

Inhaling menthol may improve cognitive function in Alzheimer's disease

May 10 2023



Graphical Abstract Olfaction is becoming a central player in the pathophysiology of several brain disorders. Actually, smell may play a role in the prediction of the future brain diseases including Parkinson or Alzheimer. Also, the role of the immune system in these illnesses is a becoming issue to be considered as well. In our work we tried to shed light on the many intricate interactions between olfaction, immune system and nervous system. We have found that the stimulation of the immune system through exposure to certain fragrances, such as menthol, can have a beneficial effect on cognition. On the contrary, anosmia induced by methimazole treatment has a deleterious impact in cognitive capacity. We have demonstrated that menthol inhalation or Treg depletion improved cognitive skills in healthy mice and more importantly, in Alzheimer's disease murine models. We have seen that downregulation of IL-1 β expression in the brain is a common feature induced by menthol inhalation or



Treg inhibition. Notably, IL-1 receptor inhibition by Anakinra administration improved cognitive capacity both in healthy and in an Alzheimer's disease murine model. The link between impaired olfaction and immune system in neurologic diseases remains to be understood but it opens the door for its potential use in therapies for CNS-related diseases. Credit: *Frontiers in Immunology* (2023). DOI: 10.3389/fimmu.2023.1130044

Researchers from Cima University of Navarra (Spain) have shown in animal models of Alzheimer's disease that inhaling menthol improves cognitive ability. This study discovered that repeated short exposures to this substance can modulate the immune system and prevent the cognitive deterioration typical of this neurodegenerative disease.

When analyzing its mechanism of action, they observed that when smelling this aroma, the level of interleukin-1-beta (IL-1b), a critical protein mediating the inflammatory response, was reduced. Furthermore, by inhibiting this protein with a drug approved for the treatment of some autoimmune diseases, they were also able to improve cognitive ability in these diseased mice.

This research highlights the potential of odors and immune modulators as therapeutic agents. Furthermore, it opens the door to developing therapies based on stimulating and training the <u>olfactory system</u> to prevent or alleviate the effects of Alzheimer's and other diseases of the central nervous system. *Frontiers in Immunology* published the results of this study in its latest issue.

Brain, smell, and immune system connection

The functional balance of the brain depends on <u>complex interactions</u> between various types of nerve cells, immune cells, and neural stem



cells. In this complex web of interactions, several studies have addressed the immunomodulatory and neurological effects of odorants. Other previous works have also shown a correlation between the loss of the sense of smell and the appearance of the first symptoms of Alzheimer's disease.

"We have focused on the olfactory system's role in the immune and central nervous systems, and we have confirmed that menthol is an immunostimulatory odor in animal models. But, surprisingly, we observed that short exposures to this substance for six months prevented <u>cognitive decline</u> in the mice with Alzheimer's and, what is most interesting, also improved the cognitive ability of healthy young mice," says Dr. Juan José Lasarte, director of the Immunology and Immunotherapy Program at Cima and principal author of the investigation.

Another result noted by the researchers is that "blocking the activity of T regulatory cells, one type of <u>immune cells</u> with immunosuppressive activity, also improved the cognitive ability of mice with Alzheimer's disease and also caused a clear benefit in the cognitive ability of healthy young mice," explains Dr. Ana García-Osta, a researcher at Cima's Gene Therapy of Neurological Diseases Program and principal co-author of this work.

"Both menthol exposure and Treg cell blockade caused a decrease in IL-1b, a protein that could be behind the cognitive decline observed in these models. In addition, the specific blockade of this protein with a drug used in treating some autoimmune diseases also improved the cognitive capacity of healthy mice and mice with Alzheimer's."

"This study is an important step toward understanding the connection between the <u>immune system</u>, the central nervous system and smell, as the results suggest that odors and immune modulators may play an important



role in the prevention and treatment of Alzheimer's and other diseases related to the central nervous system," points out Dr. Noelia Casares, also a researcher at the Immunology and Immunotherapy Program and first author of the article.

More information: Noelia Casares et al, Improvement of cognitive function in wild-type and Alzheimer's disease mouse models by the immunomodulatory properties of menthol inhalation or by depletion of T regulatory cells, *Frontiers in Immunology* (2023). DOI: 10.3389/fimmu.2023.1130044

Provided by Universidad de Navarra

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