Enhancement of neural regeneration as a therapeutic strategy for Alzheimer's disease (Review)

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Abstract. Alzheimer's disease (AD), the most common cause of dementia worldwide, has gradually become a global health concern for society and individuals with the process of global ageing. Although extensive research has been carried out on AD, the etiology and pathological mechanism of the disease are still unclear, and there is no specific drug to cure or delay AD progression. The exploration of enhancing nerve regeneration in AD has gradually attracted increasing attention. In the current review, the existing therapeutic strategies were summarized to induce nerve regeneration which can increase the number of neurons, and improve the survival of neurons, the plasticity of synapses and synaptic activity. The strategies include increasing neurotrophic expression (such as brain-derived neurotrophic factor and nerve growth factor), inhibiting acetylcholinesterase (such as donepezil, tacrine, rivastigmine and galanthamine), elevating histone deacetylase levels (such as RGFP-966, Tasquinimod, CM-414 and 44B), stimulating the brain by physiotherapy (such as near-infrared light, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation) and transplanting exogenous neural stem cells. However, further evaluations need to be performed to determine the optimal treatment. The present study reviews recent interventions for enhancing adult neurogenesis and attempts to elucidate their mechanisms of action, which may provide a theoretical basis for inducing nerve regeneration to fight against AD.

Contents

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is a central neurodegenerative disease characterized by progressive cognitive impairment and memory loss. The main pathological features include intracellular neurofibrillary tangles (1) and extracellular β-amyloid (Aβ) peptide aggregation (2) to form senile plaques. These pathological changes lead to clinical manifestations characterized by memory loss, impairment of abstract thinking, numeracy deficits, and changes in personality and behavior (3). According to previous studies, the pathogenesis of AD mainly includes the following: Abnormal accumulation of Aβ (4), τ-protein hyperphosphorylation (5), neuroinflammation (6), cardiocerebral cascade (7), cholinergic deficiency (8), excitatory amino acid toxicity (9). At present, there is no treatment to cure or delay the process of the disease. However, with the increasing number of patients with AD, AD has become one of the main medical and health societal issues. To address the lack of effective drugs and the failure of continuous clinical trials, the current research focus is on therapeutic strategies for inducing the regeneration of neural stem cells (NSCs). In recent years, research on promoting targeted neural regeneration has received increasing attention. Therefore, the current review is focused on the mechanisms of induced nerve regeneration in the treatment of AD.

2. Role of nerve regeneration in restoring cognitive performance in AD

Neural regeneration is the process of generating new neurons or restoring neuronal structure, which mainly refers to the proliferation and differentiation of neural progenitor cells, and the synaptic plasticity of neurons against memory disorders

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and the ageing-related decline of learning and memory (10). In 1965, Altman and Das (11) first demonstrated that new neurons could be generated in the adult mammalian brain. Since then, continuous studies have found that nerve regeneration in the brains of adult mammals mainly occurs in two regions, namely, the subgranular zone in the dentate gyrus of the hippocampus and the subventricular zone (12,13). Nerve regeneration may also occur in other brain areas, such as the neocortex (14) and striatum (15). However, neurogenesis in these areas seems to occur at lower levels. To explore whether neurogenesis in humans lasts a lifetime, Tobin *et al* (16) examined the brains of 18 cadaver donors with a mean age of 90.6 years in 2019. Among them, not only proliferating neural precursor cells (Nestin$^+$/PCNA$^+$), undifferentiated neural stem cells (Nestin$^+$Sox2$^+$) and proliferating neural stem cells (Nestin$^+$/Sox2$^+$/Ki67$^+$), but also newborn immature neurons [Doublecortin (DCX)$^+$/PCNA$^+$], were found in the brains of patients with AD, which indicated that hippocampal neurogenesis persisted in the aged and diseased human brain (16). In addition, the study found a clear association between the number of newborn immature neurons and the cognitive scores of these donors. The more DCX$^+$/PCNA$^+$ cells that are produced, the more cognitive performance is improved, suggesting that the number of neurons is positively associated with cognitive function (16). The level of cognitive function also depends to some extent on the integrity and transmission efficiency of synapses. Synapses are the sites where functional connections form between neurons, and they are also the key places for information transmission. Synapses are structurally unstable and dynamic, which can mean that they are susceptible to nutrient levels such as those affected by brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), diseases such as AD and other factors such as inflammation and oxidative stress. An increasing number of studies have shown that the loss of synapses in the hippocampus and neocortex is an early symptom of AD and one of the main causes of cognitive dysfunction (10,17). Synaptic damage is one of the most important causes of cognitive decline in AD. Therefore, inducing nerve regeneration might fundamentally treat cognitive dysfunction in AD. In recent years, research on nerve regeneration has been extensive, but generally, it has aimed to solve two main issues: How to replenish missing or damaged neurons, and how to re-establish neural connections. In various transgenic (Tg) rodent models, nerve regeneration ability could be improved by external interventions such as treatment with different types of drugs such as escitalopram, trodusquemine, agomelatine, silibinin, esculentoside A and butyrate (18-23), the transplantation of human NSCs (hNSCs) (24,25) and electrical stimulation (26), which have been proven to increase the number of neuronal precursor cells, and ameliorate the degree of τ-phosphorylation and AD-related memory loss. The effects of different external interventions on inducing nerve regeneration in various Tg rodent models in recent years are summarized in Table I. New mature neurons induced by external interventions from the migration of existing NSCs in certain regions or the generation of NSCs can replenish the missing or damaged cells, which contributes to restoring part or even all of the neural network (18-26).

In conclusion, cognitive function is closely related to the number of neurons and synaptic integrity. Therefore, the recovery of damaged neurons and increase in the number of neurons induced by nerve regeneration is expected to improve cognitive levels, and allow more efficient treatment of AD.

3. Nerve regeneration induced by neurotrophins in the treatment of AD

BDNF-induced nerve regeneration in the treatment of AD. Among the neurotrophin family factors, BDNF is the most widely distributed in the central nervous system (CNS). BDNF mainly exists in the hippocampus, cortex and basal forebrain, and plays a key role in synaptic plasticity, neuronal survival, neuronal differentiation and neuronal development (27). Reduced levels of BDNF are associated with different categories of neurological disorders, including neurodegenerative disease, such as AD (28) and Parkinson's disease (29), neurodevelopmental disorders, such as developmental delays (30), and neurobehavioural and neuropsychiatric disorders (31), such as depression and anxiety. Studies have shown that decreased BDNF levels lead to a lack of neuronal nutritional support, resulting in the degeneration of specific neuronal populations in the basal forebrain cholinergic system in AD (32,33). With continuous studies on the role of BDNF, it has been found that BDNF has a physiological effect on the inhibition of neuronal apoptosis and the treatment of cognitive impairment, suggesting that increasing BDNF levels might be a promising target for the treatment of cognitive decline in patients with AD. When BDNF nutrient solution was injected into the medial entorhinal cortex (120 μg/side, once a day) of aged Fischer rats with cognitive degeneration, their spatial learning and memory abilities were markedly improved (34). In addition, invasive gene therapy to overexpress BDNF has been successfully demonstrated to enhance synaptic protein expression and neuronal proliferation, as well as to attenuate amyloid load in APP/PS1 transgenic mice (35). Similar conclusions were obtained when the studies were extended to non-human primates. Neuronal apoptosis in the endodermis of monkeys was induced with bilateral radiofrequency lesions in the perforant path. The monkeys were then stereotaxically injected with a lentiviral vector expressing BDNF into the entorhinal cortex. Stereological quantification revealed that the lesions of the perforant path without BDNF treatment resulted in the loss of 45.9±8.5% of neurons in layer II of the entorhinal cortex in the lateral region compared with that in intact monkeys. However, the monkeys in which lesions of the perforant path were treated with BDNF were able to maintain 85.4±7.1% of the neurons on the lesion side, and their brains continued to function normally, suggesting that BDNF can also notably prevent neuronal death in non-human primates (34). There was little correlation between BDNF levels and cognitive decline in patients with a clinical diagnosis of mild cognitive impairment. However, a high level of BDNF expression could effectively slow the rate of cognitive decline in patients with AD (36). BDNF affects neuronal plasticity by inducing neurotransmitter release (37), increasing vesicle docking and enhancing the glutamate-induced postsynaptic response (38). BDNF binds to the high-affinity tropomyosin-related kinase

Table I. Effects of different interventions on nerve regeneration in mouse models of AD.

Strain name	Age, months	Interventions	Neurogenesis assessment	Effect of intervention	(Refs.)
P301L[a]	10	Intraperitoneally injected with 1 mg/ml escitalopram[b] (10 mg/kg/day) for 4 weeks	Western blotting, immunohistochemical analysis	Markedly decrease τ phosphorylation, and increased PSD95 and PSD93	(7)
hAPP-J20[c]	4.5	Intraperitoneally injected with trodusquemine[d] for 6 consecutive weekly doses of 2.5 mg/kg	Morris water maze, whole-cell patchclamp recording	Rescue synaptic plasticity and spatial memory	(8)
APP/PS1	6	Intraperitoneally injected with agomelatine[e] (50 mg/kg/day) for 30 days	Immunohistochemical analysis for p-τ	Decrease hippocampal p-τ (T181) expression	(9)
APP/PS1	8	Administered silibinin[f] every day for 4 weeks	Daily injection of bromodeoxyuridine for 5 days	Increase the number of newly generated microglia, astrocytes, neurons and neuronal precursor cells	(10)
3xTg-AD[g]	8	Intraperitoneal treatment of either 5 or 10 mg/kg esculentoside A[h] for 8 consecutive weeks	Immunofluorescence assay, western blotting	Decrease Aβ generation, reduce the levels of oxidative stress and mitigate neuronal apoptosis	(11)
Institute of Cancer Research[i]		Administered different concentrations of sodium butyrate[j] orally for 21 days before establishing an AD mouse model	Immunofluorescence assay, behaviour test	Improve the cognitive impairments, promote differentiation into astrocytesx	(12)
P301L[a]	10	NSCs extracted from the hippocampus of wild-type C57BL/6 suckling mice were cultured and transplanted into the CA1 region of bilateral hippocampus	Behaviour test, western blotting	Reduce abnormal aggregation of τ, markedly improve short-term memory	(13)
Tg2576[k]	5-7	Bilateral intrahippocampal human NSC	Immunohistochemistry	Increase the number of of doublecortin+ cells in the dentate gyrus	(14)
Wistar rats[l]	4-5	2 and 50 Hz electroacupuncture once a day, over a course of 7 days for two courses, with a day off between courses	Electrophysiological experiments	Stably increase the population spike amplitude	(15)

[a]P301L, tauopathy model mice; [b]Escitalopram, selective serotonin reuptake inhibitor; [c]hAPP-J20, Tg mice expressing APP; [d]Trodusquemine, a protein tyrosine phosphatase-1b selective inhibitor; [e]Agomelatine, an agonist of melatonergic MT1 and MT2 receptors and a selective 5-hydroxytryptamine 2C receptor antagonist; [f]Silibinin, a flavonoid extracted from the medicinal plant *Silybum marianum*; [g]3xTg AD, APP/PS1/Tau Tg mice; [h]Esculentoside A, a neuroprotective saponin-isolated from *Phytolacca esculenta*; [i]Institute of Cancer Research, Aβ$_{25-35}$ was injected into the lateral cerebroventricular to establish a mouse AD model; [j]Sodium butyrate, a type of short-chain fatty acid; [k]Tg2576, APP Tg mice; [l]Wistar rats, AD was induced in Wistar rats by Aβ1-42 injection. AD, Alzheimer's disease; PSD-95, postsynaptic density protein 95; p-, phorsphorylated; NSC, neural stem cells; Tg, transgenic; APP, amyloid β precursor; Aβ, β-amyloid; PS1, presenilin-1.

B (TrkB) receptor, and then induces Trk dimerization and autophosphorylation (39), thus activating the downstream cascades of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) intracellular signal transduction pathways (40). Akt is phosphorylated through its interaction with PI3K and attaches to the inner surface of the plasma

membrane (41). Phosphorylated Akt terminates cell apoptosis and induces the survival of nerve cells by inhibiting the activity of the tumour suppressor gene p53 or directly blocking the activity of the apoptosis pathway (41). Under normal conditions, cytochrome c (cyt-c) exists in the lacunae between the inner and outer membrane of mitochondria, and the stimulation of apoptotic signals causes the release of cyt-c from the mitochondrial lacunae into the cytoplasm (42). Before the release of cyt-c, phosphorylated (p)-Akt regulates the activity of Bcl-2 family members and controls the release of cyt-c from the mitochondria into the cytoplasm. After the release of cyt-c, p-Akt can also modulate the components of the apoptosome and inhibit the formation of the apoptosome, thereby blocking the apoptosis pathway mediated by the mitochondria (43). Together, BDNF mediates the activity of the PI3K/Akt pathway by binding to the membrane receptor TrkB, thereby regulating cell survival and synaptic function, and making the BDNF/TrkB/PI3K/Akt signalling pathway a potential therapeutic target for neurodegeneration (44). Furthermore, the BDNF protein is a charged, yet net hydrophobic molecule with a low molecular weight, causing it to have a short half-life (t1/2) in humans, which makes it a non-ideal biological drug candidate (45). Previous studies have shown that zinc finger E-box-binding homeobox 85, a potent and full agonist of human TrkB, plays a role in neuroprotection and neurorestoration (45,46). 7,8-Dihydroxyflavone (7,8-DHF), a potent TrkB agonist, has also been shown to have therapeutic effects on AD (47). In addition, it has been demonstrated that LMDS-1, another agonist of TrkB, can improve the pathological phenotype of early AD mice by upregulating the expression of BDNF. Moreover, LMDS-1 is more effective than 7,8-DHF in alleviating the behaviour and pathological characteristics of mice with AD (48).

In conclusion, previous studies have found that the expression level of BDNF is positively correlated with the cognitive level in rats, non-human primates and humans. BDNF mainly regulates the survival of nerve cells and synaptic plasticity by triggering the BDNF/TrkB/PI3K/Akt signalling pathway, and ultimately improves cognitive ability. In addition, other TrkB agonists play a functional role in neuroprotection and cognitive function, similar to BDNF.

NGF-induced nerve regeneration in the treatment of AD. NGF is one of the earliest discovered and most well-studied nerve cell growth regulators among neurotrophic factors; it has dual biological functions of nourishing and promoting neurite growth of neurons (49). NGF also plays an important role in the development, differentiation, growth, regeneration and function of central and peripheral neurons (50). Recent studies have shown that mice lacking NGF exhibit deposits of Aβ plaques, τ-hyperphosphorylation, synaptic dysfunction and other typical pathological features of AD (51,52).

Treatment targeting NGF not only reduces pathological changes in AD but also contributes to the survival and axonal regeneration of injured neurons in AD (53). The knockout of the NGF gene resulted in a 55% reduction in basal forebrain cholinergic neurons and a 62% reduction in hippocampal cholinergic neurons in the CNS of adult mice, suggesting that NGF deficiency may be an important factor in neuron loss (54). Increasing NGF may be an effective strategy to reduce Aβ deposition and improve clinical cognitive impairment in AD. In the brain, NGF is tonically secreted in its precursor form, proNGF, which is then cleaved by the extracellular protease into mature NGF (mNGF) (55). Interfering with NGF transport or reducing NGF processing may lead to the overexpression and abnormal accumulation of proNGF and a deficiency of mNGF. mNGF is required for the growth and plasticity of cholinergic neurons (56). NGF bioactivity is mediated by binding to the high-affinity TrkA receptor and the low-affinity tumour necrosis factor neurotrophin receptor (p75NTR) on the plasma membrane (57). NGF produced by hippocampal and cortical neurons binds to TrkA and p75NTR, and then forms dimeric complexes that maintain the normal activity of neurons, suggesting that NGF maintains the normal function of neurons through the TrkA/p75NTR-mediated signalling pathway (58). In the absence of TrkA, a combination of NGF and p75NTR accelerates apoptosis by activating p53, ceramide and c-Jun N-terminal kinase pathways (59). It was found that the proNGF level in the parietal cortex of patients with AD was twice as high as that of healthy subjects, suggesting that the degeneration of cholinergic neurons in patients with AD may be associated with a deficiency of mNGF (60). After treatment with NGF, the activity of choline acetyltransferase (ChAT) in the cerebrospinal fluid of patients with AD is markedly enhanced, while the activity of ChAT in the cerebrospinal fluid is associated with cognitive function, suggesting that NGF may improve cognitive function by mediating ChAT activity (60). At present, there are animal experiments and clinical trials of NGF with different infusion modes, including direct intracerebral infusion of NGF (61), peripheral administration of NGF using nasal (62) or intraocular (63) delivery and NGF delivery using viral vectors (53,64). Although these methods have been proven to be effective, there are drawbacks such as pain, weight loss and difficulty controlling the dose. It has been found that the sustained release of NGF can be induced by redirected implantation of NGF into the basal forebrain through encapsulated cell biodelivery of NGF (NGF-ECB), in which the encapsulated cells are made from fibroblasts (65). In addition, elevated NGF can regulate the exocytosis of presynaptic terminal vesicles and induce BFCN electrochemical signalling, suggesting that high levels of NGF may alter AD-related synaptic failure and neurotransmission defects (66). NGF-ECB implantation in patients with mild to moderate AD can obviously repair the degeneration of BFCN, and reduce the rate of brain atrophy and cognitive decline; importantly, the safety of the treatment has been demonstrated (67). Furthermore, the long-term release of NGF by implanted transmitters would need to be optimized to achieve a more predictable and stable effect in the treatment of AD. In addition, agonists of TrkA neurotrophin receptors such as doxycycline (68) or NGF-mimicking drugs such as LM11A-31 (69) were reported to have NGF-like effects.

In conclusion, NGF is closely related to the proliferation, differentiation, regeneration and electrophysiological function of central and peripheral neurons. Interference with NGF transport or processing may impair the normal function of neurons. In the AD brain, targeted drug therapy or gene therapy can induce the release of mNGF or increase the expression level of NGF, and then NGF activates the NGF-TrkA signalling

pathway in neurons, which can ameliorate the issues of synaptic failure and neurotransmission defects, and ultimately improve the cognitive level of patients with AD.

4. Nerve regeneration induced by inhibitors in the treatment of AD

Nerve regeneration is induced by acetylcholinesterase inhibitors. As the 'Cholinergic hypothesis of Alzheimer's disease' was proposed by Bartus *et al* (70) in 1982, cholinergic deficiency was accepted as one of the early pathogenesis factors of AD. According to this theory, a deficiency of acetylcholine (ACh), a neurotransmitter in the synapses of neurons, is considered to be a key factor leading to cognitive dysfunction in patients with AD. ACh and Ach esterase (AChE) are two major elements in the cholinergic nervous system. AChE is a key enzyme in the hydrolysis of ACh. Both ACh and AChE are widely distributed in the CNS, and are necessary for learning and memory formation (71). At present, there are four types of AChE inhibitors (AChEIs) that are most widely used for the clinical treatment of AD, including donepezil, tacrine, rivastigmine and galanthamine (72). Although all of these drugs can inhibit the activity of AChE, they work by different mechanisms. Donepezil is a specific and reversible AChEI. Rivastigmine is a pseudoirreversible AChEI. Galanthamine is a selective, reversible AChEI. Tacrine is a non-competitive and reversible AChEi that was withdrawn in 2013 due to its hepatotoxicity (73). The effects of these drugs are different; donepezil is more active than tacrine, whereas donepezil is safe and reliable, and the first choice for the treatment of patients with mild to moderate AD, as it has fewer side effects such as nausea, vomiting, diarrhea and dizziness (74). The effectiveness of galantamine is superior to that of rivastigmine, and is second only to that of donepezil (75). Rivastigmine is a relatively effective drug for patients with advanced-stage AD (74). Clinical studies have shown that these drugs can not only delay the onset of dementia in patients with AD, but also improve mental behaviour and the ability to carry out daily living activities (75,76).

In the pathological process of AD, the activity of AChE in the brain is notably increased, which leads to the hydrolysis of ACh and the loss of cholinergic neurons. Moreover, the high levels of glutamate in the synaptic cleft of neurons activate the N-methyl-D-aspartic acid receptor, which opens Ca^{2+} channels and increases Ca^{2+} influx, leading to neuronal necrosis (77). Most AChEIs inhibit AChE activity and reduce the decomposition of ACh, which effectively protects neuronal survival and alleviates AD symptoms (78,79). Donepezil can also protect neurons from glutamate-induced neurotoxicity by directly or indirectly activating nicotinic ACh receptors (nAChRs). The combination of nAChR antagonists and donepezil markedly reduced the neuroprotective effects of donepezil, suggesting that donepezil exerts neuroprotective effects in foetal Sprague-Dawley rats by binding to nAChRs (80). Donepezil can also prevent Aβ-induced neural cell death by activating the PI3K pathway (80). The activation of nAChRs can trigger downstream PI3K and thereby catalyse the production of p-Akt, which enhances the activation of the PI3K pathway (81). In addition, it was found that the phosphorylation levels of Akt were notably increased

in astrocytes after treatment with donepezil (10 mM) for 6 h (82). The therapeutic effect of donepezil was alleviated when donepezil was used in combination with a PI3K inhibitor (30 mM) or an Akt inhibitor (1 mM), suggesting that donepezil plays a neuroprotective role in the brain through the PI3K/Akt signalling pathway (82). In summary, donepezil plays a neuroprotective role by either inhibiting AChE or activating nAChRs and their downstream PI3K/Akt pathway. It has also been shown that the neuroprotective effect of AChEI drugs is achieved by engaging in the upregulation of the antiapoptotic Bcl-2 protein. When AChEIs are combined with HA14-1, a drug that inhibits Bcl-2, the neuroprotective effect of AChEIs is weakened, suggesting that AChEIs exert neuroprotective effects by upregulating the target gene Bcl-2 (83). The different concentrations of AChEIs have various degrees of effectiveness in preventing apoptosis. Galantamine, donepezil and rivastigmine show the highest neuroprotective effects at 0.3, 1 and 3 M, respectively. With the increase in concentration, galantamine and donepezil exhibit a well-characterized U-shaped neuroprotective curve with the percentage of cell death in longitudinal coordinates. High concentrations of galantamine block nAChRs, and lead to the absence of neuroprotective effects on cell death caused by Aβ in the human neuroblastoma SH-SY5Y cell line (83).

In conclusion, AChEI drugs have been widely used in the clinical treatment of AD. One main capability of AChEI drugs is to reduce the decomposition of ACh by inhibiting AChE, and the other is to activate nAChRs and improve glutamate transport, thereby activating the PI3K/Akt pathway and upregulating the downstream target protein Bcl-2. Therefore, AChEI drugs induce the survival of nerve cells, enhance the connection between synapses and eventually attenuate AD symptoms.

Nerve regeneration induced by histone deacetylase (HDAC) inhibitors. Histone acetylation is an epigenetic modification that alters gene expression without changing the DNA sequence. HDACs catalyze not only histone deacetylation, but also a variety of non-histone protein deacetylations, maintaining the dynamic equilibrium between acetylation and deacetylation, and regulating gene expression (84). The HDAC family, composed of 18 isoforms, is divided into five groups on the basis of phylogenetic characteristics: Class I (HDAC1, HDAC2, HDAC3 and HDAC8), class IIa (HDAC4, HDAC5, HDAC7 and HDAC9), class IIb (HDAC6 and HDAC10), class III (silent information regulator 2) and class IV (HDAC11). The function of HDACs is to deacetylate the lysines on histone tails, causing the condensation and subsequent repression of chromatin (85).

HDACs are involved in chromatin remodelling, gene expression, and synaptic formation and plasticity, and have been used as targets for improving synaptic function (86). The degree of histone deacetylation is closely related to the pathological phenotype of AD. High levels of HDAC (HDAC6) expression can be seen in the hippocampus and the cortex of patients with AD (87). HDAC1 plays a role in neurodegeneration, HDAC2 participates in modulating synaptic plasticity and long-lasting changes in neural circuits, and HDAC3-11 and class III HDACs are beneficial for their neuroprotective effects (88). The loss of HDAC1

in neurons causes DNA damage and cell death, while the lack of HDAC2 in mice improves learning and memory, enhances synaptic plasticity, and increases dendritic spine density and synapse number (89). RGFP-966, a selective HDAC3 inhibitor, can increase H3 and H4 acetylation and BDNF acetylation, resulting in increased BDNF expression, reduced τ and Aβ1-42 accumulation, and improved spatial learning and memory in 3xTg-AD mice (90). In a previous study, a notable increase in HDAC4 expression was responsible for neurotoxic Aβ deposition in neuronal cells in a dose-dependent manner (91). Tasquinimod, a selective HDAC4 inhibitor, can partly rescue the expression of genes related to synaptic plasticity and neuronal memory, and shows the effect of an HDAC4-targeting treatment (92). Owing to a notable increase in HDAC6 expression in the hippocampus and cortex of patients with AD and AD animal models, HDAC6 inhibitors are being investigated for the treatment of AD (93). Moreover, a phosphodiesterase type 5 (PDE5) inhibitor was shown to markedly activate cAMP/cGMP responsive element binding, which improved the long-term potentiation mechanism following hippocampal damage in amyloid β precursor (APP)/presenilin-1 (PS1) mice. The synergistic effect of PDE5 inhibitors and HDAC enzyme (class I HDACs and HDAC6) inhibitors can be more effective in the treatment of AD, which has proven to be a potential new therapeutic approach (93). CM-414, a dual inhibitor of PDE5 and HDACs, not only reduced the levels of Aβ and p-τ in the brain, but also increased the density of dendritic spines in hippocampal neurons and alleviated cognitive deficits in Tg2576 mice (93). Furthermore, 44B, another dual compound inhibitor of PDE5 and HDACs, markedly reduced the level of hAPP by 55% and the level of p-τ proteins by 30% *in vitro*, suggesting that 44B directly inhibited hAPP and p-τ production (94). In addition, an *in vivo* study showed that 2 weeks of treatment with the dual compound inhibitor 44B (40 mg/kg) could recover partial memory impairment in elderly (16-month-old) Tg2576 mice (94).

In conclusion, HDACs are involved in synaptogenesis and cognitive function by increasing deacetylation modifications of histones or genes associated with memory such as BDNF. The synergistic effect of PDE5 and HDAC enzyme inhibitors can not only induce the acetylation of histones and synapse-related genes, but also inhibit the levels of Aβ and p-τ, which has a better therapeutic effect on AD.

5. Nerve regeneration induced by brain stimulation in the treatment of AD

In recent years, physical intervention in the treatment of AD has gradually received widespread attention. Using physical intervention to induce neurogenesis is expected to be an effective therapeutic treatment for AD. Currently, there are two major and reliable non-traumatic brain stimulations used in the clinic, namely, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).

TMS refers to the process of stimulating cortical neurons with electromagnetic fields and then activating neuronal circuits in the CNS (95), which can recover the function of synaptic transmission in the cerebral cortex, and is considered a non-invasive and painless treatment technology (96).

rTMS is the continuous administration of repetitive electromagnetic stimulation to reduce the imbalance between excitatory and inhibitory signals, thereby mediating synaptic activity and neuroplasticity (97). Previous studies showed that rTMS markedly promoted the cognitive level and language ability of patients with AD, especially patients with mild AD, indicating that treatment with rTMS could effectively improve the clinical manifestations of AD (98,99). Research suggests that rTMS has positive therapeutic effects on the nerves and psychology of patients, as assessed by a neuropsychological quantitative scale such as the World Health Organization-University of California Auditory Word Learning Test (WHO-UCLAAVLT) (98), AD Assessment Scale-Cognitive Section (ADAS-Cog) (99), Mini-Mental State Examination (MMSE) (100) and Montreal Cognitive Assessment Scale (MoCA) (99). These results suggest that rTMS improved the cognitive ability and mental behaviour of patients with mild to moderate AD. However, variations in the intensity and location of rTMS lead to different therapeutic effects. A randomized controlled trial showed that high-frequency rTMS (20 Hz) markedly improved cognitive impairment, while low-frequency rTMS (1 Hz) had no obvious effect in patients with mild to moderate AD (101). Moreover, studyhas proven that the cognitive function of patients selectively deteriorates after 10 min of low-frequency rTMS (1 Hz) (102). These results suggested that only high-frequency rTMS has a positive effect on ameliorating cognitive impairment. Research on different stimulus locations found that there was a notable improvement in the cognition and memory of patients with mild or moderate AD who received rTMS in the right or bilateral dorsolateral prefrontal cortex (DLPFC), but not in those who received rTMS in the left DLPFC (103).

tDCS is the direct use of a weak electrical current (usually 1-2 mA) to stimulate specific areas of the brain, leading to a change in resting membrane potential in neurons, and thus inducing the excitability of brain cells. The excitability of neurons was increased by the depolarization of anodic current stimulation and decreased by the hyperpolarization of cathodic current stimulation (104). The level of γ-aminobutyric acid in the motor cortex decreased after anodic current stimulation, whereas there was no change in the γ-aminobutyric acid level in the motor cortex with cathodic current or sham stimulation, suggesting that anodic current stimulation might elicit neuronal excitation by inhibiting the level of γ-aminobutyric acid (105). The experimental results showed that the expression of BDNF mRNA induced by tDCS was 9.5 times higher than that of the control group, suggesting that tDCS might be conducive to brain health by enhancing the level of BDNF (106). Clinical experimental results showed that visual recognition memory scores had increased by 8.9% when the temporal cortex of patients with AD was stimulated by tDCS for 30 min for 5 days, but these beneficial effects lasted only 1 month after the end of stimulation regimens (107). Although increasing the strength of an electric current might lead to excitatory changes in a larger area of the cortex, the highest strength clinically used is 2 mA for safety purposes. The findings of another study have suggested that increasing the strength of tDCS did not necessarily improve the curative effect, as tDCS enhanced

electrical signals only in the existing neural network and did not stimulate action potentials from the resting state of neurons (108). The therapeutic effect of tDCS depends on the current physiological state of the brain, and even increasing the intensity of electrical current cannot form a new neural network in the brain (109). Therefore, these results suggest that the therapeutic effect of tDCS might be limited in patients with advanced AD, who have a reduction in both synaptic plasticity and long-term potentiation.

Although both rTMS and tDCS can improve the cognitive function of patients with AD to a certain extent, they also have limitations. First, the electric current only reaches the cerebral cortex, and it is difficult for the current to reach the medial prefrontal cortex, insula, cingulate gyrus and other deep brain regions. Second, repeated use of rTMS may also induce epilepsy; therefore, rTMS is potentially harmful to the human body (110). rTMS stimulates a wide range of brain areas, and therefore lacks specificity and accuracy. Previously, light therapy has been gradually favoured by clinicians due to its fewer side effects and deep treatment area. Studies have shown that 1,072-nm near-infrared (NIR) light can protect immune cells by limiting the toxic effects of ultraviolet-A on them, and prevents cell apoptosis (111). After 1,072-nm NIR light treatment, the expression of heat shock proteins was markedly increased, and the levels of Aβ and p-τ protein were notably decreased (112). Furthermore, other wavelengths of light in the range from red to infrared light have also been shown to improve AD symptoms (113,114). Iaccarino et al (110) found that the treatment of AD mice with a 40-Hz light-emitting diode could enhance γ brainwaves and reduce Aβ deposition in the brain; however, the benefit lasted for only 1 week once therapy was discontinued. In addition, intermittent flickering light therapy shows much promise for mild cognitive impairment and patients with mild AD who suffer from both sleep disturbances and cognitive deficits, including memory loss, mental behavior abnormalities and a reduced ability to perform daily tasks (115). The aforementioned study showed that a 40-Hz flicker can not only increase γ brainwaves in the visual cortex, decrease Aβ deposition, and reduce both APP and p-tau protein expression in the hippocampus, but that it can also have a positive impact on the circadian rhythms of patients with AD.

In summary, as physical therapies for AD, rTMS and tDCS can improve the cognitive function of patients with AD by activating the synaptic activity of neuronal circuits in the CNS. However, the treatment effects of those electrical stimulations are transient, and the stimulations have numerous side effects. Light therapy has gradually attracted the interest of researchers. Research suggests that infrared light and wavelengths in the range from red to infrared light are effective in the treatment of AD with the advantage of having few side effects.

6. Nerve regeneration induced by the transplantation of neural stem cells with or without the administration of neurotrophins in the treatment of AD

Nerve damage and insufficient endogenous nerve regeneration in the brains of patients with AD lead to neuronal depletion and the disruption of neural circuits, ultimately causing cognitive decline (116). Although the induction of nerve regeneration has been proven to fundamentally solve the issue of neuronal loss in AD, the number of endogenous NSCs in the adult brain is limited; therefore, it is anticipated that NSC transplantation will induce nerve regeneration (117). Stem cell therapy emerged in the early 2000s and has been explored as a potential treatment for various diseases, especially neurological diseases, including AD, Parkinson's disease, Huntington's disease, multiple sclerosis and stroke (118). In recent years, successes in the culture and transplantation of NSCs have provided a new vision for brain injury repair and AD treatment (119). NSCs have the characteristics of self-renewal and multidirectional differentiation potential (120). Therefore, after NSCs are implanted into the brain, surviving NSCs migrate and differentiate into neurons and glial cells. Newborn neurons integrate into functional neural circuits, which can alleviate learning and memory disorders (121). Exogenous NSCs are mainly derived from three sources: Direct extraction from embryonic or foetal nerve tissue (122), transdifferentiation of induced multipotent stem cells (iPSCs) (123) and the differentiation of mesenchymal stem cells (MSCs) (124). Some issues are encountered after the transplantation of NSCs extracted from embryonic or foetal nerve tissue, such as immune rejection and teratomas, and these problems, along with various ethical issues, limit the application of these NSCs in vivo. iPSCs are induced by the transduction of four reprogramming factors, Qct3/4, Sox2, Klf4 and c-Myc, in the dermal fibroblasts of the patient (125). NSCs originating from iPSCs lack ethical and histocompatibility problems, but there are still issues such as a low induction rate and the risk of triggering tumours (126). MSCs are derived from bone marrow, umbilical cord, foetal blood and adipose tissue. MSCs have the ability to differentiate into different tissue types and cells, such as nerve cells, osteocytes and cardiomyocytes. The advantages of MSCs are their wide range of sources, easy isolation and culture, and lack of ethical issues and immune rejection, but they also have issues such as difficulty differentiating into functional neurons in vivo (127).

A large number of studies have confirmed that the transplantation of exogenous NSCs can induce nerve regeneration (128-130), but the mechanism is not fully understood. Studies have found that exogenous NSCs transplanted into the brain not only have the role of replacing lost and injured neurons, but also have the auxiliary role of secreting neurotrophic factors to improve nerve regeneration and immunity (131,132). Secreted neurotrophins play important roles in the proliferation, survival, migration and differentiation of NSCs, thereby participating in neuroprotective and repair functions (132). However, there are still existing issues with the low survival rate and neuronal differentiation rate of transplanted NSCs due to the harsh environment in the brain (133). Both BDNF and NGF are conducive to neuroprotection and the differentiation of endogenous or exogenous NSCs into neurons. Therefore, a combined method of BDNF and NSCs or NGF and NSCs for the treatment of AD has been explored. Intracerebral injection is not ideal for this combined method due to the short half-life of BDNF and NGF. Therefore, a nano-delivery system of BDNF or NGF

encapsulated by liposomes, polymer micelles or nanoparticles could be used to establish a long-term, continuous, slow-release and controlled drug delivery mode. Although some results have been obtained with this system, it is still in the animal phase of research testing, and a clinical application is thus lacking (134,135). There is a double therapeutic effect for gene therapy using NSCs as a carrier. Exogenous genes for BDNF or NGF are transfected into NSCs, and BDNF and NGF are thus continuously overexpressed with the proliferation of NSCs. On the one hand, BDNF and NGF are widely expressed during cell migration. On the other hand, the expression of BDNF and NGF contributes to promoting the differentiation of NSCs into neurons (136,137). Exosomes (EXOs) are one of the smallest extracellular vesicles released by cells. Transplanted exogenous MSCs can secrete EXOs to regulate the pathological microenvironment and neural plasticity, indicating that EXOs are involved in nerve repair and regeneration (138). The aforementioned study found that NSCs derived from human iPSCs secreted EXOs, which could reduce the inflammatory response, ameliorate oxidative stress and facilitate NSC differentiation, suggesting that NSC-derived EXOs could be used as a supportive adjuvant for NSC transplantation (139). Another study found that induced neural progenitor cells (iNPCs) from mouse fibroblasts and astrocytes abundantly released EXOs, which could promote the proliferation of neural progenitors and release of growth factors via activating the downstream extracellular signal-regulated kinase pathways, indicating that iNPC-derived EXOs played a critical role in functional rehabilitation of brain lesions (140). Moreover, the combination of exogenous NSCs with induced EXOs could alleviate the injury of brain tissue, and promote the recovery of motor function, suggesting that NSCs together with EXOs have potent therapeutic effects in neurological disorders (139). Furthermore, the involvement of microRNAs (miRNAs/miR) in biological activities, including cell growth and metabolism, has been well documented. EXOs have been used as novel biological vehicles to transfer different miRNAs, and the delivery of EXO-mediated miRNAs had an effect on treating neurological diseases (141). miR-21a is enriched in EXOs at high levels, and has key roles in the generation of neurons and mediating the neurogenic potential of EXOs (138). A One study demonstrated that EXOs with miR-21a overexpression had a greater capacity for the promotion of neuronal differentiation and the inhibition of gliogenesis, indicating that EXOs may achieve a therapeutic effect in neurogenesis promotion via the transference of miR-21a (138). miR-455-3p was found to have protective effects on the regulation of APP, levels of amyloid-β, mitochondrial biogenesis and dynamics, synaptic activity and the viability or apoptosis of the cell (142). EXOs released from MSCs alleviated hippocampal neuronal injury through transferring miR-455-3p (143). Injecting miR-133b EXOs preserved neurons and promoted the regeneration of axons (144), and EXOs harvested from miR-133b-overexpressing MSCs were shown to improve neural plasticity and functional recovery (145), suggesting that the transfer of EXO-mediated miR-133b represents a novel therapeutic approach for the treatment of neurological diseases. An animal study indicated that transplantation of NSCs could protect basal forebrain cholinergic neurons and restore synaptic impairment, eventually leading to improvements in learning and memory functions in APP/PS1 Tg mice (146). Stem cell therapy for human subjects with AD has been conducted since 2011. In a phase I clinical trial in Korea, 9 patients with mild to moderate AD were studied to assess the safety and dose-limiting toxicity of a stereotactic brain injection of human umbilical cord blood-derived MSCs (147). There were no serious adverse events, such as fever, during the follow-up period of 24 months (147). Despite this lack of adverse events, the feasibility and safety of stem cell therapy need to be evaluated further in larger trials.

In conclusion, transplanted NSCs can not only directly replenish lost neurons, but also indirectly ameliorate the pathological environment by secreting neurotrophic factors or EXOs, which affect the survival, proliferation, differentiation and synaptic density of neurons. Treatment with BDNF combined with NSCs or NGF combined with NSCs has been proven to efficiently induce nerve regeneration, the level of which is better than that with NSC transplantation alone. However, in clinical applications, issues with brain mechanical injury, graft location, efficacy and safety are still encountered in NSC transplantation.

7. Conclusions

According to the World Alzheimer Report 2021 (148), the total estimated annual worldwide cost of dementia is ≥1.3 trillion US dollars, and the figure is forecast to rise to 2.8 trillion US dollars by 2030. There is no efficacious drug that can halt AD progression. The high cost and limited efficacy of AD treatment have caused a burden on numerous patients with AD and their families. Therefore, it is necessary to find an effective and low-cost therapeutic strategy. Inducing neuronal regeneration could improve synaptic plasticity and functional recovery in patients with AD. There are various external interventions that accelerate nerve regeneration, and they have been proven to alleviate the pathological symptoms and memory disorders of AD to a certain extent, but there are still issues to be solved.

Although nerve regeneration was first proven to exist in the mammalian CNS in the 1960s (11), the enhancement of nerve regeneration as a treatment strategy for AD has been gaining traction only in recent years. A growing number of studies have shown that inducing nerve regeneration can fundamentally improve the self-care ability and cognitive impairment of patients with AD (103,107). However, inducing nerve generation is still a difficult, yet key point of intervention methods in the clinical treatment of diseases. Previous research in AD has shown that endogenous nerve regeneration can be improved by increasing the expression levels of BDNF and NGF, inhibiting AChE, activating nAChRs, increasing acetylation modifications of histone and memory-related genes such as BDNF, increasing the synaptic activity of neuronal circuits by electrical stimulation, and transplanting exogenous NSCs (Fig. 1). Currently, there is no clear conclusion on the therapeutic effect of different interventions due to the lack of comparison and rating scale evaluations. Moreover, the conclusions on interventions are mostly based on the results of animal experiments, and the
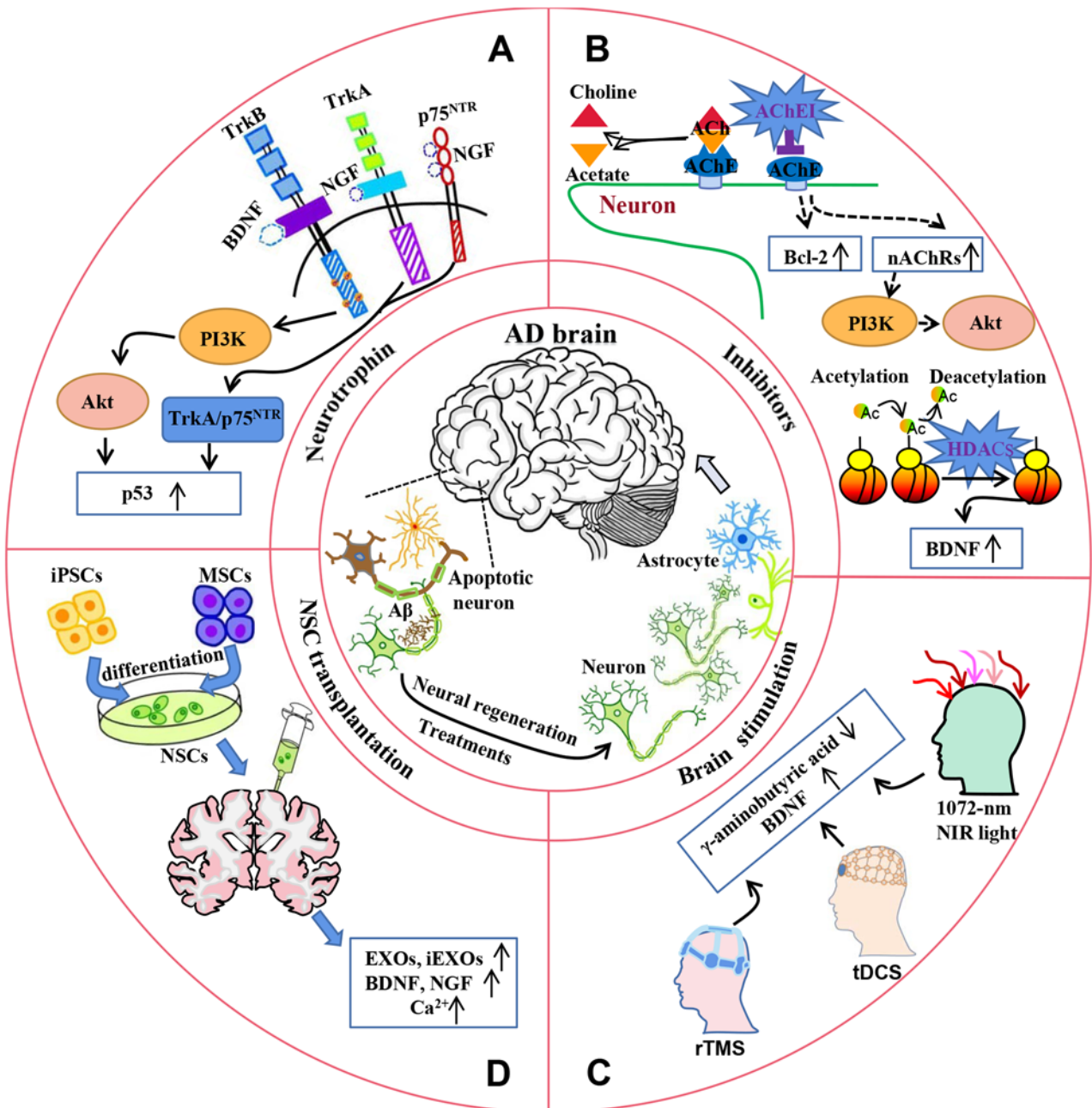
Figure 1. Different interventions enhance nerve regeneration for the treatment of AD. The quarter labeled 'A' shows nerv.sse regeneration induced by neuro-trophins in the treatment of AD. BDNF mediates the activity of TrkB/PI3K/Akt signalling pathway to regulate the survival of nerve cells and synaptic plasticity, marking it as a potential therapeutic target for neurodegeneration. NGF triggers the activity of the NGF-TrkA or NGF-p75NTR signalling pathway to maintain the normal activity of neurons, which can ameliorate the problems of synaptic failure and neurotransmission defects in patients with AD. The quarter labeled 'B' shows nerve regeneration induced by inhibitors in the treatment of AD. AChEI drugs, on the one hand inhibit AChE activity and reduce the decomposition of Ach, but on the other hand activate nAChRs and improve glutamate transport, thereby activating the PI3K/Akt pathway and upregulating the downstream target protein Bcl-2, and therefore inducing the survival of nerve cells, enhancing the connection between synapses. HDAC enzyme inhibitors increase acetylation modifications of histones and the expression of BDNF genes, which have a better therapeutic effect on AD. The quarter labeled 'C' shows nerve regeneration induced by brain stimulation in the treatment of AD. rTMS, tDCS and 1072-nm NIR light raise the synaptic activity of neuronal circuits in the brain via an increase in γ-aminobutyric acid and BDNF. The quarter labeled 'D' shows nerve regeneration induced by the transplantation of neural stem cells in the treatment of AD. Exogenous NSCs, iPSCs or MSCs are transplanted into the diseased brain region, which not only have the role of replenishing lost neurons, but also have the auxiliary role of secreting neurotrophic factors such as BDNF and NGF or EXOs and iEXOs to improve nerve regeneration. AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase B; PI3K, phosphatidylinositol 3-kinase/protein kinase B; NGF, nerve growth factor; p75NTR, neurotrophin receptor; AChE, acetylcholine; AChEI, acetylcholine esterase; nAChR, nicotinic acetylcholine receptor; HDAC, histone deacetylase; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; NSCs, neural stem cells; iPSCs, induced pluripotent stem cells; MSC, mesenchymal stem cells; EXOs, exosomes; NIR, near-infrared.

clinical therapeutic effects need to be further confirmed. Furthermore, physical therapies such as rTMS, tDCS and light therapy show a curative effect, but also have side effects on the human body, and the optimal stimulation intensity and duration need to be further investigated. Therefore, further studies are needed to determine the effectiveness of different

interventions and elucidate the mechanisms for interventions inducing nerve regeneration. In addition, the combination of interventions with different modes of action, such as chemical stimulation and physical stimulation, may be a more robust and effective treatment plan.

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LL conceived and planned the article. JG drafted the manuscript, drew the figure and created the table. JG and LL carried out the literature review, and contributed equally in revising the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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