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THEMED ISSUE REVIEW

Adipose tissue as a therapeutic target for vascular damage in Alzheimer's disease

Miriam Bettinetti-Luque[1] | Laura Trujillo-Estrada[1,2] | Eduardo Garcia-Fuentes[3,4] | Juana Andreo-Lopez[1] | Raquel Sanchez-Varo[1,2,5] | Lourdes Garrido-Sánchez[6,7] | Ángela Gómez-Mediavilla[8] | Manuela G. López[8,9] | Melissa Garcia-Caballero[10] | Antonia Gutierrez[1,2] | David Baglietto-Vargas[1,2]

[1]Departamento de Biología Celular, Genética y Fisiología, Instituto de Investigación Biomédica de Málaga (IBIMA)-Plataforma BIONAND, Facultad de Ciencias, Universidad de Málaga, Málaga, Spain

[2]CIBER de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain

[3]Unidad de Gestión Clínica Aparato Digestivo, Hospital Universitario Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga (IBIMA)-Plataforma BIONAND, Málaga, Spain

[4]CIBER de Enfermedades Hepáticas y Digestivas (CIBEREHD), Instituto de Salud Carlos III, Madrid, Spain

[5]Departamento de Fisiología Humana, Histología Humana, Anatomía Patológica y Educación Física y Deportiva, Facultad de Medicina, Universidad de Málaga, Málaga, Spain

[6]CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain

[7]Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga (IBIMA)-Plataforma BIONAND, Málaga, Spain

[8]Departamento de Farmacología, Facultad de Medicina. Instituto Teófilo Hernando para la I+D de Fármacos, Universidad Autónoma de Madrid, Madrid, Spain

[9]Instituto de Investigaciones Sanitarias (IIS-IP), Hospital Universitario de la Princesa, Madrid, Spain

[10]Departamento de Biología Molecular y Bioquímica, Instituto de Investigación Biomédica de Málaga (IBIMA)-Plataforma BIONAND, Facultad de Ciencias, Universidad de Málaga, Málaga, Spain

Correspondence
David Baglietto-Vargas, Department of Cell Biology, Genetics and Physiology, Faculty of Sciences, University of Malaga, Campus Teatinos 29071, Málaga, Spain.
Email: d.baglietto@uma.es

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Adipose tissue has recently been recognized as an important endocrine organ that plays a crucial role in energy metabolism and in the immune response in many metabolic tissues. With this regard, emerging evidence indicates that an important cross-talk exists between the adipose tissue and the brain. However, the contribution of adipose tissue to the development of age-related diseases, including Alzheimer's disease, remains poorly defined. New studies suggest that the adipose tissue modulates brain function through a range of endogenous biologically active factors known as adipokines, which can cross the blood–brain barrier to reach the target areas in the

Abbreviations: AD, Alzheimer's disease; AgRP, agouti-related peptide; AMPK, AMP-activated protein kinase; APOE, apolipoprotein E; APP, amyloid precursor protein; AQP4, aquaporin 4; AT, adipose tissue; BAT, brown adipose tissue; BBB, blood-brain barrier; BMP8p, bone morphogenetic protein 8b; CBF, cerebral blood flow; CSF, cerebrospinal fluid; dSAT, deep subcutaneous adipose tissue; EC, endothelial cell; FGF21, fibroblast growth factor 21; GLUT4, glucose transporter type 4; GSK3β, glycogen synthase kinase-3β; HIF, hypoxia-inducible factor; IRS-1, insulin receptor substrate 1; KI, knock-in; LRP-1, low-density lipoprotein receptor-related protein 1; LTP, long-term potentiation; MMP, matrix metalloproteinase; NMN, nicotinamide mononucleotide; NMR, nicotinamide riboside; NPY, neuropeptide Y; POMC, propiomelanocortin; RAAS, renin–angiotensinogen–aldosterone system; RAGE, receptor for advanced glycation end products; sSAT, superficial subcutaneous adipose tissue; TBI, traumatic brain injury; TEER, transendothelial electrical resistance; UCP-1, uncoupling protein-1; VSMCs, vascular smooth muscle cells; WAT, white adipose tissue; WT, wild-type.

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brain or to regulate the function of the blood–brain barrier. In this review, we discuss the effects of several adipokines on the physiology of the blood–brain barrier, their contribution to the development of Alzheimer's disease and their therapeutic potential.

KEYWORDS
adipokines, adipose tissue, Alzheimer's disease, amyloid, inflammation, tau, vascular

1 | INTRODUCTION

Crosstalk between the brain and peripheral organs is central for cerebral health and disease and, thus, this topic is emerging as an exciting field of investigation. In fact, diabetes, obesity and other metabolic disorders contribute to cognitive impairment and brain malfunction (Baglietto-Vargas et al., 2016; Biessels & Despa, 2018; Dove et al., 2021; Nguyen et al., 2014). The global burden of these metabolic diseases has risen significantly in recent years, and it is projected to increase in the coming decades (Malenfant & Batsis, 2019; Prospective Studies et al., 2009; Zamboni & Mazzali, 2012). Obesity leads to metabolic abnormalities in adipose tissue (AT), a complex organ involved in the maintenance and homeostatic balance of a wide range of biological functions, including energy homeostasis, reproduction, protection and insulation (Kahn et al., 2019; Rosen & Spiegelman, 2014; Tseng, 2023). This critical organ has generated more interest during the last decades, especially after the discovery of the hormone '**leptin**' (Caron et al., 2018). Indeed, new findings have recognized the AT as a major endocrine organ that releases a variety of different bioactive molecules called adipokines, which communicate with and regulate the function of several other organs such as liver, heart, muscle, lung and brain (Kahn et al., 2019; Kusminski et al., 2016; Rosen & Spiegelman, 2014; Tseng, 2023). In the past few years, particular attention has been paid to understanding the interactions and connections between AT and the brain. This aspect is gaining more importance as novel evidence has shown that adipokines play a critical role in a wide range of brain functions, such as synaptic plasticity, memory formation and consolidation, neurogenesis, neuroinflammatory processes and the maintenance of the blood–brain barrier (BBB) (Caron et al., 2018; Lee et al., 2019; Parimisetty et al., 2016).

Notably, recent studies suggest that alterations in the production or levels of these adipokines are related to several brain disorders (Lee et al., 2019; Parimisetty et al., 2016). In this context, one of the major brain disorders that has particular is affecting significance for the ageing human population is Alzheimer's disease (AD), a progressive and fatal neurodegenerative condition, which is associated with profound metabolic disturbances (Ardanaz et al., 2022; Baglietto-Vargas et al., 2016; Merlo et al., 2010; Poddar et al., 2021). Indeed, AD has been proposed as 'Type 3 diabetes' because insulin resistance in the brain is a pathological feature of this disorder (de la Monte & Wands, 2008; Kandimalla et al., 2017; Nguyen et al., 2020). Likewise, more than 80% of AD patients manifest cerebrovascular damage, suggesting that disruption of the BBB and alterations of the neurovascular system contribute to disease progression (Govindpani et al., 2019; Klohs, 2019; Yu et al., 2020). Given the fact that there are no effective disease-modifying treatments able to halt or retard the clinical course of AD, and considering that the number of cases is increasing exponentially, novel pathogenic mechanisms are needed to disclose new targets and design promising therapies for AD.

This review focuses on the biology of the adipose cells and its interactions with the brain and vascular system, as mediated by the adipokines. Moreover, this work aims to summarize the mechanisms involved in the disruption of the cerebrovascular system that may contribute to AD pathogenesis. Finally, we will highlight the most recent evidence about the effects of the AT on the initiation and progression of AD, with special attention to the dyshomeostasis of the BBB, as a potential therapeutic target for disease intervention.

2 | ADIPOSE TISSUE IN HEALTH AND DISEASE

The AT, commonly named 'body fat', is metabolically dynamic and complex, being the largest endocrine organ in the entire body. Besides adipocytes, it is composed of vascular cells, fibroblasts and resident cells of the immune system, which are in constant communication among them (Herrada et al., 2021; Rosen & Spiegelman, 2014). Depots of AT, visceral and subcutaneous, display a different profile of biological functions, including adipokine secretion, rates of lipolysis, triglyceride synthesis and immune cell infiltration (Herrada et al., 2021; Rosen & Spiegelman, 2014). Overall, these studies and others suggest that the marked heterogeneity of adipose fat pads is

associated with the variety of biological functions of these cells (Chouchani & Kajimura, 2019; Herrada et al., 2021; Kusminski et al., 2016; Rosen & Spiegelman, 2014). Interestingly, certain diseases affect the AT in a specific manner, for example, some types of congenital lipodystrophy cause the loss of metabolically related fat depots, whereas mechanical fat is not affected (Garg, 2011). Conversely, obesity and Type 2 diabetes are associated with the prominent increase of visceral omental fat depots, which are metabolically more active than subcutaneous fat (Chouchani & Kajimura, 2019; Ibrahim, 2010). Importantly, recent studies have investigated the critical role of these fat depots and their implication in metabolic diseases, cognitive impairment and neurodegenerative disorders (Caron et al., 2018; Kahn et al., 2019; Kusminski et al., 2016; Rosen & Spiegelman, 2014). Therefore, acquiring greater knowledge of the different types of adipose cells, their location and function, is needed for a better understanding of how these cells change their biological response under different metabolic disturbances that, ultimately, may be the cause or predispose the brain to the development of many brain disorders, including AD.

2.1 | The three types of adipose cells

In general, the adipose cells are mainly classified into two types: white adipocytes and brown adipocytes (Luong et al., 2019). The white adipose cells are composed of a unilocular lipid droplet and derive from paired box protein 7 and myogenic factor 5 negative stem cells (Pax7−/Myf5−). These cells are specialized in the storage of lipids as a long-term energy reserve (Macotela et al., 2012). In addition, the white adipocytes participate in the homeostasis of energy metabolism through the secretion of multiple adipokines such as leptin, **adiponectin** or resistin, all of them molecules that cross the BBB and generate a hypothalamic response to the peripheral energy state (Henry et al., 2012; Luong et al., 2019) (Figure 1).

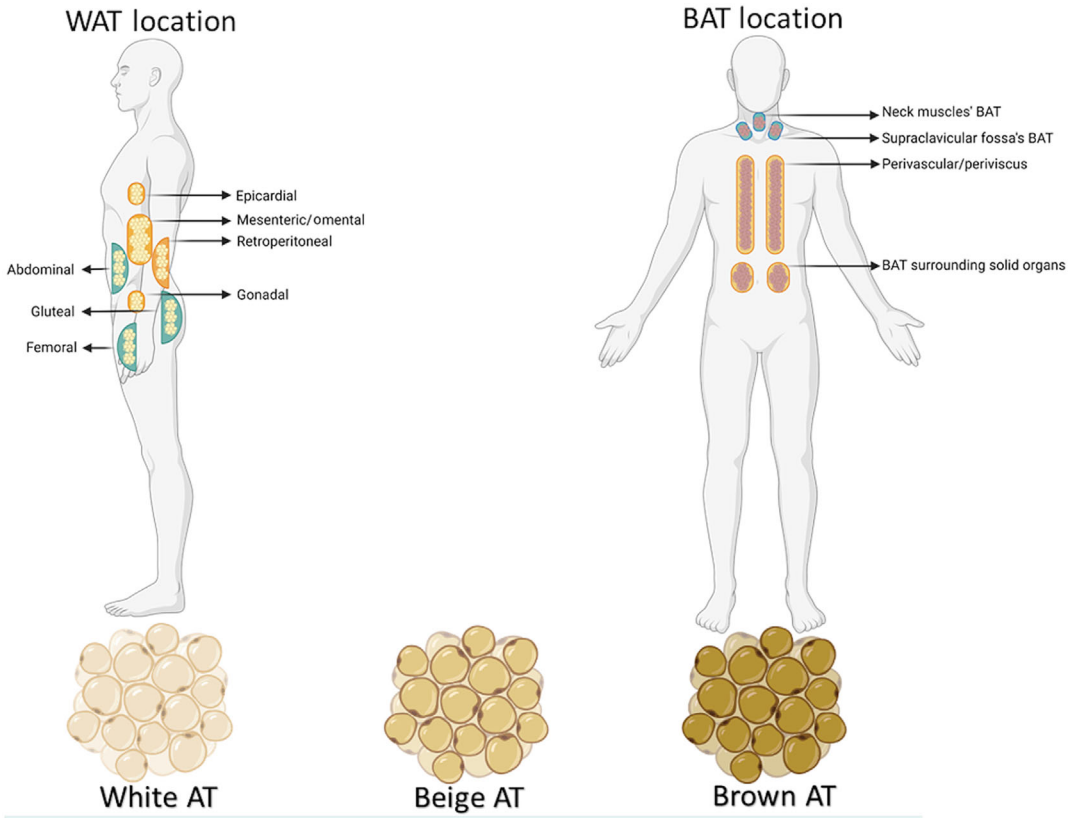
On the other hand, the multilocular brown adipocytes derive from Pax7+/Myf5+ cells, have principally a thermogenic function and exist primarily in hibernating mammals (Macotela et al., 2012) (Figure 1). This activity can be thermoregulatory in response to cold, or metaboregulatory according to the energy state of the organism (Enerback, 2010). In both cases, their biological activity involves **uncoupling protein-1 (UCP-1)**, a transporter located in the mitochondria of brown adipocytes that increases the conductance of the inner mitochondrial membrane and ultimately facilitates heat generation (Fedorenko et al., 2012). Of note, the thermoregulatory view has changed in the past few years due to the recent discoveries showing that brown adipocytes are also involved in the regulation of metabolic processes through the release of adipokines. This group of molecules includes some interleukins and the hormone irisin and are collectively known as batokines (Villarroya, Gavalda-Navarro, et al., 2017).

Furthermore, this binary classification has been modified since 2012 due to the discovery of a third type of adipose cells, named as beige or brite (brown and white) adipocytes, that does not quite belong to either of the previous groups (Wu et al., 2012). Specifically, these UCP-1+ cells are observed within white adipose tissue (WAT) deposits in both rodents and humans, as a consequence of prolonged exposure to cold, and they had been misidentified as brown adipocytes for decades (Xue et al., 2007). Following further analysis, the abundance of these inducible cells was found to vary between different body-fat depots, and their expression profile overlapped and differed from that of brown adipocytes. Beige adipocytes, like white adipocytes, derive from the Pax7−/Myf5− cell lineage; however, they express UCP-1, like brown adipocytes (Figure 1). These cells exhibit a specific genetic profile including the transmembrane protein 26 (Tmem26), **tumour necrosis factor receptor superfamily member 9 (TNFRSF9** or CD137) or T-box transcription factor 1 (Tbx1) that has been used to differentiate them from the brown adipocytes. In addition, the brown adipocytes also express epithelial V-like antigen 1 or zinc finger protein of cerebellum 1 (Eva1 or Zic1) which is absent in the beige cells (Walden et al., 2012; Wu et al., 2012). These studies suggest that the beige adipocytes, which possess features from white and brown adipocytes, are a unique type of inducible cell that participates in the maintenance of energy homeostasis, until they receive an appropriate thermogenic stimulus and switch their function to heat production (Walden et al., 2012; Wu et al., 2012).

2.2 | Heterogeneity of adipocyte biology

Apart from the existence of three major types of adipose fat pads, the adipocytes are widely distributed, and their regionalization implicates different structural and functional characteristics (Rosen & Spiegelman, 2014). It is commonly known that the WAT is not only an energy storage organ, but also participates in multiple key biological processes, including the maintenance of energy homeostasis, regulation of appetite, induction of the production of sex hormones and protection of vital organs, among others (Rosen & Spiegelman, 2014; Villarroya et al., 2018). Likewise, we must consider the WAT as a highly mouldable tissue, which changes over time, and is easily altered in metabolic disorders such as obesity or Type 2 diabetes (Hajer et al., 2008; Kusminski et al., 2016).

According to the location, the WAT has been generally described as subcutaneous or visceral fat. Subcutaneous fat is distributed throughout the entire body surface. Specifically, it is found in the hypodermic layer of the skin and is organized into two clearly distinguished layers: superficial and deep subcutaneous adipose tissue (sSAT and dSAT, respectively) (Smith et al., 2001; Walker et al., 2007). Likewise, there are three main areas of subcutaneous fat deposits in the body: abdominal, gluteal and femoral areas (Figure 1) (Chait & den Hartigh, 2020; Sbarbati et al., 2010). At the structural level, sSAT has a very compact lamellar organization, while that of dSAT is more loose (Cancello et al., 2013). In terms of cellular composition, the dSAT displayed an 'inflammatory' molecular profile, reflecting a greater infiltration of immune cells, compared with the sSAT (Cancello et al., 2013).Both types of tissue also displayed different densities of blood vessels, with higher densities in the dSAT (Cancello et al., 2013).



	White AT	Beige AT	Brown AT
Derived from	Pax7−/Myf5− stem cells	Pax7−/Myf5− stem cells	Pax7+/Myf5+ stem cells
Cell morphology	Unilocular lipid droplets UCP1−	Multilocular lipid droplets UCP1+	Multilocular lipid droplets UCP1+
Function	Energy storage Regulation of energy metabolism Endocrine funtion	Energy expenditure (adaptative thermogenesis)	Energy expenditure (thermogenesis) Endocrine funtion
Location	Multiple depots	Heterogeneous depots (transition fr m WAT)	Multiple depots

FIGURE 1 Characteristics of the different types of adipose cells in white (WAT), beige and brown adipose tissue (BAT). On the left, the locations of subcutaneous WAT depots are shown in green and the visceral WAT depots in orange. On the right, the locations of the BAT depots are shown. In the table below, the lineage, cell morphology and function of the three types of AT are summarised. Data shown apply to adipose tissue in the adult human (created with BioRender.com).

The second type of WAT is the visceral AT, which is mainly distributed into two regions: epicardial and abdominal, the latter being the most representative (Smith et al., 2001; Wronska & Kmiec, 2012). The epicardial AT is located below the visceral layer of the pericardium, providing fatty acids, the energy substrate of the myocardium, to the coronary arteries (Sanchez-Gurmaches et al., 2016; Wronska & Kmiec, 2012). It also protects the heart either against mechanical or metabolic damage by producing adiponectin and other adipokines. Nevertheless, under altered metabolic conditions, the epicardial AT can release a variety of pro-inflammatory cytokines that may contribute to atherosclerosis (Sanchez-Gurmaches et al., 2016; Wronska & Kmiec, 2012). Moreover, the amount of epicardial AT in humans correlated with the development of insulin resistance and metabolic syndrome, suggesting that this WAT may contribute significantly to the development of cardiovascular diseases (Kawai et al., 2021; Wronska & Kmiec, 2012). On the other hand, the abdominal WAT represents the majority of visceral fat depots in humans and regionally can be divided into gonadal, retroperitoneal, omental and mesenteric fat depots (Figure 1) (Wronska & Kmiec, 2012).

In general, visceral AT displays higher lipolytic and lipogenic activities, as well as a greater oxidative rate of fatty acids than subcutaneous AT. In addition, visceral AT adipocytes appear to show a faster metabolic response to fasting compared with subcutaneous AT (Lafontan & Langin, 2009; Wronska & Kmiec, 2012). However, the metabolic activity of this tissue can change depending on its location. For example, different AT depots have distinct cytokine expression profiles (Dodson

et al., 2014). Gene expression studies carried out in patients with Type 2 diabetes show that leptin, **PPARγ**, **fatty acid translocase** (FAT/CD36) and **11β-hydroxysteroid dehydrogenase** expression were significantly increased in mesenteric fat, compared with omental fat depots (Belfiore et al., 2019). This up-regulation seems to indicate that mesenteric fat would have a more prominent role in the development of metabolic syndrome, compared with other visceral fat depots (Belfiore et al., 2019). In addition, the abundance of adipose tissue macrophages varies up to seven-fold between the different fat depots, which participates in the variation of the adipokine secretion profile (H. M. Zhang et al., 2009). Increased infiltration of adipose tissue macrophages in omental fat has also been correlated with the development of insulin resistance, obesity and metabolic syndrome, and it does not occur with the subcutaneous fat (Villafuerte et al., 2000).

With regard to the adipokine secretion, there are important differences between subcutaneous and visceral ATs. For instance, subcutaneous AT is the main leptin producer of the body, and it is also largely involved in the synthesis of adiponectin, which participates in the maintenance of glucose tolerance and insulin sensitivity (Turer et al., 2011). In the absence of adiponectin, **AMP-activated protein kinase** (AMPK) is dephosphorylated and, in turn, certain serine residues of the **insulin receptor substrate 1** (IRS-1) are phosphorylated, leading to its inactivation, which then prevents the externalization of **glucose transporter type 4 (GLUT-4)** and induces insulin resistance (Y. Wang et al., 2019). Taking this into account, subcutaneous AT has been proposed to play a protective role against the development of insulin resistance and, therefore, Type 2 diabetes. Conversely, visceral AT seems to be a major contributor to metabolic disorders (Buemann et al., 2006; Rosenbaum et al., 2001; Turer et al., 2011).

Unlike WAT, brown adipose tissue (BAT) exhibits mainly thermogenic activity (Marlatt & Ravussin, 2017). In fact, newborns rely on BAT to maintain body temperature for their first few months of life (Marlatt & Ravussin, 2017), a necessity that rapidly disappears in time (Sacks & Symonds, 2013). For this reason, in adult humans, the BAT surface area/volume ratio decreases by half compared with newborns, which makes it difficult to identify this tissue in the adult human body. However, several intriguing studies using post mortem analysis and positron emission tomography (PET) detection have provided a better understanding of the regionalization of this tissue (Sacks & Symonds, 2013; Santhanam et al., 2018; H. Wang et al., 2020).

Similarly to WAT, the BAT can be classified as visceral or subcutaneous (Sacks & Symonds, 2013). Visceral BAT can be found around certain blood vessels (perivascular) and surrounding muscular organs (periviscus), as well as in solid organs such as the pancreas, kidney, adrenal, liver, thoracic paravertebral and hilum of spleen (Sacks & Symonds, 2013; Villarroya et al., 2018). The perivascular BAT is located around the aorta, brachiocephalic artery, carotid artery, epicardial coronary artery, cardiac veins, among other vessels (Sacks & Symonds, 2013; Villarroya et al., 2018). BAT not only protects blood vessels against cold but also releases **vascular endothelial growth factor** (VEGF) proteins, some of the most important angiogenic factors. In addition, brown adipocytes increase the expression of **nitric oxide** (NO) in response to cold, which has a vasodilatory action. All this seems to indicate that BAT plays a fundamental role in cold acclimatization by modifying the cardiovascular system at various levels (Cannon & Nedergaard, 2004). Moreover, BAT in its active state promotes the combustion of triglycerides and glucose-derived free fatty acids, improves cardiometabolic health and prevents AT dysfunction and the development of obesity and insulin resistance (Chen et al., 2021; Scheja & Heeren, 2019). The major locations of BAT perivisceus are surrounding the heart, in the trachea, main bronchi, oesophagus, colon and greater omentum.

On the contrary, the subcutaneous BAT is found between the anterior neck muscles and supraclavicular fossa, although it has also been detected under the clavicles, in the axilla, in the anterior abdominal wall and in the inguinal fossa (Kusminski et al., 2016; Rosen & Spiegelman, 2014). Overall, there are many places in which BAT is located but the functional differences between the distinct BAT deposits remain an unexplored area of great interest.

Currently, it is known that BAT functions extend beyond thermogenesis, as it has been associated with improved glucose metabolism, insulin sensitivity and lipid metabolism (Villarroya, Gavalda-Navarro, et al., 2017). The activation of this tissue through cold exposure or pharmacological means leads to increased glucose uptake and enhanced insulin sensitivity. Interestingly, BAT transplantation studies have shown that this type of AT can improve systemic metabolism and release secreted factors, suggesting a paracrine or endocrine role of BAT in physiology (Khan et al., 2020).

Indeed, WAT and BAT have distinct functional and morphological properties, leading to differences in their secretory profiles. WAT, the predominant form of AT in the body, is known for its role in energy storage (Rosen & Spiegelman, 2014; Villarroya et al., 2018). WAT secretes a variety of adipokines, including leptin, adiponectin, resistin, omentin, **adipsin**, visfatin, **retinol-binding protein 4** (RBP4) and inflammatory cytokines such as **tumour necrosis factor-α** (TNF-α), **interleukin-6** (IL-6), plasminogen activator inhibitor (PAI-1) and the chemokine **CCL2** (Clemente-Suárez et al., 2023). On the other hand, BAT, which is primarily involved in energy expenditure and thermogenesis, has a unique secretory profile compared with WAT. Some molecules, such as **bone morphogenetic protein 8b** (BMP8b), **fibroblast growth factor 21** (FGF21), irisin, **neuregulin 4** (NRG4), nesfatin-1, meteorin-like protein, **chemerin**, IL-6, **IL-8** and **IL-10**, have been identified as batokines (Clemente-Suárez et al., 2023). The first one, BMP8b, participates in the regulation of brown adipocyte differentiation and thermogenesis, stimulating the expression of UCP-1 and other thermogenic genes. It enhances energy expenditure, increases body temperature and promotes lipid metabolism, thereby potentially protecting against diet-induced obesity and metabolic dysfunction (Khan et al., 2020).

FGF21, a hormone-like protein secreted by many tissues including BAT, modulates glucose and lipid metabolism. FGF21 expression is induced by various physiological and pathological conditions such as fasting, cold exposure and metabolic stress. It exerts beneficial effects on metabolic health, including improved insulin sensitivity, enhanced fatty acid oxidation and reduced body weight and adiposity. FGF21 also stimulates brown adipocyte thermogenesis and augments energy expenditure. Moreover, it promotes the browning of WAT,

leading to the conversion of white adipocytes into brown-like adipocytes with thermogenic properties. Additionally, FGF21 plays a role in appetite regulation and food intake, contributing to overall energy balance (Khan et al., 2020).

Another batokine is irisin, which increases energy expenditure and improves glucose homeostasis. This hormone is a derivative of the cleavage of fibronectin type III domain-containing protein-5, and its production is elevated under cold exposure or exercise (Boström et al., 2012).

Even though significant progress has been made during the past decade to understand the biological implications of the distinct secretory profiles between WAT and BAT, they are still poorly defined and much remains to be discovered. Understanding the unique secretory profiles of WAT and BAT can provide insights into the distinct physiological functions of these ATs and their potential implications in metabolic diseases, allowing the discovery of innovative targets for therapeutic interventions.

2.3 | Adipose tissue expansion, extracellular matrix and cell infiltration changes in lean and obese condition

It is well known that AT has the ability to modify its dimensions depending on the energy state of the organism (Cox et al., 2019; Vishvanath & Gupta, 2019). Thus, in mice under overnutrition, the adipocytes first experience an increase in size (hypertrophy) and then proliferate and differentiate into preadipocytes (hyperplasia) (Koenen et al., 2021; Rosen & Spiegelman, 2014). In humans, overfeeding for a prolonged period mainly leads to hypertrophy and, to a lesser extent, hyperplasia (Rosen & Spiegelman, 2014). However, once hyperplasia occurs, it is difficult to decrease the number of adipocytes. Contrary to what has been established, weight loss is not associated with a decrease in the number of adipocytes, but in their size (Cox et al., 2019; Vishvanath & Gupta, 2019). The number of adipocytes remains quite stable because production and elimination rates are relatively similar (Rosen & Spiegelman, 2014). Nevertheless, this equilibrium may be disrupted under several metabolic diseases such as obesity, in which the AT experiences an accelerated cell expansion (Figure 2). This massive increase in the adipocytes size also gives rise to an elevated rate of cell death (Iyengar et al., 2016; Strissel et al., 2007).

One of the causes linked to the high rate of cell death in AT is the hypoxic environment that occurs during its expansion, known as AT hypoxia (Figure 2). Even though AT can promote its own vascularization, it does not seem to be enough because of the rapid expansion of adipose cells, especially the visceral fat, and under obesity (Rosen & Spiegelman, 2014; Wronska & Kmiec, 2012). Specifically, AT cells express a wide variety of matrix proteins such as collagen, fibronectin and laminin and therefore a large number of enzymes that allow their remodelling and breakdown, whose expression is highly dependent on energy requirements (Ruiz-Ojeda et al., 2019). For the healthy expansion of adipocytes, proper relaxation of the extracellular matrix is

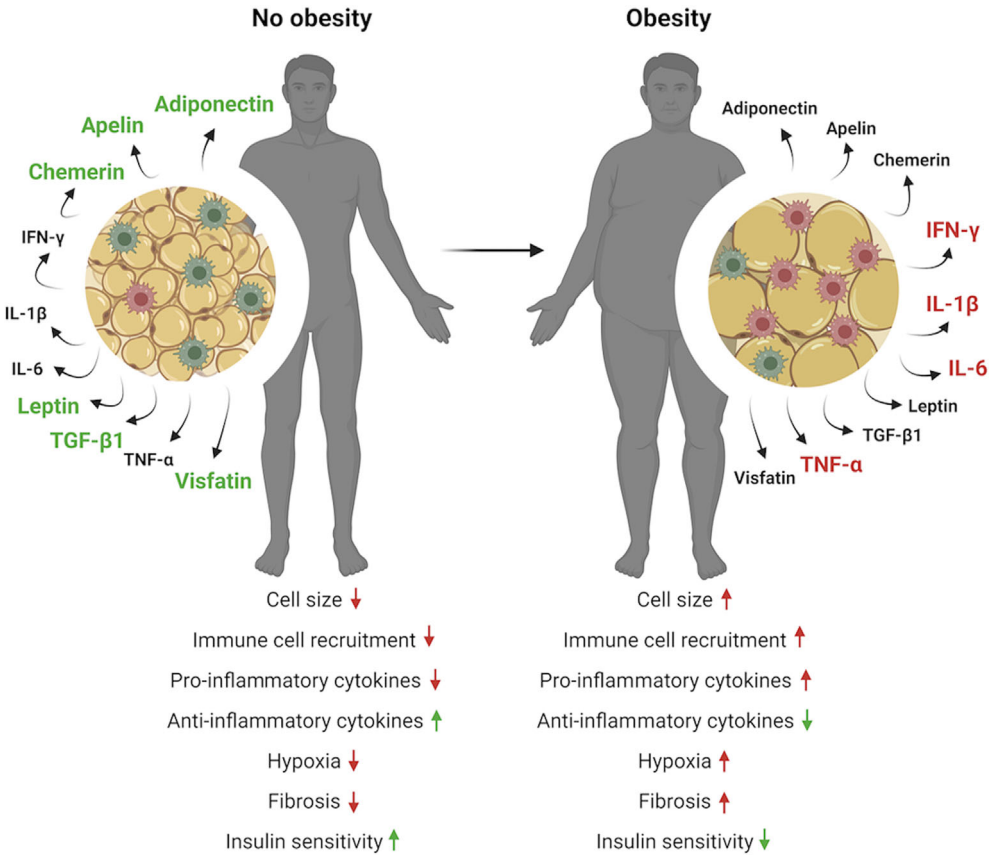


FIGURE 2 Functional and morphological changes in adipose cells in lean and obese conditions. Obesity is accompanied by severe changes in the adipose tissue in terms of cell size and hypoxia levels. In addition, cellular matrix content is significantly changed, which alters the level of fibrosis in the tissue. Furthermore, secretion of adipokines and infiltration of immune cells also is modified by obesity into a pro-inflammatory state (created with BioRender.com).

necessary. However, under metabolic disturbances, an increase in matrix rigidity leads to the activation of signalling pathways related to cellular stress and inflammation (Sun et al., 2012, 2013). For instance, the oxygen-sensitive transcription factor, HIF-1, is increased during metabolic distress and plays a critical role in the response of the AT to a hypoxic environment. The expression of HIF-1 correlates with a pro-fibrotic transcriptional programme that involves the production of collagen, **metallopeptidase inhibitor protein** and **lysyl oxidase**. The accumulation of collagen fibres then leads to fibrosis, a hallmark of metabolic dysfunction in AT (Figure 2) (Sun et al., 2013; Warbrick & Rabkin, 2019).

Another important feature of hypertrophic adipocytes is the high expression profile of pro-inflammatory molecules (Figure 2). Specifically, an increase in **granulocyte-macrophage colony-stimulating factor** (GM-CSF), IL-6, IL-10, **IL-1α**, **IL-1β**, the chemokines **CCL3** and **CXCL1**, and TNF-α was observed in epididymal fat depots of rats given a high fat diet for 7 weeks (Poret et al., 2018; Roy et al., 2022). This high level of pro-inflammatory cytokines has been correlated with elevated number of adipose tissue macrophages infiltrated from the peripheral system (Figure 2). Under normal conditions, the adipose tissue macrophages represent only 5% of AT cells, while in obese patients this proportion increases to 50%, suggesting that the resident macrophages of the AT may make an important contribution to the development and progression of the metabolic syndrome (Herrada et al., 2021; Koenen et al., 2021; Q. A. Wang et al., 2013).

The adipose tissue macrophages are classified into the classic activation states M1 and M2 (Herrada et al., 2021; Rosen & Spiegelman, 2014). While cells with the M1 phenotype are characterized by having a pro-inflammatory expression profile (TNF-α high, IL-1 high, IL-12 high, IL-10 low and **TGF-β** low), M2 macrophages are characterized by displaying an anti-inflammatory expression profile (TNF-α low, IL-1 low, IL-12 low, IL-4 high, IL-10 high and TGF-β high) (Figure 2). This nomenclature enables us to distinguish two phenotypic extremes of macrophages, although there is considerable heterogeneity between them (Herrada et al., 2021; Rosen & Spiegelman, 2014). In healthy individuals, macrophages express an M2 phenotype characterized by the secretion of anti-inflammatory cytokines. Conversely, people with obesity show an imbalance between the activation of M1 and M2 macrophages, generating a pro-inflammatory environment. Commonly, these macrophages are located surrounding the dead or dying adipocytes, forming 'crown-shaped structures' which are found abundantly in the visceral AT of people with obesity (Herrada et al., 2021; Rosen & Spiegelman, 2014).

Additionally, other cells of the immune system, including neutrophils, mast cells, B lymphocytes and some types of T lymphocytes, can infiltrate the AT and participate in the pro-inflammatory state during obesity (Russo & Lumeng, 2018). At the same time, other cellular types such as eosinophils and innate lymphoid cells (ILC2) are also present, and mitigate this pro-inflammatory environment. In addition, regulatory T-cells (Tregs) are increased in the visceral fat of rodents and participate in the control of the adipose tissue macrophages. A recent study has shown that its depletion contributes to the development of insulin resistance (Janani & Ranjitha Kumari, 2015). Considering that both Tregs and M2-type macrophages express PPARγ, it has been hypothesized that the net result of the pleiotropic effects of PPARγ ligands is improving the insulin sensitivity (Janani & Ranjitha Kumari, 2015). However, the precise time sequence of immune cell infiltration into AT remains unclear.

2.4 | Secretory profile of adipose tissue under obese condition

Under diverse metabolic states, the AT experiences a significant alteration in the secretion profile of many bioactive factors or adipokines (Figure 2) (Bluher, 2019; Choe et al., 2016; de Oliveira Leal & Mafra, 2013). In general, the adipose cells can produce a huge variety of adipokines (comprising lipids, hormones and proteins) that target several systemic organs and regulate crucial homeostatic functions in the body, such as energy homeostasis, fat distribution, insulin sensitivity, immune response and blood pressure (Bluher & Mantzoros, 2015; Clemente-Suárez et al., 2023; Fasshauer & Bluher, 2015). Thus, several factors such as adipose hypertrophy, fat expansion, hypoxia level or immune cells phenotype, markedly influence the adipose cell biology and its secretion profile (Bluher & Mantzoros, 2015; Clemente-Suárez et al., 2023; Fasshauer & Bluher, 2015). Here, we summarize how the AT modifies the expression of some of the most well-known adipokines under different metabolic states, although a more profound description has been recently published (Bluher & Mantzoros, 2015; Clemente-Suárez et al., 2023; Fasshauer & Bluher, 2015).

Leptin, primarily secreted by adipocytes, acts as a key regulator of energy balance and appetite control (Friedman, 2019). This adipokine normally acts as a satiety signal, suppressing appetite and reducing food intake (Friedman, 2019). However, in obesity, leptin levels are elevated and leptin resistance is associated with body-fat mass (Friedman, 2019). In the presence of leptin resistance, this appetite-suppressing effect is diminished, leading to increased hunger and overeating. Thus, hyperleptinaemia disrupts energy homeostasis, promotes inflammation and contributes to metabolic dysregulation (Investigators, 1990; Myers et al., 2008). The exact mechanisms underlying this phenomenon are not fully understood but may involve disturbances in leptin transport across the BBB or impaired intracellular signalling cascades (Myers et al., 2008; Obradovic et al., 2021). With this regard, recent evidences have indicated that dysregulation of suppressor of cytokine signalling 3 (SOCS3), a negative regulator of leptin downstream signalling, may be involved. In obesity, elevated levels of pro-inflammatory cytokines induce the expression of SOCS3, which acts as an inhibitory feedback loop, interfering with **leptin receptor** signalling. Increased SOCS3 expression reduces the sensitivity of target cells to leptin, contributing to leptin resistance (Morris & Rui, 2009; Munzberg & Myers, 2005). Another possible mechanism is related to the chronic low-grade inflammation, a characteristic feature of obesity. Increased levels of pro-inflammatory cytokines, such as TNF-α and IL-6, can interfere with leptin signalling pathways (Hotamisligil, 2017). These cytokines activate intracellular signalling pathways, such as the **Janus kinase–signal transducer and activator**

of transcription (JAK–STAT) pathway, leading to the inhibition of leptin receptor signalling and the subsequent leptin resistance (Kwon et al., 2016; Wauman & Tavernier, 2011).

Adiponectin is another main adipokine produced by the AT that exhibits insulin-sensitizing and anti-inflammatory properties (Engin, 2017; Parida et al., 2019). Importantly, adiponectin levels are reduced in obesity (Engin, 2017). This reduction occurs through several molecular mechanisms, which contribute to the development of metabolic dysfunction and related health complications (Engin, 2017; Rizzo et al., 2020). Increased AT mass during obesity conditions leads to the infiltration of immune cells, such as macrophages, which secrete pro-inflammatory cytokines such as TNF-α and IL-6 that suppress the production and release of adiponectin by adipocytes (Choi et al., 2020). Specifically, TNF-α and IL-6 can activate certain transcription factors, such as NF-κB and **STAT3**, which can bind to specific regions of the adiponectin gene promoter. This binding leads to the inhibition of adiponectin gene transcription, resulting in reduced adiponectin synthesis (Feng et al., 2020). As noted earlier, AT expansion during obesity can outpace its blood supply, leading to AT hypoxia. This condition triggers the release of **hypoxia-inducible factors** (HIFs) that inhibit the expression of adiponectin (Saito et al., 2019). Besides, obesity is commonly associated with insulin resistance, a condition that affects adipocytes and impairs adiponectin production. Insulin signalling pathways involved in the regulation of adiponectin, such as the **Akt** and AMPK pathways, are disrupted in insulin-resistant states, leading to reduced adiponectin synthesis (Schinner et al., 2005).

Another adipokine produced by the AT is resistin, which initially has been implicated in insulin resistance, chronic inflammation and obesity-related complications (Antuna-Puente et al., 2008). Elevated resistin levels in obesity are associated with impaired glucose metabolism and may contribute to the development of insulin resistance and the progression of metabolic dysfunction (Antuna-Puente et al., 2008; Li et al., 2009). One of the underlying factors driving the increase of resistin is the chronic low-grade inflammation observed in obesity and the associated production of pro-inflammatory molecules (Antuna-Puente et al., 2008). TNF-α exerts its effects by binding to its receptor, **TNF receptor 1** (TNFR1), on adipocytes (Cawthorn & Sethi, 2008; Horiuchi et al., 2010). This interaction activates intracellular signalling pathways, including NF-κB and mitogen-activated protein kinases, such as **c-Jun N-terminal kinase (JNK)** and **p38MAPK** (Stan et al., 2011). The activation of these pathways leads to the induction of resistin gene expression and subsequent production by adipocytes (Stan et al., 2011). Moreover, the pro-inflammatory cytokine IL-6 acts through its receptor, **IL-6 receptor**, which forms a complex with the signalling receptor **glycoprotein 130** (gp130) (Kuźmicki et al., 2014). Binding of IL-6 to this complex triggers the activation of JAK and STAT3 signalling pathways (Kuźmicki et al., 2014). The activated STAT3 translocates to the nucleus and binds to specific promoter regions of the resistin gene, promoting its transcription and subsequent resistin synthesis. Several transcription factors, such as PPARγ and CCAAT/enhancer-binding protein α (C/EBP-α), can modulate the expression of resistin (Ghafouri-Fard & Taheri, 2021; L. Wang et al., 2022). In obesity, there may be alterations in the expression and activity of these transcription factors, leading to increased resistin production.

Chemerin is one of the most recently described adipokines that is involved in adipogenesis, inflammation and metabolic regulation, and it has gained attention for its role in obesity-related metabolic dysregulation (Ernst & Sinal, 2010). During obesity, TNF-α and IL-1β, released by immune cells, stimulate the production and secretion of chemerin by adipocytes (Kirichenko et al., 2022). Thus, this inflammatory milieu contributes to the increased levels of chemerin observed in obesity. In addition, chemerin participates in adipocyte differentiation and the regulation of adipogenesis, the process by which preadipocytes mature into adipocytes (Muruganandan et al., 2011; Villarroya, Cereijo, et al., 2017). This adipokine acts as an autocrine and as a paracrine factor, promoting adipocyte differentiation and increasing adipocyte size and number (Muruganandan et al., 2011; Villarroya, Cereijo, et al., 2017). The up-regulation of chemerin during obesity may be a consequence of enhanced adipocyte differentiation and expansion. Chemerin is also involved in the recruitment and activation of immune cells, such as macrophages and dendritic cells, thus perpetuating the inflammatory response (Ernst & Sinal, 2010). The increased chemerin levels in obesity contribute to the chronic low-grade inflammation observed in AT, further exacerbating metabolic dysfunction (Kawai et al., 2021). Overall, the increase in chemerin during obesity involves inflammatory processes, adipocyte differentiation and insulin resistance (Ernst & Sinal, 2010). The elevated levels of chemerin contribute to AT dysfunction, impaired glucose metabolism, dysregulated lipid metabolism and triggering of the inflammatory response.

These and other adipokines play crucial roles in mediating the crosstalk between AT and various organs, contributing to metabolic dysregulation and obesity-related complications. Changes in their secretion during obesity disrupt physiological processes and contribute to the pathogenesis of obesity-related health problems, including cancer, asthma, cardiovascular problems, non-alcoholic fatty liver disease and mental disorders (Bluher, 2019; Miethe et al., 2020; Piche et al., 2020; Polyzos et al., 2019; Selman et al., 2022; Zhou et al., 2023).

3 | ADIPOSE TISSUE AND BRAIN CROSSTALK

Far from being merely a fat storage organ, the AT is a fundamental endocrine organ for the entire body (Scheja & Heeren, 2019). Therefore, alterations in the secretion and systemic level of these adipokines may contribute to the development of many health problems as previously described, including numerous neurodegenerative diseases such as AD (de A Boleti et al., 2023).

Probably, this relationship between the adipose cells and the brain has gained more attention after the discovery of leptin, the first adipokine identified in 1949, which is secreted primarily by WAT and whose plasma level correlates with adiposity and caloric intake (Caron et al., 2018). In the brain, the main target area of this adipokine is the

hypothalamus, participating in the regulation of energy balance, food intake, satiety and, subsequently, body weight (Caron et al., 2018; Obradovic et al., 2021). Specifically, leptin acts on several neuronal populations found in the arcuate nucleus of this brain region, where it activates anorexigenic neurons that express propiomelanocortin (POMC) while inhibiting orexigenic neurons containing **neuropeptide Y** (NPY) and **agouti-related peptide** (AgRP) (Ahima et al., 1996; Coll et al., 2007; Morrison, 2009). This anorexigenic effect occurs after ingestion and ultimately suppresses leptin synthesis. On the other hand, under fasting conditions, plasma leptin levels increase, which stimulates orexigenic action and induces appetite (Ahima et al., 1996).

Furthermore, leptin receptors have been described in the hippocampal and cortical area of mice brain (Stranahan et al., 2008), and this adipokine is needed for cognitive functions and neuroplasticity of these regions (Stranahan et al., 2008). The db/db mice, which are homozygous for the diabetes spontaneous mutation ($Lepr^{db}$), show decreased proliferation of neuronal progenitor cells, as well as a reduction in dendritic spines and neuronal atrophy at the hippocampal level (Stranahan et al., 2008). In addition, in vivo studies using mouse models have shown that hippocampal or systemic injection of leptin improves spatial memory and learning (Kanoski et al., 2011; Perez-Gonzalez et al., 2011). Even though the mechanism by which these cognitive improvements occur remains unclear (Kanoski et al., 2011), leptin has been proposed to decrease oxidative stress in the hippocampus. In fact, in hippocampal neurons, leptin receptors are coupled to the JAK/STAT and **PI3K**/Akt-mediated signalling cascades, and their activation involves the production of the enzyme manganese superoxide dismutase (Mn-SOD) and **anti-apoptotic protein** Bcl-xL. Both enzymes are essential to stabilize the potential of the mitochondrial membrane, decreasing oxidative stress and inducing an increase in proliferation of hippocampal neurons (Guo et al., 2008; Kanoski et al., 2011; Suarez et al., 2019). Collectively, these findings strongly suggest that leptin acts as a major regulator of brain structure and functions, exerting neuroprotective effects under altered metabolic and neurotoxic conditions.

Furthermore, recent findings have shown that multiple adipokines also reach the brain and modulate important physiological functions. For example, the adiponectin receptors (**Adipo1** and **Adipo2** receptors) are widely expressed in the brain, especially in the hypothalamus, cortex and hippocampal areas (Chandran et al., 2003; Kawano & Arora, 2009). Among their functions, adiponectin plays a fundamental role by modulating the energy homeostasis and food intake (Chandran et al., 2003; Kawano & Arora, 2009). With this regard, this adipokine promotes the activity of anorexigenic POMC neurons in the arcuate nucleus of the hypothalamus, and leptin potentiates the excitatory effect of the adiponectin. In turn, adiponectin induces the inhibition of NPY/AgRP orexigenic neurons (Kubota et al., 2007; Sun et al., 2016; Suyama et al., 2017; Yau et al., 2014). However, this adipokine can exhibit an opposite effect by inhibiting the activity of POMC neurons under high-glucose conditions (Suyama et al., 2016).

In addition, certain in vivo studies have shown that adiponectin increases hippocampal progenitor cell proliferation (Liu, Liu, Wang, et al., 2020; D. Zhang et al., 2011). In culture, adiponectin treatment also increases the proliferation of adult human neural stem cells. Specifically, adiponectin activates the AMPK and p38MAPK signalling pathways, inducing the phosphorylation of **glycogen synthase kinase-3 beta** (GSK3β) which triggers the proliferation of these progenitor cells (Suyama et al., 2016). On the other hand, deficiency of this adipokine leads to a reduction in the length and dendritic branching in the neurons of the hippocampal dentate gyrus and cognitive dysfunction (Song, Kang, et al., 2015; D. Zhang et al., 2016). Moreover, adiponectin deficiency induces cerebral insulin resistance in knock-out mice (Ng et al., 2016). This defect in insulin signalling has been related to cognitive impairment, hindering learning and memory and decreasing synaptic plasticity.

Another adipokine that has been recently described with a major role in the brain is resistin. This adipokine seems to have an anorexigenic effect because it acts at the hypothalamic level, inhibiting NPY and AgRP neurons. Resistin, like the adipokines already mentioned, also seems to be involved in neurodegeneration, as shown by an increase of this cytokine in the cerebrospinal fluid (CSF) of patients with cognitive impairment. In addition, higher resistin levels are observed in patients with traumatic brain injury (TBI) or AD (Brunetti et al., 2004; Hu et al., 2010; Vázquez et al., 2008). Increased resistin levels are also associated with mitochondrial dysfunction, reducing the mitochondrial transmembrane potential and causing irreversible damage to this organelle. Hyperesistinaemia is also correlated with high levels of TNF-α and IL-6, at the same time associated with cognitive decline (Garcia-Escudero et al., 2013; Trifunovic & Larsson, 2008). Furthermore, this adipokine has been shown to increase the risk of developing metabolic syndrome and cardiovascular diseases (Garcia-Escudero et al., 2013; Trifunovic & Larsson, 2008). Therefore, these studies suggest that resistin is a neuroinflammatory inducer that may affect the development and progression of neurodegenerative diseases such as AD.

Finally, chemerin is another adipokine produced by WAT, with both pro-inflammatory and anti-inflammatory functions whose receptors are also widely expressed within the brain (Zabel et al., 2005), highlighting the effects of molecules produced by the AT in the CNS. One of the regions with a large number of these receptors is the hypothalamus, where chemerin plays a crucial role and participates in the regulation of appetite, although the mechanism remains unclear (Rourke et al., 2014).

4 | CEREBROVASCULAR SYSTEM, ADIPOSE TISSUE AND ALZHEIMER'S DISEASE

The BBB is a highly specialized and selective interface that protects the CNS from blood-borne agents and tightly regulates the exchange of nutrients, waste products and other molecules between the blood and the brain (Kadry et al., 2020). However, growing evidence suggests that AT-secreted molecules, known as adipokines, may reach the systemic circulation and interact with the BBB and the neurovascular system, compromising its integrity and potentially influencing

the development of neurological disorders including AD (Pan & Kastin, 2007). Also, breakdown of the BBB is an important pathological feature in AD, worsening the clearance of **amyloid-β** (Aβ) peptides, microglial activation and astrogliosis (Sousa et al., 2023).

The current and the next section of this review aim to explore the intricate interactions between adipokines, the BBB and the neurovascular unit in the context of neurological disorders, focusing on the potential therapeutic implications of these interactions for the treatment of cerebral dysfunction. Understanding the molecular mechanisms and crosstalk between these systems may pave the way for the development of innovative and effective therapies to combat AD and improve the brain health of patients, in general.

4.1 | The blood–brain barrier and the neurovascular system

The BBB is considered the largest interface for blood–brain exchange, as the surface area in adults is approximately between 12 and 18 m^2, based on an average microvessel surface area of 150 and 200 cm^2 per gram of tissue (Kadry et al., 2020). The BBB is formed by microvascular endothelial cells (ECs) lining the cerebral capillaries present in the brain and spinal cord of mammals and other living organisms with a well-developed CNS (Kadry et al., 2020). This endothelium displays morphological, structural and functional properties that are clearly distinct from those of the endothelium lining peripheral blood vessels (Kadry et al., 2020). Among these different features it is worth highlighting the following: (i) flattened appearance; (ii) expression of highly specialized intercellular junctions between adjacent ECs, which restricts the transcellular flow and prevents the unregulated passage of polar (water-soluble) molecules between the blood and the brain; (iii) presence of very few caveolae at the luminal surface and a high number of mitochondria; (iv) presence of active transport mechanisms to regulate the nutrient exchange and the elimination of toxic metabolites; (v) absence of fenestrations; and (vi) lack of pinocytic activity. Moreover, the brain microvascular ECs have a basement membrane and pericyte covering that reinforce the blood barrier function (Kadry et al., 2020). Therefore, the BBB plays a critical role in protecting the brain parenchyma from blood-borne agents and provides a significant obstacle to the entry of drugs and other exogenous compounds into the CNS.

The brain possesses a unique vascular network, the neurovascular system, which is structurally and functionally different from that of peripheral organs (Sweeney, Kisler, et al., 2018). This system tightly controls the cerebral blood flow (CBF) and the integrity of the BBB, which determines normal brain function (Yu et al., 2020). This regulation guarantees an effective and uninterrupted provision of oxygen and nutrients to the brain, while also ensuring the elimination of toxic metabolites (Ahmad et al., 2020). The increase or reduction in neuronal requirements entails fluctuations in blood supply, which are mediated by the neurovascular unit, a functional unit encompassing neurons, glial cells (microglia, oligodendroglia and astrocytes) and vascular cells (ECs, vascular smooth muscle cells and pericytes) (Yu et al., 2020; Zlokovic, 2011) (Figure 3). The integrity of the neurovascular unit is maintained by tight and adherens junctions between the ECs. The tight junctions play a crucial role by limiting the paracellular permeability of the BBB, preventing free diffusion of proteins and sealing the space between ECs (Chasiotis et al., 2012). Transmembrane proteins, including claudin, occludin, junctional adhesion molecule and zonula occludens-1 (ZO-1), are involved in constructing such tight junctions (McNeil et al., 2006; Otani & Furuse, 2020). The adherens junctions are mediated by vascular endothelial cadherin, facilitating intercellular adhesion and promoting cell maturation (Harris & Nelson, 2010). Both tight and adherens junctions are essential in regulating endothelial permeability (Sukriti et al., 2014). Together these cell types constitute the neurovascular unit, being intricately and effectively functionally connected (Muoio et al., 2014; Schaeffer & Iadecola, 2021).

4.2 | Adipose tissue and the vascular system

As described previously, AT is a dynamic organ that performs a key endocrine regulation in many biological processes throughout the entire body (Kahn et al., 2019; Rosen & Spiegelman, 2014; Tseng, 2023). Over the past decade, research has focused on the critical role of the AT in the vascular system. Taking into consideration that vascular damage is an important feature of many neurodegenerative disorders, understanding the link(s) by which the AT may modify the vascular system and consequently promote brain disorders is a matter of great interest.

Indeed, a new set of studies have highlighted that the AT can be located near and surrounding most of large blood vessels, providing an important mechanical protection and modulating the vascular tone, density and angiogenic processes (Galley et al., 2022; Opatrilova et al., 2018; Vliora et al., 2023). Besides this direct contact between the AT and vascular tissue, a paracrine or endocrine communication mediated by the secretion of many adipokines regulates the vascular function. For example, leptin appears to modulate vascular tone, angiogenesis and platelet aggregation (Mellott & Faulkner, 2023). Adiponectin increases NO production and regulates endothelium-dependent vasodilation (Galley et al., 2022). Resistin promotes angiogenic processes by triggering the production of VEGF (Pang et al., 2013). Visfatin is a recent discovered adipokine, also known as extracellular nicotinamide phosphoribosyl transferase (eNampt) or pre-B-cell colony-enhancing factor 1 (PBEF1), that promotes proliferation of the ECs and migration through activation of ERK1/2 signalling pathways (S. R. Kim et al., 2007). Although these adipokines have revealed a strong relationship between AT and vascular system, such communication was emphasized by the discovery of the regulation of the renin–angiotensinogen–aldosterone system (RAAS) by the AT (Briones et al., 2012; Yasue et al., 2010). The RAAS regulates blood osmolarity and pressure throughout the body and the AT modulates this system at several points, such as the production of angiotensinogen and by expressing aldosterone (Briones et al., 2012; Yasue et al., 2010). This critical communication between the AT and the

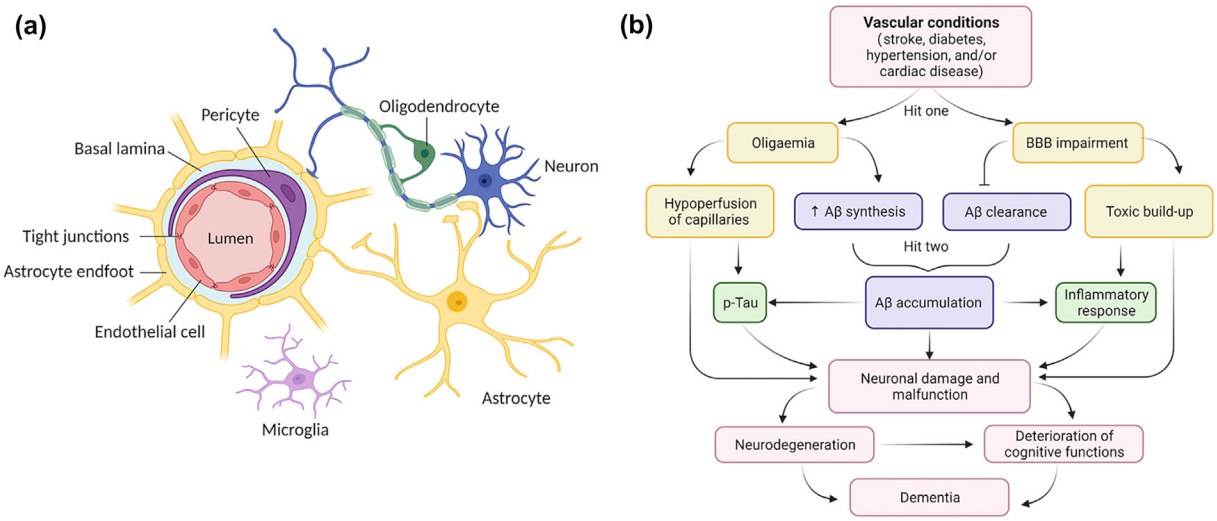


FIGURE 3 The neurovascular unit and two-hit hypothesis of Alzheimer's disease (AD). (a) At the level of the cerebral capillaries, endothelial cells are bound together by tight junctions and surrounded by pericytes, both comprising the capillary wall. This structure is attached to the basal lamina and encased by astrocyte end-feet processes, which are additionally connected to neurons whose myelin sheath consists of oligodendrocytes. Homeostatic microglia are ramified and can detect neuronal lesions. (b) Vascular conditions (Hit 1) induce a decrease in cerebral blood flow (CBF) (oligaemia) along with impairment of the blood–brain barrier (BBB) constituting the non-amyloid-β [Aβ] pathway, shown in yellow. Neuronal damage and malfunction are early prompted by hypoperfusion of capillaries together with toxic build-up. Through the Aβ pathway (shown in violet), Aβ synthesis is increased, and its clearance is reduced, leading to accumulation of the Aβ peptides (Hit 2). This hypothesis defines that tau pathology occurs as a result of both hits. In this regard, hypoperfusion of capillaries and accumulated Aβ promote the hyperphosphorylation of tau (p-Tau) and, eventually, the formation of neurofibrillary tangles. In addition, dysfunction of the BBB together with the accumulation of Aβ induce infiltration of neurotoxins and immune cells creating a neuroinflammatory environment which eventually converge in neuronal damage and malfunction, strengthening the propagation of the disease. Created with BioRender.com.

vasculature can be altered under pathological conditions such as obesity or any other metabolic disorder, leading to the development of important negative effects that may cause many vascular abnormalities, including endothelial dysfunction, vascular stiffness and elevated blood pressure (Galley et al., 2022; Opatrilova et al., 2018; Vliora et al., 2023). Therefore, AT-mediated vascular damage may be considered a therapeutic target not only for metabolic, but also for neurological diseases, such as AD.

4.3 | Cerebrovascular pathology, obesity and Alzheimer's disease

AD is neuropathologically characterized by two major protein lesions, the aggregation of Aβ into extracellular deposits called amyloid plaques and the intraneuronal aggregation of the hyperphosphorylated microtubule-associated protein **tau** into neurofibrillary tangles (Iadecola, 2016).

Much evidence correlates cerebrovascular dysfunction and AD. Around 50% of AD patients present vascular abnormalities, which increase with age (Sweeney et al., 2019). Vascular risk factors such as metabolic syndrome and atherosclerosis contribute to brain hypoperfusion and the probability of AD. Most of these factors are related to vascular ageing, resulting in changes that negatively affect the brain, as it critically depends on blood supply for structural and functional integrity (Cortes-Canteli & Iadecola, 2020).

Metabolic syndrome (obesity, diabetes and hypercholesterolaemia) has been related to cognitive impairment and AD (de Bruijn & Ikram, 2014). The study by Meakin et al. reported that diet-induced obesity in mice increased plasma and vascular Aβ42, which correlated with decreased NO bioavailability, endothelial dysfunction and increased blood pressure. In humans, these results were confirmed, as plasma Aβ42 correlated with diabetes and endothelial dysfunction (Meakin et al., 2020). Interestingly, in a mouse model combining features of Type 2 diabetes (morbidly obese and diabetic db/db mice) and AD (PS1P264L/P264L knock-in [KI] mice), cognitive decline was increased compared with single db/db or PS1P264L/P264L KI mice. These animals also showed severe cerebrovascular pathology, including aneurysms and small strokes (Niedowicz et al., 2014). In humans, in different large-scale studies, obesity was correlated to cognitive decline (Benito-Leon et al., 2013; Elias et al., 2005; Gunstad et al., 2010). On the other hand, atherosclerosis and lifestyle/genetic risk factors can cause cerebrovascular damage and breakdown of the BBB, marked by inflammation and hyper-connectivity (Kisler et al., 2017). This vascular damage leads to neurovascular dysfunction, reduction of CBF and potentially may initiate Aβ pathology by a reduction in amyloid clearance.

Increased Aβ production has been implicated in diverse processes of vascular dysfunction in AD, as it generates vascular inflammation and deregulation of vascular tone contributing to the impairment of the BBB (Govindpani et al., 2019). On the contrary, vascular anomalies have been reported to appear before Aβ accumulation, functional

decay, dysregulation of metabolism and brain deterioration (Solis et al., 2020). These findings suggested the two-hit neurovascular hypothesis of AD which postulates disruption of Aβ and of the neurovascular unit as separate predisposing elements that trigger a cascade of events presaging dementia (Figure 3) (Apátiga-Pérez et al., 2022; Zlokovic, 2011).

Taken together, the recognized pathological hallmarks of AD such as Aβ and vascular risk factors related to the metabolic syndrome have a marked effect on vascular dysfunction. These factors can influence the BBB and CBF that, in the long term, may contribute to AD development and progression.

4.4 | Apolipoprotein E, cerebrovascular dysfunction and risk of Alzheimer's disease

Recent genetic studies have shown that the risk of developing AD is significantly enhanced by various cardiovascular risk genes (Broce et al., 2019) which in turn are related to elevated Aβ levels in the brain (Rabin et al., 2018). For example, the level of apolipoprotein E (APOE) is the most important genetic risk factor for AD. This multifunctional protein is involved in the regulation of important neuronal and vascular functions such as cholesterol transport, lipid metabolism and Aβ clearance, among others (Mahley & Rall, 2000). Of the three isoforms of APOE (APOε2, APOε3 and APOε4), APOε4 is the one that significantly increases the risk for late-onset AD (Chartier-Hariln et al., 1994). The link between APOε4 and CBF is controversial, although there is evidence for such a relationship from studies investigating the contribution of APOε4 to preclinical risk of AD. For instance, APOε4 carriers with normal cognition showed higher perfusion deficits with age in brain regions especially vulnerable to pathological changes in AD such as frontal, parietal and temporal cortices (Thambisetty et al., 2010; Wierenga et al., 2013) when compared with non-APOε4 carriers.

The APOε4 genotype also influences BBB breakdown in AD patients because APOε4 homozygotes exhibit a thinner capillary basement membrane (Salloway et al., 2002) and increased leakage of plasma proteins (Zipser et al., 2007). Such data relate to the findings in human APOε4 KI mice that exhibit BBB impairment (Nishitsuji et al., 2011). Furthermore, AD patients carrying APOε4 are more susceptible to pericyte dysfunction than non-APOε4 carriers, and their pericytes are more prone to Aβ1–40 toxicity (Verbeek et al., 2000). Taken together, these results could explain, at least in part, the major susceptibility of APOε4 carriers to AD dementia.

4.5 | Neurovascular dysfunction in Alzheimer's disease

Under certain neurodegenerative disorders such as AD, the BBB integrity is impaired (Huang, Wong, et al., 2020). Breakdown of the BBB in AD has been shown through the detection of plasma-derived proteins in brain tissue (Sengillo et al., 2013; Takechi et al., 2010). For instance, post mortem cortical tissues of AD patients contain plasma proteins, and their leakage is more common in individuals with at least one APOε4 allele (Halliday et al., 2016). Additionally, dynamic contrast-enhanced magnetic resonance imaging has revealed increased BBB permeability in patients with mild cognitive impairment compared with healthy controls (M. Li et al., 2021). Moreover, BBB dysfunction in AD leads to decreased clearance of Aβ, contributing to amyloid burden in the brain (Deane et al., 2009).

At the molecular level, several mechanisms are associated with BBB dysfunction in AD. For instance, there is decreased expression of LRP-1 and P-glycoprotein (P-gp), both essential for Aβ transport across the BBB (Mohamed et al., 2016). LRP-1 facilitates Aβ internalization on the abluminal side of ECs and its subsequent degradation or transcytosis. Besides, P-gp, located on the luminal surface of ECs, is an ATP-dependent efflux transporter that reduces Aβ accumulation in the brain (Hartz et al., 2010). Conversely, increased expression of the **receptor for advanced glycation end products** (RAGE) also promotes the entry of Aβ into the brain by mediating its transport across the BBB (Candela et al., 2010; Wan et al., 2014). RAGE also interacts with hyperphosphorylated tau proteins and accelerates the progression of tau pathology in neurons, leading to behavioural deficits in tauopathies, such as AD (Y. Kim et al., 2023).

In terms of the cellular components of the neurovascular unit, one of the principal cell types affected under Alzheimer's pathogenesis are the ECs, which show different abnormalities, as reduced expression of tight junction proteins, increased permeability of the BBB and impaired transport mechanisms (Sweeney, Sagare, & Zlokovic, 2018). These alterations contribute to the accumulation of toxic substances in the brain and compromise the homeostatic environment necessary for neuronal functioning (Kadry et al., 2020; Zlokovic, 2011). In addition, decreased pericyte coverage, impaired contractility and abnormal interaction with ECs are also observed in AD (Procter et al., 2021). These changes lead to microvascular instability, increased BBB permeability and compromised regulation of CBF, which contributes to cerebral hypoperfusion and impaired clearance of Aβ peptides (Procter et al., 2021; Winkler et al., 2014). Furthermore, dysfunctional vascular smooth muscle cells (VSMCs) also contribute to the development of cerebral small vessel disease, which is commonly observed in AD and characterized by the deposition of Aβ in cerebral vessels, vascular calcification and vessel wall thickening (Frismantiene et al., 2018; Hayes et al., 2022). A functional change in VSMCs causes a decrease in contractility and an increase in stiffness, also contributing to cerebral hypoperfusion and impaired CBF regulation (Ahmad et al., 2020; Yazdani et al., 2020).

Microglia also display a fundamental role in the neurovascular unit due to their significance in maintaining brain homeostasis and participation in immune responses (da Fonseca et al., 2014). The communication and coordination between endothelial and microglial cells are vital for maintaining the integrity and functionality of BBB (Haruwaka et al., 2019). However, microglial activation is a prominent feature of AD, and it can significantly affect the function of the neurovascular unit in several ways (Huang et al., 2023). The microglial cells located near the BBB and ECs engage in continuous two-way

communication, and a strong spatiotemporal correlation between microglial activation and BBB impairment in AD has been found (da Fonseca et al., 2014).

One of the primary pathways involved in this process is NF-κB signalling pathway. When microglia is activated in response to inflammatory molecules, such as Aβ and other pathological stimuli, the NF-κB signalling pathway is activated in these cells, triggering the promoter regions of several pro-inflammatory genes, including those encoding cytokines such as IL-1, IL-6 and TNF-α (da Fonseca et al., 2014). These pro-inflammatory cytokines secreted by activated microglia can have detrimental effects on the ECs of the BBB (Rochfort & Cummins, 2015b; W. Y. Wang et al., 2015). For example, IL-1 and TNF-α can induce the production of matrix metalloproteinases, particularly **MMP-2** and **MMP-9**, in ECs. These enzymes degrade the extracellular matrix, including components of tight junctions, leading to increased BBB permeability (Song, Wu, et al., 2015). Additionally, microglia can promote the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) through the activation of enzymes such as **NADPH oxidase** and **inducible nitric oxide synthase** (iNOS). The excessive production of ROS and RNS can cause oxidative stress and damage to the ECs of the BBB (Song, Wu, et al., 2015). These ROS can attack lipids and proteins within the cells, leading to the release and activation of cytokines and proteases, including certain interleukins, which contribute to vascular damage. In the context of AD, IL-17 induced ROS production through NADPH oxidase or **xanthine oxidase** (XO) pathways. The resulting oxidative stress triggers the activation of the endothelial contractile machinery and down-regulates the expression of occludin, involved in tight junction formation (Lehner et al., 2011).

Astrocytes play a vital role as a crucial component of the neurovascular unit or the extended BBB. Positioned strategically between neurons and ECs within the neurovascular unit, astrocytes extend end-feet processes and, thus, closely monitor and adjust CBF in response to dynamic shifts in neuronal metabolism and synaptic activity. However, in pathological situations, reactive astrogliosis becomes dominant, triggered by a wide range of molecular signals such as cytokines, ATP, BMP, endothelin, FGF2, sonic hedgehog and thrombin. These molecular signals form the basis for communication among neurons, the BBB and microglia/macrophages (Filosa et al., 2016; Liu et al., 2018; Liu, Liu, Bao, et al., 2020).

While activated microglia are primarily responsible for producing pro-inflammatory cytokines that can contribute to BBB disruption during neuroinflammation, reactive astrocytes can also secrete certain molecules affecting BBB permeability (Lecuyer et al., 2016). The most notable molecule is **VEGF**, a potent angiogenic factor that plays a critical role in promoting blood vessel formation. In the context of neuroinflammation, reactive astrocytes can up-regulate the expression of VEGF (J. I. Alvarez et al., 2013; Linnerbauer & Rothhammer, 2020) which can directly act on the ECs of the BBB, leading to increased vascular permeability (J. I. Alvarez et al., 2013; Li et al., 2014; Linnerbauer & Rothhammer, 2020). VEGF binds to its receptors, such as **VEGFR-2**, present on the surface of ECs. This binding triggers a series of intracellular signalling events that result in the disruption of tight junction proteins between ECs (J. I. Alvarez et al., 2013; Lange et al., 2016). VEGF signalling can lead to the internalization and down-regulation of tight junction proteins like occludin and claudins, leading to the loosening of intercellular junctions (J. I. Alvarez et al., 2013; Lange et al., 2016). The loss of tight junction integrity increases the paracellular permeability of the BBB, allowing molecules and immune cells to enter the brain more easily. Consequently, this disruption of BBB tight junctions can facilitate the infiltration of pro-inflammatory cytokines, immune cells and other neurotoxic molecules into the brain parenchyma, contributing to neuroinflammation and altering the function of the neurovascular unit (Coisne & Engelhardt, 2011). It is important to note that while reactive astrocytes can contribute to BBB disruption through VEGF release, the primary mediators of neuroinflammation and BBB dysfunction are pro-inflammatory cytokines produced by activated microglia. The interaction and communication between active microglia and astrocytes play a vital role in orchestrating the neurovascular response in various brain disorders, including AD (J. I. Alvarez et al., 2013; Coisne & Engelhardt, 2011; Lange et al., 2016).

In addition, the mRNA expression of astrocytic end-feet water channel **aquaporin 4 (AQP4)** in the perivascular zone in the frontal cortex of AD patients is decreaased (Mader & Brimberg, 2019). AQP4 not only supports CSF flux into the brain parenchyma but also aids in the clearance of different solutes through bulk interstitial fluid. Deficiency of AQP4 impaired the clearance of Aβ42 through BBB, contributing to the progression of AD pathology (Yamazaki & Kanekiyo, 2017). In addition, astrocytic end-feet dysfunction in AD could increase the Aβ burden associated with blood vessels and within the brain parenchyma by reducing its clearance through the lymphatic system (Nedergaard & Goldman, 2020). Moreover, recent in vitro studies demonstrate that IL-1β disrupts the protective influence of astrocytes on BBB by inhibiting the production of sonic hedgehog and increasing the production of some pro-inflammatory chemokines, including CCL2, CCL20 and CXCL2, which attract immune cells and induce BBB disruption and neuroinflammation (Y. Wang et al., 2014).

Overall, these mechanisms postulate the importance of the constituents of the neurovascular unit as potential therapeutic targets, for these brain and vascular disorders (Muoio et al., 2014).

5 | EFFECTS OF ADIPOKINES ON THE BRAIN AND CEREBROVASCULAR SYSTEM: POTENTIAL THERAPEUTIC TARGETS FOR ALZHEIMER'S DISEASE

AD is a major neurodegenerative disorder and increasing studies have determined an important link between the incidence and progression of this disease and metabolic dysfunction (Cai et al., 2012). The AT plays an endocrine role by synthesizing and secreting bioactive compounds called adipokines, being closely linked to metabolic regulation. These adipokines may be involved in the regulation of different neurodegenerative disorders, although their functions in AD are not fully understood. The relationship between AD and obesity is well known,

although controversial (Emmerzaal et al., 2015; Qizilbash et al., 2015). Different studies have shown that excess body weight in subjects with overweight and obesity was related to a higher risk of developing AD (Kivipelto et al., 2005; Whitmer et al., 2007).

Among all the adipokines, leptin and adiponectin have been the most studied. However, their effects on the maintenance and disruption of the BBB are mostly unknown. Therefore, the aim of this section is to summarize the existing literature on the potential neuroprotective effects of the main obesity-related adipokines, their effects on the BBB integrity and function and their possible therapeutic effects in AD (Table 1).

5.1 | Leptin

As previously described, leptin is one of the main adipokines synthesized by AT and regulates body weight by suppressing hunger via its cognate receptor in the hypothalamus. The activation of leptin receptors triggers different intracellular signalling pathways related to inflammation, cognition, neurogenesis, synaptogenesis, neuronal excitability and neuroprotection, mechanisms that play an important role in the development and progression of AD (Flores-Cordero et al., 2022). Different studies have shown that circulating leptin levels were lower in AD patients compared with non-AD individuals with similar body mass index (Bigalke et al., 2011).

Studies in animal models support the neuroprotective effects of leptin and the administration of exogenous leptin as a possible therapy for AD (Hamilton & Harvey, 2021) (Table 1). Even though there are no clinical trials in humans, a study carried out in congenital cases of leptin deficiency (Paz-Filho et al., 2015) suggests leptin administration may be a safe treatment. Studies in animal models of AD showed that, in general, leptin has beneficial cognitive effects. Leptin administration to wild-type (WT) animals improved cognitive performance in a variety of behavioural assays of hippocampus-dependent learning and memory (McGregor & Harvey, 2019). In fact, an improvement in spatial and contextual learning and memory was found after bilateral injection of leptin into the dorsal hippocampus of SAMP8 mice with memory deficits due to Aβ overexpression (Farr et al., 2006). Other studies concluded that intracerebroventricular leptin administration improved hippocampal synaptic plasticity and spatial memory (Harvey et al., 2006; Tong et al., 2015). Furthermore, synaptogenesis is also promoted by leptin, by increasing the expression of microRNA-132 (Dhar et al., 2014). Even peripheral leptin administration in healthy male mice enhanced neuroplasticity and cognitive function, promoting hippocampal cell proliferation and survival of newborn neurons (Garza et al., 2008).

Chronic leptin treatment decreases both Aβ and tau pathology in a transgenic rodent model of AD (Greco et al., 2009). Several studies suggest that leptin reduces the toxic neuronal accumulation of Aβ either by directly reducing its generation (Fewlass et al., 2004) or by promoting its degradation (Marwarha et al., 2010). Other authors found that leptin promotes neuronal clearance of toxic Aβ through APOE-dependent Aβ uptake in human neuroblastoma cells (Fewlass et al., 2004). There is evidence that treatment with low concentrations of leptin protects against the acute and chronic actions of Aβ on synaptic plasticity (Malekizadeh et al., 2017). Furthermore, leptin also reduced the expression and phosphorylation of tau (Greco et al., 2010).

Leptin (a neuroprotective hormone) has also been used in combination with **pioglitazone** (an anti-inflammatory agent) as anti-Aβ therapy in APP/PS1 mice, with more effective results than leptin monotherapy alone (Liu, Hanson, McCormack, et al., 2020). Even a small leptin-derived fragment ($leptin_{116-130}$) counteracted the deleterious effects of Aβ at excitatory synapses, limited the extent of Aβ-induced neuronal cell death, reproduced the cognitive-enhancing effects of leptin and improved performance in episodic-like memory tasks in rodents (Malekizadeh et al., 2017).

Taken together, there is good evidence supporting the cognitive benefits of leptin in animal models of AD, although for its use in AD clinical trials several unresolved questions remain to be answered, such as the possible presence of leptin resistance. In this context, the mechanisms that regulate the transport of leptin through the BBB and its integrity are essential for understanding the development of leptin resistance and leptin effects on the brain. In b.End3 cells, which are derived from mouse brain endothelium, leptin can promote an alteration in the transcriptional expression of cytoskeletal components, proteasome subunits, translation elongation factors, ribonucleoproteins and others (Pan & Kastin, 2007). These effects could modify the BBB integrity. On the other hand, the development of leptin resistance in individuals with overweight and obesity may contribute to increase the risk of AD. A study performed in leptin-resistant rodents (db/db mice; fa/fa rats) suggests that they have an impaired ability to perform spatial memory tasks (Winocur et al., 2005). Although the molecular mechanism involved in the leptin resistance is unknown, it has been attributed to receptor saturation effects exerted by the excess of leptin or to the reversible inhibition caused by circulating factors as triglycerides, which can inhibit leptin transport across the BBB in a dose-dependent manner (Banks et al., 2018). Other mechanisms include defects in the capacity of the BBB to transport leptin. Several strategies to overcome leptin resistance include the modification of the structure of leptin (leptin analogues) and the development of new leptin receptor agonists with increased BBB permeability (Banks, 2001). Also, analogues of leptin, such as PEG-modified leptin, which is unable to pass through the BBB, and leptin modified with amphiphilic pluronic triblock copolymers, glucidic residue or PASylation of leptin may be able to overcome leptin transport resistance at the BBB (Izquierdo et al., 2019).

5.2 | Adiponectin

Adiponectin, the most abundant adipocytokine secreted by AT, plays a role in the regulation of insulin sensitivity, energy expenditure and inflammation. BBB and brain have **Adipo1** and **Adipo2** receptors for adiponectin (Thundyil et al., 2012), with different binding affinities for various types of adiponectin and different functional signalling

TABLE 1 Effects of adipokines on Alzheimer's disease pathology, the blood-brain barrier and promising therapies.

Adipokine	Effect on AD pathology	References	Effect on BBB	References	Therapy	References
Adiponectin	• Improvement of spatial memory, rescue of synaptic loss and reduction of Aβ levels and inflammation. • Reduction of synaptotoxicity, tau hyperphosphorylation and apoptosis.	Liu, Liu, Wang, et al. (2020); Ng et al. (2021)	• Reduction of VSMC proliferation and migration. • Decrease of VCAM-1 and ICAM-1 levels. • Decreased NO, IL-6, IL-8, TNF-α and CCL2 production.	Bloemer et al. (2018); Kawanami et al. (2004); Lee, Xu, et al. (2014); Song et al. (2017); Spranger et al. (2006)	• AdipoRon and osmotin: both compounds lower Aβ level, decrease accumulation of hyperphosphorylated tau, improve cognitive and synaptic function and reduce pro-inflammatory responses.	Ali et al. (2015); Liu, Hanson, McCormack, et al. (2020); Ng et al. (2021); Shah et al. (2017)
Apelin	• Facilitation of memory formation. • Amelioration of Aβ load and neurodegeneration. • Reduction of inflammation and the levels of IL-1β, TNF-α, MPO and ROS.	Luo et al. (2019); Nasseri et al. (2020); Wan et al. (2022); W. Xu et al. (2019)	• Modulation of tight junction opening, endothelial cell swelling and BBB permeability. • Promotion of endothelial cell proliferation and migration. • Induction of vasodilation by production of NO.	Cheng et al. (2019); Chu et al. (2017)		
Chemerin	• Prevention of neuronal apoptosis and neurodegeneration. • Facilitation of memory formation and amelioration of Aβ-induced memory impairment.	Lei et al. (2020); Y. Zhang et al. (2019)	• Inhibition of NF-κB and NO production. • Increase of CCL2, IL-8, TNF-α, VCAM-1, ICAM-1, E-selectin and monocyte-endothelial adhesion molecules.	Dimitriadis et al. (2018); Neves et al. (2015); Yamawaki et al. (2012)		
Chemokines	• Opposing effects depending on disease stage and chemokine type.	Wojcieszak et al. (2022)	• CCL2 causes redistribution of tight junction proteins. • CCL2 induces loss and redistribution of tight junction proteins.	Dimitrijevic et al. (2006); Stamatovic et al. (2005, 2006, 2009)		
IL-1β	• Promotion of tau hyperphosphorylation and NFTs. • Reduction of synaptic plasticity and learning processes. • Regulation of APP production and processing.	Mrak and Griffin (2000); Sheng et al. (2000)	• Increase in levels of CXCL1 and CXCL2 induces MMP-9 production. • Loss of occludin and ZO-1 expression. • Reduction of claudin-5 expression. • Decrease of sonic hedgehog expression in astrocytes.	Alvarez et al. (2011); Beard et al. (2014); Bolton et al. (1998); Chapouly et al. (2015); McColl et al. (2007, 2008); Y. Wang et al. (2014)	• IL-1β antibodies (canakinumab) and IL-1 receptor antagonists (anakinra). • Reduction of tau and Aβ pathology.	Cho et al. (2014)

(Continues)

TABLE 1 (Continued)

Adipokine	Effect on AD pathology	References	Effect on BBB	References	Therapy	References
			• Induction of VEGF-A production by astrocytes.			
IL-6	• Promotion of Aβ production. • Increase in NFT formation. • Cognitive impairment.	Ait-Ghezala et al. (2007); Lyra e Silva et al. (2021); Quintanilla et al. (2004)	• Decrease of transendothelial electrical resistance. • Decreased expression of tight junction proteins (claudin-5, occludin and ZO-1). • Autocrine effect on receptor glycoprotein 130 (gp130).	Brett et al. (1995); de Vries et al. (1996); Dohgu et al. (2011); Gopinathan et al. (2015); Rochfort et al. (2014, 2016); Voirin et al. (2020)	• Tocilizumab (humanized anti-IL-6R Mab).	Rubbert-Roth et al. (2018)
Leptin	• Reduction of Aβ load and tau phosphorylation in the hippocampus. • Reversal of Aβ-induced memory and learning deficits. • Inhibition of Aβ production and tau phosphorylation. • Increase of APOE-dependent Aβ uptake.	Fewlass et al. (2004); Greco et al. (2009, 2010); Tong et al. (2015)	• Inhibition of the BBB permeability, ICAM-1 expression and brain infiltration of neutrophils. • Increase in arterial pressure and heart rate. • Triggers release of the vasoconstrictor endothelin-1. • Induction of angiogenesis.	Banks (2001); Banks et al. (2018)	• Metreleptin (leptin A-100), for congenital or acquired generalized lipodystrophy or hypothalamic amenorrhea. • RmetHuLeptin stimulates the inflammatory and platelet responses in humans under caloric deprivation.	Paz-Filho et al. (2015)
NLRP3	• Reduction of Aβ accumulation. • Improvement of cognitive function.	Dempsey et al. (2017); X. F. He et al. (2020)				
TGF-β1	• Reduction of Aβ plaques. • Protection of neurons from Aβ toxicity. • Contribution to tau pathology. • Detrimental effects on AD pathology through astrocyte reactivity.	Lesné et al. (2003); Luterman et al. (2000); Ren and Flanders (1996); Tesseur et al. (2006); Wyss-Coray et al. (1997, 2000, 2001)	• Strengthen BBB. • Increase in permeability by phosphorylation of VE-cadherin and claudin-5.	Dohgu et al. (2004); Shen et al. (2011)		
TNF-α	• TNFR1 signalling is required for Aβ-induced neuronal death. • Increase Aβ deposition. • Decrease Aβ degradation.	Chang et al. (2017); X. Cheng et al. (2010); P. He et al. (2007); Smith et al. (2012)	• Induction of MMP-9 release by pericytes, which have proteolytic active over tight junction proteins.	Aslam et al. (2012); Bauer et al. (2010); Candelario-Jalil et al. (2007); Forster et al. (2008); Nagyőszi et al. (2015); Ni et al. (2017); O'Carroll et al.	• TNF inhibitors (TNFIs): monoclonal antibodies (infliximab, adalimumab, golimumab, dertolizumab) and	Chang et al. (2017); Cheng et al. (2014); McAlpine et al. (2009); Shi et al. (2011); Tobinick et al. (2006)

TABLE 1 (Continued)

Adipokine	Effect on AD pathology	References	Effect on BBB	References	Therapy	References
			• Increased expression of ICAM-1, VCAM-1 and NLRP3 in endothelial cells. • Decreased expression of ZO-1, claudin-3, claudin-5 and occludin.	(2015); Rochfort et al. (2014); Rochfort and Cummins (2015b); Versele et al. (2022); Y. M. Zhang et al. (2012)	recombinant fusion proteins (etanercept). • Improvement of cognitive functions. • Reduction of Aβ pathology. • Decrease in tau pathology.	
Visfatin	• Block of Aβ production. • Decreased Aβ accumulation and chronic neuroinflammation. • Improvement of cognitive function and synaptic plasticity.	Gong et al. (2013); Xie et al. (2019); Yao et al. (2017)	• Induction of endothelium-dependent vasodilation. • Trigger VSMC proliferation and migration. • Increase in vascular production of several inflammatory cytokines such as IL-6 and IL-8	Zhao et al. (2015)		

Abbreviations: APOE, apolipoprotein E; BBB, blood-brain barrier; MPO, myeloperoxidase; NFTs, neurofibrillary tangles.

preferences. While **PPARα** signalling was increased in AdipoR1$^{-/-}$ livers, where AdipoR2 was elevated, no increase in basal PPAR signalling was detected in AdipoR2$^{-/-}$ mice, suggesting that other signalling pathways are involved (Bjursell et al., 2007).

Elevated serum adiponectin has been associated in the Framingham Heart Study with an increased risk of developing AD in women but not in men (Wennberg et al., 2016). In addition, in a study conducted in AD patients, adiponectin was co-localized with p-tau in neurofibrillary tangles, which would explain the reduction in adiponectin levels in CSF and its positive correlation with Aβ plaques (Waragai et al., 2017). This suggests that the actions of adiponectin may be detrimental to the brain. However, the increase of adiponectin might be trying to counteract the damage caused by the progress of AD. Consistent with clinical evidence, low levels of adiponectin and Adipo1 receptor signalling in the brain of APP/PS1 and Adipo$^{-/-}$ mice increased Aβ (M. W. Kim et al., 2017), negatively affecting cognition and leading to increased levels of AD pathogenic markers (Bloemer et al., 2018), impaired learning and memory performance in fear conditioning, object recognition, Y-maze tests and spatial memory (Ng et al., 2016; D. Zhang et al., 2017). This activation of Adipo1 receptors may reduce AD neuropathology by increasing synaptic protection in HFD mice in in vivo and in vitro AD models (Ng et al., 2021; Ng & Chan, 2017). Furthermore, intracerebroventricular infusion of adiponectin increased neurogenesis (D. Zhang et al., 2016). In addition, adiponectin injection into the hippocampal dentate gyrus showed a beneficial effect on memory, characterized by an increase in excitatory post-synaptic potential slope (Pousti et al., 2018), and a reduced pro-inflammatory response of LPS-stimulated microglia (Nicolas et al., 2017).

In addition, adiponectin may ameliorate BBB disruption in AD patients. Although adiponectin does cross the BBB, Adipo1 and Adipo2 receptors have been found in ECs from the BBB (Spranger et al., 2006). Adiponectin might be involved in regulating the function and promoting the role of endothelial progenitor cells. Moreover, adiponectin may have essential functions, such as vascular endothelial protection, anti-inflammatory and vasodilatory properties. Moreover, adiponectin improved cognitive function, microvascular density, neuroinflammation and structural damage in ageing rats, suggesting it may influence disorders of the CNS (Huang, Hou, et al., 2020). Different mechanisms have been proposed for the possible beneficial effects of adiponectin on the BBB. On the one hand, adiponectin may alleviate AD pathogenesis by protecting BBB disruption and suppressing Aβ toxicity-induced inflammation through its interaction with Adipo1 receptors. Adiponectin decreased the production of NO, IL-6, IL-8, TNF-α and CCL2 in brain ECs under Aβ-induced toxicity (Lee, Ji, et al., 2014; Spranger et al., 2006) and suppressed the loss of tight junction proteins and the increase of RAGE (Song et al., 2017). Moreover, adiponectin inhibits vascular endothelial hyperpermeability through cAMP signalling (S. Q. Xu et al., 2008). In addition, adiponectin increases the transportation of Aβ into brain and amyloid clearance by enhancing the expression of the low-density lipoprotein receptor-related protein 1 (LRP-1) and suppressing the level of RAGE in brain ECs (Song et al., 2017). On the other hand, several effects could be

mediated by Adipo2 receptors, such as the inhibition of the induction of **vascular cell adhesion molecule-1** (VCAM-1) and **intracellular cell adhesion molecule-1** (ICAM-1) (Kawanami et al., 2004), which bind to leukocytes and initiate EC injury.

These effects of adiponectin can be mimicked by other molecules with a potential agonist effect on adiponectin receptors, such as osmotin and AdipoRon (Table 1, Figure 4). Osmotin has shown a protective effect in transgenic AD mouse models (Ali et al., 2015). Intraperitoneal osmotin treatment improved Y-maze spontaneous alternations performance, reduced Aβ accumulation and reduced tau hyperphosphorylation in mice that received an intracerebroventricular injection of Aβ42 (Ali et al., 2015). Moreover, osmotin reduced LPS-induced neuroinflammation and memory impairment via the **TLR4**/NF-κB signalling pathway (Badshah et al., 2016) and improved hippocampal long-term potentiation (LTP) and performance in Morris water maze of APP/PS1 mice (Shah et al., 2017). However, like adiponectin, this molecule has a limited use as a therapeutic agent in clinical studies, because of its large size. A novel osmotin-derived adiponectin mimetic nonapeptide (Os-pep) can cross the BBB and improve synaptic plasticity and memory functions in AD and Adipo$^{-/-}$ mice (Ali et al., 2021). Meanwhile, the effects of AdipoRon, which can cross the BBB, depend on the dose used. A low dose of intraperitoneal AdipoRon promoted hippocampal cell proliferation, whereas a high dose produced detrimental effects on hippocampal function (Lee et al., 2021). Furthermore, chronic oral treatment with AdipoRon improved spatial memory functions and rescued neuronal and synaptic loss in 5xFAD and 5xFAD; APN$^{-/-}$ mice (Ng et al., 2021). Similar results were found in APP/PS1 transgenic mice, in which AdipoRon

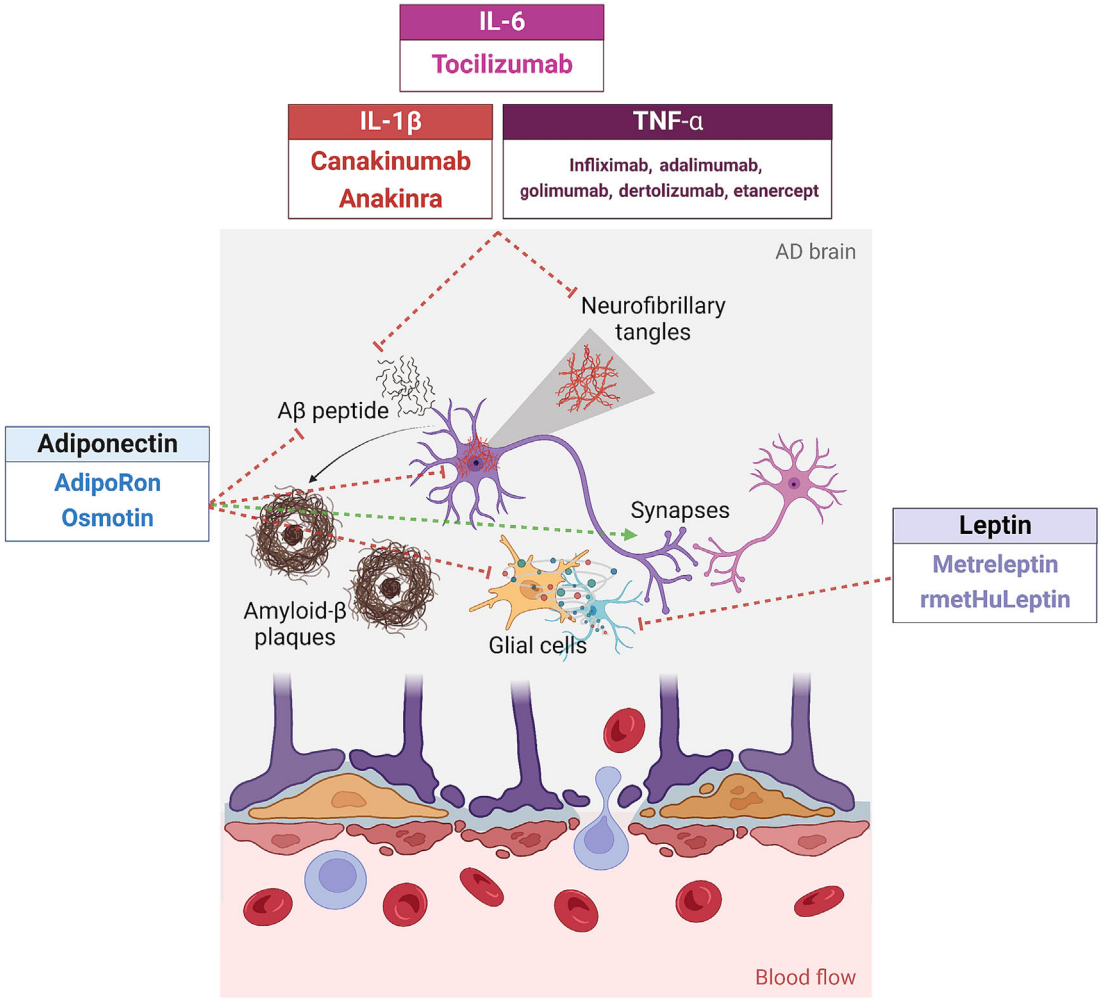


FIGURE 4 Schematic overview of different therapeutic targets and drugs related to the actions of adipokines in the brain and the blood–brain barrier. The adiponectin agonists AdipoRon and osmotin can act to decrease levels of amyloid-β (Aβ) and hyperphosphorylated tau, as well as ameliorating the pro-inflammatory response and improving synaptic function. Similarly, leptin analogues such as Metreleptin and rmetHuLeptin can simulate the effects of the endogenous adipokine leptin in the Alzheimer's disease (AD) brain, thereby reducing the pathological effects of AD. On the other hand, blockers of IL-1β action, such as the IL-1β antibody canakinumab and the IL-1β receptor antagonist anakinra, can improve AD brains by reducing both Aβ and tau pathologies. In addition, blockers of IL-6 action such as tocilizumab, a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody, can counteract the detrimental effects of IL-6. Finally, TNF-α inhibitors such as infliximab, adalimumab, golimumab and dertolizumab (monoclonal antibodies), can improve AD pathology, as well as some new drugs based on recombinant fusion proteins such as etanercept. Created with BioRender.com.

improved cognitive dysfunction, inhibited Aβ deposition and restored the impaired proliferation of hippocampal neurons (Liu, Hanson, McCormack, et al., 2020).

Other analogues of adiponectin are the C1q/TNF-related proteins (CTRPs). This family has structural and biochemical characteristics similar to those of adiponectin. Intranasally, rCTRP9 produced an activation of Adipo1 receptor, with the consequent improvement of neurological functions and preservation of BBB integrity through the APPL1/AMPK/**Nrf2** signalling pathway in ICH mice (Zhao et al., 2021).

5.3 | Chemerin

Chemerin is another adipokine that can act on different tissues by binding to various receptors, such as **chemokine-like receptor 1** (CMKLR1). The expression of this receptor is up-regulated in AD patients, showing a col-ocalization with Aβ42 in hippocampal neurons of APP/PS1 AD mice (Peng et al., 2015). This receptor is also involved in the processing and clearance of Aβ. Intranasal administration of recombinant human chemerin (rhChemerin) exerts neuroprotective effects that enhance cognitive and sensorimotor performance in a rat model of neonatal hypoxia-ischaemia brain injury (Y. Zhang et al., 2019). Furthermore, an intracerebroventricular injection of chemerin in mice facilitated memory formation, prolonged memory retention and ameliorated Aβ-induced memory impairment (Lei et al., 2020). Therefore, modulation of the chemerin/CMKLR1 axis might be a potential new strategy for AD therapy (Table 1).

However, there are contradictory results regarding its effects on the vascular endothelium. The administration of 400 and 800 ng per mouse of rhChemerin in a mouse model of stroke minimized the BBB opening, spatial memory and neurological impairment. Furthermore, 800 ng per mouse of rhChemerin suppressed expression of NF-κB, TNF-α and IL-1β and up-regulated IL-10 and VEGF in the cortex and hippocampus of the mice (Abareshi et al., 2021). Also, chemerin might play an anti-inflammatory role by preventing TNF-α-induced VCAM-1 expression and monocytes adhesion in vascular ECs (Yamawaki et al., 2012). On the contrary, other studies found that chemerin exerts pro-apoptotic, pro-inflammatory and proliferative effects in human vascular cells (Baglietto-Vargas et al., 2016; Neves et al., 2015). In addition, it increased the expression of inflammatory factors, as induced NF-κB activation, and the secretion of EC adhesion molecules, namely, E-selectin, VCAM-1 and ICAM-1, leading to enhancement of monocyte-endothelial adhesion (Dimitriadis et al., 2018).

5.4 | Apelin

Apelin is a hormone secreted by adipocytes, primarily involved in the regulation of glucose homeostasis. This hormone also plays an important role in neuronal protection (Pope et al., 2012) and the presence of apelin receptors has been described in the brain of rodents (Pope et al., 2012) (Table 1). One of the bioactive forms of apelin, **apelin-13**, seems to modulate different mechanisms related to AD. On the one hand, the intracerebral infusion of apelin-13 decreases the BBB permeability after cerebral ischaemia (Chu et al., 2017) and could reduce brain oedema, BBB disruption and neurofunctional deficits after subarachnoid haemorrhage in rats (W. Xu et al., 2019). Apelin-13 promotes proliferation and repair of ECs by activating **endothelial nitric oxide synthase** (eNOS), AMPK, ERK1/2/PI3K/**P70S6K**, PI3K/Akt and MAPK (J. Cheng et al., 2019) and reduces apoptosis of vascular endothelial cells(Azizi et al., 2015).

In addition, apelin-13 appears to directly affect the brain. It is involved in ameliorating AD symptoms by regulating autophagy, Aβ-induced apoptosis, neuron synaptic plasticity and inhibition of microglia and astrocyte activation (Luo et al., 2019; Wan et al., 2022). In addition, it could reduce Aβ deposition in the stroma, neurodegeneration and AD progression (Wan et al., 2022). In a rat model of streptozotocin-induced AD, apelin-13 protects neurons by decreasing neuroinflammation through activation of the **BDNF-TrkB** signalling pathway (Luo et al., 2019) and attenuating streptozotocin-induced learning and memory impairment by modulating the necroptosis signalling pathway (Nasseri et al., 2020). Furthermore, apelin-13 can protect against passive avoidance memory deficiency and **scopolamine**-induced neuronal loss in male rats (Gazmeh et al., 2022).

5.5 | Visfatin

Nicotinamide phosphoribosyl transferase (NAMPT/visfatin) is an enzyme that catalyses the biosynthesis of nicotinamide adenine dinucleotide (NAD^+) in mammals. NAD^+ acts as a neuroprotective agent to prevent ATP depletion (Zhu et al., 2015). Visfatin is a neuroendocrine factor, although it is uncertain whether visfatin can cross the BBB. Transgenic mice overexpressing NAMPT globally had increased neuronal survival in the hippocampal dentate gyrus and showed improved learning and memory performance in the water maze test upon middle cerebral artery occlusion (Zhao et al., 2015).

Different NAD^+ precursors, including nicotinamide mononucleotide (NMN) and nicotinamide riboside (NMR), might be a potential treatment for AD progression (Table 1). NAD replenishment with NMN maintains the integrity of the BBB and ameliorates tPA-induced haemorrhagic transformation in brain ischaemia (Wei et al., 2017). In the brain of an AD rat model, intraperitoneal administration of NMN improved learning and memory performance in the water maze task (X. Wang et al., 2016). Furthermore, NMN treatment in AD transgenic mice reduced cognitive impairment, significantly decreased Aβ production, amyloid plaque load, synaptic loss and inflammatory responses by the inhibition of JNK activation (Yao et al., 2017). Supplementation of APP/PS1 transgenic mice with NMR, a safe NAD precursor with high oral bioavailability, improved short-term spatial memory and the contextual fear memory (Xie et al., 2019). In addition, NMR inhibited astrocyte activation, Aβ accumulation and astrocyte migration. This precursor also exhibited a pro-cognitive function,

restored LTP deficit in the hippocampal CA1 region of the Tg2576 AD mouse model and could prevent Aβ accumulation in the brain (Gong et al., 2013).

5.6 | IL-6

IL-6 is a critical inflammatory cytokine involved in the acute phase of inflammatory response (Aliyu et al., 2022). Many relevant studies have shown that this specific cytokine is closely related with metabolic disorders such as obesity. With this regard, elevated IL-6 is detected in obese humans and rodents (Bastard et al., 2000) and IL-6 expression decreases in the AT and plasma after weight loss (Bastard et al., 2000). Overall, these findings have clearly demonstrated an important crosstalk between IL-6 and metabolic alterations.

IL-6 can be produced by many different cells in many different organs, including adipocytes, fibroblasts, vascular ECs, macrophages and T-cells (Aliyu et al., 2022) that contribute to the production and accumulation of this cytokine in the circulatory system. In the CNS, IL-6 is produced mainly by microglial cells, although astrocytes and ECs from brain microvessels can release significant amounts of this cytokine (Fabry et al., 1993; Lieberman et al., 1989). IL-6 produced at peripheral level may also cross the BBB, being found in both CSF and brain parenchyma (Banks et al., 1994), contributing to cerebral IL-6 levels. Thus, peripheral IL-6 may facilitate cognitive damage, because there is an inverse association between peripheral plasma IL-6 levels and hippocampal grey matter volume (Bradburn et al., 2017; Marsland et al., 2008). In addition, IL-6 produced impairments in synaptic development and dendritic spine formation (Wei et al., 2012), altering the synaptic plasticity (Yaffe et al., 2004).

The molecular and cellular mechanisms by which IL-6 dysregulates the BBB function remain poorly defined. However, IL-6 was able to disrupt the BBB by decreasing the transendothelial electrical resistance (TEER) (de Vries et al., 1996). Moreover, IL-6 increased endothelial permeability in the brain by reducing the expression of the tight junction proteins such as claudin-5, occludin and ZO-1 (Rochfort et al., 2014; Voirin et al., 2020). This reduction was mediated by rROS generation in ECs (Rochfort et al., 2014). Within the BBB, IL-6 is secreted by ECs and contributes to barrier integrity dysfunction in an autocrine manner through its co-receptor gp130 (Dohgu et al., 2011; Rochfort et al., 2016). IL-6 is also secreted by pericytes under inflammatory conditions (Jansson et al., 2014). Nevertheless, the results obtained when analysing the local effects of IL-6 on the BBB seem contradictory. On one hand, IL-6 can promote abnormal angiogenesis with scarce pericyte coverage and barrier dysfunction (Brett et al., 1995; Gopinathan et al., 2015). On the other hand, IL-6 could stimulate pericyte migration to enhance vascular coverage (Ricard et al., 2014). In this regard, oncostatin M is a cytokine of the IL-6 family that activates the JAK/STAT 3 pathway in pericytes, contributing to BBB disruption (Takata et al., 2018, 2019). Moreover, oncostatin M can contribute to increase BBB permeability by other mechanisms as **its receptors** are expressed by ECs and were shown to reduce claudin-5 expression (Takata et al., 2018).

IL-6 plays a critical role in the pathogenesis of inflammatory disorders such as AD, which is associated with high levels of this cytokine in brain (Bauer et al., 1991; Hull, Berger, et al., 1996; Rothaug et al., 2016). In fact, the expression of IL-6 is increased around Aβ plaques and in CSF of AD patients (Hampel et al., 2005; Hull, Strauss, et al., 1996). In human, the −572C/G polymorphism of the IL-6 gene promoter region might be associated with AD risk (M. X. He et al., 2010). IL-6 promotes Aβ production through JAK activation of NF-κB via PI3K/Akt pathway as NF-κB is able to bind the **amyloid precursor protein** (APP) (Ait-Ghezala et al., 2007). Moreover, the transcription and synthesis of APP is stimulated by IL-6 (Ringheim et al., 1998). In turn, Aβ can activate glial cells inducing the production of inflammatory cytokines such as IL-6 (Song et al., 2001) increasing the detrimental effect of this interleukin on Aβ production. However, despite the effect of IL-6 on Aβ toxicity shown in vitro, IL-6 may be beneficial at early stages of the disease by enhancing plaque clearance through activation of astrocyte and microglia (Chakrabarty et al., 2010). On the other hand, IL-6 increases formation of neurofibrillary tangles (Quintanilla et al., 2004) by activation of JAK/STAT3 and MAPK. IL-6 is also related to cognitive impairment as an APP/PS1 model administered with IL-6 neutralizing antibody exhibited similar performance in cognitive test compared with WT mice (Lyra e Silva et al., 2021).

As IL-6 plays a major role in neurological disorders, the blockade of IL-6 signalling may be an interesting candidate for AD treatment (Rothaug et al., 2016). **Tocilizumab** is a humanized anti-IL-6R Mab approved by FDA for the treatment of rheumatoid arthritis (Table 1, Figure 4) (Rubbert-Roth et al., 2018). There are other anti-IL mAbS that are in different phases of clinical trials (Kaur et al., 2020). The efficiency of this treatment in prevention of inflammation has been successfully shown in patients with juvenile idiopathic arthritis (Brunner et al., 2015). However, their elevated cost and high possibility of immunogenicity have limited their use. Therefore, other IL-6 inhibitors, such as IL-6 production inhibitors, IL-6 expression inhibitors, IL-6 receptor antagonists and IL-6/JAK/STAT3 signalling pathway inhibitors, are in development (Kaur et al., 2020).

5.7 | TNF-α

TNF-α is a cytokine implicated in chronic inflammation. In the periphery, TNF-α is produced by adipocytes and macrophages and can cross the BBB (Di Simone et al., 2006). In the brain, TNF-α can be produced by astrocytes, microglia and neurons (Lieberman et al., 1989; Morganti-Kossman et al., 1997) where it controls synaptic transmission and neurogenesis (Beattie et al., 2002; Pickering et al., 2005) and exerts neurotoxic effects by damaging myelin and oligodendrocytes (Selmaj & Raine, 1988), facilitating glutamate excitotoxicity (Pickering et al., 2005), altering adult neurogenesis (Cacci et al., 2005) and triggering processes such as apoptosis (Montgomery & Bowers, 2012; Pickering et al., 2005).

TNF-α levels are elevated in the plasma and hypothalamus of obese rodents and humans (Mousa, 2005; Thaler et al., 2012). In

obese individuals, excessive production of TNF-α by WAT may decrease adult neurogenesis, impair LTP and increase **glutamate** excitotoxicity (Penn et al., 2013). In addition, TNF-α administration results in BBB failure (Candelario-Jalil et al., 2007). Brain pericytes express receptors for TNF-α (Matsumoto et al., 2014; Navarro et al., 2016), which induces the release of **MMP-9** (Takata et al., 2011). MMP-9 in the brain leads to BBB impairment through proteolytic activity over tight junction-associated proteins (Bauer et al., 2010; Y. M. Zhang et al., 2012), increasing endothelial permeability. An in vitro study using cultured ECs showed that TNF-α interact with its receptor (Lucas et al., 1998) increasing BBB permeability. TNF-α increased transcellular and paracellular passage, through up-regulation of ICAM-1, VCAM-1 and **NLRP3** in ECs (Nagyőszi et al., 2015; Versele et al., 2022). Moreover, TNF-α decreased the expression of tight junction-associated proteins ZO-1 (Rochfort & Cummins, 2015a), claudin-3 and occludin (Forster et al., 2008; Ni et al., 2017; Rochfort et al., 2014; Versele et al., 2022). Activation of NF-κB and PI3K are implicated in BBB dysfunction mediated by TNF-α, because this cytokine reduces claudin-5 promoter activity and mRNA expression through the NF-κB pathway (Aslam et al., 2012). PI3K inhibition attenuated the TNF-α-induced loss of claudin-5 expression in ECs (Camire et al., 2015). In addition, TNF-α stimulated the production of various inflammatory mediators, including IL-6, IFN-γ and CCL2 in ECs leading to BBB disruption (Matsumoto et al., 2014; Rochfort et al., 2016).

IL-1, IL-6 and TNF-α levels are associated with AD risk (Tan et al., 2007), and TNF-α is particularly important in the development of this disorder as participates in the spread of inflammation and the pathophysiology (Chang et al., 2017). One observation supporting the involvement of TNF-α in AD is its presence around Aβ plaques in post mortem human AD brains (Dickson, 1997). Accordingly, several studies have shown that TNF-α levels are higher in AD patients than in healthy people (A. Alvarez et al., 2007; Tarkowski et al., 2003), who usually display very low levels. Moreover, **TNFR1** signalling is required for Aβ-induced neuronal death (X. Cheng et al., 2010), and several studies have shown an elevation of TNF-α levels in CSF and serum of AD patients, whose levels correlated with disease progression (A. Alvarez et al., 2007; Paganelli et al., 2002; Tarkowski et al., 2003). Elevated TNF-α levels were also observed in AD transgenic mice brain (Sly et al., 2001) that were associated with intraneuronal Aβ immunoreactivity and correlated with cognitive deficits (Billings et al., 2005). TNF-α is related to abnormal APP processing and plaque deposition. In fact, deletion of TNFR1 in AD mice lowered Aβ formation, Aβ plaque deposition and cognitive deficits (P. He et al., 2007). TNF-α expression increased after Aβ1–40 injection in mice and worsened cognitive function (Medeiros et al., 2007). This molecule has been demonstrated to decrease Aβ degradation (Smith et al., 2012) and increase its production through up-regulation of β-secretase expression. In addition, chronic neuronal TNF-α expression resulted in neuronal cell death (Chang et al., 2017).

TNF inhibitors (TNFIs) have been tried in patients with ankylosing spondylitis resulting in a protective role for AD risk (Watad et al., 2022). The most potent TNFIs are biologic drugs that are approved by FDA for the treatment of peripheral inflammatory conditions such as Crohn's disease, psoriatic arthritism and rheumatoid arthritis (Chang et al., 2017). These TNFIs include TNF-α-specific monoclonal antibodies (**infliximab**, **adalimumab**, **golimumab** and **certolizumab**) and recombinant fusion proteins (**etanercept**) (Table 1 and Figure 4) (X. Cheng et al., 2014). These drugs have shown protective effects in AD improving cognitive impairment and reducing Aβ and tau pathology (Chang et al., 2017; McAlpine et al., 2009; Ou et al., 2021; Shi et al., 2011; Tobinick et al., 2006). Etanercept, which is in Phase II clinical trials, reduces neuroinflammation, TNF level and amyloid plaque accumulation and improves cognitive functions (Figure 4) (Tufan & Tufan, 2015; Zhou et al., 2020). Moreover, this compound is able to increase PSD95 expression and reduce p-tau, microgliosis and neuron loss in the hippocampus of PS19 mice (Ou et al., 2021).

5.8 | Interleukin-1β

As mentioned above, adipocytes can also produce IL-1β, which is another pro-inflammatory cytokine able to increase BBB permeability (Blamire et al., 2000). Systematic IL-1β administration exacerbates ischaemic brain injury and BBB disruption. However, this process can be reversed by the treatment with IL-1 receptor antagonist (**IL-1ra**) (Betz et al., 1995; Garcia et al., 1995; Pradillo et al., 2012, 2017). IL-1β also affects BBB permeability by increasing circulating levels of the chemokines **CXCL1** and CXCL2, leading to more neutrophil infiltration which produce MMP-9 (McColl et al., 2007, 2008). Moreover, IL-1β induces the expression of other inflammatory mediators such as TNF-α, CXCL10, IL-8, IL-6, CCL2, G-CSF, VEGF and GM-CSF in ECs (Krasnow et al., 2017; O'Carroll et al., 2015). Brain parenchymal injection of IL-1β showed that this cytokine leads to the loss of tight junction-associated protein occludin and ZO-1 expression at ECs, which coincide with paracellular leakage and neutrophil recruitment to vessels (Bolton et al., 1998). In this sense, a 6-h exposure of ECs to IL-1β led to brain endothelial barrier dysfunction associated with elevated phosphorylation of XO-1 through activation of **protein kinase C** (Ralay Ranaivo et al., 2012). A 24-h exposure reduced claudin-5 expression through transcriptional repression of **β-catenin** and FoxO1 (Beard et al., 2014).

IL-1β acts not only on ECs but also on astrocytes to increase the BBB permeability. IL-1β released by microglia decreases astroglial expression of sonic hedgehog, which regulates tight junction proteins in ECs. Sonic hedgehog can strengthen BBB integrity by up-regulating these proteins, whereas IL-1β decreases expression of sonic hedgehog by down-regulating the tight junction proteins (J. I. Alvarez et al., 2011; Y. Wang et al., 2014). Moreover, IL-1β increases pro-inflammatory chemokine production in astrocytes such as the chemokines CCL 2, CCL20 and CXCL2, which in turn exacerbates BBB disruption (Y. Wang et al., 2014). In addition, IL-1β can also induce astrocytic production of **VEGF-A** and thymidine phosphorylase, which reduce the expression of tight junction proteins in ECs (Chapouly et al., 2015).

IL-1β is elevated in AD brains and can be associated with the progression and early onset of this disorder (Sanchez-Mejias et al., 2020). IL-1β production is mediated by NLRP3 activation. Once microglia are stimulated by Aβ, NLRP3 recruits adaptor protein ASC and procaspase-1 into an inflammasome complex, to generate **caspase-1**. Subsequently, the pro-inflammatory cytokines, especially pro-IL-18 and pro-IL-1β, are cleaved by caspase-1 into mature forms of IL-18 and IL-1β (Liang et al., 2022). Excessive NLRP3 activation and elevated IL-1β levels in microglia promote tau hyperphosphorylation and formation of neurofibrillary tangles, thus affecting synaptic plasticity and learning processes in AD (Mrak & Griffin, 2000; Sheng et al., 2000). Moreover, IL-1β also regulates APP production and processing (Mrak & Griffin, 2000). In turn, Aβ fibrils trigger the activation of microglia and enhance their production of IL-1β (Barger & Harmon, 1997), exacerbating its toxic effect. Several researchers have suggested that blocking IL-1β signals via IL-1β antibodies and IL-1R antagonists could be a possible therapeutic strategy for AD. Currently, the soluble IL-1 trap **rilonacept**, the IL-1R antagonist **anakinra** and the neutralizing monoclonal anti-IL-1β antibody **canakinumab** have been investigated against IL-1β-mediated neuroinflammation and AD (Table 1, Figure 4) (M. H. Cho et al., 2014). Multiple non-inflammatory and inflammatory disorders have been successfully treated with anakinra to specifically suppress the activity of IL-1β, including familial Mediterranean fever, rheumatoid arthritis, gout, cyopyrin-associated periodic syndrome, heart failure, Type 2 diabetes and AD (O'Hanlon, 1988). The long-term treatment of 3xTg-AD mice with an IL-1R blocking antibody improved cognition, reduced cerebral inflammation, alleviated tau pathology and lowered fAβ levels (Kitazawa et al., 2011).

In vivo studies testing specific inhibitors of NLRP3 have yielded promising results, such as a decrease of tau and Aβ aggregates and amelioration of the cognitive impairment (Barczuk et al., 2022). Small-molecule NLRP3 inhibitors such as **MCC950** have been shown to improve cognitive function and reduce Aβ accumulation (Dempsey et al., 2017; X. F. He et al., 2020). In this sense, MCC950 and **inzomelid** (a related NLRP3 inhibitor) will soon move to Phase II for a range of neurodegenerative diseases including AD (Onyango et al., 2021). JC124 is an NLRP3 inhibitor that blocks IL-1β secretion. This small molecule reduces Aβ load and neuroinflammation in APP/PS1 mice along with an improvement in cognitive function (Onyango et al., 2021). Moreover, JC124 decreased Aβ levels and oxidative stress (Yin et al., 2018) in a CRND8 AD model.

5.9 | Chemokines

Chemokines constitute a family of low-molecular-weight proteins related to leukocyte recruitment and cellular activation. Overexpression of chemokines disrupts the integrity of BBB, facilitating the infiltration of immune cells into the brain. The chemokines **CCL2** (MCP-1), **CCL3** (MIP-1α) and **CXCL12** (SDF-1) play an important role in BBB disruption (Dimitrijevic et al., 2007; Eugenin & Berman, 2003). As commented, adiponectin regulates CCL2 levels, which cause tight-junction proteins redistribution in ECs affecting BBB permeability both in vitro and in vivo models (Dimitrijevic et al., 2006; Stamatovic et al., 2005). Accordingly, CCL2 causes loss of tight junction proteins expression and redistribution (Stamatovic et al., 2006, 2009).

Within the brain, chemokines may be released by neurons, astrocytes or microglia and contribute to neurogenesis, synaptic plasticity and also to neuroinflammation (Wojcieszak et al., 2022). **CX3CL1** (fractalkine) is a chemokine expressed by neurons whose decreased signalling leads to pro-inflammatory microglial activation (L. Zhang et al., 2018). Reduced levels of CX3CL1 were found in brains (Cho et al., 2011) and CSF (Perea et al., 2018) from AD patients. Conversely, other studies showed increased levels of CX3CL1 in AD brains (Dworzak et al., 2015). In animal models, genetic ablation of the receptor **CX3CR1** eliminates microglial activation and cognitive deficits in Aβ-treated rats (Wu et al., 2013). Inhibition of CX3CL1 signalling produces opposite effects on Aβ and tau pathologies in mouse models of AD. APP/PS1 mice deficient in CX3CL1 showed enhanced tau phosphorylation and reduced Aβ pathology (Lee, Xu, et al., 2014). Overexpression of CX3CL1 in neurons of mice with tau mutation reduced neurodegeneration and improved cognitive functions (Fan et al., 2020). A reduction of Aβ deposition was observed in APP/PS1 and APP mice deficient for CX3CR1 (Lee et al., 2010) and also in APP/PS1 mice heterozygous for CX3CR1 (Hickman et al., 2019).

Concerning CCL2, elevated levels of this chemokine were found in plasma, CSF and brain of AD patients (Correa et al., 2011; Lee et al., 2018). Increased expression of CCL2 was also observed in several mouse models of AD such as 5xFAD (Manji et al., 2019), Tg2576, 3xTgAD and APP/PS1 (Hartlage-Rübsamen et al., 2015; Reale et al., 2018; Zaheer et al., 2013). In APP mice, overexpression of CCL2 results in increased Aβ deposition (Kiyota et al., 2009; Yamamoto et al., 2005). In rTg4510, up-regulation of CCL2 promotes microglial activation and exacerbates tau pathology (Joly-Amado et al., 2020). Moreover CCL2 silencing can also aggravate AD pathology in mouse models. For example, in APP/PS1 mice, knock-out of **CCR2** accelerates Aβ accumulation and cognitive decline (Naert & Rivest, 2011). Thus, CCL2 plays a protective role against amyloidosis at physiological levels but at late stages of AD may aggravate Aβ pathology (Wojcieszak et al., 2022).

5.10 | Transforming growth factor β1

TGF-β1 is a potent anti-inflammatory agent that can be produced by adipocytes and plays a major role in inflammation resolution. At the BBB level, TGF-β1 is produced by pericytes. The inhibition of TGF-β1 by pericytes leads to BBB dysfunction (Takata et al., 2007), which might be explained by its contribution to tighten the BBB and enhance P-gp efflux transporter activity in ECs of mouse brain capillaries (Dohgu et al., 2004). TGF-β1 increases permeability of vascular endothelium by tyrosin phosphorylation of VE-cadherin and claudin-5 (Shen et al., 2011).

TGF-β1 levels are low in the healthy CNS but increase after injury and neurodegenerative disorders (Tesseur et al., 2006). TGF-β1 can

be synthetized by microglia and astrocytes, and its concentration has been reported to be elevated in AD brains (Ueberham et al., 2003). This molecule can reduce Aβ deposits by activating microglia (Wyss-Coray et al., 2001) and also protect primary cultures neurons from Aβ toxicity (Ren & Flanders, 1996). In fact, TGF-β1 levels are reduced in the hippocampus of Aβ-injected mice (Torrisi et al., 2019) and TGF-β deficiency promotes Aβ deposition and neuronal loss in a mouse model of AD (Tesseur et al., 2006). In cultured cells, TGF-β1 signalling impairment leads to neuronal degeneration and increased Aβ and APP levels (Tesseur et al., 2006). Moreover, TGF-β1 signalling participates in tau pathology and neurofibrillary tangle formation (Luterman et al., 2000). Astrocytic TGF-β1 signalling can facilitate microglial Aβ uptake (Tichauer & von Bernhardi, 2012). TGF-β1 overexpression can restore hippocampal synaptic plasticity and improve memory function (Hu et al., 2019). In the hippocampus of AD model mice, a decrease in TGF-β1 expression causes reduction in spine density, synaptic plasticity and memory function (Hu et al., 2019).

Given that TGF-β1 promotes cell survival and cell renewal, whereas impairments of TGF-β1 pathway increase neuroinflammation and decrease Aβ clearance, it may be considered as a target for AD treatment (Yang & Xu, 2023). On the contrary, TGF-β1 signalling in astrocytes seems to be detrimental (J. Luo, 2022) as induces inflammatory astrocyte reactivity promoting amyloid angiopathy in the frontal cortex and meninges (Wyss-Coray et al., 1997, 2000) and increases the production of Aβ40/42 by astrocytes in GFAP-TGF-β1/APP mice (Lesné et al., 2003). Interestingly, TGF-β1 drives APP production only in astrocytes and not in neurons (Lesné et al., 2003).

6 | CONCLUSIONS

Multiple in vitro, animal and clinical studies have been conducted to identify molecular targets capable of preventing or slowing AD progression. However, a highly effective therapeutic target is still to be discovered. There is increasing evidence for the effects of AT endocrine activity in the context of metabolic disorders such as obesity and its correlation with AD risk. Several adipokines and related molecules could be considered of interest in the search for new mechanisms acting on neuronal and BBB protection for AD. However, the pathways regulating the biology of these adipokines are not fully understood. Given their wide expression and cellular activity in different tissues, their safety and efficacy must be established so they can be considered as a treatment for AD patients, avoiding unexpected side effects. Finally, the evaluation of combined strategies would also be necessary to develop new and more effective therapeutic approaches.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to Pharmacology (http://www.guidetopharmacology.org) (Alexander, Christopoulos et al., 2021; Alexander, Cidlowski et al., 2021; Alexander, Fabbro et al., 2021a, b; Alexander, Kelly et al., 2021a, b; Alexander, Mathie et al., 2021).

AUTHOR CONTRIBUTIONS

M. Bettinetti-Luque: Conceptualization; writing—original draft (equal); writing—review and editing (equal). **L. Trujillo-Estrada:** Writing—original draft (equal); writing—review and editing (equal). **E. Garcia-Fuentes:** Conceptualization; supervision; writing—original draft (equal); writing—review and editing (equal). **J. Andreo-Lopez:** Writing—original draft (equal); writing—review and editing (equal). **R. Sanchez-Varo:** Supervision; writing—original draft (equal); writing—review and editing (equal). **L. Garrido-Sánchez:** Writing—original draft (equal); writing—review and editing (equal). **Á. Gómez-Mediavilla:** Writing—original draft (equal); writing—review and editing (equal). **M. G. López:** Conceptualization; supervision; writing—original draft (equal); writing—review and editing (equal). **M. Garcia-Caballero:** Conceptualization; supervision; writing—original draft (equal); writing—review and editing (equal). **A. Gutierrez:** Conceptualization; supervision; writing—original draft (equal); writing—review and editing (equal). **D. Baglietto-Vargas:** Conceptualization; supervision; writing—original draft (lead); writing—review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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ORCID

Miriam Bettinetti-Luque https://orcid.org/0009-0002-5177-9264
Laura Trujillo-Estrada https://orcid.org/0000-0001-6696-4505
Eduardo Garcia-Fuentes https://orcid.org/0000-0002-3491-2724
Juana Andreo-Lopez https://orcid.org/0000-0003-2180-0560
Raquel Sanchez-Varo https://orcid.org/0000-0001-5296-9786

Lourdes Garrido-Sánchez https://orcid.org/0000-0003-0756-9606
Ángela Gómez-Mediavilla https://orcid.org/0000-0001-9636-771X
Manuela G. López https://orcid.org/0000-0003-4461-8788
Melissa Garcia-Caballero https://orcid.org/0000-0002-4263-5536
Antonia Gutierrez https://orcid.org/0000-0002-6264-6152
David Baglietto-Vargas https://orcid.org/0000-0003-1441-3175

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