergic). Furthermore, non-pharmacological measures can be used to provide an improvement in the quality of life of the patient and their family/caregiver, which aim to establish the most efficient use of memory, through multidisciplinary care strategies, with mnemonic or learning techniques, compensatory strategies, reality orientation therapies and the therapeutic approach with groups of families and caregivers (Brown et al., 2003). Furthermore, the use of anti-inflammatory drugs has been suggested as a possible treatment for the disease and, given this, the objective of this research was to explain the use of non-steroidal anti-inflammatory drugs as a therapy for Alzheimer's Disease.

2. Methodology

This is a descriptive research of the systematic literature review type. To develop the research question, the PICOT strategy (Acromion for *Patient, Intervention, Comparison, Outcome and Time*) was used . Using this strategy to formulate the research question when conducting review methods enables the identification of keywords, which help to locate relevant primary studies in databases. Thus, the delimited research question was: “What is the evidence regarding the use of anti-inflammatories as a therapy for Alzheimer’s Disease?” In this way, it is understood that P = patients with Alzheimer's Disease;

I = patients with Alzheimer's disease who use NSAIDs as therapy for the disease; Co = patients with Alzheimer's disease who do not use NSAIDs as therapy for the disease, and T = two months of data collection.

After establishing the research keywords, the descriptors were crossed, in English: *"Alzheimer's disease", "non-steroidal anti-inflammatory", "NSAID", "pharmacotherapy", "coxibs"* and in Portuguese: *"Alzheimer's disease", "non-steroidal anti-inflammatory", "NSAIDs", "pharmacotherapy", "coxibs"* in the following databases: *National Library of Medicine* (PubMed MEDLINE), *Scientific Electronic Library Online* (Scielo) , Cochrane Database of Systematic Reviews (CDSR), Google Scholar, Virtual Health Library (VHL) and EBSCO *Information Services* . The bibliographical research was exploratory in nature, starting from the identification, selection and evaluation of works and scientific articles considered relevant to provide theoretical support for the classification, description and analysis of results.

The search was carried out in the months of October and November 2021. Studies published in the period between 2001 and 2021 were considered. The article selection strategy followed the following steps: search in the selected databases; reading the titles of all articles found and excluding those that did not address the subject; critical reading of article summaries and full reading of articles selected in the previous stages. Relevant sources inherent to the topic, original and international, were analyzed. After careful reading of the publications, 3 articles were not used due to the exclusion criteria. Thus, there were a total of 13 scientific articles for the systematic literature review, with the descriptors presented above. After this selection, articles from the last two years and articles in English and Portuguese were filtered. As inclusion criteria, original articles were considered, which addressed the researched topic and allowed full access to the study content, from 2001 to 2021, in English and Portuguese.

3. Results and Discussion

Cyclooxygenase (COX) is the main enzyme in the biosynthesis of prostaglandins. It exists in two isoforms, constitutive COX-1 (responsible for physiological functions) and inducible COX-2 (involved in inflammation). COX inhibition explains the therapeutic effects (COX-2 inhibition) and side effects (COX-1 inhibition) of nonsteroidal anti-inflammatory drugs (NSAIDs). In other words, NSAIDs act through the competitive inhibition of cyclooxygenase (COX), an enzyme linked to the biotransformation of arachidonic acid into prostaglandins. While the COX-1 isoform is constitutively expressed in various tissues, COX-2 is expressed as a consequence of induction by stimuli such as pro-inflammatory cytokines, lipopolysaccharides and mitogens. From this perspective, an NSAID that selectively inhibits COX-2 is likely to retain maximal anti-inflammatory efficacy combined with less toxicity (McGeer et al., 2006).

Based on evidence that inflammatory processes are involved in the pathogenesis of Alzheimer's disease, research has observed the use of non-steroidal anti-inflammatory drugs and steroidal glucocorticoids as treatment options for patients with the disease. Furthermore, it is known that inflammatory phenomena occur secondarily throughout maturation and in the vicinity of senile plaques, as part of the b-amyloid cascade, and, thus, the accumulation of microglial cells occurs around the plaques, acute phase reactions. mediated by local cytokines and activation of the complement cascade. Furthermore, studies with transgenic mice have suggested that indomethacin and ibuprofen can even reduce the formation of b-amyloid (Gyvengesi et al., 2020).

Therefore, it is acceptable to assume that anti-inflammatory drugs may also exert a neuroprotective effect, modifying the pathogenesis and, thus, the risk and the therapy itself of AD. Furthermore, epidemiological studies conducted at the end of the last decade suggested that prolonged use of non-steroidal anti-inflammatory drugs would be associated with a reduction in the incidence of AD, but would not affect the risk of vascular dementia. This benefit would be restricted to chronic users of these medications, such as those with rheumatic and orthopedic diseases, as, otherwise, this supposed neuroprotective effect would be outweighed by the risks of continuous exposure to anti-inflammatories (Aisen et al., 2003). Other important findings

linking inflammation to AD pathology are the identification of activated complement fragments, including the membrane attack complex, as well as inflammatory cytokines in association with the lesions. Furthermore, *in vitro*, activated microglia would release toxic factors for neurons, which could be partially blocked by NSAIDs (Forlenza, 2005).

(Aβ) levels above 80% in cell culture. As not all non-steroidal anti-inflammatory drugs showed this effect, it is believed that this reduction occurred through a process independent of the anti-inflammatory activity on COX-1 (Aisen et al., 2003). Furthermore, a study by Gyengesi et al. (2020) also demonstrated that neurons treated with COX-1 inhibitors, such as ibuprofen and acetylsalicylic acid, were more resistant to the effects of Aβ, compared to neurons treated with COX-2 inhibitors. The study also demonstrated a reduction in the production of prostaglandins in neurons treated with COX-1 and COX-2 inhibitors. Furthermore, indomethacin was able to suppress the expression of numerous pro-inflammatory genes in monocytes, in addition to microglia (Scali et al., 2003). The administration of indomethacin also produced neuroprotection by inhibiting the induction of COX-2, which was capable of potentiating excitotoxicity and increasing the production of free radicals and tumor necrosis factors (Sereniki et al., 2008).

From this perspective, the results of some epidemiological studies, which used anti-inflammatory agents, suggest that neuroinflammation may play an initial role in the pathogenesis of Alzheimer's disease; however, clinical studies, especially involving selective COX-2 inhibitors, have been disappointing (Moore et al., 2002). Furthermore, other factors, such as, for example, the complement system for nicotinic receptors, which is implicated in the inflammatory process associated with Alzheimer's disease, demonstrate that there are still many mechanisms related to the pathology that need to be understood (Reines et al., 2004). Other factors to consider are that many of the participants in the inflammatory process, such as microglia and astrocytes, may have both neuroprotective and neurodegenerative functions, making their roles difficult to determine in the disease process (Parihar et al., 2004).

Of patients with Alzheimer's disease, anti-inflammatory drug users performed better on neuropsychological test scores than non-users. However, there were no significant differences in the amount of inflammatory glia, plaques, or tangles in either diagnostic group (Brown et al., 2003). Furthermore, the association of immune proteins and immunocompetent microglial cells with senile plaques (SP) in AD and normal aging suggests that these drugs may be capable of modifying the course of AD, either by interfering with SP formation or by suppressing inflammation (Tuppo et al., 2005).

However , one of the controversial factors regarding the use of non-steroidal anti-inflammatory drugs to reduce the risk of developing Alzheimer's disease is the toxicity associated with these medications, given that non-steroidal anti-inflammatory drugs have been recognized to cause problems gastrointestinal, renal, hematological, cardiovascular and on the central nervous system, with the elderly population, which would use these medications, being more susceptible to toxic effects (Hoozemans et al., 2003) . Overall, these studies suggest that alternative hypotheses exist for mechanisms of cognitive improvement with NSAIDs, particularly if cerebrovascular processes play a more significant role. Morphological and biochemical changes in the cerebral vasculature can affect cerebral perfusion and the permeability of the blood-brain barrier and thus affect cognition. These factors appear to underlie the clinical effects observed with NSAID use, rather than a direct action against pathological changes in the brain (Mackenzie, 2001).

4. Final Considerations

Anti-inflammatories have been suggested as a possible treatment for Alzheimer's disease (AD). It is clear that given this entire panorama in which AD is inserted, it is necessary to highlight that the last 100 years have seen unprecedented advances in the understanding of the dynamics of the brain and its possibilities for rehabilitation after a brain injury. In this scenario, there are favorable and promising perspectives for the treatment of Alzheimer's dementia and, even if it is not yet possible to cure this disease, it is possible, at least, to alleviate and delay the impacts it causes on the lives of those with it. and

family members, promoting a better quality of life during the stage in which the clinical condition is evolving. Therefore, further studies are now needed to test all possible hypotheses for the drug's action and increase our understanding of any protective mechanisms against the disease process.

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