Short Review of Current Research on the Physiology and Pathology of Olfactory Detection

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Received date: November 10, 2015; Accepted date: March 25, 2016; Published date: March 30, 2016

Abstract

Most concepts related to physiology and pathology of olfaction has been related to abnormalities in neural function related to changes in central nervous system disorders or in disorders of olfactory nerves. While these events have been useful in understanding olfactory physiology and pathology most pathology of olfactory detection lies in problems related to olfactory receptor function not to the neural correlates per se. This brief review introduces pertinent information which relates to the role that olfactory receptors, their physiology and their pathology play in olfactory function.

Keywords: Olfaction; Olfactory receptors; Growth factors; Phosphodiesterase inhibitors; Theophylline

Introduction

Smell function involves a tripartite system involving the brain, nerves and receptors. Olfactory detection, which involves each of these systems, depends initially on the function of olfactory receptors through which the initial events in this sensory system occur. These events occur at the receptor membrane. These membrane proteins in which the receptors, ion channels and cell transponders reside comprise nearly 30% of the proteins in eukaryotic cells. They also constitute more than 50% of all cellular drug targets. It is the purpose of this review to discuss sensory function of the olfactory receptors, particularly in relationship to the pathology encountered in human loss of smell function, and its subsequent treatment to restore this function through specific drug effects. The changes observed by these pathological events lend insight into the physiology of olfactory detection.

Olfactory Receptor Function

Olfactory receptors have been studied anatomically and physiologically for many years [1] and are involved in the initial coding in the olfactory system [2]. These receptors are unique in that they have no blood vessels, no lymphatics, do not exhibit mitosis but turnover structurally rapidly, many over a 24-hour period, some in a few days and others in less than a month [3]. This rapid turnover depends upon the continual stimulation of stem cells in both olfactory epithelium (and in taste buds) with growth or transcription factors that stimulate these stem cells to induce the growth, maturation and perpetuation of the panoply of receptor cells necessary for receptor function in smell (and taste) [4]. Any interference with secretion of these growth or transcription factors inhibits smell (and taste) function. These growth or transcription factors comprise multiple chemical moieties but major among these are sonic hedgehog (Shh) [5] and carbonic anhydrase (CA) VI [6]; cAMP and cGMP are also important moieties in receptor function in several ways [7,8]. Each of these factors play multiple roles in receptor function with secretion of each factor enhanced by phosphodiesterase (PDE) administration [3].

Olfactory Receptor Growth Factors

There is multiple growth and transcription factors that play a role in olfactory receptor function [4]. However, there are several of these factors that play dominant roles. It is important to recognize the multiple roles each of these moieties play in receptor function both individually and together. cAMP and cGMP are the final activating steps after the binding of sensory stimuli to G-protein coupled receptors (GPCR) at the cellular membrane followed by the subsequent stimulation of adenyl cyclase III with its downstream products cAMP and cGMP responsible for amplification of the receptor generator potential to induce depolarization and subsequent initiation of the neural response initiated at the receptor with subsequent transmission of this signal along the sensory nerves to the brain [9]. The binding of the olfactory stimulus to the GPCR activates, via the G-protein Golf, adenyl cyclase resulting in an increase in cAMP which elicits opening of cation channels directly gated by cAMP. This induces an increase in intracellular Ca+ concentration which activates a Cl- current which, owing to an elevated reversed potential for Cl-, induces depolarization of the olfactory neurons. Amplification of the receptor generated potential leads to the subsequent generation of the action potential which conveys the chemosensory information along the olfactory fila into the olfactory bulb and ultimately to the brain [9]. This olfactory signal transduction pathway is modulated by cGMP which plays an important role in regulating function of olfactory signaling [10-13] as does calcium itself [14]. Any interference with cAMP and cGMP presence inhibits activation of the receptor signal with inhibition of smell function [3]. Both moieties may also play a role in stem cell stimulation and act as second messengers in receptor growth and development. The PDE inhibitor theophylline increases both cAMP and cGMP in patients with loss of smell (hyposmia) which activates this system and thereby improves hyposmia [1,15]. These results emphasize the role of Ca2+-calmodulin-dependent phosphodiesterase localized to olfactory cilia in this system [14,16].
Olfactory Receptor Pathology

There are also other effects of the PDE inhibitor theophylline in maintaining taste and smell receptor function. Although its mechanism(s) of action on receptor function is complex much is known about these actions particularly emphasized by pathology which affect patients with several types of smell dysfunction [3]. Indeed, recent studies have demonstrated that many people have lost ability to detect, and thereby lost ability to recognize olfactory stimuli, through the action of various pathologies which interfere with olfactory detection [3]. These pathologies involve viral-type infections [18], allergic and other immunological abnormalities [19], head injuries [20] and a variety of other pathological processes [3].

Treatment or Repair of Olfactory Receptor Pathology

It has been useful to develop therapies to correct these pathological factors which interfere with olfactory detection. Patients who develop zinc deficiency for a variety of causes lose ability to detect olfactory signals primarily through the loss of gustin or CA VI which is a critical growth or transcription factor to maintain taste and smell receptor function [6,21]. Indeed, absence of this growth factor is associated with anatomical distortion of taste bud receptors [17] which is restored following zinc repletion [17]. By analogy, similar events can occur in the olfactory receptors. Treatment of zinc deficient patients with zinc ion increases secretion of these growth factors with restoration with both taste and smell receptor function [6]. Zinc depletion also decreases the activity of calmodulin regulated cAMP which is another activity of cAMP in olfactory receptor function.

Another major pathology which contributes to loss of olfactory receptor function relates to the inhibition of secretion of Shh. Patients with smell loss exhibit significant inhibition of nasal mucus Shh [5]. However, treatment with phosphodiesterase (PDE) inhibitors, particularly theophylline either orally or intranasally, activates secretion of nasal mucus Shh or thereby improves receptor activity in these hyposmic patients [5].

Still another major cause of loss of olfactory receptor function relates to inhibition of secretion of adenyl cyclase and its downstream components cAMP and cGMP. Inhibition of secretion of these moieties causes loss of olfactory receptor function with subsequent loss of smell function [3]. Treatment with PDE inhibitors, particularly theophylline either orally or intranasally, activates secretion of cAMP and GMP and thereby increases both receptor function and ability to detect olfactory signals [1,10].

Conclusion

These pathological events affecting smell function in humans have their action mainly by inhibition of olfactory receptor function through inhibition of secretion of these well-known growth factors which directly stimulate stem cell function to enhance growth, development and perpetuation of the elegant repertoire which comprises olfactory receptors and thereby their function.

It is through these pathological events that several important aspects of the physiology of olfactory receptor function can be elucidated.
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