Life Sciences 231 (2019) 116483

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Tackling Alzheimer's disease: Hypothetical synergism between anti-inflammatory and anti-diabetic agents☆

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ARTICLE INFO

Keywords:
Alzheimer's disease
Dementia
Insulin
Hypoglycemic agents
Anti-inflammatory agents
Drug synergism

ABSTRACT

Alzheimer's disease (AD) remains one of the greatest global concerns. Current treatment of AD – the acetylcholinesterase inhibitors – provides temporary improvement of cognitive functions, but does not affect the core of the underlying pathological process. There is still the need for alternative approaches, preferably ones based on the upstream events in the AD pathogenesis. The nature of AD pathogenesis remains complicated and not entirely explained. It is assumed to comprise of many interrelated events which can sequentially lead to further pathologies — as a kind of vicious cycle. The solution in this case could be to interact with these processes on multiple levels at the same time. The proposed approach hopes to achieve the state of equilibrium between two pathological pathways via reducing their dynamics on appropriate levels. The first step is to inhibit Tumor Necrosis Factor signaling related to inflammatory response. The second is to take advantage of the influence of insulin signaling on amyloid-β processing to restore its proper clearance. Employing two only partially-beneficial approaches into a novel approach aims at breaking the "vicious cycle" and eliciting synergistic effect via working on different levels simultaneously. The effect of such therapy could allow physicians to completely inhibit neural damage. The proposed strategy may prove easily introducible as an efficacious clinical approach employing novel anti-TNF agents in combination with anti-diabetic agents. Data is needed on its influence on cognitive functions, any occurrence of adverse effects, and the development of models of optimal doses and their temporal location.

1. Introduction

Alzheimer's disease (AD), the most common type of dementia, remains one of the greatest global concerns. With the numerous advances in the field of medicine, population aging is an increasing problem worldwide. WHO reports that 5.5 million people aged 65 and more are affected by AD in the US alone. This number is expected to triple by 2050 and this trend is observed globally [1,2]. Such prognosis requires an intensifying of efforts to search for new therapeutic strategies or prophylaxis for dementia. The issue is considered to be one of society's greatest social and economic burdens, and poses a great challenge for modern medicine.

Current treatment of AD is based on the use of acetylcholinesterase inhibitors, such as donepezil, galantamine or rivastigmine, and *N*-methyl-D-aspartate (NMDA) receptor antagonist, memantine, which is indicated in moderate and severe AD [3]. These drugs provide temporary improvement of cognitive functions, but do not affect the core of the underlying pathological process. Their beneficial effects are elicited by substituting the inadequate cholinergic signaling which is essential for memory-related processes and reducing L-glutamate excitatory neurotoxicity. However, the constant existence of neuroinflammation and neural necrosis leads to tissue degradation beyond repair, and at a certain time, the sole use of these drugs does not suffice to maintain even the most basic level of cognitive functions. Hence, the issue of effective AD treatment still remains unsolved and the search goes beyond the sole cholinergic substitution.

Amyloid deposits in the brain are one of the hallmarks of AD. Amyloid-β (Aβ) of various lengths — especially 40 and 42 amino acid chains — is a by-product of Amyloid Precursor Protein (APP) processing [3]. It appears in two main forms, fibrillar and oligomeric, with the latter probably causing greater inflammatory response [4,5]. Importantly, Aβ clearance is dependent on insulin signaling [6–9]. Its transport from blood to brain was proved to be mediated mainly by Receptor for Advanced Glycation Endproducts (RAGE), but additional

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
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https://doi.org/10.1016/j.lfs.2019.05.039
Received 9 April 2019; Received in revised form 13 May 2019; Accepted 14 May 2019
Available online 15 May 2019

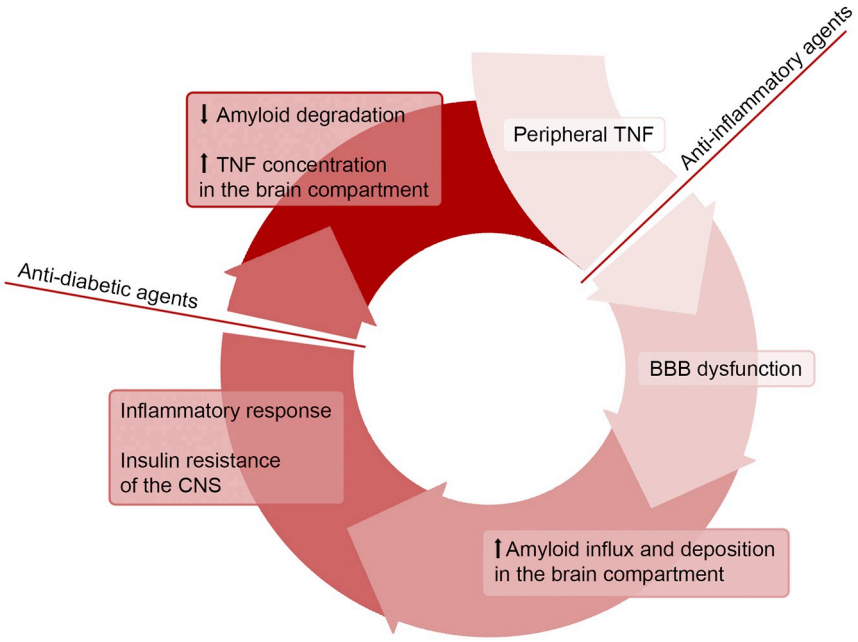

Fig. 1. Vicious cycle in AD pathology.
Peripheral Tumor Necrosis Factor (TNF) circulating in the blood acts on Blood-Brain Barrier (BBB) decreasing its integrity. This results in increased Aβ influx into the brain compartment and formation of amyloid deposits in the brain parenchyma. TNF produced in response to Aβ or amyloid deposits and peripheral TNF disrupt insulin signaling pathways favoring insulin resistance of the Central Nervous System (CNS). The results of insulin resistance in the brain are decreased insulin-dependent amyloid clearance and further increase in TNF concentration.
The potential points of action have been marked. Anti-inflammatory agents bind peripheral TNF in the blood, acting at the earliest step of the vicious cycle. Anti-diabetic agents restore insulin signaling allowing for insulin-dependent amyloid clearance.

ways of entry similar to its cellular uptake may also exist [10,11].

The previous focus on amyloid theory resulted in an approach aimed at managing AD by decreasing the amyloid burden in the nervous tissue. Various novel methods emerged based on this theory, an example being the antibody bapineuzumab which binds neurotoxic amyloid peptides and increases their clearance [12]. However, as it transpires, solely reducing the amyloid burden does not improve the cognitive functions or the overall prognosis [13]. There is still the need for alternative approaches, preferably ones based on the upstream events in the AD pathogenesis.

The nature of AD pathogenesis remains complicated and not entirely explained. It is assumed to comprise of many interrelated events which can sequentially lead to further pathologies — as a kind of vicious cycle (Figs. 1 and 2) [14].

The solution in this case could be to interact with these processes on multiple levels at the same time. This solution could inhibit the reciprocal acceleration between the inflammatory response of the Central Nervous System (CNS) and dysfunctional amyloid processing, the interplay believed by many to lie at the core of AD [14].

2. Hypothesis

The proposed approach hopes to achieve the state of equilibrium between two pathological pathways via reducing their dynamics on appropriate levels. The first step is to inhibit Tumor Necrosis Factor (TNF, previously described as TNF-α) signaling which is related to inflammatory response [13]. This can be achieved with the use of biological anti-TNF agents, such as infliximab or etanercept. The second is to take advantage of the influence of insulin signaling on Aβ processing to restore its proper clearance with the use of anti-diabetic agents.

The innovative perspective in relation to AD treatment is the synergistic combination of anti-inflammatory and anti-diabetic agents. This two-way approach aims to both stop the inflammatory response connected with Aβ deposition and also to allow dysfunctional insulin signaling — a consequence of the inflammatory response — to regain its normal function which could in turn result in constant decrease of the amyloid burden (Fig. 3).

Patients with more severe AD symptoms could also benefit from complementary cholinergic substitution. Inhibiting core pathology of AD and thereby, reducing further loss of neurons, could potentially prolong the advantageous effects of acetylcholinesterase inhibitors. While numerous reports emphasize the importance of the inflammatory and metabolic interplay, no strategy based on balancing these dysfunctions has so far been proposed.

3. Discussion

Both the inflammatory response and insulin signaling affect the Blood-Brain Barrier (BBB) which grants the brain environment its unique metabolic properties. Thus, BBB plays a pivotal role in the development of AD.

3.1. The inflammatory pathway

TNF levels in the cerebrospinal fluid of AD patients are 25-fold increased [15]. The TNF stimulation can derive from the previously-deposited Aβ in the CNS, but also from the peripheral inflammatory response. Peripheral TNF enters the CNS via transcytosis which requires involvement of two Tumor Necrosis Factor Receptor (TNFR) types [16]. TNF is also produced by immunocompetent cells which migrate through BBB or local cells, such as astrocytes or microglia, especially in response to Aβ and peripheral TNF [16–18]. While the literature suggests that peripheral TNF may have greater significance in the development of AD rather than its advancement, it may also accelerate the above-mentioned vicious cycle and disrupt attempts of the CNS to regain homeostasis, but further studies are needed in order to determine it [14].

TNF signaling activates c-Jun N-terminal Kinase (JNK) pathway in astrocytes and microglia spiraling the inflammatory response [19–21]. In the brain it influences the insulin signaling leading to insulin resistance of the CNS and favors amyloid deposition [13,17,22]. Additionally, TNF affects expression of BBB proteins and significantly lowers its integrity in vitro [23–25].

These phenomena may be responsible for the development of AD in cases of chronic inflammatory response such as ones connected to rheumatic diseases or even obesity. The change of fat tissue distribution related to aging results in elevated inflammatory mediators in the blood, which is described by the term “in-flamm-aging” [26]. Moreover, patients with chronic inflammatory diseases such as rheumatoid arthritis are found to be at increased risk of developing AD [27]. This data implies the importance of tackling the inflammatory response in the elderly in order to sustain intact cognitive functions.

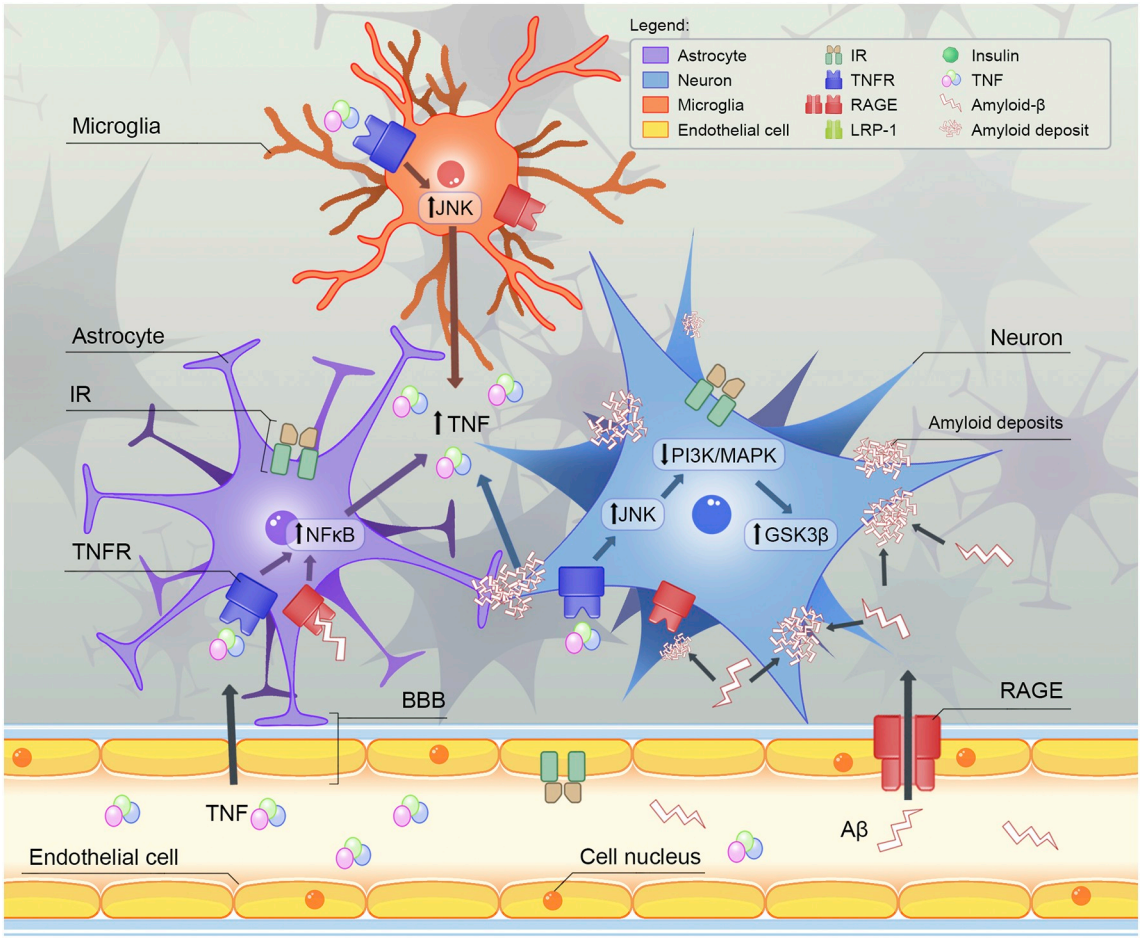

Fig. 2. Selected pathways of the Alzheimer's disease pathology.
Figure presents a focused summary of the essential mechanisms and molecular pathways involved in the pathology of the disease. Tumor Necrosis Factor (TNF) circulates in the blood and enters the brain compartment through the Blood-Brain Barrier (BBB) via transcytosis. Next, TNF affects local cells via Tumor Necrosis Factor Receptor (TNFR) stimulation and causes activation of c-Jun N-terminal Kinase pathway (JNK) and Nuclear Factor κ-light-chain-enhancer of activated B cells (NFκB) cascade which leads to increased TNF production. Peripheral amyloid-β (Aβ) enters the brain compartment e.g. via Receptor for Advanced Glycation Endproducts (RAGE) adding to the amyloid burden resulting from local production. There it acts on RAGE causing further production of TNF by astrocytes which is mediated by NFκB cascade. The amyloid deposits impair synaptic function and cause an inflammatory response which leads to additional TNF signaling. The inflammatory response may also result from the microglial attempts to phagocyte deposits (not illustrated). Further, the TNF signaling in neurons disrupts insulin signaling mediated by Phosphoinositide 3-Kinases (PI3K) and Mitogen-Activated Protein Kinases (MAPK) leading to increased activity of Glycogen Synthase Kinase 3β (GSK3β) which favors amyloid deposition. Altogether, these processes affect the neuron function and lead to local brain atrophy.

Experimental studies support the use of anti-TNF agents. They are proven to be well-tolerated in AD patients [28] and some case reports of their perispinal use (Tobinick et al.) demonstrate significant improvements of cognitive functions lasting up to one month [29–31]. Admittedly, the limitation of the above-mentioned studies is the lack of control groups to account for the potential placebo effect. Yet the authors suggest that excess TNF affects synaptic function — which can be rapidly normalized with the perispinal administration of anti-TNF agents. However, their isolated peripheral use did not provide a well-established method of AD treatment so far, possibly because it does not affect the previously dysregulated Aβ metabolism sufficiently [28].

The beneficial influence of anti-TNF agents may derive from the biological properties of TNF. It is proven to increase the γ-secretase and inducible Nitric Oxide Synthase (iNOS) activity resulting in higher generation of Aβ and free radicals [32–34]. Additionally, anti-TNF agents reduce the abnormally increased function of glutamatergic neurons and NMDA excitotoxicity, which characterize early AD pathology [13]. In the mouse model of amyloid-induced cognitive deficits, peripheral administration of anti-TNF agent resulted in the normalization of hippocampal TNF levels and counteracted the cognitive impairment, such as working and long-term memory deficits [35]. Interestingly, in accordance with the fact that TNF favors development of insulin-resistance [13], infliximab also affects the glucose metabolism countering this effect [36].

3.2. Insulin regulation

Insulin is an endogenous hormone which enters the brain via receptor-mediated active transport [37]. It has anti-apoptotic influence on neurons in vitro and also modifies the expression of transport proteins and therefore the function of the BBB [38].

The abnormalities detected in insulin signaling are the reason for naming AD type 3 diabetes [39], which puts emphasis on the utmost importance of CNS insulin-resistance in the development of AD. In fact, there is over 80% coincidence between AD and occurrence of pre-diabetes or type 2 diabetes [40]. Other similarities are apparent in regional amyloid deposition and altered profiles of cytokines and immune mediators [38]. Research shows that development of the insulin-resistance in the CNS predates the cognitive decline up to a decade or even more, allowing for detection of early, asymptomatic AD based on modern imaging techniques, such as Positron-Emission Tomography (PET) [41–43].

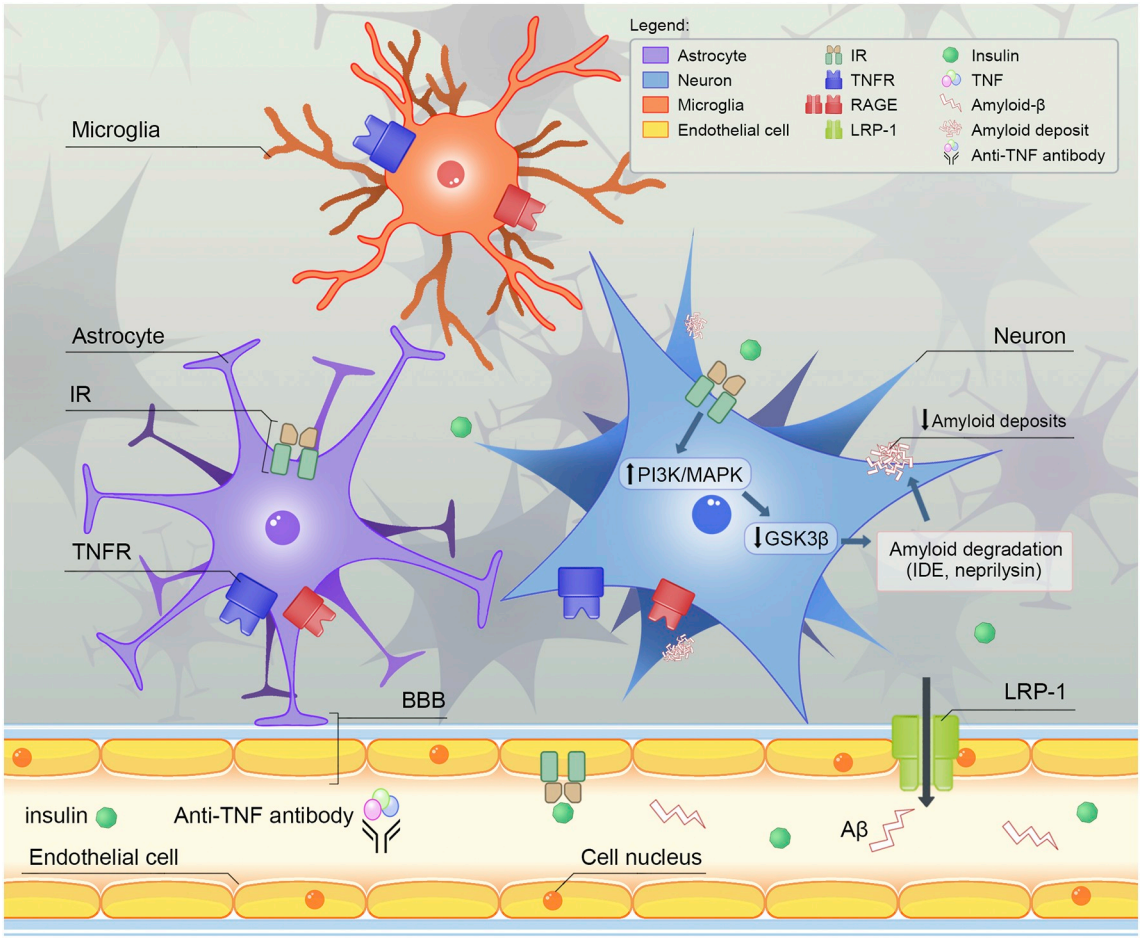

Fig. 3. The mechanism of action of the proposed synergistic treatment.
Figure presents a focused summary of the anti-diabetic and anti-inflammatory agents on the molecular mechanisms involved in Alzheimer's disease pathology. The anti-TNF antibodies bind circulating Tumor Necrosis Factor (TNF) and prevent it from entering the brain compartment diminishing the inflammatory response. Insulin from the blood crosses Blood-Brain Barrier (BBB) by active transport (not illustrated) and binds Insulin Receptors (IR) which is followed by Phosphoinositide 3-Kinases (PI3K) and Mitogen-Activated Protein Kinases (MAPK) activation and leads to decreased activity of Glycogen Synthase Kinase 3β (GSK3β). GSK3β decreased activity alters the protein expression and can favor amyloid-β degradation via Insulin Degrading Enzyme (IDE) or neprilisin and — in endothelial cells — its transport to the blood e.g. via Low density lipoprotein Receptor-related Protein 1 (LRP-1). The consequence of these changes can be reduced amyloid burden and, in turn, improved overall neuron function.

Insulin-resistant CNS is characterized with altered Aβ transport and metabolism. These effects are mediated by lack of physiological insulin signaling, conducted by Phosphoinositide 3-Kinases (PI3K) and Mitogen-Activated Protein Kinases (MAPK) pathways. The inadequate insulin stimulation results in increased Glycogen Synthase Kinase 3β (GSK3β) activity which is characteristic of diabetes, altered protein expression and Aβ processing [44,45]. GSK3β in absence of insulin stimulation favors the development of the lesions characteristic of AD by decreasing the integrity of BBB [38]. Various membrane transporter proteins which enable Aβ transport remain dependent on insulin signaling. Insulin-resistance, among others, leads to decreased expression of Low density lipoprotein Receptor-related Protein 1 (LRP-1) resulting in reduced efflux of the harmful metabolite and also increased expression of RAGE allowing for higher influx of amyloid peptides in animal models [6,7]. The latter, RAGE, is especially significant as its activation by Aβ mediated by Nuclear Factor κ-light-chain-enhancer of activated B cells (NFκB) cascade results in further TNF production in astrocytes and microglia [46–48]. Moreover, degradation of regional Aβ is dependent on neprilisin and Insulin Degrading Enzyme (IDE), catalytic enzymes which activities rely on insulin signaling [8,9]. Altogether, the molecular effects of insulin-resistance favor amyloid deposition and, consequently, neuroinflammation.

Currently many studies are trying to counter these phenomena by trying to affect the cognitive functions with anti-diabetic agents. The newly-developed systems for transnasal insulin application are a prime example. Although they avoid side effects resulting from hypoglycemia, they also circumvent the BBB, limiting the potential effects of insulin stimulation [49]. Studies performed on animal models show that insulin and various anti-diabetic agents such as metformin, exenatide or glibenclamide can improve the BBB integrity and subsequently enhance cognitive functioning [22,50,51]. Of the aforementioned, metformin remains in the scope of special interest, as it affects MAPK pathway but also decreases the inflammatory response, reduces acetylcholinesterase activity and amyloid aggregation and has antioxidant effect [48,52–54]. However, experimental studies deliver conflicting results so far [55,56]. With numerous studies exploring the exact influence of anti-diabetic agents on a molecular level, no spectacular success has been noted so far in the area of cognitive functions and further prognosis of AD patients. Nevertheless, a recent meta-analysis concerning 6 anti-diabetic drugs indicates that all of them had significant positive effect on cognition compared to placebo [57]. This suggests that this approach may prove beneficial in dealing with AD, even if insufficient as an isolated intervention.

3.3. Combined therapy

So far no individual approach has proved efficacious in tackling AD. While the restored insulin signaling may affect the temporal processing of the amyloid, and in turn result in decreased amyloid burden, the upstream pathology – possibly the one connected to peripheral inflammatory response [14] – remains, causing further dysregulation again. Similarly, reducing the TNF signaling may result in stopping the further development of insulin-resistance but it does not influence the current pathological processes connected with amyloid metabolism in the brain.

The complex, intermingled relations between inflammatory response and insulin-resistance of the CNS are apparent in AD pathology. Hereby, employing two only partially-beneficial approaches into a novel approach which aims at breaking the “vicious cycle” and eliciting synergistic effect via working on different levels simultaneously, may provide a solution.

3.4. Consequences of the hypothesis

The proposed strategy may prove easily introducible as an efficacious clinical approach employing novel anti-TNF agents in combination with anti-diabetic agents. The benefit of this approach could be inhibiting the currently inevitable decline in cognitive functions, and possibly even restoring some of them — suppressing the inflammatory response is proven to influence signaling in various neural networks and thus affect overall neural function [58].

The method of treatment employable at the earliest phases of dementia can bear great significance for the constantly-increasing number of patients and their care-givers. The sustainable effect of such therapy could allow physicians to completely inhibit neural damage, conserving in patients features such as self-reliance or the ability to work. With aging populations an increasing reality, the prognosis is that most societies are going to spend a disproportionate part of their gross domestic product on the costs related with providing care for elderly, with special emphasis on dementia patients. Additionally, such strategy is also relevant for care-givers of AD patients.

On the other hand, the proposed treatment would first require long-term multicenter clinical trials. Data is needed on its influence on cognitive functions, any occurrence of adverse effects during the combined therapy, and the development of models of optimal doses and their temporal location. Considering the lack of such studies and probable low risks or toxicity of the proposed strategy, the issue seems worthy of further exploration.

Declaration of Competing Interest

The authors have no conflict of interest to report.

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