IBRO Neuroscience Reports 14 (2023) 64–76

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

Review of Alzheimer's disease drugs and their relationship with neuron-glia interaction

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ARTICLE INFO

Keywords:
Alzheimer
Inflammation
Galantamine
Dextromethorphan
Alphoscerate
Neuron-glia

ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia worldwide. Because Alzheimer's disease has no known treatment, sufferers and their caregivers must concentrate on symptom management. Astrocytes and microglia are now known to play distinct physiological roles in synaptic function, the blood-brain barrier, and neurovascular coupling. Consequently, the search for drugs that can slow the degenerative process in dementia sufferers continues because existing drugs are designed to alleviate the symptoms of Alzheimer's disease. Drugs that address pathological changes without interfering with the normal function of glia, such as eliminating amyloid-beta deposits, are prospective treatments for neuroinflammatory illnesses. Because neuron-astrocytes-microglia interactions are so complex, developing effective, preventive, and therapeutic medications for AD will necessitate novel methodologies and strategic targets. This review focused on existing medications used in treating AD amongst which include Donepezil, Choline Alphoscerate, Galantamine, Dextromethorphan, palmitoylethanolamide, citalopram, resveratrol, and solanezumab. This review summarizes the effects of these drugs on neurons, astrocytes, and microglia interactions based on their pharmacokinetic properties, mechanism of action, dosing, and clinical presentations.

Introduction

Chronic inflammation in the central nervous system (CNS) is a hallmark of neurodegenerative illnesses such as Alzheimer's disease (AD) (Madeira et al., 2015; Kostrzewa, 2014; Skaper et al., 2013). Anatomically, the CNS is partitioned by threefold barricades viz; the Blood-brain barrier (BBB) or blood-spinal cord barrier (BSCB); the blood-cerebrospinal fluid barrier at the choroid plexus (CP), and the arachnoid barrier (Hampel et al., 2015). The vulnerability of different anatomical regions of the body to neuroinflammatory occurrences may be directly proportional to contrast in the structures of the BBB and BSCB, also variations in the cranial and spinal meninges, in white and grey matter (Stephenson et al., 2018). Indisposition of the above-mentioned barriers is recognized to happen in neuro-inflammatory diseases such as multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), stroke, epilepsy, and traumatic brain injury (TBI) and is related to activated endothelial cells that show a modified phenotype and a dwindle in tight junction proteins (Stephenson et al., 2018).

The etiology of neurodegeneration is diverse, and evidence suggests that extrinsic variables such as lifestyle and chemical exposures are connected to the development of these disorders. Neurotoxic metals have been linked to AD due to their potential to increase beta-amyloid (Aβ) peptide levels and phosphorylation of tau protein (P-tau), resulting in senile/amyloid plaques and neurofibrillary tangles (NFTs), both of which are symptoms of the disease (Chin-Chan et al., 2015). The prevailing neurodegenerative condition majorly examined is dementia with the maximum cases being Alzheimer's disease type. Paramount risk factors of AD are age greater than 60 years, low schooling (lower than 6 years of education), family background, and rural residence. Alzheimer's disease is responsible for two-third of all dementia cases worldwide ("2020 Alzheimer's Disease Facts and Figures, 2020). Its

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https://doi.org/10.1016/j.ibneur.2022.11.005
Received 9 May 2022; Accepted 16 November 2022
Available online 19 November 2022

prevalence rises with age, reaching as high as 40 % by the age of 85 years, and is expected to rise in lockstep with the population's average age (Tayeb et al., 2013). However, much has not been done in Africa to determine the prevalence of Alzheimer's disease in the general population (Adeloye et al., 2019; Namuli, 2015).

Alzheimer's disease is the most frequent cause of dementia worldwide, as well as the fifth-greatest cause of mortality among Americans aged 65 years and over (Tayeb et al., 2013). Dementia is thought to impact about 20 million individuals globally in 2006, with that figure projected to rise to 40 million by 2020, and then double every 20 years after that, reaching an estimated 80 million by 2040 (Brodaty et al., 2006). However, according to Malik & Robertson (2017), dementia affects roughly 47 million people worldwide, with the number expected to rise to 75 million by 2030 and 131 million by 2050, with the highest increases expected in low- and middle-income nations. By 2050, one out of every 85 persons on the planet will have Alzheimer's disease (Tayeb et al., 2013).

The overall prevalence of Dementia in Nigeria has been estimated to be 5 % (Adeloye et al., 2019). Among other dementia subtypes, Alzheimer's disease (AD) has the greatest incidence of 2 %, with the former having prevalence rates lesser than 1 % in Nigeria (Adeloye et al., 2019; Olawande et al., 2020). When compared to African Americans, Yoruba Africans have a 2–3 times lower rate of Alzheimer's disease (Olawande et al., 2020). In 2015, Uganda's population was predicted to be 35 million, with 2.1 % and 4.6 % of the population being over 65 and 60 years old, respectively (Namuli, 2015). In their study on aged adults in rural areas of Uganda, Mubangizi et al. reported a significantly high prevalence (20 %) of dementia when compared with other sub-Saharan African countries including 6.4 % in Tanzania with a much older population and an 8 % prevalence rate in South Africa (Mubangizi et al., 2020). Dementia and depression are the two most frequent psychiatric disorders in Uganda, accounting for 13.2 % of cases resulting in the admission of older individuals over the age of 60 years according to a study conducted at Mulago National Referral hospital (Namuli, 2015).

Cholinergic neuron depletion has been documented in 70 % of AD patients and 40 % of vascular dementia (VaD) patients in neuropathological studies. Attenuated acetylcholine (ACh) levels in the cerebral cortex, hippocampus, striatum, and cerebrospinal fluid (CSF) have been documented in VaD patients (Tomassoni et al., 2006). A buildup of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) is thought to be the cause of neurodegeneration in Alzheimer's disease (Kostrzewa, 2014). Because of their toxicity, Aβ plaques cause synaptic dysfunction and neuronal death and increase tau phosphorylation. NFTs are generated when phosphorylated tau aggregates and play a role in neuronal dysfunction and cell death (Kostrzewa, 2014). The deposition of Aβ and NFTs disrupts glutamate transmission at synapses, and the resulting increase in glutamate at axon terminals is linked to cognitive impairment (Kobayashi et al., 2018).

Because there is presently no cure for AD (Zhao et al., 2019), both patients and their caregivers must focus on symptom management (Brodaty et al., 2006). Microglia and astrocytes are the primary glial types involved in inflammatory reactions (Carson et al., 2006). Astrocytes play a role in synaptic information transmission and plasticity, neurotransmitter metabolism, metabolic, trophic, and antioxidant support for neurons, and brain homeostasis, among other things (Bobermin et al., 2019). Furthermore, astrocytes are immunocompetent players, generating a wide range of inflammatory mediators, including pro-and anti-inflammatory cytokines and chemokines, in response to diseased or injury conditions (Bobermin et al., 2019; Madeira et al., 2015). As a result, novel anti-inflammatory medications are primarily directed at these cells. Although these cells ordinarily provide nourishment and growth factors to neurons, disease-specific events can cause glial production of neurotoxins. Reduced glia-mediated inflammation has been proposed as a way to reduce a neuronal loss (Madeira et al., 2015). In addition, gene changes that alter inflammatory pathways have been related to lower cognitive performance in the elderly, and there are currently no effective treatments for preventing or reducing inflammation (Madeira et al., 2015). Until recently, the role of astrocytes in Alzheimer's disease progression was generally ignored. Astrocytes are essential for optimal brain function, and astrocyte reactivity is a symptom of Alzheimer's disease that could be used as a target for preclinical diagnosis and treatment (Carter et al., 2019).

The goal of this study is to look at the effects of Alzheimer's medications on brain tissues by looking at the interactions between neurons, astrocytes, and microglial cells. Given their various targets, specific medications from the current list of Alzheimer's disease treatments were chosen for this review article. Drugs considered include Donepezil (a cholinesterase inhibitor), Galantamine (a nicotinamide acetylcholinesterase receptor modulator), Choline alphoscerate (a cholinergic modulator), Dextromethorphan (a N-Methyl-D-aspartate receptor inhibitor), Palmitoylethanolamide (a peroxisome proliferator-activated receptor-α activator), Citalopram (a selective serotonin reuptake amyloid beta sequester). This review looks at how astrocytes and microglia protect neurons in normal situations, how interactions between neurons, astrocytes, and microglia regulate inflammatory responses and stressor handling, and when these glia cells lose their protective ability for neurons and become harmful in the case of Alzheimer's disease. The drugs were further evaluated based on their pharmacokinetic properties (drug absorption, distribution, metabolism, and excretion), mechanisms of action, dosing as documented by previous experimental and clinical research, effects on clinical presentations, and documented pathologies.

Neuron-glia interaction

According to Kim et al., neuron-glia interactions may be dysfunctional in the pathophysiology of neurodevelopmental disorders. They proposed that the identification of novel treatment targets for neurodevelopmental diseases will be aided by a better knowledge of the mechanisms governing neuron-glia interactions during synapse development and maturation (Kim et al., 2020). It has been revealed that several newly discovered characteristics of glial cells, like the release of gliotransmitters and cytokines, promote their interaction with neurons throughout brain development (Kim et al., 2020). Glutamate and gamma-aminobutyric acid (GABA) are examples of gliotransmitters in addition to cytokines that are known to function at tripartite synapses and may either directly or indirectly affect the wellbeing of neurons (Kim et al., 2020). Therefore, it is important to look at how neuron-glia interactions affect the synaptic abnormalities caused by glia which may provide a better therapeutic approach to slowing down neurodegeneration.

It would be necessary to study the interconnections of both glia and neurons in current brain science. Glia, rather than nerve cells, have become the focus of several kinds of research on dementia and aging. Specifically, astrocytes and microglia, which were formerly assumed to exclusively serve as neuronal assistance, are now understood to perform unique physiological functions in synapse function, the blood-brain barrier, and neurovascular coupling (Ishiguro et al., 2021; Xapelli et al., 2020). The deranged or defective interplay between neurons and glia can throw off the balance of normal brain physiology (Lana et al., 2017). Goshi et al. (2020) posited that the inflammatory responses to injury in the central nervous system are governed by relationships existing among neurons, microglia, and astrocytes. Though neurons are thought to constitute the fundamental principal components of the CNS, findings reveal that microglia perform a critical role in the normal functioning of the neuron-glia triad, which is crucial for the brain's appropriate organization (Cerbai et al., 2012; Ugolini et al., 2018).

Astrocytes are the mass innumerable subtypes of glial cells within the central nervous system (CNS). The cell body and the vital processes of astrocytes are enhanced with glial fibrillary acidic protein (GFAP) that forms intermediate filaments (Ricci et al., 2009). Astrocytes are an essential component of synaptic transmission, modulate brain energetics, and moderate cerebrovascular function and therefore are crucial

for the organization and maintenance of neuronal health (Delekate et al., 2014). Reactive astrogliosis is a principal emblem of essentially every form of acute or chronic neuronal injury such as AD, however, the functional outcomes of this transition from the typical to the reactive phenotype have remained greatly unrevealed (Delekate et al., 2014; Ricci et al., 2009). Astrocytes in the healthy brain are assembled into dynamic networks. Significantly the expression of molecular constituents that control these networks namely connexin channels is reshaped under pathological situations, disclosing that homogenous to neuronal ensembles. AD is also related to a perturbation of astrocytic network activity activated by reactive astrogliosis (Delekate et al., 2014). In AD, pathological studies in human patients and mouse prototypes have disclosed that astrocytes encircle plaques and can perform a vital function in Aβ accumulation and clearance (Delekate et al., 2014; Kuchibhotla et al., 2009). This revealed the great effect of Aβ accumulation on surrounding neuronal calcium homeostasis and synaptic role (Kuchibhotla et al., 2009).

Through the use of widefield calcium imaging of neurons and resting-state functional magnetic resonance imaging (rsfMRI), Shah et al. recently discovered the importance of astrocytes in maintaining large-scale networks in the healthy brain. They also showed their involvement in early functional connectivity disruptions in AD (Shah et al., 2022). They explained the elevated calcium signals in the astrocytes of AD models as being caused by increased astrocyte reactivity in response to plaques, which led to hyperactivity of astrocytic calcium, altered purinergic receptor regulation, increased calcium efflux from mitochondria by reactive oxygen species production, and aberrant ATP release (Shah et al., 2022). Long before amyloid plaques were present, they discovered decreased in vivo calcium signaling in astrocytes. They also observed decreased astrocytic IP3R2 expression in AppNL-F mice, which suggests impaired calcium release from internal storage. Additionally, they verified a reduction in GLT-1 expression, which was previously proposed as a potential mechanism controlling the neuronal calcium hyperactivity in AD. They found that astrocytes with intact calcium signaling systems were able to control neuronal hyperactivity produced by GLT-1 malfunction back to basal levels in their assessment of the regulatory role of astrocyte calcium signaling. Overall, these findings highlight the critical function of astrocytes in the early stages of AD and confirm that, in the absence of amyloid pathology, astrocytes continue to play a regulatory role in network activity. This is confirmed by the recovery of astrocyte-neuron interaction through astrocyte calcium signaling.

Based on the density and distance of Aβ, Lines et al., also observed reduced sensory-evoked astrocyte responsiveness in AD mice. Responses indicated aberrant calcium dynamics characterized by spontaneous astrocyte hyperactivity but hypo-responsive to sensory stimulation (Lines et al., 2022). According to their research, astrocyte network disruption in AD mice may dysregulate cortical electrical activity and cause cognitive deterioration.

Inflammation and other stressors can affect neuron-astrocyte-microglia connections, a mechanism that could be involved in brain aging or AD (Cerbai et al., 2012; Mercatelli et al., 2016; Ugolini et al., 2018). In the dentate gyrus (DG), Choi et al., 2021 found an increase in astrocyte activities during hippocampus-dependent long-term memory consolidation via contextual fear conditioning. One of the continuous pathological alterations shown by reactive astrocytes in the hippocampus DG region in an Alzheimer's disease model is an increase in the number of processes. According to Choi et al., STAT3 phosphorylation suppression caused the decreased colocalization of astrocytes and neurons in 5XFAD animals to return. Cognitive impairment in early-stage AD may be partially explained by a decrease in the number of astrocyte-neuron connections during the reactive state of astrocytes (Choi et al., 2021). An innovative therapeutic approach for AD in its early stages may be provided by medications that directly suppress STAT3 phosphorylation in astrocytes.

Microglia and astrocytes are neuroprotective in some situations, but they can also be harmful to neuronal health (Lana et al., 2017). In rat models of brain inflammation, normal aging, and chronic hypoxia, for example, astrocytes and microglia in Cornu Ammonis (CA1) actively collaborate in removing apoptotic neurons and neuronal debris (Cerbai et al., 2012; Lana et al., 2014, 2017). In mice models of AD, Ugolini et al. (2018) demonstrated an increase in the number of reactive astrocytes, particularly around Aβ plaques, as well as a decrease in size and a decrease in the number of primary branches of astrocytes. According to them, the response of Astrocytes to the same stimulus may change in different brain regions, resulting in variable neuronal survival status. This could explain why astrocyte atrophies and astrogliosis do not appear in all brain regions at the same time in AD. Lana et al. also discovered that numerous microglia cells form triads with astrocytes to phagocytose degenerative or apoptotic neurons in the stratum radiatum of treated rats with two-vessel occlusion vehicle and two-vessel occlusion dipyridamole.

Another study found that injecting Lipopolysaccharide (LPS) stimulates microglia, which then diffuse and disperse throughout the brain, matching the spread of LPS across the cerebral hemispheres in a short period (Cerbai et al., 2012; Kostrzewa, 2014). Activated microglia serve as scavenger cells in the CNS (Kostrzewa, 2014), but their multiplication and activation surrounding Aβ plaques are characteristic of AD (Díaz-Lucena et al., 2018). When microglia cells fail to respond to their normal regulatory feedback, resulting in a decreased ability to remove Aβ, they may become mainly cytotoxic. As a result, decreased Aβ uptake and elimination may raise the risk of AD (Ugolini et al., 2018; Wang et al., 2015). Microglia activation and recruitment were formerly thought to be a negative mechanism that led to the buildup of neurotoxic phagocytes, but new research has revealed that it is a reversible process that has neuroprotective effects (Lana et al., 2014). Transforming-polarization of microglia within certain periods could help treat neurodegenerative disorders (Ugolini et al., 2018).

Because microglia and astrocytes are involved in amyloid-beta clearance during the initial phases of AD development, activation is beneficial (Kaur et al., 2019). However, when the situation worsens, active microglia cause neurotoxicity in the adjoining brain regions by overproducing pro-inflammatory cytokines such as interleukins (IL-1, IL-6), and tumor necrosis factor (TNF). As a result, Aβ clearance by microglia declines, leading to Aβ accumulation in the brain and neuroinflammation (Kaur et al., 2019). As a result, enhanced pro-inflammatory cytokine production causes Aβ accumulation. By shedding their neurotrophic functions, reactive astrocytes acquire a harmful function and demonstrate neurotoxic consequences. Astrocyte dysregulation is characterized by elevated secretion of cytokines and inflammatory mediators, neurodegeneration, reduced glutamate uptake, loss of neuronal connections, and lastly, cognitive impairments in Alzheimer's disease (Kaur et al., 2019).

Increased production of proinflammatory molecules, glial toxic metabolites, excitatory molecules like glutamate, and reduced discharge of neurotrophic substances from glia can cause harm to normal adjoining neurons in neuroinflammation. Drugs, that combat these pathological alterations without compromising the glia's physiological activity, such as removing amyloid-beta deposits, are promising possibilities for treating neuroinflammatory disorders (Madeira et al., 2015). Degeneration of cholinergic basal forebrain neurons (Deyn and Dam, 2011) that innervate the brain cortex has been linked to cognitive function deficits in AD (Courtney, 2004). In Alzheimer's disease, presynaptic cholinergic cellular impairment reduces the quantity of acetylcholine approaching postsynaptic cholinergic nerve cells (Brodaty et al., 2006). This has prompted the development of cholinesterase inhibitors, which upregulate acetylcholine in the brain by blocking enzymes that process this chemical (Zhao et al., 2019).

Numerous acetylcholinesterase inhibitors had already been researched for their potential to manage symptoms of Alzheimer's disease, and there is some data to indicate their involvement in preserving or improving cognitive, behavioral, and motor functioning (Brodaty

et al., 2006; Madeira et al., 2015). The inhibition of acetylcholinesterase was the first pharmacological target that showed therapeutic efficacy on cognition, behavior, and functioning daily activities (Fernández-Bachiller et al., 2010). Acetylcholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, are drugs utilized to manage AD patients (Villarroya et al., 2007).

Numerous distinct operations of the brain function require a cholinergic system in which in the hippocampus part of the brain, cholinergic activity regulates neuronal, and network activity, also synaptic transmission and plasticity (Navarrete et al., 2012). A report from Navarrete et al., 2012 disclosed that the results extrapolated presently in vivo and in vitro studies reveal that hippocampal long-term potentiation (LTP) a cellular fundamental in learning and memory, elicited by cholinergic action was related to Ca^{2+} boosting in astrocytes and both operations are regulated by muscarinic acetylcholine receptors (mAChRs) (Navarrete et al., 2012; Takata et al., 2011).

Elevation of astrocytic Ca^{2+} activity occurs during the following actions; pharmacological strengthening of the neural task, sensory stimulation, or the triggering of the locus coeruleus. Furthermore, it has been revealed that activating nucleus basalis of meynert (NBM) the chief origin of cholinergic innervation to the cortex can occur via the above actions which increases astrocytic Ca^{2+} through mAChRs (Takata et al., 2011). Hence, cholinergic drugs that directly or indirectly target cholinergic glial interactions may be used to treat neurodegenerative conditions like Alzheimer's disease by controlling neuroinflammation and oxidative stress because neuronal cholinergic signaling is thought to be anti-inflammatory and anti-oxidative (Gamage et al., 2020).

Donepezil

Introduction

Donepezil hydrochloride is a well-known anti-dementia medication that works by inhibiting acetylcholinesterase, which raises acetylcholine levels (Kim et al., 2014). It is an acetylcholinesterase inhibitor (AChEI) that is now used to maintain AD symptoms (Kwon et al., 2014). It is the foremost cholinesterase inhibitor drug to be authorized in the United Kingdom (UK) in march 1997, succeeded by rivastigmine and galantamine, and is the only one endorsed for the therapy of full-spectrum Alzheimer's disease (mild, moderate, and severe) (Courtney, 2004; Lee et al., 2015).

Pharmacokinetics (absorption, distribution, metabolism, and excretion of the drug)

Absorption is adequate via oral administration with 100 % of relative oral bioavailability in which it attains peak plasma concentration (C_{max}) in 3–4 h (Adlimoghaddam et al., 2018; Kim et al., 2014). According to Matsui et al., (1999) absorption of donepezil was fast and complete, and a total of 86.8 % of systemic bioavailability and excretion ratio via the liver was 0.16 % when administered orally in rats. However, in humans the absorption rate of donepezil in the gut is slow and it attains the peak concentration within 3–4 h which could be attributed to diverse designs of donepezil namely orally disintegrating tablets or an oral film-coated tablet (Bae et al., 2021).

Excretion of donepezil via the kidney seems insignificant regarding 1.65 % of renal-excreted donepezil into urine for twenty-four hours in donepezil hydrochloride groups which connotes that while excretion of some donepezil is via urine in mice, the metabolism of donepezil may be the major channel of its elimination. This was corroborated by the report from Matsui et al., (1999) that the hepatic metabolism of donepezil is a principal route of excretion (Bae et al., 2021). Transdermal drug delivery procedures have various benefits juxtaposed to oral methods and injection namely enhanced systemic bioavailability, avoidance of hepatic first-pass metabolism, lower administration frequency, a prolonged period of action, dwindled side effects, and excellent patient adherence (Shin et al., 2020). Optioning to a transdermal patch from oral or injection procedures could be potent for AD therapy (Shin et al., 2020).

Mechanisms of actions documented by previous experimental and clinical research

Donepezil is one of the cholinesterase inhibitors whose mechanism of action involves binding with enzymes such as acetylcholinesterase thereby blocking the hydrolysis of acetylcholine to boost cholinergic neurotransmission (Adlimoghaddam et al., 2018). The binding and deactivation of AChE by donepezil causes acetylcholine (ACh) hydrolysis to be suppressed, resulting in an increase in ACh buildup at cholinergic synapses (Sahoo et al., 2018). Donepezil also prevents Aβ-induced cytotoxicity by enhancing oligodendrocyte differentiation by activating the phosphatidylinositol-3-kinase (PI3K)/Akt route (Bae et al., 2021). In addition, donepezil activates the sigma-1 receptor with disaffects the suppressive action of Aβ on long-term potentiation in the hippocampus of the rat (Bae et al., 2021). Donepezil has been discovered to have a high affinity for the Sigma-1 receptor, which regulates a variety of cellular activities including Ca^{2+} signaling, neurotransmitter release, and cellular defense against Aβ-induced neurotoxicity, among others (Bae et al., 2021; Solntseva et al., 2014).

Dosing documented by previous experimental and clinical research

A study by Birks and Harvey (2018), found that 10 mg donepezil improved cognitive function slightly more than 5 mg; however, pharmacological studies found little difference between these doses. As a result, both doses were recommended, and a new high-dose of one-per-day 23 mg tablet was endorsed for treating Alzheimer's disease patients with mild to moderate symptoms. It has also been hypothesized that inhibition of cortical acetylcholinesterase (AChE) function is 20–40 % using 5 mg and 10 mg thereby indicating that AChE inhibition is directly proportional to the dose of donepezil (Courtney, 2004; Lee et al., 2015). Patients with Alzheimer's disease who have low body weight, a history of gastrointestinal bleeding, or a poor appetite are not candidates for this new treatment (Adlimoghaddam et al., 2018; Lee et al., 2015).

Effects on clinical presentations and documented pathologies (histopathology, neurochemical pathology, pathophysiology)

After six months of medication, the effects of donepezil on clinical biomarkers of AD demonstrated a decrease in serum content of amyloid-beta (Aβ) in AD patients. In addition, donepezil improved cognitive performance by slowing hippocampal atrophy and lowering total tau protein expression after 48 weeks of treatment (Zhang and Gordon, 2018). Because of the significance of a high-fat diet (HFD) in causing neuropathology and its substantial link with the progression of age-related neurodegenerative illness, Dasuri et al. investigated donepezil's ability to attenuate HFD-induced impact on brain disease (Dasuri et al., 2016). When mice were fed a high-fat diet (HFD), their levels of AChE enzyme increased significantly compared to those fed a low-fat diet (LFD) (Dasuri et al., 2016). They also observed that donepezil medication lowers HFD-induced inflammation in the cortical regions of the brain, as well as microglial activation (Dasuri et al., 2016). They discovered that donepezil can protect the brain against the initial stages of HFD-induced inflammatory responses, which are expected to perform a role in the progression of neuropathology in the elderly and age-related neurodegenerative diseases (Dasuri et al., 2016).

Also, another group of researchers compared astrocyte-multiplication caused by Naturido to that elicited by zonisamide, donepezil, galantamine, and serine, all of which are used in treating Parkinson's disease and Alzheimer's disease, respectively (Ishiguro et al., 2021). The drug zonisamide, which boosts C6 cells and is used to

treat Parkinson's disease in the clinic, did not affect astrocyte growth. Donepezil, eserine, and galantamine, and the other three medications, did not affect astrocyte proliferation. There appear to be few studies that have looked into the effects of donepezil on neuron-glia interactions. As a result, more research may be needed to determine the exact dose of donepezil that can affect glia cells, such as suppression of microglial cell activation and astrocyte activation.

Galantamine

Introduction

Galantamine is a natural substance derived from the bulbs of various *Amaryllidaceae* species and the Caucasian snowdrop. It is an allosteric nicotinamide acetylcholinesterase receptor (nAChR) modulator and a selective, reversible, competitive inhibitor of acetylcholinesterase inhibitors (AChEI) (Villarroya et al., 2007). Galantamine is an acetylcholinesterase inhibitor that also increases acetylcholine release, which allosterically amplifies the effect of acetylcholine at nicotinic receptors (Brodaty et al., 2006; Kelly et al., 2008). Galantamine is the most recent AChEI to be licensed for the clinical management of AD in Europe and the United States. In comparison to other inhibitors now used to manage AD, its effect as an AChEI is minor (Villarroya et al., 2007).

Pharmacokinetics (absorption, distribution, metabolism, and excretion of the drug)

Galantamine has been shown in many studies to boost the secretion of other neurotransmitters like glutamate, Gama amino butyric acid (GABA), and various monoamines via this allosteric mechanism. These galantamine responses could be the rationale for improved performance in AD patients because dopamine and serotonin, not ACh, are implicated in these behavioral symptoms (Saito et al., 2019; Villarroya et al., 2007).

Mechanisms of actions documented by previous experimental and clinical research

Galantamine has been shown to block astrocyte activation, lower intracellular tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) expression, and reduce the total amyloid load in the hippocampus of amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice (Wu et al., 2015). Galantamine therapy, on the other hand, inhibited the generation of proinflammatory cytokines through neurotoxic microglial activation from the pre-plaque phase (Saito et al., 2019). As a result, galantamine therapy beginning in the pre-plaque period may have clinical value in the prevention of Alzheimer's disease. Galantamine also improved microglial function to increase Aβ clearance, lowering the amount of insoluble Aβ in the brain and reducing the Aβ-positive area in the cortex (Saito et al., 2019; Wu et al., 2015).

Dosing documented by previous experimental and clinical research

One research conducted by Gaudig et al. (2011), revealed in-vitro data that galantamine may give neuroprotection against the amyloid-beta peptide, which is involved in the etiology of Alzheimer's disease. If galantamine is stopped in patients with mild to moderate AD who have shown cognitive gains from up to 5 months of treatment with galantamine, there is an apparent natural progression of AD (Gaudig et al., 2011). Drug discontinuation, on the other hand, does not appear to be linked to any safety issues.

Effects on clinical presentations and documented pathologies (histopathology, neurochemical pathology, pathophysiology)

Brodaty et al. found that 70 % of galantamine-treated patients improved their cognition, as judged by the "Mini-Mental State Examination (MMSE) scale", especially after 6 months. On the 'Clinician's Interview-Based Assessment of Change (CIBIC) plus scale', 86 % of patients over 6 months had a favorable overall impression of response (defined as unchanged, or minimally, much, or very much improved) (Brodaty et al., 2006). In the investigations of Raskind et al. and Tariot et al., the CIBIC-plus scores of around 70 % of participants receiving galantamine 16 or 24 mg/day remained unchanged or improved (Brodaty et al., 2006; Raskind et al., 2000; Tariot et al., 2000). Over six months, the majority of the patients in their study showed no decrease in behavioral evaluation. These findings are also in line with those of Raskind et al. and Tariot et al., even though they utilized different assessment methodologies (Brodaty et al., 2006; Raskind et al., 2000; Tariot et al., 2000). They concluded that the majority of galantamine-treated patients who finished the trial had acceptable cognition, behavior, or function at the end of the 6-month treatment period (Brodaty et al., 2006). According to Saito et al., galantamine administration during the pre-plague phase improved memory in the 'Morris water maze test and new object identification test. The use of electron paramagnetic resonance (EPR) imaging to monitor the redox condition of the brain revealed that galantamine treatment improved the unbalanced redox state (Saito et al., 2019).

Furthermore, the findings of Saito et al. (2019), show that EPR imaging can be used to quickly and quantitatively assess the efficacy of disease-modifying medications for Alzheimer's disease. Patients with advanced moderate AD and those who have been pronounced non-responsive by the CIBIC-plus test may benefit from continuing galantamine medication (Gaudig et al., 2011). Galantamine therapy alone enhanced metabolism in the right precuneus, right inferior parietal lobule, and right middle occipital gyrus (Smith et al., 2009). The synergistic interplay of cholinergic and serotonergic systems is suggested by the joint cerebral metabolic responses of galantamine and citalopram (Smith et al., 2009). Although galantamine is useful in the management of AD symptoms, further research is required to determine its exact role in modifying the numerous metabolic pathways linked to disease progression.

Choline alphoscerate

Introduction

Choline alphoscerate (L-α-glyceryl phosphorylcholine, α-GPC), a semi-synthetic derivative of phosphatidylcholine (PDC or lecithin) (Tomassoni et al., 2006), is a remarkable new cholinergic drug that has been shown in pre-clinical studies to increase and cause the release of acetylcholine in the rat hippocampus, improve learning and memory in animal archetypes, and boost brain transduction operations.

Pharmacokinetics (absorption, distribution, metabolism, and excretion of the drug)

Choline alphoscerate has been identified as a cholinergic progenitor that contains cytidine 5'-diphosphocholine (CDP-choline) and has a high penetration rate, allowing it to pass past the Blood-Brain Barrier (Parnetti et al., 2001; Scapicchio, 2013; Tomassoni et al., 2006). As proposed by studies, damaged brain cholinergic transmission contributes greatly to the degeneration of cognitive function in AD patients, and various curative techniques have been suggested to restore cholinergic transmission in dementia disorders. Integration of ACh progenitors, activating ACh release, activation of muscarinic or nicotinic receptors, and acetylcholinesterase suppression are among them (Tomassoni et al., 2006).

Mechanisms of actions documented by previous experimental and clinical research

While responding to endotoxin, high quantities of choline have been

found to activate nAChR in circulating immune cells and prevent the production of pro-inflammatory cytokines (Tayebati et al., 2017). Other choline precursors and GPC have been shown to inhibit astroglial growth in both in vitro and in vivo experiments, suggesting that they may have a protective role in the brain (Tayebati et al., 2009, 2017; Tomassoni et al., 2006).

Dosing documented by previous experimental and clinical research

According to Scapicchio (2013), With twenty-four (24) hours of assimilation, injection, or oral administration of Alpha (α)-GPC leads to an increase in free plasma choline, which is incorporated into brain phospholipids. Co-administration of alpha (α)-GPC with cholinesterase inhibitor (galantamine) has been disclosed to evoke neuroprotective upshots greater than the effect of a single compound (Tayebati et al., 2009). Their simultaneous treatment has been linked to an increase in the release of ACh induced by alpha-GPC, as well as overexpression of the protective protein Bcl-2, which is controlled by alpha-7 nicotinic Ach receptors (nAChRs) (Scapicchio, 2013; Tayebati et al., 2009).

Effects on clinical presentations and documented pathologies (histopathology, neurochemical pathology, pathophysiology)

In an animal model study by Tayebati et al. (2009), choline alphoscerate was found to prevent hypertension-related neuronal loss and glial response in the hippocampus, confirming previous studies and bolstering the idea that choline alphoscerate may work as a neuroprotectant in vascular dementia. Reactive astrocytosis is caused by injury or disease to the central nervous system, and reactive astrocytes play a role in the healing and defense of neurons (Tomassoni et al., 2006). Choline alphoscerate increases cholinergic neurotransmission, which may protect against glutamate neurotoxicity by activating nicotinic acetylcholine receptors and the phosphatidylinositol 3-kinase cascade. Modulation of the α-7 nicotinic receptor may disrupt inflammatory responses of the central nervous system, the amplitude of which is controlled by astrocytes (Tomassoni et al., 2006).

Treatments with choline and GPC without any specific pro-inflammatory events, on the other hand, did not change the expression of endothelial adhesion molecules and pro-inflammatory cytokines in normal brain circumstances (Tayebati et al., 2017). Further research may explore this option by conjugating choline precursors and derivatives with additional therapeutic targets including beta-APP (amyloid precursor protein) cleaving enzymes (BACE), due to its capacity to traverse the blood-brain barrier. Future research may focus on the anti-inflammatory characteristics of conjugates of choline alphoscerate and the cascade of responses that occur after it is administered as an Alzheimer's disease intervention.

Dextromethorphan

Introduction

Dextromethorphan (DM; d-3-methoxy-17-methylmorphinan) is a cough suppressant and received FDA approval for its use in 1958 (Oh et al., 2022). Although it has been around for a long time as an over-the-counter decongestant, the underlying pathway through which it works to stop coughing is unknown (Taylor et al., 2016; Yang et al., 2006).

Pharmacokinetics (absorption, distribution, metabolism, and excretion of the drug)

DM has complicated pharmacology that goes beyond blocking N-Methyl-D-Aspartate receptors (NMDAR) and inhibiting glutamate excitotoxicity (Yang et al., 2006). Serotonin transporters, noradrenaline (NA) transporters, sigma-1 receptors (Sig1-R), α3β4 nicotinic acetylcholine receptors, and N-Methyl-D-Aspartate receptors (NMDARs) are all involved in the pharmacology of DM. These proteins are found in a variety of neurotransmitter systems that are used to treat neurological and psychiatric conditions. DM has no meaningful activity at opioid receptors, despite its structural similarity to opioid agonizts (Chen et al., 1990; Taylor et al., 2016). TNF-α, IL-6, NO, and superoxide anion (O_2^-) are only a few of the inflammatory mediators that have been demonstrated to be inhibited by DM. DM has been found in several studies to attenuate glia-mediated neuroinflammation and may have neuroprotective properties. In vitro, DM reduced microglia-mediated dopaminergic neuron degeneration as well as the production of TNF-α, NO, and O_2^-. DM is also an antagonist of the N-Methyl-D-Aspartate receptor (NMDAR) (Chechneva et al., 2011; Madeira et al., 2015).

Mechanisms of actions documented by previous experimental and clinical research

The use of DM/Q may potentially generate agonist activity at sigma-1 receptors via antagonizing nicotinic acetylcholine receptors, particularly those made of α3β4 subunits (Lisak et al., 2020; Liu et al., 2019; Sałaciak and Pytka, 2021; Taylor et al., 2016).

Dosing documented by previous experimental and clinical research

Lisak et al. found that DM had considerable effects on glial proliferation in less mature cultures compared to minor variable effects in mature cultures; 1 μM DM promoted OPC proliferation by 4-fold, microglia (MG) proliferation by 2.5-fold, and astroglia (AS) proliferation by 2-fold. Treatment of OPC with DM for 3 days raised the percent of OPC relative to OL, with a lesser difference by 5 days, suggesting that OPC maturation to OL was "catching up" by 5 days, in agreement with enhanced OPC proliferation (Lisak et al., 2014). Both OL and OPC were protected by DM at 2 and 20 μM from glutamate, NMDA, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), quinolinic acid, staurosporine, and reactive oxygen species (ROS). DM did not affect kynurenic acid and only had a minor effect on NO. At the concentrations employed, these drugs and DM were not harmful to astrocytes or microglia. As a result, DM promotes OPC proliferation while also protecting both OL and OPC from excitotoxic and inflammatory assaults (Lisak et al., 2014).

The fast metabolization of DM to dextrorphan (DX) has impeded the development of DM therapies. Due to quick and widespread conversion to DX, when DM is given orally (30 mg) to extensive metabolizers, only modest plasma levels (unbound plasma concentrations of 2–4 nM) are attained (Chen et al., 1990; Lauterbach et al., 2016; Taylor et al., 2016). DX is glucuronidated by uridine diphosphate-glucuronosyltransferase to generate dextrorphan-O-glucuronide, with the O-glucuronide accounting for 97–98 % DX in plasma (Ouzzine et al., 2014). Because dextrorphan-O-glucuronide is irreversibly charged and less permeable to the blood-brain barrier than unconjugated DX, even though it may be present at higher total (bound and unbound) plasma concentrations than DM, it is unlikely to produce significant pharmacological effects in the brain at clinically used doses (Ouzzine et al., 2014; Taylor et al., 2016). Co-administration of DM with a low dose of quinidine (Q) reduces DM metabolism, increases bioavailability, and allows for a more targeted assessment of DM's therapeutic characteristics other than its metabolites (Taylor et al., 2016). The findings imply that DM/Q disrupts NMDA receptors and inhibits serotonin and norepinephrine reuptake with rapid kinetics (Liu et al., 2019; Taylor et al., 2016).

Effects on clinical presentations and documented pathologies (histopathology, neurochemical pathology, pathophysiology)

Madeira et al. found that DM reduced lesion size and neuronal cell death, potentially via lowering microglial activation. NMDAR-mediated excitotoxic brain damage induced by inflammation was reduced by low

dosages of DM without affecting neuronal death. DM has been demonstrated to inhibit NOX-2 transcription and O_2 generation in microglia in animal models of multiple sclerosis (Butovsky, 2006; Díaz-Lucena et al., 2018; Madeira et al., 2015). As a sigma receptor agonist and NMDA receptor antagonist, dextromethorphan protects neurons from glutamate excitotoxicity, hypoxia, and ischemia, as well as inhibiting microglial activation (Lisak et al., 2014; Liu et al., 2019; Sałaciak and Pytka, 2021). This is important in protecting oligodendroglia (OL) to prevent demyelination and preserve axons (Sałaciak and Pytka, 2021), as well as protecting oligodendroglial progenitor cells (OPC) to optimize myelination during development (Lisak et al., 2014, 2020).

Clinical researchers are investigating DM's therapeutic potential in illnesses such as pain and epilepsy, as a neuroprotectant for acute brain injury or stroke, and in neurodegenerative disorders due to its receptor pharmacology (especially at NMDARs) (Taylor et al., 2016). Dextromethorphan can be used with various inhibitors to stop its activities in certain receptors due to its effect on diverse receptors. Following its usage in the treatment of dementia and other neurological disorders, more research may be needed to look into the molecular interaction of dextromethorphan-quinidine and its metabolite in neural tissue (Lisak et al., 2020; Liu et al., 2019; Sałaciak and Pytka, 2021; Taylor et al., 2016).

Palmitoylethanolamide

Introduction

Palmitoylethanolamide (PEA), a natural compound from peanut meal, egg yolk, and soybean lecithin, is an analog of anandamide (Casale et al., 2021; Lambert et al., 2002). PEA, like other endogenous N-acylethanolamine compounds, is known to mimic several endocannabinoid-driven actions even though it does not bind to cannabinoid receptors. As a result, PEA and other endogenous N-acylethanolamine compounds bind to the peroxisome proliferator-activated receptor (PPARα) expressed on neurons and astrocytes with a relatively high affinity (Casale et al., 2021; Scuderi et al., 2012).

Pharmacokinetics (absorption, distribution, metabolism, and excretion of the drug)

Glial cells produce palmitoylethanolamide (PEA) (Scuderi et al., 2012), a lipid messenger that arises naturally as an amide of ethanolamide and palmitic acid (Beggiato et al., 2020). PEA is thought to affect local cells, degranulation, and the creation of various inflammatory mediators such as neurotrophic factors (like nerve growth factor) and TNF-α (Casale et al., 2021; Lambert et al., 2002; Skaper et al., 2015).

Mechanisms of actions documented by previous experimental and clinical research

PEA therapy generates a considerable reduction in astrocyte activation with matching neuronal protection in both mixed neuroglial and organotypic hippocampus cells, according to their findings. Skaper et al. (2015) previously demonstrated that inhibiting NF-κB in rat astrocytes with PEA lowers the release of inflammatory chemicals and cytokines, resulting in a substantial down-regulation of reactive astrocytes. They concluded that the reduction of reactive gliosis and, as a result, the prevention of neuronal injury is solely dependent on PPARα activity.

Dosing documented by previous experimental and clinical research

Palmitoylethanolamide (PEA), as an endogenous lipid mediator, has been regarded to be a favorable pharmacological representative as it has disclosed potency in dwindling neuroinflammation and neurodegeneration in various in-vitro and in-vivo prototypes (Beggiato et al., 2020). Preclinical confirmation in-vitro studies disclosed the therapeutic factor in AD which examine the capability of PEA (10^{-7} M) to attenuate Aβ (Aβ1–42;1 ug/ml) -induced astrogliosis in primary cultures of rat astrocytes (Beggiato et al., 2019). In in vivo studies, the administration of PEA was done once a day (3–30 mg/kg, via subcutaneous mode) starting 3 h after $A\beta_{25–35}$ administration for 1 or 2 weeks. Using water-maze, water-maze working memory, and novel object recognition tests to evaluate cognitive functions with dose-dependent, the 10 mg/kg of body weight dwindle and 30 mg/kg of body weight of PEA prevents the cognitive damages induced by $A\beta_{25–35}$ peptide injection.

It has been established by a previous study that PEA (0.1 μM) exercise a neuroprotective impact in opposition to Amyloid-Beta ($A\beta_{1–42}$) fragment ($A\beta_{42}$) -influenced toxicity in primary cultures of cortical neurons or astrocytes from wild-type (non-Tg) and a triple-transgenic murine archetype of AD (Beggiato et al., 2020).

The feasible neuroprotective impacts of PEA were primarily examined on the emergence of Aβ25–35 induced learning deficiency in which administration of 3,10 or 30 mg/kg once per day was done for seven days with therapy starting 3 h after the intracerebroventricularly (i.c.v) administration of the Aβ25–35 peptide. Seven days after the administration of PEA its 30 mg/kg dose was disclosed to be the most energetic causing total safeguarding of the presence of Aβ25–35 induced spontaneous alternation shortage (D'Agostino et al., 2012). Indicating that the protective outline of PEA is dose-dependent and the dose of 30 mg/kg completely hinders the working memory-like damage examined via Y-maze alternation performance (D'Agostino et al., 2012).

Effects on clinical presentations and documented pathologies (histopathology, neurochemical pathology, pathophysiology)

PEA has been demonstrated to be neuroprotective in models of Parkinson's disease, spinal cord injury, traumatic brain injury, and stroke, and has been implicated in the preservation of cellular homeostasis in cases of inflammation (Skaper et al., 2015). PEA has been shown to protect primary rat astrocytes against reactive gliosis produced by Aβ following PPARα interaction, according to Scuderi et al. They tested whether Aβ regulation of reactive gliosis leads to rebound protection on neurons using mixed neuroglia co-cultures and hippocampus organotypic slices treated with Aβ in the presence or absence of PEA (Scuderi et al., 2012; Skaper et al., 2013). Inhibition or manipulation of the enzymatic breakdown of PEA could be one of the therapeutic approaches to neuroinflammation (Skaper et al., 2015). Chronic therapy with PEA was shown to reduce the presence of activated astrocytes and pro-inflammatory responses in the frontal brain of Alzheimer's disease rats (Bronzuoli et al., 2018). PEA also restored the abnormalities in trophic support in neurons of the frontal cortex whose neuronal viability had not yet been compromised (Bronzuoli et al., 2018). More research into the benefits of palmitoylethanolamide and its metabolites as a potential Alzheimer's disease therapy is needed, with a focus on the uptake and reuptake mechanisms as they relate to the neuron-astrocyte-microglia interaction.

Citalopram

Introduction

Citalopram is a selective serotonin reuptake inhibitor (SSRI), which is a type of antidepressant. It is commonly used to treat depression and, on rare occasions, panic attacks. A growing body of research suggests that using a selective serotonin reuptake inhibitor (SSRI) like citalopram changes the biochemical and behavioral responses to dopaminergic drugs, as well as the dopaminergic neurons' basal activity (Sekine et al., 2007). As reported in a study conducted by Schipke et al. (2011), Selective serotonin reuptake inhibitors (SSRIs) namely Citalopram and fluoxetine directly regulate the role of astrocytes. Following the administration of the SSRIs, non-synchronized calcium transients were documented similar to the event following the introduction of serotonin

(Schipke et al., 2011). Therefore, conjectured that SSRIs at the minimum cause induction of calcium signaling in astrocytes slightly through 5-hydroxytryptamine (5-HT) binding locations (Schipke et al., 2011). Also, 5-HT_{2B}-mediated signaling and energy metabolism in astrocytes are regulated by fluoxetine as disclosed in the culture result (Schipke et al., 2011).

Pharmacokinetics (absorption, distribution, metabolism, and excretion of the drug)

Repeated administration of SSRIs tends to enhance the behavioral response to dopamine (DA) receptor agonizts like quinpirole. DA may play a key part in the antidepressant activity of SSRIs, according to several studies employing diverse animal models of depression (Sekine et al., 2007). SSRIs modify DA receptor binding characteristics, according to receptor binding studies. The injection of citalopram into rats regularly considerably increases D3 receptor binding in the limbic system (Sekine et al., 2007; Zamudio et al., 2005).

Mechanisms of actions documented by previous experimental and clinical research

Citalopram is a powerful selective inhibitor of serotonin reuptake and surges extracellular serotonin concentrations in the hippocampus of rats however has zero impact on the uptake of noradrenaline and dopamine (Neumeister and Riepe, 2012). In immortalized mouse primary hippocampus cells (HT22) expressing mutant Amyloid precursor protein(APP) mutations, citalopram has a protective effect against impaired mitochondrial dynamics, non-functioning mitochondrial biogenesis, malfunctioning mitophagy, and synaptic disorder (Reddy et al., 2021).

Therapy of mAPP-HT22 cells with citalopram juxtaposed with untreated cells disclosed dwindled degrees of the mitochondrial fission genes, surged fusion, biogenesis, autophagy, mitophagy, and synaptic genes through the use of the following methods quantitative Real-time Polymerase Chain Reaction (RT-PCR), immunoblotting, biochemical methods, and transmission electron microscopy. The fragments of mAPP and C-terminals were also diminished in citalopram treated cells (Reddy et al., 2021). These results propose that citalopram lessens mutant APP and Aβ and mitochondrial toxicities and may have a safeguarding function of mutant APP and Aβ-induced injuries in victims with depression, anxiety, and AD (Reddy et al., 2021).

Dosing documented by previous experimental and clinical research

SSRI dosing dramatically affects striatal D2 receptor binding and DA uptake transporter levels when compared to controls, according to neuroimaging studies in humans (Sekine et al., 2007; Vulink et al., 2012).

Effects on clinical presentations and documented pathologies (histopathology, neurochemical pathology, pathophysiology)

There were immediate decreases in cerebral glucose metabolism in Alzheimer's disease patients after the injection of citalopram (Aboukhatwa et al., 2010; Smith et al., 2009). Citalopram reduced glucose metabolism in the middle frontal gyrus (bilaterally), left middle temporal gyrus, and right posterior cingulate to a higher extent than the controls (Aboukhatwa et al., 2010). Citalopram, on the other hand, enhanced metabolism in the right middle frontal gyrus, right post-central gyrus, right superior and middle temporal gyrus, and right cerebellum under citalopram plus galantamine administration. The synergistic interplay of cholinergic and serotonergic systems is suggested by the combined cerebral metabolic effects of galantamine and citalopram (Smith et al., 2009).

Furthermore, Tosto et al. found favorable outcomes with citalopram treatment for hypersexuality in Alzheimer's disease in 2008. Total sexual outlets (TSA; more than 20 or the number of orgasms each week) were significantly reduced (< 2) after 60 days of 40 mg/day citalopram, as was dissatisfaction when his wife refused (Tosto et al., 2008). After 12 months (TSA = 2), the positive effect is still present. Another patient who received citalopram for 60 days demonstrated improvement in both obsessive sex act seeking and dissatisfaction when denied (Tosto et al., 2008).

Resveratrol

Introduction

Resveratrol (3,5,4'-trans-trihydroxystilbene, RSV) is a polyphenol found in grapes, wines, peanuts, and berries in nature. The antioxidant, anti-inflammatory and neuroprotective properties of this chemical are well known (Bobermin et al., 2019). Its ability to control and protect glial cells, hence protecting the functional integrity of the brain, is one of its positive effects on the CNS (Bobermin et al., 2019). Resveratrol, a naturally occurring polyphenolic substance, is a neuroprotective molecule linked to glial function modification. Caffeine and specific adenosine receptor antagonists, on the other hand, blocked the anti-inflammatory effects of resveratrol (Bobermin et al., 2019; Genade and Lang, 2013).

Pharmacokinetics (absorption, distribution, metabolism, and excretion of the drug)

Resveratrol's anti-inflammatory effect in glial cells has been shown, and it is thought to be linked to a variety of signaling pathways, including nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), p38, and extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK) (Bobermin et al., 2019). Previous research have demonstrated that resveratrol can modify the adenosinergic system in a range of tissues, including the cardiovascular and brain, even though the underlying processes remain unknown (Bobermin et al., 2019).

Mechanisms of actions documented by previous experimental and clinical research

Preclinical studies with resveratrol demonstrate that it imitates the advantageous impacts of caloric diminution through pharmacologic stimulation of sirtuins (SIRT1). It has also been disclosed that resveratrol traverses the BBB leading to noticeable however low concentrations of the parent molecule in the brain while greater concentrations of resveratrol metabolites are discovered in the blood (Sawda et al., 2017). Resveratrol surges cerebral arteriole dilations in animal-like rats possibly through stimulation of nitric oxide (NO) regulated vasodilation which enhances post-ischemic cerebral perfusion but a homogenous study with human subjects did not disclose enhancement (Sawda et al., 2017). Further preclinical confirmation reinforces the idea that resveratrol may exhibit function in the therapy and safeguarding of neurodegenerative diseases namely Huntington's disease, Parkinson's disease, and AD via SIRT1 simulation it will shield neurons from reactive oxygen species (ROS), hydrogen peroxide free radicals, Aβ and other intra and extracellular toxins and damages related with neurodegenerative diseases (Sawda et al., 2017).

Resveratrol is a polyphenol established in red grapes, red wines, and other plant foods. and growing confirmation of the neuroprotective effects of red wine revealed various bioactive molecules such as quercetin, myricetin, catechin, tannins, anthocyanidins, ferulic acid, and resveratrol (Sawda et al., 2017).

Dosing documented by previous experimental and clinical research

Clinical evaluations of resveratrol in AD disclosed its safety and enhancement of brain volume through its use for 52 weeks by 119 participants at a dosage of 500–1000 mg once daily, and also for 48 weeks at 150 mg dosage in 18 participants resveratrol influenced refinement of cognition and inborn immune functions (Kou and Chen, 2017; Moussa et al., 2017).

Effects on clinical presentations and documented pathologies (histopathology, neurochemical pathology, pathophysiology)

Resveratrol protects DA neurons from LPS-induced neurotoxicity by decreasing microglia activation and proinflammatory factor production (Zhang et al., 2010). These neuroprotective effects of resveratrol are thought to be achieved at least in part by preventing the activation of MAPKs and the NF-κB cascade signaling pathways, as well as lowering the activity of NADPH oxidase (Sandhir et al., 2015; Zhang et al., 2010). Taherian et al. argued that treatment of cultured astrocytes with RSV enhanced the ammonia, ischemia, and trauma-induced cell swelling, likely through the exacerbation of intercellular signaling kinases and ion transporters (Taherian et al., 2020). They concluded that vigilance should be maintained while utilizing RSV to treat these neurological disorders, especially if brain edema is suspected. More research is needed to determine the underlying mechanism of action of resveratrol and how it suppresses glial cell activation during inflammatory insults.

Solanezumab

Introduction

Solanezumab is a monoclonal antibody made from humanized immunoglobulin G1 that binds to the Aβ peptide's mid-domain. It was created to enhance the clearance from the brain of soluble Aβ peptides (Chu and Liu, 2019) that could have harmful effects on synapses before the fibrillary form of the protein was deposited (Honig et al., 2018).

Pharmacokinetics (absorption, distribution, metabolism, and excretion of the drug)

Solanezumab binds to the core, a more hydrophobic portion of the human Aβ peptide (against 16–24 residues of Aβ) (Imbimbo et al., 2012; Panza et al., 2011). Multiple clinical trials for the prevention of Alzheimer's disease are underway (Bouter et al., 2015). Eli Lilly and Co.'s Solanezumab is another monoclonal amyloid antibody that has advanced to Phase III clinical studies (Panza et al., 2011). Solanezumab's biochemical features are distinct from those of other monoclonal antibodies currently being investigated as passive immunotherapeutics (Panza et al., 2011). First, the m266 monoclonal antibody recognizes the core domain of Aβ (Panza et al., 2011), and it has been proposed that this characteristic makes it more successful than other antibodies at clearing N-terminal shortened or modified variants of the Aβ peptide (Imbimbo et al., 2012). This distinguishes solanezumab from bapineuzumab, which targets the Aβ peptide's N-terminal part (amino acid residues 1–5) (Imbimbo et al., 2012).

Mechanisms of actions documented by previous experimental and clinical research

Solanezumab, like bapineuzumab, prefers to bind to the soluble form of Aβ and has little or no affinity for senile plaques (SPs) (Panza et al., 2011). It is thought that soluble oligomeric Aβ is more neurotoxic than Aβ fibrils or deposits (Imbimbo et al., 2012). It detects epitopes in the center of the Aβ (Aβ13–28), which are different from those targeted by bapineuzumab, and binds to soluble forms of Aβ more effectively than those deposited in senile plaques (Panza et al., 2011). Based on the effects of solanezumab on plasma and CSF Aβ levels, it is hypothesized that solanezumab works on peripheral amyloid, disrupting the equilibrium between plasma and CSF amyloid (Panza et al., 2011) and causing amyloid outflow from the CNS into a 'peripheral sink' (Tayeb et al., 2013). The amyloid-β hypothesis has been the most widely accepted theory for Alzheimer's disease (AD) and has served as a foundation for the development of new therapeutic techniques (Bouter et al., 2015; Kostrzewa, 2014).

Increased Aβ synthesis or decreased Aβ clearance, according to the theory, leads to the accumulation of hydrophobic Aβ40 and Aβ42 and the creation of insoluble extracellular plaques. Plaques then set off a chain reaction of harmful events that lead to synapse loss, neuron loss, brain shrinkage, and dementia. If the amyloid hypothesis is right, interrupting the cascade and eliminating Aβ from the brain should stop cell death and cognitive impairment. Reducing Aβ production, helping Aβ clearance, and preventing Aβ aggregation are the main therapeutic intervention techniques for Aβ (Bouter et al., 2015; Sumner et al., 2018; Tayeb et al., 2013). The immunohistochemistry staining profile of solanezumab revealed a strong binding affinity to plaques, identifying N-terminally modified Aβ peptides Aβ4–42 and pyroglutamate Aβ3–42 and strongly interacting with amyloid plaques (Bouter et al., 2015). Roher et al. argued that solanezumab immunotherapy provided no apparent relief in the clinical evolution of dementia in this particular AD patient since there was a continuous cognitive deterioration and full expression of amyloid deposition and neuropathology.

Dosing documented by previous experimental and clinical research

Solanezumab is a mid-domain monoclonal antibody that is the humanized equivalent of the murine antibody m266.2. The drug is presently being examined in phase III assessment for its potential to hinder the development of AD (Samadi and Sultzer, 2011). Four intravenous dosing approaches of solanezumab were espoused in its phase I evaluation: 0.5,1,4 and 10 mg/kg. After a single administration of the drug, both maximum plasma concentrations and time to attain maximum plasma concentration of $A\beta_{1-40}$ and $A\beta_{1-42}$ surged with rising doses of the study drug (500 h and 1000 h respectively for the 4 mg/kg group) (Samadi and Sultzer, 2011).

Phase II study of 52 patients with mild and moderate AD who received one of four doses of solanezumab ($n = 10–11$ per dosing group), plasma, and cerebrospinal biomarker assays proposed a favorable drug effect. Two phases III evaluations of solanezumab are in advance (Samadi and Sultzer, 2011).

Effects on clinical presentations and documented pathologies (histopathology, neurochemical pathology, pathophysiology)

According to Honig et al., Solanezumab at a dose of 400 mg given every four weeks to patients with moderate Alzheimer's disease did not affect cognitive impairment. However, Roher et al. determined that the disease severity in the Apolipoprotein (APOε4) homozygote patient included in their study may have already progressed to an advanced irreversible stage when solanezumab treatment began (Roher et al., 2016). Furthermore, the widespread vascular amyloid deposits seen in this case showed reduced brain perfusion, which could have had a negative synergistic effect on the ongoing neurodegenerative processes (Roher et al., 2016). Given the quantitative and qualitative heterogeneity of the amyloid burden in AD, solanezumab treatment could potentially reduce or stabilize amyloid accumulation and improve quality of life (Roher et al., 2016).

As a result, Solanezumab may be a viable treatment for patients in the early stages of Alzheimer's disease (Keady et al., 2007). Bioinformatics techniques aid in the prediction of medications that target specific receptors, such as beta-secretase and gamma-secretase, which are key enzymes in the formation of amyloid-beta peptides. More research into medications that target the decrease of amyloid-beta buildup could

be done in this area.

Promising pharmacological targets and interventions in Alzheimer's disease

Because glia–neuron interactions are exceedingly complicated, new approaches and strategic targets should be required for the development of effective preventive and therapeutic drugs for AD and other neurological illnesses, rather than individual glia or neurons as in the past. To put it another way, novel ways to analyze this functional complexity and identify therapeutic neuroprotective compounds are required (Ishiguro et al., 2021). Inhibition of the β-secretase and γ-secretase (GS) enzymes, which are known to catalyze Aβ plaque development and the consequent AD, could prevent Aβ plaque production and the resulting AD (Salman et al., 2021).

Molecular docking was used to identify chemically related compounds for pharmacophore mapping, and the top-scoring compound was used to describe the probable inhibitors of GS (Salman et al., 2021). Ali et al. did a study to reduce the production of Aβ plaques by using gamma-secretase inhibitors (GSI) to block the action of the GS protein. They used molecular docking to target several GSI to the protein. They employed 111 GSI which were categorized as azepines, sulfonamides, and peptide isosteres. They discovered Amorpholino-amide as the 'high-affinity compound GSI' with superior interaction characteristics by molecular docking. The PubChem compound AKOS001083915 (CID:24462213), which was virtually tested, showed the greatest affinity for gamma-secretase. The reduced glymphatic function has also been linked to Aβ and tau buildup, according to recent research on the glymphatic waste clearance mechanism (Salman et al., 2021). The water channel protein AQP4, which has been associated with several CNS diseases, mediates increased bulk flow across the glymphatic system during sleep (Xie et al., 2013). Even though no single drug has been approved to effectively target AQP4, new research suggests that sleep or AQP4 modulators could be novel targets in Alzheimer's disease as an early intervention and other diseases associated with protein-misfolding.

The occurrence of oxidative damage in neuronal lipids and proteins, in particular, is a key characteristic of AD, firmly linking oxidative stress to the disease (Cheignon et al., 2018). Because signs of oxidation exist in mild cognitive impairment brain areas, oxidative stress may be an early event in the etiology of AD which can come from a variety of places, but an excess of ROS is thought to be a primary contributor (Cheignon et al., 2018). Copper and iron, which are loosely bound metal ions, are particularly efficient catalysts for the generation of ROS, and an increase in loosely bound Cu has been reported in AD (Cheignon et al., 2018; Migliorini et al., 2012). Cu ions linked to Aβ could also be contributing to the oxidative stress seen in Alzheimer's disease. Although biological validations have provided solid evidence that medicines that block BACE1's enzymatic activity are effective in the treatment of Alzheimer's disease, the early development of BACE1 inhibitors for clinical application in AD failed due to low oral bioavailability, low blood-brain barrier penetration, and liver damage (Lao et al., 2019).

Medication that addresses the control of glia-neuron connections may offer a novel therapeutic strategy for AD in its early stages. When the glia fails to respond to their normal regulatory feedback mechanism, a good medicine for the treatment of Alzheimer's disease would be effective by targeting the lowering of glial activation and recruitment. Neurodegenerative disorders may respond very well to such medications that can lessen neurotoxicity in the nearby brain brought on by activation of microglia produced by an excess production of pro-inflammatory cytokines like interleukin (IL)-1 and TNF. Additionally, glia-neuron interactions, glutamate absorption, and neuronal connections and synapses may be maintained by drug repurposing that focuses on reducing the negative effects of reactive astrocytes.

Cyclin-dependent kinase-5 (CDK5) plays an important neurodifferentiation and neuroprotective role in healthy neuronal functioning and has been associated with several neurological disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease (Xie et al., 2017). The binding of the regulating proteins p35 or p39 to CDK5 causes it to activate. The CDK5/p35 complex may hyperphosphorylate the tau protein and decrease the tau protein's interaction with microtubules, causing cytoskeletal changes and neuronal death (Xie et al., 2017). This phosphorylation has been identified as a critical step in modulating CDK5 activation.

Conclusion

This review examined how astrocytes and microglia preserve neurons in normal conditions, how connections among neurons, astrocytes, and microglia try to control inflammatory feedback and traumatic stress handling, and how these glia cells end up losing their neuroprotective effect for neurons while becoming toxic in Alzheimer's disease. The drugs were assessed according to their pharmacokinetic features, underlying mechanisms, dose as established by previous experimental and clinical research, clinical effects, and documented pathologies. Existing medications are aimed at keeping Alzheimer's disease symptoms at bay. As a result, the quest for medications that can reduce the degenerative process in dementia patients is still critical. Donepezil is capable of reducing amyloid-beta (Aβ) levels in the blood, reducing total tau protein expression, and improving cognitive function by decreasing hippocampus atrophy after 48 weeks of treatment. Donepezil and galantamine did not affect astrocyte proliferation.

Future research may look at the impact of donepezil on the interactions of neurons-glia interactions. Further research may be needed to establish the specific dose of donepezil that can alter glial cells, such as microglial cell activation suppression and astrocyte activation. Galantamine inhibits astrocyte activation, reduces intracellular TNF-α as well as IL-6 expression, and lowers the total amyloid burden in the hippocampus of an AD model. Galantamine treatment also prevents the synthesis of pro-inflammatory cytokines by activating neurotoxic microglia in the pre-plaque stage. Although galantamine is effective in treating the clinical signs of AD, further research is needed to identify its precise role in changing the multiple metabolic pathways connected to disease progression. Choline alphoscerate promotes cholinergic neurotransmission, which could mitigate glutamate neuronal damage by activating nicotinic acetylcholine receptors and the phosphatidylinositol 3-kinase cascade.

Due to its ability to cross the BBB, more research into the anti-inflammatory properties of conjugates of choline alphoscerate and the cascade of responses that follow after it is provided as an Alzheimer's disease intervention could be done. Dextromethorphan protects neurons from glutamate excitotoxicity, hypoxia, and ischemia, as well as inhibiting microglial activation. DM is an antagonist of the NMDA receptor which inhibits some inflammatory mediators such as TNF-α, IL-6, NO, and O_2^-. It attenuates glia-mediated neuroinflammation and has neuroprotective properties. Following a PPARα interaction, palmitoylethanolamide shields rat astrocytes from reactive gliosis caused by Aβ. In both combined neuroglial and organotypic hippocampal cells, PEA treatment results in a significant decrease in astrocyte activation with corresponding neuronal defense.

With respect to the neuron-astrocyte-microglia connection, more study into the advantages of palmitoylethanolamide and its metabolites as a possible AD treatment is needed. For successful drug delivery that can pass through the blood-brain barrier, more studies into pharmaceutical product conjugation that is capable of regulating reactive astrocytes and microglia activation may be required.

CRediT authorship contribution statement

Michael Kunle AJENIKOKO: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing, Visualization. **Abayomi**

Oyeyemi AJAGBE: Investigation, Writing – original draft, Project administration. **Oluwanisola Akande ONIGBINDE:** Formal analysis, Investigation, Writing – original draft, Project administration. **Akeem Ayodeji Okesina:** Formal analysis, Investigation, Writing – review & editing. **Ahmad TIJANI-ADEKILEKUN:** Formal analysis, Investigation, Writing – review & editing, Supervision.

Ethical Statement

This research does not require ethical approval as no human or animal subject is required.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgment

We thank Prof. Lukeman AJ Shittu for his comments and clarifications on molecular docking and its predictive ability in drug designs.

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