DOI: 10.1111/bph.16292

EDITORIAL

BJP BRITISH PHARMACOLOGICAL SOCIETY

From Alzheimer's disease to vascular dementia: Different roads leading to cognitive decline

As life expectancy is projected to increase in the coming years, along with an anticipated increase in the prevalence of cognitive impairment and dementia, there is a significant emphasis on preserving and promoting brain health as a primary public objective (Fuster et al., 2023). Preserving cognitive function is a crucial aspect of successful ageing, while its decline can profoundly impact quality of life, functional independence, and the risk of requiring institutional care. Alzheimer's disease (AD) and vascular dementia (VaD) are the most prevalent types of dementia in the elderly. However, it is remarkable that conditions such as 'pure AD' or 'pure VaD' are relatively uncommon, since most patients present with mixed pathology. Indeed, the coexistence in many cases of typical AD neurodegenerative hallmarks (such as amyloid plaques and neurofibrillary tangles) and vascular pathology (such as cerebral microbleeds, micro-infarcts, arteriolosclerosis, etc.) opens the door for researchers to speculate that vascular and degenerative pathways may potentially interact with one another, possibly resulting in a synergistic impact (Iadecola et al., 2019). Vascular pathology is present in 75% of individuals over 65 years of age and has an important additive role when combined with AD pathology (van der Flier et al., 2018). However, whether vascular pathology may promote or be a downstream consequence of AD development is unknown and this chicken-or-egg question probably does not have a straight unique answer for all patients. Currently, anti-amyloid strategies are showing promising effects of slowing cognitive decline in mildly symptomatic individuals, however they have not been demonstrated to effectively stop the progression of AD, and the occurrence of side effects related to vascular events has been reported (Sims et al., 2023; van Dyck et al., 2023). Thus, there is strong need for comprehensive treatments that address both AD and vascular pathology to avert the increasing global burden of neurodegenerative diseases and dementia (Figure 1).

The vascular system has a vital impact on brain function throughout life span, both in health and disease. Within this context, cardiovascular disease (CVD) is well recognized as a key contributor to VaD and a full range of cognitive syndromes, globally defined as vascular cognitive impairment (VCI). Indeed, cardiovascular risk factors (CVRFs) can chronically sustain common multiple cellular and molecular mechanisms leading to vascular pathological damages (i.e., endothelial dysfunction, arterial stiffness, vasoreactivity alterations and hypoperfusion) that, at the brain level, are likely to be implicated in neurodegenerative conditions (Iadecola et al., 2019). Remarkably, several studies have also underscored the role of CVD and CVRFs as an adjuvant for the expression of other types of dementia, including AD (Cortes-Canteli & Iadecola, 2020). Curiously, Alois Alzheimer in his first report already evidenced vascular dysfunction in the AD brain (Alzheimer et al., 1995). On the one hand, people affected by conditions such as midlife hypertension, obesity, smoking, physical inactivity, atherosclerosis, and diabetes have a higher risk to develop both VaD and AD (Iadecola et al., 2019). Notably, some of these conditions are part of the modifiable risk factors identified by the '2020 Lancet Commission on dementia prevention, intervention, and care' to be responsible for 40% of the dementia cases (Livingston et al., 2020). On the other hand, several vascular alterations including pathology of the brain microcirculation, neurovascular unit dysfunction, a pro-coagulant state and hypertensive vascular remodelling have been described in AD patients (Cortes-Canteli & Iadecola, 2020). Additionally, cerebral blood flow and glucose metabolism are reduced and the brain vascular resistance is increased in human AD and in mice over-expressing amyloid precursor protein to mimic AD, as well as in humans and mice expressing the e4 allele of Apolipoprotein E, which predisposes to an increased risk of AD (Korte et al., 2020).

CVD and CVRFs are also associated with a sustained chronic inflammatory status (Furman et al., 2019; Goldfine & Shoelson, 2017), and lead to immune system activation, including phenomena like immunothrombosis as well as derangement of bone marrow haematopoiesis (Rohde et al., 2022). Over the past decades, emerging evidence has implicated immune system activation as a key player in neurodegeneration (Endres et al., 2022; Kinney et al., 2018). Consequently, both microglia and elements of the peripheral immune system, which may potentially infiltrate the brain, are increasingly recognized as possible novel targets to enhance the effectiveness of current therapeutic approaches (Cummings et al., 2022).

This Themed Issue discusses some of these intricate interconnected pathways, and stems from the Round Table 'From Alzheimer's disease to vascular dementia: different roads leading to cognitive decline' organized with the support of the British Journal of Pharmacology and the British Pharmacological Society during the 19th Meeting of the Spanish Society of Neuroscience organized in Lleida (Spain) on 3–5 November 2021.

Readers of this Themed Issue will find a review by Toribio-Fernandez, Ceron, Cortes-Canteli and coworkers describing in detail the vascular dysfunction and pro-coagulant state contributing to AD onset and progression, with particular emphasis on their effect on the

Abbreviations: AD, Alzheimer's disease; CVD, cardiovascular disease; CVRFs, cardiovascular risk factors; VaD, vascular dementia; VCI, vascular cognitive impairment.

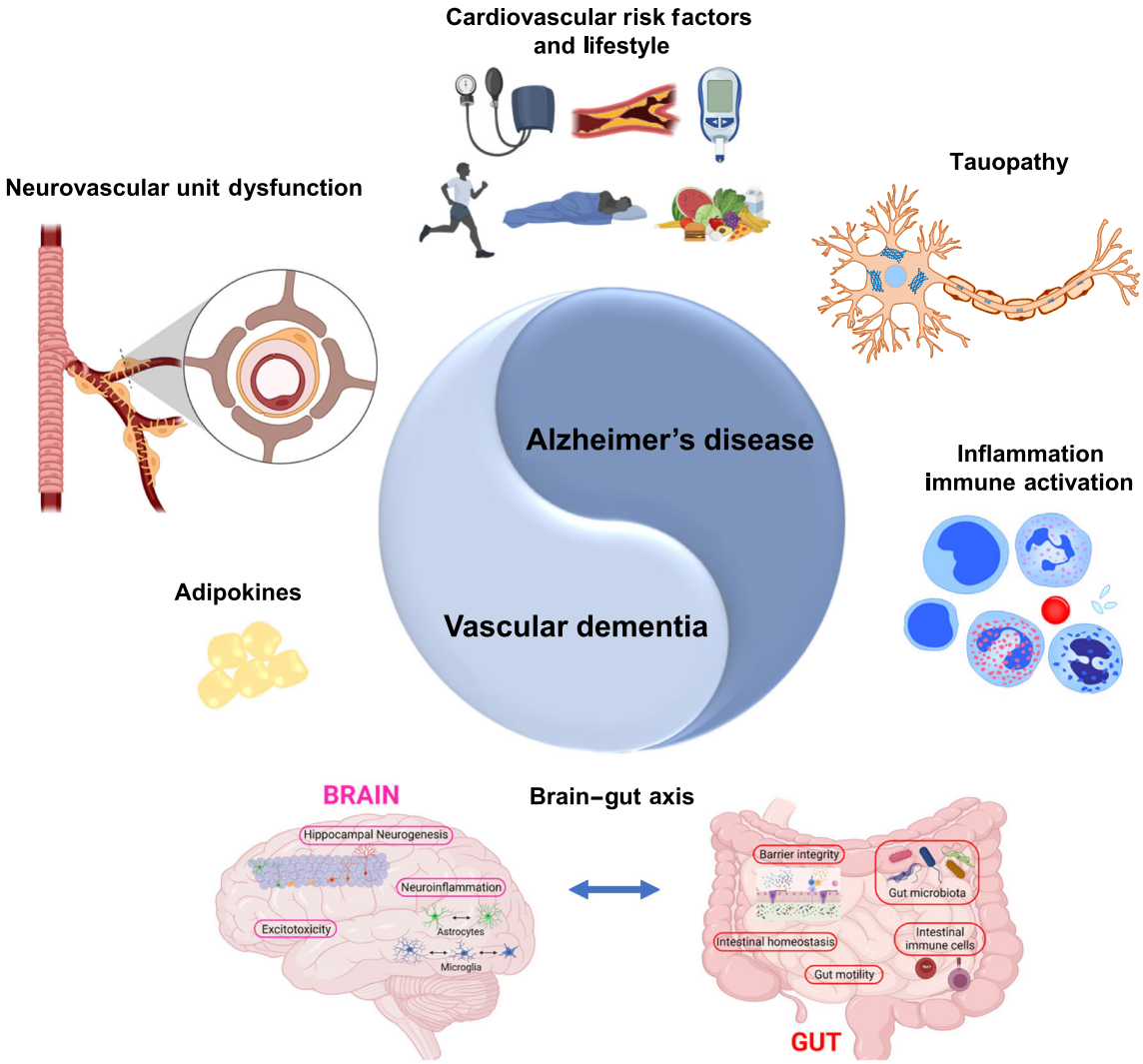

FIGURE 1 Multiple shared risk factors and pathogenetic mechanisms contribute to degeneration and cognitive impairment in Alzheimer's disease and vascular dementia. Partially created with BioRender.com.

deposition/clearance of **amyloid-β** peptide, one of the pathological hallmarks of AD (Toribio-Fernandez et al., 2023). With the idea that normalizing this abnormal thrombosis could be a plausible AD therapeutic approach, they provide a comprehensive review of clinical studies in atrial fibrillation patients using long-term anticoagulation—from the classic vitamin K antagonists (e.g., **warfarin** and **acenocoumarol**) to the direct oral anticoagulants (e.g., **factor Xa** inhibitors such as **apixaban**, **rivaroxaban** or edoxaban; and thrombin inhibitors such as **dabigatran**)—with a specific focus on dementia development. They finally discuss which would be the best strategy in a hypothetical clinical trial targeting the procoagulant state observed in AD. Moreover, this Themed Issue goes one step further and provides the first comprehensive review linking the vascular component of AD with **tau** accumulation, the other pathological hallmark of AD: Kim, Santa-Maria and collaborators summarize how tau proteostasis dysregulation contributes to vascular dysfunction and conversely, they examine the factors and pathways leading to tau pathological alterations triggered by cerebrovascular dysfunction, highlighting the role that epigenetic and epitranscriptomic factors play in regulating the integrity of the cerebrovascular system and the progression of tauopathy, including a few remarks on potential therapeutic interventions (Kim et al., 2023).

In line with the contribution of CVRFs such as diabetes, obesity and other metabolic disorders to dementia development, Bettinetti-Luque et al. dig into the cross-talk between adipose tissue and the brain. These authors specifically focus on the effect of a range of endogenous biologically active factors released by adipose tissue, known as adipokines (e.g., such as **leptin** and **adiponectin**), on inflammation, brain function, blood–brain barrier permeability and development of neurodegenerative diseases, including AD, to finally provide an overview of the potential therapeutic applications related to the actions of these adipokines on the brain's performance (Bettinetti-Luque et al., 2023).

The involvement of the immune system is increasingly acknowledged as a common theme in the pathophysiology of the development and progression of both VaD and AD. In this context, García-Culebras et al. address the contribution of both central and peripheral innate immune response to cognitive impairment,

specifically dissecting the role of cells of the myeloid lineage, mainly represented by neutrophils and monocytes, as well as resident brain microglia and border-associated macrophages (García-Culebras et al., 2023). The interactions of neutrophils with platelets, and the associated thrombo-inflammation, are highlighted as potentially relevant mechanisms in post-stroke cognitive impairment and AD. Of note, the significant role of border-associated macrophages, including their influence on neuroimmune interfaces, is pinpointed as a focal aspect for understanding how CVRFs may converge to affect the integrity of perivascular spaces and meningeal homeostasis, with ultimate impact on neurological dysfunction. Finally, novel pharmacological targets are proposed for prevention of cognitive disorders, aimed at the peripheral inhibition of neutrophil extracellular traps (NETs) formation (for instance, with **Cl-amidine**, an inhibitor of **PAD4**), and of myeloid **TLR4** receptors.

Within the immune system, adaptive immunity is also involved, as addressed by Ruiz-Fernández et al. Specifically, the role of T cells and their interplay with other immune and CNS parenchymal cells in health and disease are discussed, with an emphasis on the scenarios, mainly related to neurodegeneration and ageing (AD, Parkinson's disease, multiple sclerosis, ischemic stroke, etc.), in which disruption of these connections may lead to cognitive impairment (Ruiz-Fernández et al., 2023). The potential for the pharmacological modulation of T cells is reviewed, starting from molecules that prevent lymphocyte infiltration in the CNS (monoclonal antibodies against integrins, like **natalizumab**, or against CD49d; **$S1P_1$** receptor agonists such as **fingolimod**), with major clinical utility in multiple sclerosis, moving to modulators of the intestinal microbiota like **sodium butyrate** and **valproic acid**, with potential application in ischemic stroke, and the granulocyte-macrophage colony-stimulating factor **sargramostim** for AD.

In part by interacting with the immune system, increasing evidence suggests that commensal microbiota have a major role both in homeostasis and in pathological contexts including cerebrovascular diseases. In this vein, Cuartero et al. (2023) underscore the intricate interplay between microbiota and metabolism, immunity, brain development and function. Specifically, the possible participation of microbiota-derived products in post-stroke cognitive impairment and dementia is discussed, including potential therapeutic opportunities ranging from probiotics and prebiotics, antibiotics, and faecal microbiota transplantation. Strategies aiming at the treatment of gut dysbiosis are proposed, with special emphasis on the **aryl hydrocarbon receptor**. This transcription factor is activated by various environmental and microbial metabolites and is widely expressed in both the gut and the CNS, making it a pivotal component in the brain-gut axis.

Additional roads leading to cognitive decline include other actors. As an example, in an original article of this issue, Fan et al. (2023) report that astrocytic lactoferrin, a secreted glycoprotein, may improve cognitive capacity in AD animal models by increasing the dephosphorylation of APP, opening new lines in the search for therapeutic targets in dementia. With this Themed Issue, we intend to attract additional interest and effort to the development of a holistic approach to dementia, acknowledging the multiple brain co-pathologies associated with ageing, and highlighting the complex relationships between vascular health, immune responses, and neurodegenerative diseases. We stress the importance of this multifaceted perspective, as it opens up new avenues for lifestyle adjustments and therapeutic interventions, and is essential in addressing the mounting challenges posed by our ageing society and the increasing burden of cognitive decline and dementia.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Christopoulos et al., 2021; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, Beuve et al., 2021a; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, Boison et al., 2021b; Alexander, Kelly et al., 2021).

AUTHOR CONTRIBUTIONS

Aurora Semerano: Writing—original draft (equal); writing—review and editing (equal). **Javier Fernandez-Ruiz:** Writing—review and editing (supporting). **Marta Cortés-Canteli:** Conceptualization (equal); writing—original draft (lead); writing—review and editing (lead). **Maria Angeles Moro:** Conceptualization (equal); writing—original draft (lead); writing—review and editing (lead).

ACKNOWLEDGEMENTS

A. Semerano is supported by a la Caixa Foundation Predoctoral Fellowship (ID 100010434 and LCF/BQ/DI22/11940002) and M. Cortes-Canteli is the recipient of a Miguel Servet type II research contract (CPII21/00007) from Instituto de Salud Carlos III (ISCIII) co-funded by the European Union (Fondo Social Europeo Plus). The CNIC is supported by the ISCIII, the Spanish Ministry for Science and Innovation and the Pro-CNIC Foundation and is a Severo Ochoa Center of Excellence (grant CEX2020-001041-S funded by MICIN/AEI/10.13039/501100011033).

FUNDING INFORMATION

la Caixa Foundation Predoctoral Fellowship, Grant/Award Numbers: ID 100010434, LCF/BQ/DI22/11940002; Instituto de Salud Carlos III, Grant/Award Number: CPII21/00007; European Regional Development Fund; Spanish Ministry for Science, Innovation and Universities, Grant/Award Numbers: PID2022-140616OB-I00, MCIN/AEI/10.13039/501100011033; Pro-CNIC Foundation; Severo Ochoa Center of Excellence, Grant/Award Number: CEX2020-001041-S; Leducq Foundation for Cardiovascular Research, Grant/Award Number: TNE-19CVD01andTNE-21CVD04; European Union (Fondo Social Europeo) Plus)

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

N/A-Editorial-Themed Issue.

Aurora Semerano[1]
Javier Fernández-Ruiz[2]
Marta Cortes-Canteli[1,3]
María A. Moro[1,4]

[1]*Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain*

[2]*Instituto Universitario de Investigación en Neuroquímica (IUIN), CIBER de Enfermedades Neurodegenerativas (CIBERNED) and Instituto Ramón y Cajal de Investigación Sanitaris (IRYCIS), Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Universidad Complutense, Madrid, Spain*

[3]*Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain*

[4]*Unidad de Investigación Neurovascular, Departamento de Farmacología y Terapéutica, Facultad de Medicina, Universidad Complutense de Madrid and Instituto de Investigación Hospital, Madrid, Spain*

Correspondence

María A. Moro and Marta Cortes-Canteli, Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain.
Email: mariaangeles.moro@cnic.es and marta.cortesc@quironsalud.es

ORCID

Javier Fernández-Ruiz https://orcid.org/0000-0002-4490-0604
Marta Cortes-Canteli https://orcid.org/0000-0001-8802-4338
María A. Moro https://orcid.org/0000-0003-1010-8237

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