Neuroregeneration: New Therapeutics for Alzheimer's Dementia

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ABSTRACT

Physiological aging has become a general term in recent years that encompasses all the modifications that occur in an old-age organism. It is now clear that new health issues affecting the aging population are starting to emerge in developing and industrialised countries. Dementia is potentially one of the big issues. Different types of dementia contribute to learning deficiency, memory loss, low attention span, speech impairment, and impaired problem-solving abilities sooner or later. Normal ageing is a physiological phenomenon that often includes many neurological conditions in demented patients with the same kind of signs and consequences that many researchers are seeking to mitigate. We are trying to highlight some of the newest aspects of therapeutic techniques in this analysis that can stimulate neuroregeneration.

Neuroregeneration is a fairly new idea including neurogenesis, neuroplasticity and neurorestoration (implantation of viable cells as a therapeutic approach). In the brain of patients suffering from Alzheimer's or Parkinson's disease, neurogenesis and neuroplasticity are impaired and correlate with low endogenous defence, as a consequence of decreased expression of the growth factor. We hypothesize however that the brain has a "neuroregenerative reserve" that could be targeted by growth factor or neurorestoration therapies for stem cells, at least in the early and medium stage of disease.

In this study, through a systematic analysis of various scientific literature, we review the latest data on all three aspects of neuroregeneration in Alzheimer's disease.

INTRODUCTION

With longer life spans especially in developing and developed countries, new health issues are emerging with regard to the unique needs of the elderly. Dementia is one of the major health issues in this aspect (Mitran, Catalin, Sfredel & Balseanu, 2013). An Alzheimer's disease is the most prevalent type of dementia in the elderly and is a persistent, painful, neurodegenerative condition. Around 47 million people are affected by Alzheimer's disease and associated dementia globally, although there is no successful cure for Alzheimer's disease yet. The prevalence of Alzheimer's disease is estimated to be 135 million globally by the year 2050. An estimated 5.4 million Americans have Alzheimer's disease, including nearly 200,000 aged <65 years, have Alzheimer's disease, representing the younger-onset population with Alzheimer's disease. Statistics also suggests that another Alzheimer's disease patient is added every 68 seconds (Alzheimer' association, 2012). With symptoms increasing over time, it begins with a minor memory loss and the affected individual forgets how to perform simple everyday task such as combing their hair and brushing their teeth. They are unable to remember family members over time and need lifelong treatment, which becomes a burden to society. Alzheimer's disease, a neurodegenerative condition is characterised by memory impairment, the development of senile plaques and neurofibrillary tangles (NFTs) and the weakening of synaptic networks. Most of Alzheimer's diseases (>95%) occur sporadically, without a direct family relation, but with age as the single greatest risk factor (Sun & Alkon, 2019). Alzheimer's disease is a multifactorial and heterogenous condition, histopathologically characterized by the presence of amyloid β (Aβ) plaques and neurofibrillary tangles composed of Aβ peptides and abnormally hyperphosphorylated tau protein, respectively (Kazim & Iqbal, 2016). It is a progressive neurological disorder of wide aetiology with a significant genetic effect, and a number of factors depending on age, sex and life style (Ang, Tai, Lo, Seet & Soong, 2010).

Most degenerative diseases are characterized by cell death or damage, resulting in multiple organ dysfunction and in the loss of ability to synthesize, metabolize and properly assemble biologically active endogenous compounds (Bobkova, Poltavtseva, Leonov & Sukhikh, 2020). Neurodegeneration is a gradual process leading to a reduction in the total number of neurons, typically this process is due to apoptosis and is related to a loss of neuronal structure and function (Mitran et al., 2013). Brain aging in both neurons and glia is related to systemic and functional loss. This is commonly known as neurodegeneration. Neurons are quickly produced in early development of shape and complex complexity of the brain and peripheral nervous system. The function of neurogenesis shifts from brain growth to brain plasticity postnatally. From then on, neurogenesis takes place only in particular niches in the adult brain, in the hippocampal dentate gyrus (DG), Sub-granular zone (SGZ) and in the subventricular zone (Hollands, Bartolotti & Lazarov, 2016).

In addition to the general awareness of neurogenesis adult neuroregeneration is a dynamic concept that often involves endogenous neuroprotection leading to neuroplasticity and neurorestoration, a therapeutic approach to implantation of viable cells (Enciu et al., 2011). The modern

notion of neuroregeneration implies the presence of endogenous neuroprotection that contributes to neurogenesis and neuroplasticity, which in turn, forms the basis for neurorestoration – a therapeutic approach of grafting of viable CNS cells. Neurogenesis is recognized as a step wise process involving the proliferation, maturation, determination of fate and survival of resident CNS cells regulated by different regulatory factors (Bobkova et al., 2020). Neuroregeneration is a relatively new term that involves the implantation of viable cells as a therapeutic approach to neurogenesis, neuroplasticity and neurorestoration (Enciu et al., 2011). It is also possible to describe the concept of neuroregeneration as the superposition of three distinctive mechanisms, including neurogenesis, neuroplasticity, and neurorestoration (Mitran et al., 2013).

Objectives of the Study

General Objective

– To assess the effectiveness of neuroregeneration as new therapeutics for dementia in AD.

Specific Objectives

– To assess the prevalence of Alzheimer's Dementia

– To find out the types of Alzheimer's Dementia

– To identify the associated factors of Alzheimer's Dementia

Methodology

According to PRISMA guidelines (Moher et al., 2009) for reporting systematic reviews, the literature search was carried out. The quest included papers published between 2010 and 2020 in PubMed, Researchgate and Google Scholar. Neuroregeneration "AND" Therapeutics, OR New research, OR Neurogenesis, OR Stem cell Adult Neurogenesis OR Dementia were the search terms used. There were listed 30 publications as containing one or two keywords associated with the queries mentioned following a thorough analysis of the literature initially retrieved. Of these posts, 20 have subsequently been listed as important to the subject matter of this study. This review included only papers written in English. Unpublished documents have not been prosecuted. Publications were first chosen on the basis of titles and then imported.

RESULTS AND DISCUSSION

In order to determine the neurogenesis in the brain with Alzheimer's disease, referring to the current conflicting findings in the literature, the neurogenesis stimulating role of Alzheimer's disease drugs must also be taken into account (Enciu et al., 2011). A recent study (Haughey et al., 2002) recorded that in the dentate gyrus of amyloid precursor protein (APP) mutant mice with already developed amyloid deposits, the proliferation and survival of neuronal precursor cells was reduced. The decrease in the number of neuronal precursor cells was also associated with amyloid beta (Ab) accumulation, even in oligomeric, diffusible form (Enciu et al., 2011).

Evidence of neurogenesis in AD human brain

A recent research has documented overexpression of neurogenesis markers

(Doublecortin-DCX, Polysialylated Neuronal cell Adhesion Molecule-PSA-NCAM and TUC-4) in the hippocampus of a patient with AD without a correlated increase in mature neuronal markers (NeuN, Calbinding D28k) (Jin, Peel, Mao, Xie, Cottrell & Henshall, 2004). The theory of AD as a failed attempt of precursor cells to neuronal differentiation is confirmed by this expression disjunction (Li, Yamamori, Tatebayashi, Shafit-Zagardo, Tanimukai, Chen, Iqbal & Grundke-Iqbal, 2008), but Boekhoorn and collaborators (Boekhorn, Joels & Lucassen, 2006) argue that DCX is a nonspecific marker, increased due to reactive gliosis. Furthermore, Verwer and collaborators (Verwer, Sluiter, Balesar, Baayen, Noske, Dirven, Wouda, Van, Lucassen & Swaab, 2007) have challenged whether DCX+ cells are indeed neuroblasts, providing reasons for their astrocytic origin. Research into Musashi I immunoreactivity in Alzheimer's disease subventricular zone patients have reported impaired neurogenesis relative to controls (Ziabreva et al., 2006). In turn, although Lovell and collaborators (Lovell, Geiger, Van, Lynn & Markesbery, 2006), isolated viable neural Stem Cell from Alzheimer's disease patient's hippocampi, they obtained reduced viable neural precursor cells yields and altered division rates, relative to controls.

Unlike in vitro models using rodent neural precursor cells, in vitro studies using human neurospheres it was reported that Aβ 1-40 treatment inhibited precursor cell proliferation and differentiation (Mazur-Kolecka, Golabek, Nowicki, Flory & Frackowiak, 2006).

In order to determine neurogenesis in brain of Alzheimer's disease, adding to conflicting findings in the literature, the neurogenesis-stimulating role of Alzheimer's disease drugs must further be taken into account (Waldau & Shetty, 2008).

For example, the nerve growth factor protects cholinergic neurons from different insults, while for dopaminergic neurons, this effect is best maintained by the brain-derived nerve factor for different neuronal subpopulation (Enciu et al., 2011).

Neurogenesis in aging and disease state

Neurogenesis is significantly reduced during adulthood and further decreases during aging. The dynamics are less evident in humans. A recent research conducted by Spalding and collaborators (Spalding, Bergmann, Alkass, Bernard, Salkhpour & Huttner, 2013) suggests that there is a decline in aging neurogenesis moderately. It is still unclear, however, how this decrease affects cognitive performance in humans or whether similar paradigms of memory are controlled by adults neurogenesis as they are in rodents. Human findings using high resolution fMRI and cognitive test indicate that age-related memory loss starts in the dentate gyrus. It is assumed that these changes stem from a decrease in the support of the neurogenic niche and the intrinsic characteristics of NSC (Hollands et al., 2016).

The structure and function of the entorhinal-hippocampal circuit can be affected by defects in adult neurogenesis with age. In AD, the most prevalent type of Dementia, this area is especially susceptible and heavily affected. Alzheimer's disease is characterized by gradual memory loss and cognitive decline. Mutations in the amyloid precursor protein (APP) and presenilin-1 and *2* causes rare familial AD (FAD) (Selkoe & Wolfe, 2007). The majority of AD cases,

however, are intermittent and the greatest risk factor for AD is aging (Hollands et al., 2016).

(See Figure 1.) (See Figrue2.)

Neurogenesis as a biomarker of cognitive function and as therapeutic perspectives

Although it is clear that hippocampal neurogenesis takes place in the human brain and that the number of new neurons generated is substantial (Spalding et al., 2013), there is limited knowledge about the fate of neurogenesis in aging and cognitively impaired people. Current techniques permit the study of post-mortem neurogenesis. However, the development of methodologies for the detection of neurogenesis in live individuals would be critical because of the complex modulation that neurogenesis will undergo after various stimuli, such as progressive pathology.

Tools for the detection of neurogenesis in live humans have been limited up to now. For the estimation of the date of birth of hippocampal neurons and their quantification in post-mortem tissue, the level of 14C in genomic DNA has been used (Spalding et al., 2013). A previous research indicates that the proton nuclear magnetic resonance spectroscopy 1H-MRS can precisely detect adult neurogenesis (Manganas et al., 2007). However, Loewenbruck and collaborators (Loewenbruck, Fuchs, Hermann, Brandt, Werner & Kirsch, 2011) have challenged this approach, so further studies are needed to evaluate the specificity, sensitivity and feasibility of 1H-MRS for the detection and quantification of neurogenesis.

The link between neurogenesis decline and cognitive decline during aging, combined with neurogenesis disruption and cognitive impairment in FAD mouse model, indicates that improving neurogenesis could be a viable therapeutic strategy (see Figure 2). Effective attempts to improve rodent's neurogenesis have been defined. For instance, Sahay and collaborators (Sahay, Scobie, Hill, O'Caroll, Kheirbek & Burghart, 2011) used neurogenic pathways genetic manipulation, excising the pro-apoptotic gene Bax, to improve survival of nestin expressing cells. They observed enhanced performance in the dentate gyrus (DG)-dependent pattern separation task, where animals must differentiate between two identical contexts. Wang and collaborators (Wang, Pan, Zou, Abel & Palmitter, 2014) also increased cell survival, neuronal differentiation.

Causes and consequences of Neurodegenerative diseases and Alzheimer's disease

All neurodegenerative diseases affect various brain areas, while at the phenotypical level they display distinctive and evident characteristics, i.e. gradual loss of sensory-motor and cognitive functions (Hussain et al., 2018; Woolley et al., 2011) but universally at the cellular and molecular level they share similar etiology (Gitler et al., 2017; Hervas et al.,2012; Vadakkan et al., 2016). Evaluative scrutiny of the similarities between these disorders provides the potential for therapeutic advancements, which could treat many of these diseases simultaneously if we clearly grasp the commonalities existing between various neurodegenerative disorders (Rubinsztein et al., 2006; Thompson et al., 2008). Neurodegeneration can be seen in this regard at various stages of neuronal circuitry, ranging from intracellular protein molecule

disruption to intercellular tissue disruption and overall structures. The β-Amyloid (Aβ) protein build up and intracellular tau protein aggregation are the noxious etiological agents found in Alzheimer's disease that can induce synaptopathies, glial inflammation and eventual neuronal death in the cerebral cortex, subcortical areas, temporal and parietal lobes and cingulate gyrus (Hussain et al., 2018).

Alzheimer's disease affects the mental capacity of a patient with significant effects, including socio-economic costs, in terms of clinical manifestations. Usually, a patient with Alzheimer's disease loses normal cognitive control over time, including abilities in emotion, learning and memory processing skills, eventually leading to what is commonly called "dementia". There is the characteristic accumulation of interneuronal "Plaques" and intra-neuronal "Tangles" in terms of pathology. "Plaques" are formed outside the neuron when the peptide, β-Amyloid (Aβ) aggregates, while the "Tangles" that build up inside the cell are predominantly composed of tau protein associated with hyper-phosphorylated microtubules (Haughey et al., 2002).

Prevalence of Alzheimer's Disease

There are about 50 million people suffering from dementia in the world, according to the 2018 World Alzheimer's Survey. This number is projected to rise to approximately 82 million in 2030 and approximately 152 million in 2050. About 200 dementia subtypes, 50 percent-60 percent of all cases caused by Alzheimer's disease. Originally described by Alois Alzheimer in Frankfurt ammain in 1907, this form of dementia later became the most prevalent neurodegenerative disease (Vesic, Barth & Schmidt, 2019).

In 2015, there were approximately 46.8 million people living with AD in the world, according to Alzheimer's Disease International (ADI), which is expected to double every 20 years. The population of people with AD will therefore rise to 74.7 million in 2030 and 131.5 million in 2050. As the proportion of people with AD rises, it is estimated that the current proportion of 58 % of patients from middle- and lower-income countries will grow to 63 % by 2050. These figures indicate that each year there are around 9.9 million new cases, with a new case happening every 3.2 seconds.

Factors of AD

In the USA, the disease predominantly affects the elderly population over 65 years of age. There are cases of early onset, however the demographic profile is as follows in Singapore: 0.8 % among the 60-64-year-old cohort, to a staggering 32.2 % among people over 84 years of age. A combination of different genetic, behavioural, dietary and environmental factors results from the sporadic form of AD (>90%), so there is no single magic solution to tackle this issue. In view of extended life expectancies and increasingly rising population, this undoubtedly poses a significant issue (Haughey et al., 2002).

When one grows older, various risk factors starting from childhood IQ, middle aged obesity smoking, hypertension, elevated cholesterol and mid-life diabetes to stroke and adulthood atrophy cause elderly dementia (Mitran et al., 2013). Studies performed on elderly individuals have shown that it is harder to differentiate between a normal aged brain and a brain

affected by dementia as people grow older. Cerebral atrophy is the only objective and quantifiable diagnostic criterion still applicable in both elderly (>75 years of age) and young (<75 years of age) individuals (Mitran et al., 2013). It is well known that dementia is predominantly a sporadic age-related disorder, and hereditary mutations are the cause of just fewer than 5% of all cases. The risk of developing AD rises 14-fold between the ages of 65- 85 and affects about 47% of people over 85 years of age. The gradual loss of cognitive function is characteristics of this disorder. These patients are clinically distinguished by an impairment in short term memory that interferes with and complicates everyday life activities, followed later by impairment in other cognitive fields, such as language, rational comprehension, orientation, executive function, reasoning, actions and motor problems (Vasic et al., 2019).

(See Figure 3.)

It is clear that old age alone is the key factor in the onset of disorders of neurodegeneration. A simple concept would be that aging results in iron accumulation, which would increase oxidative stress, leading to diseases such as Alzheimer's disease and Parkinson's disease. This occurs mainly through the Fenton reaction in the development of highly reactive hydroxyl radicals that are involved in DNA, lipid, and protein damage in Figure 4 (Haughey et al., 2002).

(See Figure 4.)

Not only does iron contribute to oxidative stress in Alzheimer's disease, but it is also involved in plaque pathology and the associated oxidative damage related to plaque. This is significant because the accumulation of physiological iron in AD brain is independent of the normal increase in ferritin associated with age (Haughey et al., 2002). In summary, the role of oxidative stress relative to iron in relation to neurodegenerative disorder is important and thoroughly discussed previously by others (Haughey et al., 2002). Similarly, interesting studies indicating the role of certain pro-inflammatory cytokines (TNF-alpha) in the development of Alzheimer's disease and Parkinson's disease are also available on Figure 5.

(See Figure 5.)

Exercising, Diet, Brain Function to Prevent AD

The benefits to the brain of exercise and its cognitive functions are immense, and others have extensively reviewed them (Dishman et al., 2005; Ang. & Gomez-Pinilla, 2007; Winter et al., 2007). Recent randomized controlled trials have shown in Alzheimer's disease patient that exercise could potentially help delay the progression of the disease both directly and indirectly (Rolland et al., 2007, 2008; Lautenschlager et al., 2008). It is postulated that exercise in Alzheimer's disease patients may help clear the amyloid-beta peptide (main pathological driver) (Bates et al., 2009). The death of cholinergic neurons could be avoided and likely attenuate cognitive decline through exercise induced nerve growth factor production (Scott & Crutcher, 1994). The basal metabolism will naturally decrease with age, and it is hypothesized that this could also help to reverse some of the risk factors (such as lower testosterone) for AD with exercise.

Sometimes associated with Alzheimer's disease and Parkinson's disease, exercise may also relieve depression or depressive

mood (Peluso & Guerra de Andrade, 2005). Cerebral blood flow in seniors may also be maintained, thereby avoiding cognitive deterioration (Roger et al., 1990). Exercise induced increase in growth hormones can also play a role in promoting neuroregeneration (by increasing neural stem cell) (Blackmore et al., 2009). The effect of exercise from animal research are even more surprising. It has been reported that exercise may offer assistance with learning and memory (Winter et al., 2007). There is additionally proof to point that exercise could probably boost neurogenesis (Aberg et al., 2008; Naylor et al., 2008; VanPraag, 2008; Wu et al., 2008). Exercise, in short, is beneficial in lowering the risk of Alzheimer's disease. There are, however, still several differences between biological discoveries and the translation of that understanding into clinical and community circumstances (Garraux, 2008).

It has been recently documented that a multitude of systemic effects, including anti-inflammatory, oxidative stress reduction, promotion of synaptic plasticity and the induction of neuroprotective factors in the brain, can result from caloric restriction and exercise (Gillete-Guyonnet & Velles, 2008; Hofer et al., 2008). As a result, these molecular pathways work to increase the efficacy of free radicle neutralization in order to reduce factor of oxidative load associated with age and diseases. On another note, even though the neurological mechanism is still unclear, dietary restriction may also facilitate adult neurogenesis and thus prevent Alzheimer's disease (Levenson & Rich, 2007). It could also help the brain work by choosing a diet enriched with omega 3 fatty acids (Sinclair et al., 2007; Tassoni et al., 2008). In short, hormesis may occur when protecting the body from aging and neurodegeneration (Gomez- Pinilla, 2008; Mattson, 2008 a, b), and in this analysis we suggest that exercise combined with diet/caloric restriction may be the way of neurogenesis.

(See Table 1.)

Treatments of AD

Stem cells can be a real substitute to brain regeneration in neurodegenerative disorders such as dementia, because they are capable of being unified into a degenerative environment (the differentiation potential towards site appropriate phenotypes) and releasing neurotrophic cytokines (Mitran et al., 2013).

In neuronal self-healing some natural substances are also used. Among them, Cerebrolysin stand for a therapeutic strategy for neurological disorders like dementia, stroke and traumatic brain injury. It is a peptide preparation imitating the action of neurotrophic variables. Studies in vitro (biochemical and cell cultures) or in vivo (on animal models) manifest a lot of benefits of the natural drug as from pig brain extract (Mitran et al., 2013).

Stem cells (SCs) are undifferentiated cells capable of giving rise to any human body cell line. The new organism consists entirely of embryonic stem cells (ESCs) at the beginning of embryonic development, forming the inner cell mass of the blastocyst. SCs differentiate into somatic cells that constitute the body during the pre and postnatal development. As a result, only a limited number of adult SCs involved in the regeneration of damaged or physiologically degrading tissues (blood cells, epithelial cells, etc. are present in an adult organism (Bobkova et al., 2020).

(See Figure 6.)

Bone marrow, adipose tissue, tooth pulp, peripheral blood, and tissues acquired after natural childbirth or caesarean section (umbilical cord blood, placental tissue, Wharton's jelly) are the most widely used and available sources of autologous adult SCs in humans. Autologous cells of the patient are employed in therapy commonly since their use presents the least risk of complications. From the therapeutic point of view, the most common sources for regenerative medicine and tissue replacement after injury or disease are ESCs, fetal neural stem cells (fNSCs), adult allogeneic MSCs from the bone marrow, and hair follicle pluripotent stem cells (hfPSCs) (Bobkova et al., 2020).

(See Figure 7.)

Irrespective of the various etiopathogenic mechanisms involved in Alzheimer's disease, the neurogenic and synaptic failure are a general feature of AD that play a pivotal role in cognitive dysfunction (Kazim & Iqbal, 2016).

Neuro-regeneration Targeting Interventions for Memory Impairment

Memory decline and dementia are the result of synaptic/neuronal deficits. The intrinsic ability of neuroregeneration in the mammalian brain has been shown to be very restricted, even after eliminating several known inhibitory signals (Sun & Alkon, 2019).

Nonpharmacological Intervention

– Environmental Enrichment and Exercise

Growing evidence suggests that regulating neuronal activity might be an approach for enhancing intrinsic neuronal growth ability. The least invasive approaches that improve endogenous neuroregeneration are environmental enrichment and physical activity (Sun & Alkon, 2019).

– Brain Stimulation

Some hopes for symptomatic relief in AD has been created by brain stimulation. Brain stimulation thus has risks of interfering with memory functions, ensuing in adverse cognitive reaction (Sun & Alkon, 2019). Memory loss is the main symptom of dementia-related disorders, like the common Alzheimer's disease (AD). To date, pharmacological treatments for AD have minimal and short-lasting effects. Therefore, researchers are studying novel therapies such as deep brain stimulation (DBS) to treat or mitigate memory impairment and to reduce or stop the progression of it. Clinical and preclinical investigations have been performed and incitements of the fornix, entorhinal cortex and core basalis of Meynert have been done. The results of these studies depict that DBS has the potential to increase memory functions in patients and animal models. Release of particular neurotransmitter and neuroplasticity may be among the mechanisms underlying memory enhancement. DBS may also be disease modifying, some authors say. Regardless, the end that DBS can be utilized in the treatment of AD is as yet untimely and the field will stand by the consequences of on-going clinical preliminaries.

Pharmacological Interventions

– Antioxidants

In Alzheimer's disease pathology, synaptic dysfunction and cognitive impairment, Oxidants can play an important role.

Resveratrol (3,5,4′-trihydroxy-trans-stilbene),

Curcumin, (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)

– Anti-inflammatory Agents

There is ample evidence that anti-inflammatory therapies can produce anti-AD impacts in AD models (Sun & Alkon, 2019).

– Histone Deacetylase (HDAC) Inhibitors

Histone de-acetylation has been implicated in contributing to the AD-like phenotype

CONCLUSION

The high prevalence of neurodegeneration is found in older populations, further jeopardizing the restoration of an injured brain. Numerous disease conditions may cause dementia; however, the most common one is Alzheimer's disease. Alzheimer's disease is an incurable and debilitating chronic progressive neurodegenerative disorder. New therapeutic approaches to dementia in the elderly may be seen by elucidating the cellular and molecular basis for neurodegeneration and neuroregeneration in the aged brain. The development of novel and successful brain self-repair treatments, using either molecular mRNA expression regulation, stem cell therapy, neurotrophic factors or even drugs derived from natural sources, would potentially contribute to better dementia treatments in the elderly. Neuroregeneration is a relatively new idea comprising neurogenesis, neuroplasticity, and neurorestoration – implantation of viable cells as a therapeutic approach. Stem cell therapy bares tremendous potential for the treatment of AD. Pre-clinical analyses yielded positive results and paved the way for clinical trials.

In summary, numerous epidemiological studies have found out that exercise is effective in lowering the risk of most age-related diseases such as Alzheimer's disease. The neuregeneration therapy and treatment are more effective for Alzheimer's disease. Treatments like environmental enrichment and exercise, diet and nutrition, brain stimulation, antioxidants, anti-inflammatory agents can reduce Alzheimer's disease.

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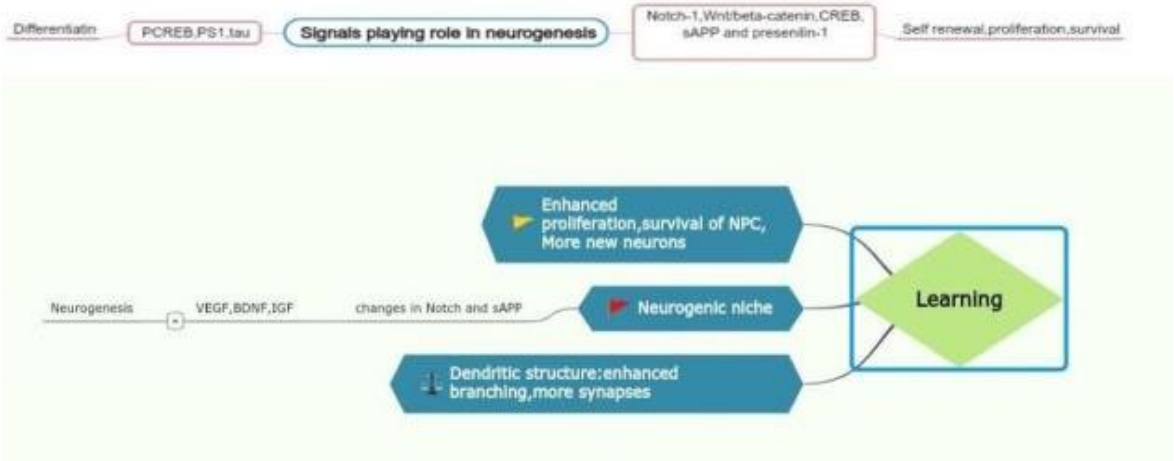
APPENDIX

Figure 1.

Common mechanisms of neurogenesis and Alzheimer's disease and the inference for learning: (A) Signals that play a role in neurogenesis, are implicated in Alzheimer's disease such as Notch-1, Wnt/β-catenin, CREB, sAPP, tau, and presenilin-1. (B) Changes in the neurogenic niche after learning comprise changes in Notch and sAPP, enhanced expression of neurotrophins such as VEGF, BDNF and IGF that enhance angiogenesis and support the neurogenic niche, contributing to increased neurogenesis. Up-regulation by neural progenitor cells and neurons of CREB signaling can promote NPCs survival and maturation. Presenilin-1 and APP can mediate increased dendritic branching of mature neurons and synaptic plasticity. In Alzheimer's disease, the factors mediating these processes are dysfunctional or compromised suggesting that hippocampal function in Alzheimer's disease may be affected by defective neurogenesis (adapted from Hollands, Bartolotti & Lazarov, 2016).



Figrue2.

Therapeutic and translational capability of neurogenesis. Methods for upgrading neurogenesis incorporate noninvasive, environmental tweaks like cognitively complex exercises and exercse, just as molecular intercessions like antidepressants, favorable to neurogenic small particles, chemicals or synapses, or different controls of the neurogenic pathways, while readouts of human neurogenesis are normally done in post-mortem tissue utilizing radioactive isotopes or investigation of neurogeneic cell markers, imaging methods, for example, fMRI, or blood biomarkers will offer non-intrusive roads to decide neurogenesis during life. (adapted from Hollands, Bartolotti & Lazarov, 2016).

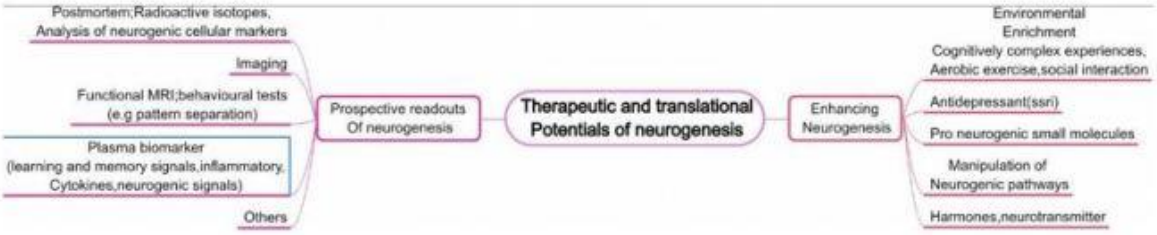


Figure 3.

AD's multifactorial existence and the presence of many different mechanisms of etiopathogenism. Familial early-onset AD triggered by APP, PS1 or PS2 mutations account for fewer than 1% of AD cases, which accounts for the remaining >99% of AD cases are largely unknown to date. Furthermore, it is hypothesized that aging alongside gene- environment interaction also contributes to this type of AD. Both types of AD contribute to amyloid plaques, neurofibrillary pathologies, synaptic dysfunction and neurodegeneration and eventually to cognitive impairment (adapted from Kazim & Iqbal, 2016).

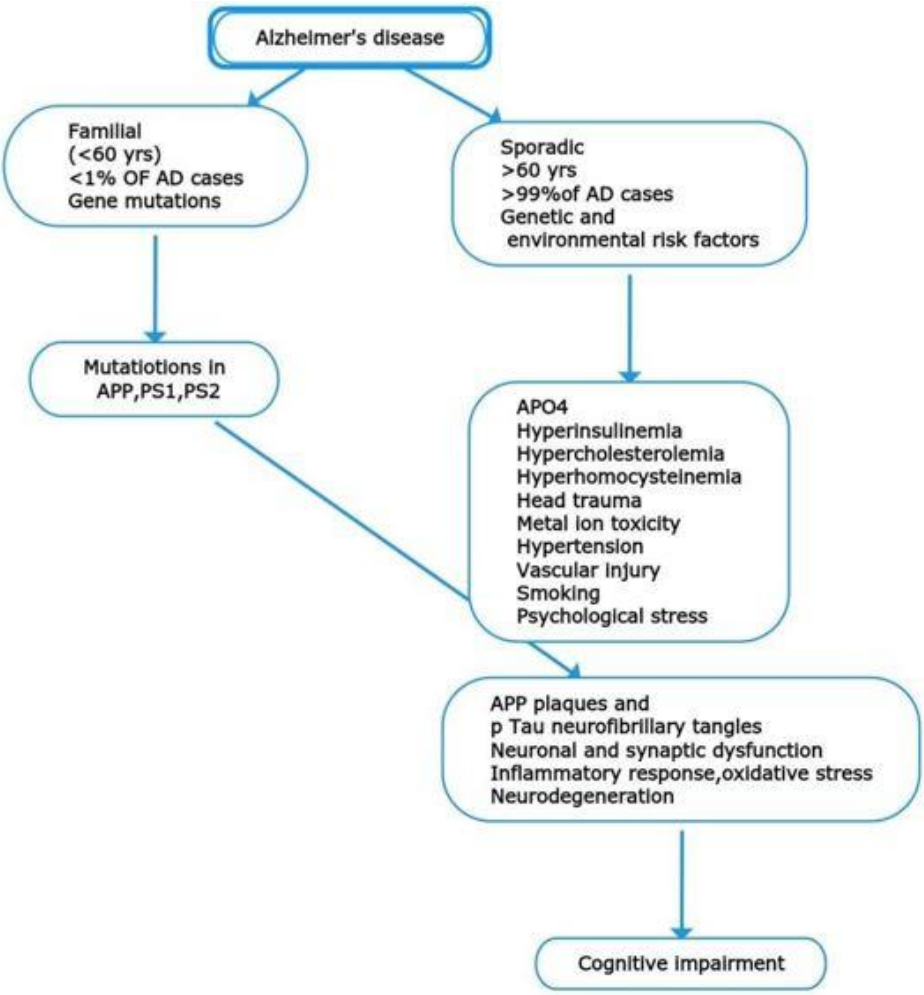


Figure 4.

Aging results in iron accumulation, which increases oxidative stress and thereby induces diseases such as AD and PD. This happens primarily through Fenton reaction in the development of the highly reactive hydroxyl radicals, which are involved in DNA, lipid and protein damage (adapted from Ang, Tai, Lo, Seet & Soong, 2010).

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\bullet}OH$

$Fe^{3+} + O_2^{\bullet-} \longrightarrow Fe^{2+} + O_2$

$H_2O_2 + O_2^{\bullet-} \longrightarrow OH^- + {}^{\bullet}OH + O_2$

Fenton reaction. This involves the conversion of iron (II)(Fe^{2+}) to iron (III) (Fe^{3+}) through the reaction with hydrogen peroxide (H_2O_2). Hydroxyl radical ($^{\bullet}OH$) is generated as a by-product. Additonally, in the presence of superoxide anion ($O_2^{\bullet-}$), Fe^{3+} can be converted back to Fe^{2+}, which in turn can go through another cycle of reaction with H_2O_2 to generate more $^{\bullet}OH$. Besides, $^{\bullet}OH$ could be generated through the reaction between H_2O_2 and O_2.

Figure 5.

Along with main genetic/environmental factors, salient signs of disease are seen here. The overlaps were purposely intended to imply a potential contribution to both scenarios by the same element (adapted from Ang, Tai, Lo, Seet & Soong, 2010).

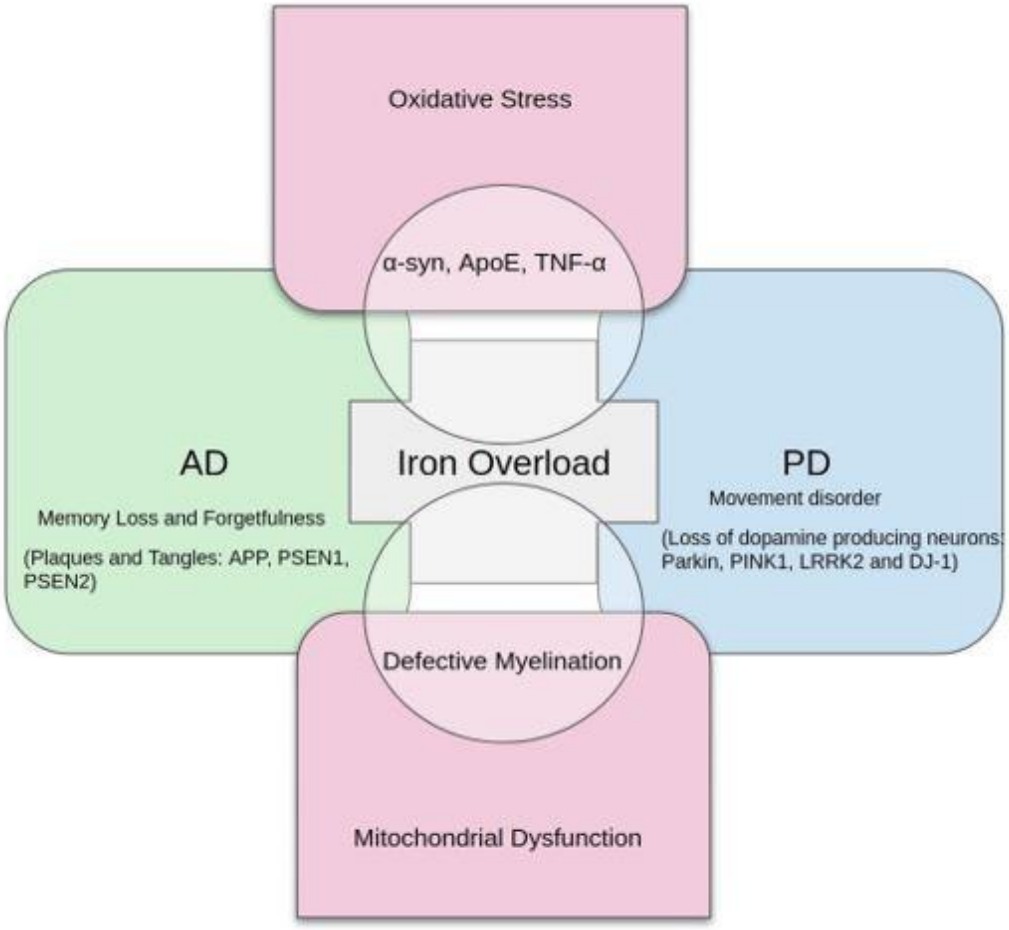


Table 1.

The nervous system is primarily made up of different cell types, neurons and glial cells. Microglia and glial cells, namely oligodendrocytes, astrocytes and progenitor cells (polydendrocytes, NG2 glia) and neurons can play an important role in AD pathogenesis, induced by their roles in neuroprotection, CNS homeostasis maintenance (ion concentration, neurotransmitter, etc.) and the brain immune system (adapted from Vasic, Barth & Schmidt, 2019).

Cellular system	Physiological system	Involvement in AD
Microglia	Cognitive function, healthy brain preservation, attack and removal of pathogens, and detritus, secretion of tissue rebuilding factors, synaptic remodeling	Involved in the generation of neuro-inflamation, imbalance of AB peptide homeostasis, decrease of phagocytic activity, release of pro-inflammatory neurotoxins and cytokines/chemokines
Astrocytes	Interactions with neurons by releasing and recycling glio-transmitter, control iron hemeostasis, energy metabolism, synaptic remodeling and the modulation of oxidative stress leading to control of neurotransmission, synaptic plasticity and the modulation of cognitive functions involved in the degradation of AB peptides	Changes in intra-and extracellular degradation of AB peptides, release of cytokines and chemokines, expression of ApoE, formation of hyperphoshorylated tau protein
Oligodendrocytes	Form together with myelin lipid layers the envelope of the neuronal axons	Specific morphological changes during AD progression, deterioration in myelin integrity and axonal destruction, killed by AB peptides
NG2-glia	Oligodendrocyte precursor cells	AB peptides-induced inhibition of wnt signaling pathway results in an inhibition of the differentiation og NG2-glia
Neurons	Expression of a large number of molecules for protection against inflammatory attacks and induction of neurological disorders	Formation of intracellular neurofibrillary tangles by hyperphosphorylated tau protein, impaired axonal transport of mitochondria resulting in energy dysfunction, generation of reactive oxygen and nitrogen species
Mitochondria	ATP synthesis, reaction to different energy demands by balanced fission and fusion processes and directed transport along axons, protection against ROS damage by elimination of defective constituents	Aggregation of hyperphosylated tau in neurofibrilliary tangles, perinuclear mis-localization resulting in ATP depletion, synaptic dysfunction, oxidative stress

Mitophagy	Degradation of organelles, proteins and lipids mediated by membranes, vesicles and lysosomes, essential for organelle turn-over, synaptic plasticity, anti-inflammatory function in glial cells, oligodendrocyte development, and the myelination process	Dysregulation leading to changes in the expression of several autophagy genes resulting in reduced energy levels, increased ROS production and impaired neuroplasticity
Endocytic processes	Internalization of materials from the cell surface by clathrin- dependent and clathrin- independent pathways, using flotillins or caveolines as the main proteins, as well as the protection against the processing of APP and AB toxicity.	Only a few data available, volume of total endosomes increases, enhanced levels of several endocytic enzymes
Mitochondria	ATP synthesis, reaction to different energy demands by balanced fission and fusion processes and directed transport along axons, protection against ROS damage by elimination of defective constituents	Aggregation of hyperphosylated tau in neurofibrilliary tangles, perinuclear mis-localization resulting in ATP depletion, synaptic dysfunction, oxidative stress
Mitophagy	Degradation of organelles proteins and lipids mediated by membranes, vesicles and lysosomes, essential for organelle turn-over, synaptic plasticity, anti-inflammatory function in glial cells, oligodendrocyte development, and the myelination process	Dysregulation leading to changes in the expression of several autophagy genes resulting in reduced energy levels, increased ROS production and impaired neuroplasticity
Endocytic processes	Internalization of materials from the cell surface by clathrin- dependent and clathrin- independent pathways, using flotillins or caveolines as the main proteins, as well as the protection against the processing of APP and AB toxicity.	Only a few data available, volume of total endosomes increases, enhanced levels of several endocytic enzymes

Figure 6.

he advancement of stem cell therapy for Alzheimer's disease. Patients with AD or healthy donors or in the case of ESCs, the blastocyst can be the source of multiple forms of stem cells that can be used for treatment development. Different processes, such as differentiation, genetic modifications, drug screening or testing on mice and other cells may further include stem cells. Eventually stem cells enter patient with AD and are used for therapeutic purposes (adapted from Vasic, Barth & Schmidt, 2019).

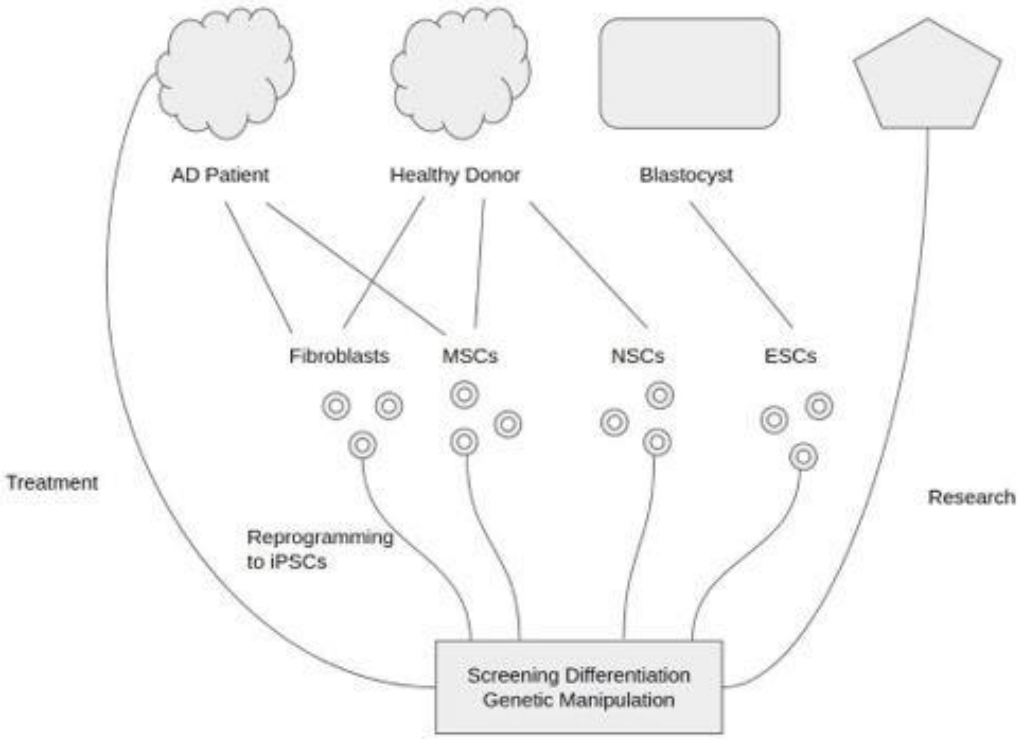


Figure 7.

In order to cure AD, there are a growing number of clinical trials using stem cell therapies, and most of them are still in progress. The principles of treatment involves the ability of transplanted stem cell to transform into damaged neuronal and glial cells, to function in a paracrine manner by secreting neurotrophic and neuroprotective agents, and to activate mechanism of endogenous repair. Due to easy harvesting, intravenous transplantation ability, lack of immune response and ethical concerns, the MSC is the most used type of cell for this purpose. Comparison between different types of stem cells are depicted in this figure (adapted from Vasic, Barth & Schmidt, 2019).