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Mini Review

Targeting PDE4 and the Brain-Lung-Olfactory Axis: Integrated Pharmacological and Nutritional Strategies for Alzheimer's Disease

Mosab Nouraldein Mohammed Hamad*

Assistant professor of Microbiology, Excellence Research Center, Elsheikh Abdallah Elbadri University, Sudan

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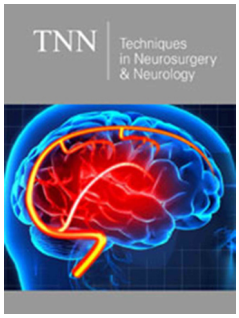

***Corresponding author:** Mosab Nouraldein Mohammed Hamad, Assistant Professor of Microbiology, Excellence Research Center, Elsheikh Abdallah Elbadri University, Berber, Sudan

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Abstract

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by β-amyloid plaques, tau-containing neurofibrillary tangles and cognitive decline. Emerging evidence suggests that chronic neuroinflammation, disrupted Cyclic Adenosine Mono Phosphate (cAMP) signaling and early olfactory dysfunction accelerate disease progression. Phosphodiesterase-4 (PDE4) inhibitors, such as roflumilast, enhance cAMP-mediated signaling and exhibit anti-inflammatory and neuroprotective effects. Complementary interventions-including flavonoids, lignans and vitamin D-may modulate the brain-lung-olfactory axis and further mitigate neuroinflammation. This review proposes an integrated pharmacological and nutritional strategy targeting systemic and central inflammatory pathways, offering a novel framework for preventive and therapeutic approaches in AD.

Keywords: Alzheimer's disease; Phosphodiesterase-4 (PDE4) inhibitors; Roflumilast; Neuroinflammation; cAMP signaling; CREB pathway; Olfactory dysfunction; Tau protein; β-amyloid; Flavonoids; Lignans; Vitamin D; Brain-lung axis; Cognitive decline; Neuroprotection

Introduction

Alzheimer's Disease (AD) is biologically defined by the accumulation of β-amyloid (Aβ) plaques and tau-containing neurofibrillary tangles in the brain, leading to synaptic dysfunction, neuronal loss and progressive cognitive impairment [1,2]. Despite extensive research, current therapeutic strategies remain limited, prompting growing interest in targeting molecular pathways involved in neuroinflammation and synaptic plasticity. One such promising target is phosphodiesterase-4 (PDE4), a key enzyme responsible for Cyclic Adenosine Monophosphate (cAMP) degradation, which plays a critical role in memory formation, learning and neuroprotection [3].

Roflumilast: Mechanism of Action and Clinical Use

Roflumilast (Daliresp®) is an orally administered selective PDE4 inhibitor approved for reducing inflammation and the risk of exacerbations in patients with severe Chronic Obstructive Pulmonary Disease (COPD) [4-6]. By inhibiting PDE4 and its active metabolite, roflumilast N-oxide, intracellular cAMP levels increase, leading to relaxation of airway smooth muscle and suppression of inflammatory mediators such as Tumor Necrosis Factor-α (TNF-α) and interleukin-17 (IL-17), thereby reducing pulmonary inflammation [4,5].

Beyond its pulmonary indications, PDE4 inhibition has demonstrated therapeutic potential in preclinical models of AD. Inhibition of PDE4-particularly the PDE4D subtype-enhances cAMP signaling, activates cAMP Response Element-Binding Protein (CREB),

improves synaptic plasticity, attenuates neuroinflammation and reverses Aβ-induced cognitive deficits [3]. Roflumilast has been shown to cross the blood-brain barrier, albeit moderately and exerts neuroprotective effects through modulation of intracellular phosphorylation pathways, including increased CREB, Akt and GSK-3β phosphorylation and reduced activation of JNK, IRE1α, p38 MAPK and SMAD3 pathways [7-9].

Olfactory Dysfunction and Neuroinflammation in AD

Olfactory dysfunction is among the earliest clinical manifestations of AD and reflects synaptic and neuronal disruption within the Olfactory Bulb (OB) [10,11]. Increasing evidence implicates Th17 lymphocytes and IL-17A in mediating olfactory deficits, with animal studies demonstrating partial restoration of olfactory function following IL-17A neutralization [12]. TNF-α further contributes to AD pathogenesis by promoting neuroinflammation, neuronal injury and Aβ production, although its effects differ depending on activation of TNFR1 versus TNFR2 signaling pathways [13,14]. PDE4 inhibitors such as roflumilast may mitigate these inflammatory cascades and restore olfactory and cognitive function.

Natural Compounds with PDE4-Inhibitory or Neuroprotective Effects

Natural compounds, including flavonoids and lignans, exhibit potent anti-inflammatory, antioxidant and neuroprotective properties. Flavonoids have been shown to reduce oxidative stress, enhance cerebral blood flow, promote neuronal survival and support cognitive performance [15]. Lignans, abundant in seeds (e.g., flaxseed and sesame) and berries (e.g., Schisandra species), can cross the blood-brain barrier and modulate inflammatory and oxidative stress pathways, thereby protecting against neurodegeneration [16]. In addition, certain plant-derived compounds such as sappanone A and licorice-derived molecules demonstrate PDE4-inhibitory activity, suggesting potential synergistic effects with pharmacological PDE4 inhibitors [17,18].

Vitamin D and the Brain-Lung Axis

Emerging evidence supports the existence of a functional brain-lung axis, with inflammation serving as a critical mediator between these organs. Vitamin D exerts immunomodulatory and anti-inflammatory effects in both the central nervous system and the respiratory tract [19,20]. Vitamin D deficiency has been associated with cognitive decline, depression and increased susceptibility to respiratory disorders such as COPD and asthma. Furthermore, racial and ethnic disparities in vitamin D status-partly attributable to differences in skin pigmentation-have been linked to an increased risk of AD among Black, Hispanic and South Asian populations [21-26].

Hypothesis and Future Directions

Based on its capacity to inhibit PDE4, suppress systemic and central inflammation and penetrate the central nervous system, roflumilast represents a promising candidate for AD prevention or therapy. Adjunctive interventions using flavonoids, lignans and vitamin D supplementation may further enhance neuroprotection and slow disease progression. We hypothesize that AD progression may be driven, in part, by chronic disruption of the brain-lung inflammatory axis and that targeted modulation of inflammatory signaling and cAMP pathways represents a viable therapeutic strategy. Further experimental and clinical studies are warranted to evaluate the safety and efficacy of these combined interventions.

Conclusion

Roflumilast, natural PDE4 inhibitors, flavonoids, lignans and vitamin D supplementation collectively represent an integrated therapeutic approach to mitigating neuroinflammation, synaptic dysfunction and cognitive decline in Alzheimer's disease. Systematic investigation of these strategies in preclinical and clinical settings may open new avenues for preventive and disease-modifying interventions in AD.

References

1. Zou Y, Gao C, Chen L (2016) Olfactory dysfunction in Alzheimer's disease. Front Neurosci 10: 155.
2. Elhabbari K, Brown S, Wilson J (2024) Olfactory deficits in aging and Alzheimer's-spotlight on early neural dysfunction. Front Neurosci 18: 1503069.
3. Miles DH, Schafer P, Zhang K (2008) Phosphodiesterase-4 inhibitors: Current status. Br J Pharmacol 155(3): 308-320.
4. Baye J (2012) Roflumilast (daliresp): A novel phosphodiesterase-4 inhibitor for the treatment of severe chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 37(3): 149-161.
5. Laura F, Bianca B, Klaus FR (2015) Roflumilast: A review in COPD. Pulm Pharmacol Ther 31: 50-58.
6. Bellamy D, Patterson S, Calverley P (2014) Roflumilast (Daliresp): Clinical pharmacology and safety. Am Fam Physicians 89(5): 300-306.
7. Sambeth A, Hooft J, Blokland A, Prickaerts J (2016) The PDE4 inhibitor roflumilast improves memory: Mechanistic insights. Maastricht University report.
8. (2024) Clinical trial protocol: A proof-of-concept study with roflumilast in mild cognitive impairment/AD (ROMEMA). Trials 25: 501.
9. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science 297(5580): 353-356.
10. Xiaozhou Y, Hong L, Lei W (2022) Interleukin 17A in Alzheimer's disease: Recent advances and mechanisms. Int J Mol Sci 23(15): 8543.
11. McEvoy CT, Hoang H, Beaglehole B (2020) Dietary and nutrient associations with cognitive function in multi ethnic cohorts. Front Hum Neurosci 14: 359.
12. Virginie L, Andres S, Jean-Pierre B (2016) Vitamin D, cognition and Alzheimer's disease: Meta-analysis and review. J Alzheimer's Dis 51(4): 1217-1230.
13. Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, et al. (2014) Vitamin D and the risk of dementia and Alzheimer disease. Neurology 83(10): 920-928.
14. Schlögl M, Holick MF (2014) Vitamin D and neurocognitive function. Clin Interv Aging 9: 559-568.

15. Williams RJ, Spencer JP (2012) Flavonoids, cognition and dementia: Actions and mechanisms. J Agric Food Chem 60(23): 5713-5721.

16. Pan M, Zhang Q, Li H (2020) Lignans: Neuroprotective effects through modulation of neuroinflammation and oxidative stress. Mol Nutr Food Res 64(2): 1900772.

17. Peng X, Li W, Zhang M (2021) Natural PDE4 inhibitors from sappanone a: Anti-inflammatory and neuroprotective effects. Phytomedicine 92: 153712.

18. Wang L, Chen Y, Zhao R (2020) Licorice-derived molecules as PDE4 inhibitors: Potential neuroprotective applications. Planta Medica 86(14): 1049-1058.

19. Wang Y, Zhang Y, Feng J (2021) Brain-lung axis: Systemic inflammation and its impact on neurodegeneration. Brain Behav Immun 95: 243-256.

20. Martineau AR, Jolliffe DA, Hooper RL (2017) Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis. Respir Res 18: 188.

21. Shuo W, Ming L, Hui C, Wei Z (2025) IL-17a induces age-related olfactory dysfunction by impairing regeneration and promoting respiratory metaplasia in mice. Nat Commun 16: 1234.

22. Irina KM, Natalia SI, Elena MP (2016) Levels of proinflammatory cytokines IL-17 and IL-23 in Alzheimer's disease, mild cognitive impairment and vascular dementia. Zh Nevrol Psikhiatr Im S S Korsakova 116(3): 39-43.

23. Spencer JP (2009) Flavonoids and brain health: Multiple effects underpinned by common mechanisms. Genes Nutr 4(4): 243-250.

24. Tobinick E, Gross H, Weinberger A (2006) TNF-α modulation as a therapeutic strategy for Alzheimer's disease. Nat Rev Neurol 2(8): 484-489.

25. Baruch K, Deczkowska A, Schwartz M (2015) Th17 cells drive neuroinflammation and olfactory dysfunction in Alzheimer's disease. Front Immunol 6: 107.

26. Annweiler C, Anne-Marie S, Berrut G, Chauvire V, Montero-Odasso M, et al. (2010) Vitamin D and cognition in older adults: Update and perspectives. J Alzheimer's Dis 20(Suppl 1): S85-S94.