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INTERVENTIONS FOR PREVENTION OF ALZHEIMER'S DISEASE: A FOCUS ON OLFACTION

Psychology

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ABSTRACT

Epidemiological research has identified loss of olfactory perception as a salient risk-factor associated with the slowly developing, but insidious, cognitive decline characteristic of late onset Alzheimer's disease (LOAD). Evidence supports the conclusion that the first appearance of neural loss associated with LOAD occurs in the periphery of the olfactory brain. These two well-supported conclusions focus attention on the nasal cavity's olfactory mucosa which contains the dendrites of the olfactory nerves whose axons ascend through the foramina of the cribriform plate to the olfactory bulb. Consequently, this review begins with a description of the physiology of the olfactory mucosal tissue, the barrier between contaminants in breathed air and the olfactory bulb. The functionality of the mucosa's innate immune system(IIS) regularly protects the olfactory bulb from infectious threats in breathed air. Therefore, any event hindering the efficiency of the IIS of the olfactory mucosa, in turn, enhances the likelihood of disease of the olfactory bulb which is where LOAD begins. Given the known of the physiology of the olfactory mucosa, an event likely disrupting the efficiency of the IIS is the wide-spread use of drugs to treat the symptoms of the common cold and insomnia. A prudent resolution to decreasing the risk of LOAD is ultimately a cognitive, behavioral issue of avoiding the use of these drugs which may seem utilitarian, but probably is not, and whose use is risky.

KEYWORDS

Alzheimer's disease; olfaction; over-the-counter drugs; sleep-aids, histamine; innate immune system (IIS); psychoneuroimmunology

INTRODUCTION

This review describes a probable sequence of events linking an insult to the vitality of the innate immune system (IIS) of the olfactory mucosa to the insidious, loss of brain tissue eventually manifesting as Alzheimer's dementia. Germane considerations: (a) loss of olfactory perception is an early harbinger of late onset Alzheimer's disease (LOAD) (Attems, Lintner, & Jellinger, 2005; Devanand et al., 2015; Doty, 2008), (b) research supports the idea that LOAD likely begins in the periphery of the olfactory brain (Daulatzai, 2015; Ethell, 2014; Franks, Chuah, King, & Vickers, 2015), and (c) a behavioral treatment is effective in treating lost olfaction due to lingering effects of infections, the most common cause of lost olfaction. Unfortunately, the new treatment is effective with only about 60% of those engaging the treatment; however, this is a vast improvement over no treatment (Altundag et al., 2015). In consideration of these findings, this question arose: What dynamics are associated with the presence of infectious material in breathed air and whether or not those infectious materials might reach the interior of the skull? Toward answering these questions, consider the functionality of the IIS of the respiratory mucosa.

Discussion of the IIS of the respiratory mucosa

This summary of the anatomy and physiology of the sinonasal cavity relies on information provided by Beule (2010), Hariri & Cohen (2016), Ethell (2014), Doty (2008) and Dasaraju & Liu (1996). Figure 1 depicts cells that populate the respiratory mucosa of the sinonasal cavity and related features. The top of the figure faces the nasopharyngeal airway. The ciliated epithelial cells act as a physical barrier preventing contaminants in air from infiltrating into the depths of the tissue. The barrier is strengthened by transmembrane proteins.

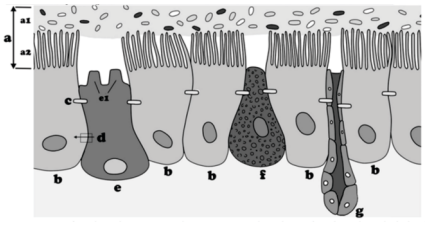

Figure 1. The cells and fluids lining the resporatory mocosa. Key. a Airway surface: liquids,: a1, mucus layer floating in that layer are mircrobes and particular matter; a2, pericillary layer; b, ciated epithellial cells; c, tight junctions; d, gap junction; e, solitary chemosensory cell: e1 bitter and sweet receptors; f, goblet cell; g, Bowman's capsule. This figure was drawn by Caroline R. Mann. It is modelled after a figure in Laryngoscope Investigative Otolaryngology, 2016 Aug; 1(4): 88-95. By Ryan M. Carey, Nithin D. Adappa, James N. Palmer, Robert J. Lee, and Noam A. Cohen. Doi: 10.1002/lio2.26 This is an open access article whose use is under the terms of Creative Commons Attribution-NonCommercial License.

Facing the airway is a layer of mucus with its antimicrobial proteins (e.g., mucins) and is often populated with viruses, bacteria and debris of incoming air. Antimicrobial proteins are sticky and tend to bind microbes and particulate matter. It is not sufficient that antimicrobial proteins bind to microbes, the complex must be moved out of the airway rather quickly to avoid infectious material from accumulating, i.e., the "garbage" needs to be taken out nearly continuously. The process for "garbage-removal" is mucociliary clearance.

The layer of mucus floats on a layer of serous fluid. Mucociliary clearance is accomplished by brush-like strokes of the cilia (accomplished by circular movements of cilia) moving through the serous fluid and moving the mucus layer toward the back of the throat. Upon arrival at the back of the throat, it is swallowed, dumping the complex into the acid bath of the stomach (destroying captured microbes). An accumulation of mucus at the back of the throat can stimulate coughing and "hacking-up" the "gunk," thereby stirring the mucus and facilitating swallowing. Coughing often expels the complex of mucus and bound microbes. The system additionally recruits sneezing and rhinorrhea for removal of contaminants.

The nearly constant "brush strokes" of the epithelial cells' cilia move the mucus layer at a speed of 2 to 25 mm/min. Faster beating by cilia moves the mucus faster. Faster beating is generated by increases in contaminants in the airway. Given the constant movement of the mucus out of the cavity along with some serous fluid, both must be continuously replaced. The glandular cells and goblet cells fulfill that function. Ultimately, the fluids of the mucosa are supplied by the extensive vascular network in the lamina propria (the tissue next to the bones of the sinonasal cavity, not depicted).

Recent research (Hariri & Cohen, 2016) has improved our knowledge of the IIS's functionalities by describing how the system senses and responds to a threat, and eventually treats that threat, thereby preventing infectious doses of bacteria and viruses from descending into the lungs and/or ascending into the brain. There are receptors associated with the epithelial cells (Hariri & Cohen, 2016) that respond to increases in numbers of microbes; and, when appropriate, facilitate the release of antimicrobial peptides, e.g., lysozyme. There are the solitary chemosensory cells which sense large concentrations of

bacteria in mucus and serous fluids (Dando et al., 2014). The bitter receptor of the cell is activated by secretions of gram-negative bacteria (i.e., a quorum sensing secretion) which, in turn, releases calcium ions which transverse a gap junction connecting the chemosensory cell to an epithelial cell. The increment in calcium flow, in turn, stimulates release of nitric oxide, a bacteria-killing toxin. Sweet receptor stimulation is activated by a plentiful supply of glucose which tends to inhibit the flow of calcium ions. When bacteria multiply, they deplete the sweet receptor stimulus; hence, reducing the inhibition of calcium flow which, in turn, increases the release of the nitric oxide, hence killing bacteria.

We provided this summary of the functionality of the IIS of the sinonasal cavity to call attention to the complex dynamics of the marvelously effective system which prevents infections of the components of the cavity as well as other tissues. A prime example of the system's utility is that it cures many instances of infections by viruses of the common cold (4-6 yearly among children; fewer among adults).The system also cures mild infections of flu-viruses and disables many pathogenic bacteria. If the system fails, bacteria can descend toward the lungs, where they might multiply in the bronchial tubes and, very problematically, in the alveoli (e.g., pneumonia). A severe infection of the depths of the lungs is the 3rd leading cause of death. Here, we discuss the possibility that a failure of the system may also lead to disease of the olfactory bulb which, in turn, could propagate another leading cause of death, LOAD.

Hindering the innate Immune system of the respiratory mucosa leaves the lungs and brain vulnerable.

Events causing dryness of the mucosa is a cause of failure of the respiratory mucosa's IIS. The system operates efficiently when the airway is sustained at its usual 100% humidity and body temperature. The air within the sinonasal cavity is warmed through circulation around and over the tissue lining the bones of the cavity, the warming associated with the frontal sinuses and the warming of exhaled air. The availability of fluids to moisturize the tissue comes from blood vessels of the lamina propria and to a lesser extent from drainage from the brain via the foramina of the cribriform plate. *A dry mucus-layer does not capture microbes and dirt.*

The mucosa is supplied with fluids by the dense vascular network of the lamina propria. Changes in vasodilation regulate the release of fluids from that vascular. Increases in vasodilation is in response to the stimulation of increased contaminants coming into the cavity. Vasodilation is, in turn, a response to a release of histamine from mast cells of the lamina propria. Also, bacterial features interact with the bitter taste receptors T2R38 in the epithelial layer and that stimulation leads to the responses of faster ciliary beating (hence faster movement of microbes out of the airway) and release of nitric oxide. Also, vasodilation increases the release of antimicrobial components floating in the blood stream. Extensive vasodilation temporarily expands the tissue of the respiratory mucosa with actions that provide sufficient moisture throughout and sufficient serous fluid to allow cilia to move and engage fast ciliary clearance. A swollen respiratory mucosa is manifest by the outward signs which can include rhinorrhea, congestion, some difficulty breathing, frequent swallowing and coughing; the symptoms of viral infections by common cold and flu viruses.

There are two kinds of events that could disable the sinonasal cavity's IIS. One, the system can be overwhelmed by inhaled particulate matter, such as caused by smoking cigarettes or other herbal products. That is, a steady supply of dirty air would produce nearly constant high levels of activity of the IIS which may eventually exhaust the production of mucus. Also, high levels of contamination of the mucosa would make it difficult to sense an increase in contamination (following the general rule of psychophysics: it takes greater intensity to produce change when intensity is already great). Consequently, during cold-season, cold viruses would not be captured and removed quickly but would linger close to epithelia cells, hence increasing the likelihood of infecting these cells.

With the threat of many cold-viruses, there is vasodilation which in turn produces the overt symptoms of the common cold. The symptoms of a common cold are unpleasant (e.g., rhinorrhea, etc.) There are currently no medicines that can cure a common cold. The only cure is due to actions of the IIS. However, there are over-the-counter (OTC) drugs purported to reduce the unpleasant symptoms of a cold. These purported medicines induce vasoconstriction. Often, their active ingredients are antihistamines, blocking vasodilation, or are agonists at the α1-adrenergic receptor, directly inducing vasoconstriction, or both. Vasodilation is a critical response of the IIS to an invasion of disease-producing microbes because vasodilation is necessary for fully bathing the fast-beating cilia in serous fluid, thereby allowing fast mucociliary movement of mucus. Vasoconstriction leads to drying of the mucosa hence muting the symptoms of infections but interfering with the functionality of the IIS to cure viral infections.

Consequences of a dried respiratory mucosa

The consequences of drying the respiratory mucosa is a mucus layer that does not move (or moves slowly with inefficient ciliary beating) and a dry mucus layer. These actions are setting conditions for increased chances of viral infections of the mucosa (viruses are not moved quickly away from epithelial cells). Recently, there has been increased interest in the role of infections in the development of LOAD (Dando et al., 2014; Devanand, 2018; Harberts et al., 2011; McEwen, Jenkins, & Martens, 2008; Wang, Tan, Yu, & Tan, 2015). Hindrance of the IIS open the possibility for bacteria not being captured and killed in the mucus and descending into the depths of the lungs (Beule, 2010). As bacteria invade and multiply in the lungs, there is a fever.

Acetaminophen, often an active ingredient in medicines advertised to treat the cold and flu, is an analgesic given to lessen pain that might be associated with a cold. Acetaminophen also reduces fever. However, generally, cold and flu viruses do not produce a fever (Dasaraju & Liu, 1996). When fever occurs, it often indicates a bacterial infection of the bronchi and lungs. So, acetaminophen might mute the warning that a viral infection has led to a bacterial infection (bacterial infections concurrent with a cold are not a rare event; George et al., 2014). The postponement of the diagnostic sign of a fever accompanied by cold and flu symptoms might reduce the chances of a prescription of an antibiotic for a bacterial infection which can be a fatal mistake.

Given what we know about the strengths and weaknesses of the IIS and the known effects of commonly used OTC drugs for treating initial symptoms of the common cold and flu, this conclusion can be drawn. These OTC drugs likely enhance the chances of bacterial infections of the lungs. That likelihood is sequela of a dry mucus caused by medications whose only effects are to relieve some unpleasantness, and only temporarily (De Sutter, Saraswat, & van Driel, 2015; De Sutter, van Driel, Kumar, Lesslar, & Skrt, 2012). Unchecked bacterial growth in depths of the lungs can be fatal sequela of flu. Unfortunately, some OTC products are advertised as medicines for both the cold and flu.

A disruption of the functionality of the mucosa also puts the olfactory bulb in jeopardy. Only the thin layer of the olfactory mucosa separates the laminae of the cribriform plate from the olfactory bulb. There is mounting evidence that infectious material can, if not dealt with by mucociliary clearance, ascend to the olfactory bulb (Dando et al., 2014; Harberts et al., 2011; McEwen et al., 2008). Infections can initiate immune processes in the bulb and if the initial response does not succeed that triggers more immune system responses which can eventually lead to deadly inflammation, hence the beginning of LOAD (Wang et al., 2015). Once inflammation in the olfactory bulb occurs, that is a setting condition for a march of brain-death from the bulb to the entorhinal cortex to the hippocampus which manifests as LOAD (Ethell, 2014; Reid, Avens, & Walf, 2017).

CONCLUSION

Because there are multiple kinds of infections and widely different circumstances surrounding any single incidence of a disease, there is no way to conclude that any one infection might have been made tragically worse by taking an OTC drug. Also, LOAD is a slowly developing disease and it is difficult to know which event may have caused the beginnings of the development of LOAD somewhere, sometime during a decade before the disease becomes manifest. Nevertheless, with the initial loss of olfaction, there should be steps taken to correct the loss.

The optimal treatment for the initial symptoms of viral infections is to avoid anything that might interfere with the ordinary functions of the IIS; e.g., avoid most OTC cold and flu drugs and carefully monitor for the development of a fever which signals bacterial infection and when to optimally use an antibiotic.

Chronic obstructive lung disease and LOAD are among the 10 leading causes of death in prosperous nations. We hold that incidences of both can be reduced significantly if *behaviors* are engaged that facilitate the health of the IIS. Cognitive behavioral interventions involving encouraging avoidance of dangerous choices seems to be the appropriate way to sustain healthy lifestyles or to improve not so healthy lifestyles. Also, certain behaviors can be avoided. For example, one might learn and then behave in a way that does not hinder the functioning of the IIS.

One can encourage the construal that the symptoms of a cold are a sign the IIS is curing a cold and appreciate that. One can encourage the construal that modern advertisements are very sophisticated technologies designed to encourage buying cheaply made and marketed OTC drugs purported to shorten the duration of a cold, and touted as even aiding and abetting the curing of a cold (the data suggest otherwise (De Sutter et al., 2015, 2012; Duncan-Lewis, Lukman, & Banks, 2011). Encouraging rational thinking is one component of cognitive behavioral interventions. The other component is to engage behavior that avoids interfering with the IIS's protection of both lungs and brain; e.g., withholding the temptation to medicate a common cold for only a small increment of relief from minor unpleasantness.

Changing a maladaptive construal and replacing it with an adaptive one is a feature of cognitive behavioral therapy. Encouraging adaptive behavior such as avoiding the temptation to quickly attempt to medicate a common cold, is also amenable to cognitive behavioral therapy. As we (Reid et al., 2017) concluded recently, biologically informed, cognitive, behavioral interventions are optimal ways of preventing the development of LOAD. Despite decades of attempting to cure LOAD through medicine, such activity has failed. That failure has left steps to prevent LOAD as the only currently available solution to manage a deadly, debilitating disease that affects a large proportion of elders. Sustaining, and not hindering, the health of the olfactory mucosa appears to be a significant contribution toward preventing the development of LOAD.

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