

Review

Skin-brain axis in Alzheimer's disease - Pathologic, diagnostic, and therapeutic implications: A Hypothetical Review

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ABSTRACT: The dynamic interaction between the brain and the skin is termed the 'skin-brain axis.' Changes in the skin not only reflect conditions in the brain but also exert direct and indirect effects on the brain. Interestingly, the connection between the skin and brain is crucial for understanding aging and neurodegenerative diseases. Several studies have shown an association between Alzheimer's disease (AD) and various skin disorders, such as psoriasis, bullous pemphigoid, and skin cancer. Previous studies have shown a significantly increased risk of new-onset AD in patients with psoriasis. In contrast, skin cancer may reduce the risk of developing AD. Accumulating evidence suggests an interaction between skin disease and AD; however, AD-associated pathological changes mediated by the skin-brain axis are not yet clearly defined. While some studies have reported on the diagnostic implications of the skin-brain axis in AD, few have discussed its potential therapeutic applications. In this review, we address the pathological changes mediated by the skin-brain axis in AD. Furthermore, we summarize (1) the diagnostic implications elucidated through the role of the skin-brain axis in AD and (2) the therapeutic implications for AD based on the skin-brain axis. Our review suggests that a potential therapeutic approach targeting the skin-brain axis will enable significant advances in the treatment of AD.

Key words: Alzheimer's disease; skin-brain axis; skin disease; neurodegeneration

1. Introduction

The skin is the first organ in the body to respond to progressive changes during aging [1]. It is the largest organ in the body and undergoes both extrinsic and intrinsic aging processes. The skin acts as a window for age-related pathophysiological changes in the internal organs through progressive immunologic dysregulation, increased thinning of the epidermal barrier, and glycosylation of dermal extracellular matrix proteins [2]. In particular, a previous study proposed the concept of a 'skin-brain axis' to describe the dynamic interaction between the brain and skin [3]. Skin alterations not only reflect the state of the brain but can also directly or

indirectly influence the condition of the brain. For example, increased systemic pro-inflammatory cytokines due to trauma or skin diseases can affect the regulation of blood-brain barrier (BBB) permeability and immunomodulation in the brain [4]. In addition, damaged skin-induced immunological changes contribute to alterations in neurotransmission and neuropsychiatric and behavioral function [4]. Conversely, long-term changes in brain conditions, including chronic stress and major depressive disorder, can modulate the immune profile of the skin and exacerbate skin diseases, such as psoriasis, through the hypothalamic–pituitary–adrenal axis and hormonal regulation [5].

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Furthermore, neurodegenerative disease-associated proteins, such as amyloid beta ($A\beta$) and α -synuclein, accumulate in the skin as well as in the brain [6]. Remarkably, the skin and brain originate from the same ectoderm and share the molecular pathways involved in aging and the onset of neurodegenerative diseases [7]. Consequently, the skin can serve as a non-invasive window for observing and understanding various neuropathologies and various neurodegenerative diseases [8].

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease among the elderly [9]. AD is characterized by the accumulation of $A\beta$ and hyperphosphorylated tau [9]. The deposition of $A\beta$ and hyperphosphorylated tau in the AD brain leads to irreversible cognitive impairment via the induction of neuroinflammation, synaptic loss, and neuronal cell death [10]. In particular, both neurodegenerative alterations in the brain and complex physiological communication between the brain and the periphery are factors that contribute to AD progression [11, 12]. Previous studies have reported a relationship between AD and skin diseases [6, 13, 14]. One study found that patients with

AD had a 2.6-fold increased risk of developing bullous pemphigoid (BP) [14]. Thus, exploring the connection between the skin-brain axis and AD pathology is a novel contribution to the study of the pathomechanisms of AD [15].

Accumulating evidence suggests that the brain and skin not only mirror each other's condition but also actively participate in maintaining homeostasis and impact health through their intricate and reciprocal interactions. The complex interactions between the brain and skin during aging and neurodegenerative processes underlie the importance of the skin as a crucial indicator and contributor to neurodegeneration. However, the importance of the skin-brain axis in the diagnosis, progression, and treatment of AD has not been clearly established. In this review, we elucidate (1) the pathological alterations mediated by the skin-brain axis in AD, (2) the diagnostic implications of the skin-brain axis in AD, and (3) the therapeutic implications of AD elucidated through the skin-brain axis. Moreover, we aimed to provide a more detailed understanding of the pathophysiological and molecular alterations observed in skin disorders related to AD.

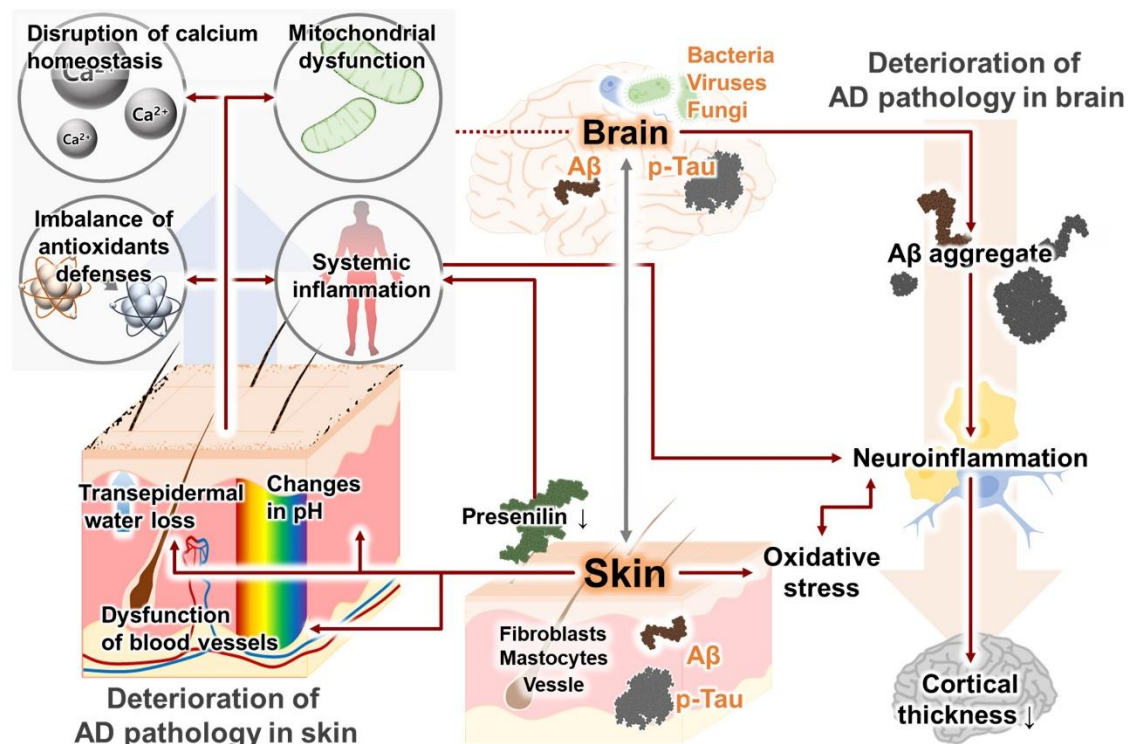


Figure 1. Overview of the association between AD-related pathologic features in the skin and brain. The solid line indicates known connections, and the dotted line indicates hypothesized connections.

2. Skin-brain axis in AD

2.1. AD-related pathological changes mediated by the skin-brain axis

Deposition of A β plaque in the brain is the hallmark pathology of AD [16]. Interestingly, the accumulation of A β also occurs in the skin, particularly in fibroblasts [17]. Recent research has suggested that antioxidant defenses are lower in skin fibroblasts from patients with familial AD than in those from controls. Furthermore, skin fibroblasts from AD patients exhibit a variety of dysfunctions, such as abnormally activated bradykinin receptor signaling, altered cholesterol ester metabolism, disrupted calcium homeostasis, and impaired mitochondrial function (Table 1) [18-21]. Moreover,

accumulated A β alters the function of blood vessels in the skin, similar to the changes that are observed in the brains of patients with AD [22, 23]. In addition, decreased expression of presenilin-1, which is involved in degrading the amyloid precursor protein (APP), has been associated with seborrheic keratosis and inflammatory skin disease in patients with AD [24]. Interestingly, A β and tau have also been shown to accumulate in skin mastocytes [25, 26]. Accumulated A β and tau have been reported to trigger epidermal keratinization-induced inflammation, pH changes, and transepidermal water loss in AD patients [27, 28]. These studies indicate the importance of understanding the skin-brain axis, as changes related to A β and tau in the skin are associated with the pathological features of the AD brain (Fig. 1).

Table 1. Pathological evidence of the skin-brain interconnection in animal models of AD and patients with AD.

Subjects	Age	Main findings	Ref.
Presenilin knock-down mice	6-month-old	Decreased expression of presenilin 1 leads to the development of seborrheic keratoses and inflammatory skin conditions	[24]
AD patients	-	A β and tau accumulated in the skin mastocytes of patients with AD. A β and tau accumulated in the mastocytes induced epidermal keratinization changes in pH, and transepidermal water loss in the skin of patients with AD.	[28]
Skin fibroblasts derived from AD patients	56.7-years-old	Skin fibroblasts derived from AD patients exhibited lower antioxidant defenses compared to those from normal subjects	[18]
Skin fibroblasts derived from AD patients	63.2-years-old	Skin fibroblasts derived from AD patients exhibit selective phosphorylation of tau protein on Ser residues.	[19]
Skin fibroblasts derived from AD patients	72.0-years-old	Skin fibroblasts from AD patients exhibited the dysregulation of cholesterol homeostasis.	[21]

Abbreviation: A β , Amyloid- β ; Alzheimer's disease, AD; potential of hydrogen, pH; serine, Ser.

Surprisingly, several studies have revealed a potential correlation between AD and skin diseases such as psoriasis, BP, and skin cancer. Patients with psoriasis tend to develop mild cognitive impairment (MCI) earlier than healthy individuals, which may be associated with a higher risk of AD onset [29, 30]. Considering that early is more strongly associated with an increased risk of progression to AD than late MCI [31], psoriasis may have important implications as a risk factor for AD. Furthermore, patients with psoriasis have decreased cortical thickness in the parahippocampal gyrus, superior temporal gyrus, and superior frontal gyrus [30, 32]. Previous studies reported that morphological changes, including reduced cortical thickness, could be potent indicators of the MCI to AD transition [33]. A genome-wide association study (GWAS) to identify genetic links between AD and psoriasis found shared genetic factors in

both diseases and suggested that psoriasis, which induces a chronic inflammatory response, may affect neuroinflammation and increase the risk of AD [34]. In addition, the association between psoriasis and AD is much stronger in middle-aged patients (40-64 years) than in older patients [35]. Patients with psoriasis treated with anti-inflammatory drugs have a lower risk of developing AD than controls without psoriasis. Furthermore, systemic administration of anti-inflammatory drugs may reduce the development of AD by reducing neuroinflammation as well as systemic inflammation. Thus, considering that patients with psoriasis have a greater tendency to develop MCI and show AD-related pathologies, such as reduced cortical thickness in certain brain regions, psoriasis and its pathologies can be considered potential risk factors contributing to the development of AD.

Blistered skin disease, an autoimmune disorder that causes large and dense blistering of the skin of older adults, has been associated with neurological diagnoses including AD, stroke, and Parkinson's disease (PD) [36]. Notably, patients with blisters have significantly lower cognitive scores than healthy controls, suggesting that patients with blisters are at a higher risk of developing cognitive impairment [37]. Surprisingly, BP autoantigens are expressed not only in the skin but also in the brain [38]. Recent studies have reported that patients with AD are more likely to be positive for BP autoantibodies than healthy controls [38, 39]. Considering the increased risk of BP development in patients with AD [39], it is believed that BP contributes to AD-related pathophysiology via autoantibodies that act on both the skin and the brain.

Interestingly, some studies have suggested that infectious diseases causing skin lesions may also be associated with AD. A number of recent studies have presented evidence supporting the 'infection hypothesis', that infection by bacteria, viruses, and fungi contributes to the pathogenesis and progression of AD [40]. Although the mechanisms by which fungal skin infections contribute to AD pathology are not fully understood, one study showed that fungal skin infections may contribute to AD progression and cognitive decline [41]. For instance, infection with *Malassezia* spp. induces skin inflammation and reduces skin barrier integrity [42]. Chronic skin deficits caused by *Malassezia* spp. infections provide an opportunity for the skin microbiome to enter the bloodstream and brain [41]. A postmortem study showed that *Malassezia globosa* and *Malassezia restricta* were distributed in the brains of patients with AD [43]. *Malassezia* spp. not only increase the levels of interleukin (IL)-17 and IL-23, but also upregulate the expression of toll-like receptor 4, activate T helper (Th)1/Th17 cells, and induce microglial phagocytic dysfunction by enhancing the expression of caspase recruitment domain family member 9 [41]. Therefore, skin infections caused by *Malassezia* spp. may contribute to A β deposition, neuroinflammation, and cognitive impairment. In addition, skin infections with *Cladosporium* spp. can contribute to AD pathology by enhancing neuroinflammation in the AD brain [41]. Next-generation sequencing studies on the postmortem brains of patients with AD support the influence of skin disease-causing fungi on AD pathogenesis [43]. Moreover, some viruses that cause skin lesions may also contribute to AD pathology and cognitive impairment. Although it remains controversial whether *Herpesviridae* directly promotes or accelerates AD pathology [44-46], some studies suggest that *Herpesviridae* infection may be a potential risk factor for AD [47, 48]. In particular, varicella zoster virus (VZV) and herpes simplex virus type (HSV)-1, which cause varicella and oral herpes, respectively [49], have been

proposed as risk factors for the progression of AD pathology [50, 51]. A recent study has shown that the superinfection of VZV on quiescent HSV-1-infected human-induced neuronal stem cells reactivates HSV-1 to contribute to A β and tau pathology [52]. In addition, VZV infection and VZV gB peptide have been reported to increase production and self-aggregation of A β in human primary astrocytes [53]. Several studies have suggested that infection by HSV-1 could exacerbate A β and tau pathology in the brain [48]. Similar to HSV-1, HSV-2 may also deteriorate A β pathology via alteration of APP processing [54]. Importantly, VZV and HSV not only infect epithelial cells and induce lesions in the skin but can also infect neurons and contribute to AD-associated neuropathology. Exploring and characterizing other skin-infecting viruses that may induce AD-associated neurodegeneration via the skin-brain axis is an interesting topic for future studies.

Previous studies have shown a significantly decreased risk for AD in patients with skin cancer [55-57]. Indeed, cancer and AD involve opposing processes: unrestrained proliferation in cancer and apoptosis in AD [58]. In other words, cancer activates signaling pathways that promote cell survival, whereas AD promotes signaling pathways that lead to increased cell death. Therefore, the signaling pathways involved in cell survival that are upregulated in skin cancer may contribute to the mitigation of neurodegeneration in AD. In skin cancer, the enzyme Pin1, which plays a role in protein folding and cell cycle control [59], is up-regulated, whereas the level of Pin1 is decreased in the brain of patients with AD [55, 60]. Particularly, Pin1 can regulate AD-related proteins including tau and APP [61, 62]. In AD, reduced activity of Pin1 decreases isomerization of APP and tau protein, leading to the development of A β - and tau-related cell death and pathology. In skin cancer, the expression of Pin1 is increased, resulting in the prevention of A β - and tau-related pathology in the brain. Moreover, the overexpression of Pin1 may attenuate neurodegeneration by activating the Wnt/beta-catenin signaling pathway [63]. Many studies investigating the relationship between skin cancer and AD have suggested that alterations in DNA methylation and the activity of the p53 tumor suppressor gene may contribute to AD pathology [57, 64, 65]. These results suggest that the pathways promoting cell survival in skin cancer may contribute to the reduced neurodegeneration observed in patients with AD. In summary, various skin diseases and causative pathogens may influence AD-related pathology.

2.2. Skin-brain axis as a diagnosis strategy in AD

The diagnostic relevance of the skin-brain axis has been emphasized in a broad spectrum of neurodegenerative

diseases. In particular, the skin reflects the pathological progression of neurodegeneration. Interestingly, skin biopsy has been suggested as an emerging new diagnostic method for PD, Lewy body dementia (LBD), and AD [28]. Measuring the seeding activity of α -synuclein aggregates in skin tissue has received much attention as a diagnostic technique for PD [66]. Surprisingly, the analysis of an autopsied abdominal skin sample using real-time quiver induction conversion succeeded in diagnosing PD with 95% sensitivity and 100% specificity [66]. In addition, measurements of phosphorylated α -synuclein deposited on autonomic skin nerve fibers clearly discriminated patients with LBD from patients with non-synucleinopathy dementia, as well as healthy controls [67]. These studies clearly show that protein-related alterations in the skin are effective diagnostic markers for neurodegenerative diseases. Several recent studies have attempted to develop an AD diagnostic method using skin biopsies [8, 28]. Transcriptomic analysis of patients with AD showed that some genes, including those in keratinocytes, fibroblasts, and endothelial cells, are differentially expressed in AD [68]. Frequent transcriptional alterations were observed in genes encoding the low-density lipoprotein receptor (LDLR), interferon-stimulated gene 15 (ISG15), galactin-3-binding protein (GAL3BP), and copine 1 (CPNE1) in the skin cells of patients with AD [68]. LDLR, which is involved in lipid and energy metabolism, is altered in the AD brain [69]. LDLR has been proposed as an important factor contributing to the progression of A β and tau pathology by interacting with apolipoprotein E [69]. Moreover, ISG15, a key regulator of interferon-related immunity, shows different expression levels in the parahippocampal gyrus of patients with MCI and AD compared to healthy controls [70]. Furthermore, GAL3BP may modulate AD pathology by blocking the β -cleavage of APP and suppressing the activity of galactin-3, which is abnormally regulated in AD [71]. A previous study suggested that GAL3BP levels in serum or cerebrospinal fluid (CSF) could be potential biomarkers for AD [71]. Collectively, the investigation of transcriptional changes in genes associated with AD, such as *CPNE1*, *ISG15*, *LDLR*, and *GAL3BP*, whose expressions are altered in the skin cells of AD patients, may contribute to the development of AD diagnostic tools and methods using the skin. The oral mucosa can also serve as a potential biomarker for diagnosing AD as it originates from ectodermal tissues similar to those of the skin and brain [72, 73]. Accumulated evidence suggests that buccal cells and fibroblast cells in AD patients display specific alterations that could be valuable in the AD diagnosis. Buccal cells from AD patients show significant differences compared to age-matched controls in both cytosolic components and DNA [74-76]. Furthermore,

studies involving buccal cytome assay on the buccal mucosa of patients with AD reported altered tissue kinetics compared to age-matched controls [76]. One study that examined telomeres in buccal cells using three-dimensional imaging revealed differences in telomere morphology between buccal cells derived from age-matched individuals and those derived from patients with AD. Furthermore, significant changes in the telomere architecture of buccal cells have been observed, depending on the stage of AD progression [77]. One study combining ATR-FTIR spectrometry and analytical algorithms demonstrated significant differences in the composition of biomolecules present in buccal cells between controls and AD patients [74]. In another study using skin punch biopsies, the use of phosphorylated ERK1/2 in fibroblasts as a biomarker was reported to potentially provide higher accuracy, sensitivity, and specificity in the diagnosis of AD than diagnosis by autopsy or clinical methods [78]. One study reported a significant increase in A β levels of oral mucosal cells through multi-parameter analysis [79]. Although relatively few studies have focused on oral mucosal epithelial cells for AD diagnosis, further research on the potential of using the oral mucosa could significantly contribute to the diagnosis of AD. Nevertheless, the reduction in the ratio of basal, karyorrhectic, and condensed chromatin cells in the buccal mucosa of AD patients suggests that AD-related physiological changes may affect the kinetics of various cells or tissues constituting the buccal mucosa. Taken together, these results suggest that AD-related changes along the skin-brain axis may be a valid approach for the diagnosis of AD.

Currently, amyloid positron emission tomography (PET) is the most effective method for diagnosing AD, and has been shown to be capable to classify healthy individuals and AD patients with high sensitivity and specificity (Table 2) [80]. Unfortunately, it has some disadvantages owing to its low accessibility and high cost [81]. Therefore, several studies have been conducted to develop simpler, safer, and more economical technologies for AD diagnosis. In particular, measuring the changes in the blood or CSF biomarkers for the AD diagnosis is considered a promising approach [82]. The sensitivity and specificity of AD diagnosis using CSF are very high [83, 84]. In particular, one study demonstrated that CSF biomarkers provide high sensitivity (81%) and specificity [81%] for diagnosing AD, with positive and negative predictive values of 87% and 72 %, respectively [84]. Moreover, recent studies on AD diagnosis using blood have shown that blood-based diagnostic tools exhibit sensitivities ranging from 83% to 96% and specificities ranging from 76% to 100% [85]. However, invasive methods have problems, such as concerns regarding side

effects such as CSF leakage and infection at the sample collection site, as well as issues related to pain, patient reluctance, and uncooperativeness during the test [86]. The establishment of skin-based AD diagnostics may provide a relatively non-invasive, low-risk, inexpensive,

and convenient means of sample collection and AD diagnosis. Therefore, the use of AD-related changes along the skin-brain axis may be a potential approach for a more beneficial and safe diagnostic strategy for neurodegenerative diseases.

Table 2. Comparison of sensitivity and specificity of diagnostic methods for AD.

Method	Biomarker	Number of participants [AD patients/controls]	Sensitivity	Specificity	Ref.
Amyloid PET (Florbetaben)	A β	81/69	80%	91%	[87]
Tau PET	Tau	6/21	100%	86%	[88]
CSF	A β _{42/40} ratio	55/34	51%	82%	[89]
	A β ₄₂	22/35	100%	80%	[90]
	A β _{42/40} ratio	22/35	95.2%	88.4%	
	A β ₄₂	48/107	94%	72%	[91]
	A β _{42/40} ratio	48/107	92%	79%	
	A β ₄₂	100/50	98.0	74.0	[92]
	A β _{42/40} ratio	100/50	85.7	78.0	
Blood	A β _{42/38} ratio	100/50	81.6	82.0	[85]
	Plasma A β ₄₂	- (Meta-analysis)	88%	81%	
	Plasma A β oligomer	- (Meta-analysis)	80%	88%	
Skin biopsy (Buccal cell) / Buccal cytome assay	Plasma tau	- (Meta-analysis)	90%	87%	[76]
	Ratio of buccal cell and micronuclei	54/66	82%	97%	
	Composition of biomolecules in buccal cell	17/12	76%	100%	
Skin biopsy (Buccal cell) / ATR-FTIR spectroscopy	DNA content and neutral lipid content	13/26	62%	100%	[74]
Skin biopsy (Buccal cell) / Laser scanning cytometry+ Oil Red O staining	Morphology of skin fibroblast	25/21	100%	100%	[75]
Skin biopsy (Skin fibroblast) / Morphometric imaging	Transketolase in skin fibroblast	38/12	69.4%	100%	[93]
Skin biopsy (Skin fibroblast) / Transketolase assay					[94]

Abbreviation: Alzheimer's disease, AD; A β , Amyloid- β ; PET, Positron Emission Tomography; CSF, cerebrospinal fluid; DNA, Deoxyribonucleic acid.

2.3. Modulation of the skin-brain axis as a therapeutic target in AD

The skin is involved in the peripheral nervous systems (PNS), autonomic nervous systems (ANS), and central nervous systems (CNS). Interestingly, in the context of skin homeostasis and disease management, substantial evidence suggests that the cutaneous PNS plays a crucial role in the skin-brain axis [95]. Several studies have demonstrated that the vagus nerve, which is distributed in the skin, can modulate the neuroendocrine and neuroimmune systems. In particular, transcutaneous vagus nerve stimulation (tVNS), an intervention that involves electrical stimulation of the vagus nerve through the skin, has provided important insights into the skin-brain axis. tVNS promotes anti-inflammatory signaling of the vagus nerve via the $\alpha 7$ nAChR/ nuclear factor kappa-

light-chain-enhancer of activated B cells (NF- κ B) signaling pathway [96]. In addition, tVNS induces microglial switching to an anti-inflammatory phenotype, and alleviates the excessive secretion of pro-inflammatory cytokines through the P2X7R/NLRP3/Caspase-1 signaling pathway in APP/PS1 mice [97, 98]. Surprisingly, recent studies are attempting to treat neurological disorders through tVNS [98]. tVNS improved locus coeruleus activity and memory performance in healthy older adults [99]. Moreover, tVNS, which stimulates the auricular branch of the vagus nerve, significantly restores cognitive dysfunction in individuals with MCI [100]. Recent literature and clinical trials (NCT number: NCT02363504) have suggested that tVNS can be applied in patients with AD to effectively ameliorate cognitive impairment [99, 101]. These findings suggest that skin stimulation via tVNS can

mitigate cognitive dysfunction by modulating neuroendocrine and neuroimmune systems through the vagus nerve and enhancing brain connectivity.

Table 3. Therapeutic interventions targeting the skin-brain axis for AD-related pathology in AD animal models and AD patients.

Therapeutic interventions	Subjects	Age	Main findings	Ref. / Trial number
Dermatological drugs	Etanercept /psoriasis, psoriatic arthritis	A β -injected Swiss mice	6-weeks-old	Treatment with etanercept attenuated cognitive impairment mediated by A β . [102]
		AD patients	76.7-years-old	Treatment with etanercept attenuated cognitive impairment. [103]
		AD patients	81-years-old	Treatment with etanercept attenuated cognitive impairment. [104]
		AD patients	72.4-years-old	Peripherally administered etanercept showed a trend toward improvement in ADL and cognitive impairment, although the difference was not statistically significant. [105] NCT01068353
	Infliximab /psoriasis, rashes, skin lesions, ulcers, hives, and swollen face or lips	APP/PS1 mice	12-months-old	Administration of infliximab reduced amyloid plaques, tau phosphorylation, and level of TNF- α . [106]
		A β oligomer-injected ICR mice	6-weeks-old	Administration of infliximab ameliorated the impairment of AD-associated recognition memory and blocked A β toxicity. [107]
		AD patients	57-years-old	Treatment of infliximab attenuated cognitive impairment and increased the concentration of A β ₁₋₄₂ and p-tau in CSF and blood. [108]
	Thalidomide /erythema nodosum leprosum	A β -injected ICR mice	-	Treatment of thalidomide attenuated cognitive impairment caused by A β . [109]
	Rapamycin /atopic dermatitis, psoriasis, skin aging	3xTg mice	6- and 12-month-old	Rapamycin administration rescued AD-related early learning and memory deficits and reduced A β and tau pathology. [110]
		J20 mice	8- and 12-months-old	Minocycline reduced A β burden and restored AD-associated cognitive dysfunction. [111]
		A β -injected rat	10-weeks-old	Minocycline decreased neuronal cell death and mitigated learning and memory impairment caused by A β . [112]
	Minocycline /pimples, red bumps	Thy1-APP mice	3-months-old	Minocycline reduced microgliosis and A β burden and inhibited BACE-1 activity. [113]
		Mu p75-SAP-injected mice	3-months-old	Minocycline reduced microgliosis and astrogliosis. Minocycline attenuated cognitive impairment. [114]
		Tg-SwDI mice	12-months- old	Minocycline reduced microgliosis and restored spatial learning memory impairment. [115]
	Celastrol	APP/PS1 mice	6-months-old	Minocycline reduced microgliosis and A β burden. [116]

	/psoriasis. atopic dermatitis				
	Bexarotene /skin cancer	APP/PS1 mice	6-months-old	Bexarotene attenuated cognitive impairment. Bexarotene reduced A β burden and rescued cortical network activity.	[117]
tVNS		APP/PS1 mice	6- and 12-months-old	tVNS induced a morphological transition of microglia from neurodestructive to neuroprotective phenotype.	[97]
		APP/PS1 mice	6-months-old	tVNS improved spatial memory and learning tVNS decreased neuroinflammatory response, A β deposits, and neurodegeneration. tVNS inhibits the hippocampal P2X7R/NLRP3/Caspase-1 signaling.	[98]
		AD patients	60~85-years-old	Modulating the locus coeruleus function through tVNS	NCT02363504
		AD patients	55~95-years-old	Rivastigmine dermal patch showed numerical improvement in CASI and MMSE scores.	[118]
Dermal patch		AD patients	-	Rivastigmine dermal patch significantly reduced blood esterase levels, specifically BuChE.	[119, 120]
		AD patients	50~85-years-old	Rivastigmine dermal patch demonstrated improvement or stability in the ADAS-Cog scores.	[121]
		AD patients	-	Rivastigmine dermal patch demonstrated restoration of cognitive dysfunction.	[122]

Abbreviation: Alzheimer's disease, AD; A β , Amyloid- β ; ADL, Activities of Daily Living; BACE-1, beta-site amyloid precursor protein cleaving enzyme 1; CSF, cerebrospinal fluid; TNF- α , tumor necrosis factor- α ; tVNS, Transcutaneous vagus nerve stimulation; CASI, cognitive assessment screening instrument; MMSE, mini-mental state examination; BuChE, butyrylcholinesterase; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale.

Moreover, a better understanding of the close relationship between AD neuropathology and increased systemic inflammatory responses or microbial invasion in skin diseases will provide opportunities to develop new therapeutic interventions for AD. Numerous studies support the beneficial effects of dermatological drugs on AD by modulating inflammatory and infectious responses, reducing A β and tau accumulation, and inhibiting neurodegeneration (Table 3). A recent study reported that patients with psoriasis treated with etanercept, or infliximab had a reduced risk of AD [123]. Etanercept or infliximab are known to be effective in the treatment of psoriasis, in which T cells and dendritic cells activated by tumor necrosis factor (TNF) accumulate and produce cytokines such as TNF- α and IL-23 [124]. Surprisingly, TNF- α , a key pro-inflammatory factor, is also known to play an important role in the pathogenesis of AD and to exacerbate A β and tau pathology [125]. It has been showed that intraventricular injection of infliximab into APP/PS1 mice reduced the levels of TNF- α , the accumulation of A β , and the phosphorylation of tau

in the brain [106]. Similarly, A β oligomer-injected ICR mice exhibited recovery of memory impairment upon intraventricular administration of infliximab [107]. Moreover, thalidomide, used to treat erythema lepromatosis, restored cognitive dysfunction in A β -injected ICR mice [109]. In a study of patients with AD, perispinal administration of etanercept resulted in significant recovery of cognitive decline [103, 104], and intrathecal administration of infliximab resulted in the restoration of cognitive dysfunction [108]. Furthermore, etanercept has been shown to slow cognitive decline and improve activities of daily living in patients with AD in phase 1 and 2 clinical trials (NCT number: NCT01068353) [105]. Thus, there is both preclinical and clinical evidence to suggest that exploiting the mechanisms of skin disease drugs, such as administration of TNF- α inhibitors, may be an effective strategy for treating AD. However, since the TNF- α inhibitors used to treat skin diseases, such as etanercept and infliximab, do not cross the BBB, it is difficult for them to act directly in the brain. Nevertheless, the TNF- α inhibitor etanercept, is

known to regulate the immune response within the CNS and AD pathology, despite its poor BBB permeability [126, 127]. Recent studies have revealed that etanercept alleviates neuroinflammation through the inhibition of c-Jun N-terminal kinase and NF- κ B pathways and exerts neuroprotective effects in AD [128]. In addition, etanercept reduced microgliosis, tau phosphorylation, and neuronal loss in the brains of PS19 transgenic mice, a model of tauopathy [129]. Interestingly, TNF- α inhibitors, whether or not they penetrate the BBB, have been shown to suppress tau-related neuroinflammation and neurodegeneration [129]. This result suggests that etanercept may alleviate AD-related pathology by reducing systemic TNF- α levels, rather than by directly affecting glial cells in the brain [129]. Similarly, TNF- α inhibitors have been reported to attenuate A β accumulation independent of BBB penetration [127]. Interestingly, BBB-penetrating TNF- α inhibitors have been shown to regulate AD-associated pathology independently of inflammation modulation associated with Iba-1 or CD11b reduction [127]. These results indicate that TNF- α inhibitors, independent of BBB permeability, may alleviate the pathophysiology of AD by reducing systemic inflammation and skin infections.

Notably, it is well known that the fungi that cause skin disorders destroy the epithelial barrier of the skin and enter the brain through systemic infection [41]. *Candida* spp., *Malassezia* spp., *Cladosporium* spp., and *Alternaria* spp. are among the most common fungi found in the brain of patients with AD. Fungi are believed to contribute to AD pathogenesis in the brain through amyloidogenic processing and gliosis [130, 131]. These four fungi may contribute to inflammatory responses and degeneration of both the brain and skin. Interestingly, a recent study investigated the utility of miconazole, an antifungal skin ointment widely used to inhibit fungal cell membrane synthesis, in the treatment of lipopolysaccharide (LPS)-induced AD in animal models [132]. Miconazole ameliorates memory decline by inhibiting the expression of inducible nitric oxide synthase and alleviates neuroinflammation by downregulating the level of the NF- κ B protein in LPS-treated AD mice [132]. Although miconazole was not used to treat fungal infections in an AD-induced mouse model, these experiments suggest that targeting changes in the skin-brain axis can ameliorate the AD pathology. These results suggest a potential dual role for miconazole in the treatment of AD pathology and fungal infections.

Since most treatments for skin diseases target inflammatory responses, it is reasonable to assume that they also exert therapeutic effects on AD. In AD, A β overproduction and tau hyperphosphorylation lead to the formation of A β /tau aggregates, which are neurotoxic and induce immune responses in microglia. Microglial

activation results in the release of pro-inflammatory cytokines and neurotoxic factors, such as TNF- α and IL-1 β , which not only amplify the inflammatory response but also trigger neuronal cell death. When neurons are destroyed, microglial activity is further enhanced by the release of microglial activating factors, such as laminin and neuromelanin. This self-perpetuating cycle contributes to the escalation of inflammatory responses in AD [133]. Breaking this cycle by administering dermatological drugs that inhibit inflammation may potentially slow the pathological deterioration and contribute to the treatment of AD. It has been suggested that drug repositioning for AD could potentially be facilitated by the conjugation of BBB transporters to various TNF- α inhibitors used for skin diseases or by chemical modification of drugs to increase BBB permeability. For example, a chemically modified BBB-permeable version of thalidomide has been found to exert neuroprotective effects [134]. Rapamycin and minocycline, known for their high BBB permeability, have been reported to improve BBB dysfunction in other disease models [135, 136]. In addition, Celestrol, which penetrates the BBB, may directly mitigate AD pathology by activating transcription factor EB (TFEB)-mediated autophagy in the brain. Furthermore, bexarotene nano-encapsulated to facilitate drug delivery effectively alleviated A β pathology [137].

The presence of amyloid in the skin could plausibly trigger protein aggregation, including A β and tau, in the brain, influencing AD pathology. The established skin-brain connection offers a promising avenue for investigating drug delivery via skin administration as a safe and simple approach for treating AD. Recent research has actively focused on the development of therapeutic agents using transdermal drug delivery systems such as dermal patches. Dermal patches are medical devices that deliver drugs through the skin, facilitating gradual release which facilitates absorption into the bloodstream. This method offers the advantage of efficiently delivering the required drug doses to patients with AD, particularly to those who may experience gastrointestinal side effects or face challenges with drug administration owing to swallowing difficulties and memory impairment. In particular, rivastigmine, a cholinesterase inhibitor, is an agent for which a transdermal delivery system has been developed, and is currently prescribed and used for patients with mild to severe AD. The rivastigmine dermal patches have shown several beneficial effects, including reduced blood esterase levels, particularly BuChE, and increased food intake in patients with AD [119, 120]. Furthermore, some studies have demonstrated that using a rivastigmine transdermal patch in patients with AD can help to restore cognitive dysfunction [118, 122]. Notably, a transdermal patch of rivastigmine was found to have

equivalent efficacy to rivastigmine capsules [122], suggesting that the transdermal delivery of rivastigmine through the patch may offer therapeutic benefits for patients with AD. Collectively, recognizing the importance of the interconnection in the skin-brain axis in AD and utilizing skin disease drugs may provide new approaches for the treatment of AD.

3. Limitation and perspective

As AD is a complex disease characterized by multiple pathologies, it is important to identify any potential associations with various factors such as A β , tau, neuroinflammation, and mitochondrial dysfunction to clarify the role of the skin-brain axis in AD. However, most existing studies on the skin-brain connection have focused on the correlation between skin conditions and the incidence of AD, or skin conditions and AD-related genes, rather than adequately addressing the direct association of skin conditions with AD pathology. Previous studies made it difficult to integrate and standardize the function of the skin-brain axis in AD. Large-scale prospective studies with longer follow-up periods are therefore required to clarify the complex

relationships between AD and various skin diseases. Clinical studies in the medical domain aimed at exploring interventions targeting the relationship between the skin and the brain have potential to offer valuable insights into potential therapeutic and diagnostic approaches for AD. Additional non-clinical studies are also needed to better understand the skin-brain axis. To explore the mechanisms underlying the relationship between skin disease and the progression of AD, examining the changes in AD-related pathology, including A β pathology, hyperphosphorylated tau, neuroinflammation, neurodegeneration, and mitochondria dysfunction, by triggering skin cancer or skin disease in AD animal models, are still need. Moreover, it is essential to investigate changes in both the skin and brain from the early developmental stages to the onset of AD. Studies examining changes in skin disease models injected with A β or tau may suggest a relationship between skin disease and the development of AD. Furthermore, collaboration among dermatologists, neurologists, and neuroscientists is essential to ensure a comprehensive and multidisciplinary approach to understanding the pathological, diagnostic, and therapeutic role of skin-brain relationships in AD.

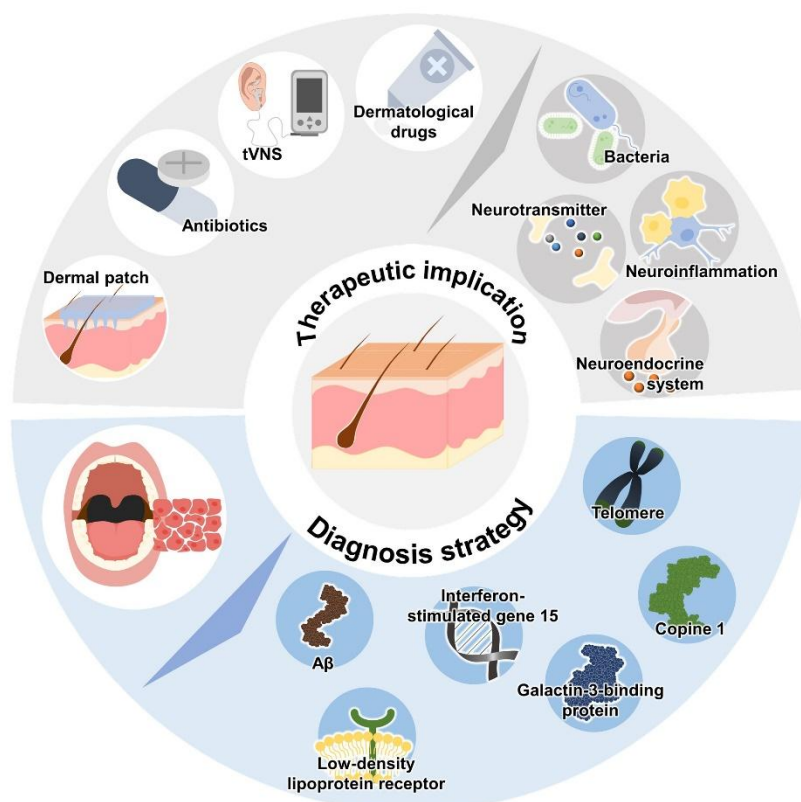


Figure 2. Strategies for the diagnosis and treatment of AD *via* targeting of the skin-brain axis.

In terms of the development of AD diagnostic technologies, the most significant barriers and challenges faced by existing AD diagnostic technologies include: (1) distinguishing between MCI and healthy individuals, (2) distinguishing between MCI and AD, (3) early prediction of MCI progression to AD, (4) invasive methods (5) high cost, and (6) low accessibility for participants. In this study, we propose that skin biopsy can help to address the issue of the high cost of AD diagnostic technology and offers a more non-invasive approach compared to existing methods. Unfortunately, it has not yet been established whether the diagnostic method of AD through skin biopsy can also be used to distinguish between patients with MCI and those with AD with high sensitivity and specificity. Future research should validate whether skin biopsy can differentiate between MCI and AD, as well as predict the progression from MCI to AD. In addition, although skin biopsy has advantages over traditional diagnostic methods in the diagnosis of AD in terms of invasiveness, cost, and convenience, more evidence is required before it can be commercially applied. Furthermore, more detailed studies on the mechanisms by which skin cells exhibit specific changes in AD are needed to establish reliable biomarkers for AD. Further mechanistic studies are also needed to compare the accuracy, sensitivity, and specificity of newly discovered skin AD biomarkers.

4. Conclusions

In this review, we elucidated the pathophysiological relationship between the skin and brain in AD. In addition, we describe the possibility of applying skin-based diagnostic and therapeutic approaches that reflect the role of the skin-brain axis in AD (Fig. 2). Although the skin and brain are usually considered distinct organs, they share a common embryological origin and pathophysiological characteristics such as inflammation. Skin changes may serve as indicators of brain changes that reflect the onset and progression of AD and vice versa. Therefore, it is important to identify the AD-related pathological changes mediated by the skin-brain axis, and utilizing the skin-brain axis may be helpful in the diagnosis and treatment of AD. Moreover, the repurposing of drugs for the treatment of AD-related skin diseases may be an interesting avenue for the development of novel therapeutic strategies for AD.

Declaration of Competing Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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