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REVIEW ARTICLE

Olfaction, pheromones and life

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Abstract

Background: From an evolutionary standpoint, olfaction is one of the oldest senses, and one that affects all aspects of life. This review discusses the influence of olfaction and pheromones on life.

Methods: A literature search was conducted using MEDLINE (1966–2012), Embase (1988–2012), The Cochrane Library (1993–2013) and Ovid (1966–2012).

Results: Olfaction plays an important role in life, from infancy through to adulthood and declining health in old age. Culture, memories and emotions, which add to life's complexity and overall enjoyment, are also influenced by olfaction.

Conclusion: Olfaction has a chronological influence on life, affecting all aspects from the cradle to the grave; it plays a role in the quality of life as a key ingredient of human evolution, survival and enjoyment.

Key words: Smell; Pheromones; Life

Introduction

'Providence made us noses to smell with', Socrates declared circa 400 BCE,[1] thus showing a basic comprehension of olfaction – one of the oldest senses, phylogenetically speaking.[2] Olfaction affects all aspects of life that can be thought of as the 'seven stages of man', from infant to old age or second childhood 'sans everything', as described in Shakespeare's *As You Like It*.[3] Olfaction also plays a key role in an individual's decline in health either from ageing or a specific disease process affecting the olfactory cleft or the projection pathways of the brain. In addition to the chronological influence of olfaction, life is a rich tapestry with multiple interwoven experiences, decorated by odours that evoke memories and emotions, thereby influencing the overall quality of life.

The sense of olfaction is ubiquitous in the animal kingdom; it arises from the nasal cavity in vertebrates and the sensory cells of the antennae in invertebrates. Humans are capable of detecting more than 10 000 different odours and distinguishing between 5000^4 odours at low concentrations – an acuity that exceeds manufactured analytical instruments.[5] Volatile odorants dissolve on the mucous layer that overlies receptors on the epithelial surface. Odours then bind to receptor cells, initiating G protein-coupled transduction by opening nucleotide-gated ion channels. Signal transduction occurs by altering the resting potential of olfactory cells and transmitting signals via action potential propagation to the olfactory bulb and onwards to the olfactory cortex. Neural projections then reach the other areas of the brain including the limbic system, where signals are integrated and interpreted, influencing behaviour and emotions.[6]

Most vertebrates, including humans, detect odours as well as pheromones. The latter is a term that was introduced by Peter Karlson and Martin Lüscher in 1959 to describe a volatile substance that is secreted and produces a specific behavioural response in another animal.[7] The term 'pheromone' is derived from the Greek *pherein* ('to convey') and *hormōn* ('to impel, set in motion'). Pheromone detection in animals is mediated by the vomeronasal organ (or Jacobson's organ), which was identified in snakes by Frederik Ruysch prior to 1732 and then as a pit on the inferior nasal septum in humans by Ludwig Jacobson in 1813.[8] There is evidence that humans have a vomeronasal organ,[9] but its function in pheromone detection has been disputed.[10] This is supported by the degeneration of neuronal projections from the vomeronasal organ in human fetal development.[11] Odour and pheromone detection is thought to be mediated by similar pathways in humans and other vertebrates.[12]

Odours have influenced cultural life from antiquity to contemporary times, contributing to spiritual and ritualistic behaviour. In ancient Egypt, the burning of incense was central to the worship of the gods and large quantities of incense were burned every day in temples throughout Egypt.[13] The first textbook on

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surgery, described in the Edwin Smith Papyrus[14] (dating to circa 1500 BCE), used olfactory cues in patient examination and Cleopatra is reputed to have used perfume comprising of rose and orange oils for seductive purposes. In the Tudor period, smells were used to stimulate cognition, with Queen Elizabeth I wearing rotten apples with cloves on a necklace for this purpose.[2]

The *olfactory revolution* in the eighteenth and nineteenth centuries, which developed as the result of sanitisation and improved personal hygiene, resulted in a relative deprivation of the olfactory system.[15] In the twentieth century, Sigmund Freud pioneered the hypothesis that olfaction in humans was becoming relegated in its sensory importance. This was based on its cyclical nature and the erect upright posture of humans, which created a reliance on visual stimulation over olfaction.[16] Darwin's theories of inter-racial variation also supported the declining importance of olfaction.[17] However, from the latter part of the twentieth century, there has been increased research into olfaction leading to a greater understanding of this sense. Alexander Graham Bell popularised the idea that it was difficult to measure a smell; in 1914, he stated that 'If you are ambitious to find a new science, measure a smell.' In 2004, advances in the field were recognised by the Nobel Prize being awarded to Richard Axel and Linda Brown Buck for discovering odorant receptors and the organisation of the olfactory system. This review aims to show the evidence that olfaction has a diverse and important influence on the quality of life enjoyed by humans and indeed, to a certain extent, on life itself.

Methods

To research the influence of olfaction and pheromones on life, a search was conducted using MEDLINE (1966–2013), Embase (1988–2013), The Cochrane Library (1993–2013) and Ovid (1966–2013). Combinations of the following search terms were used: olfaction, pheromones, anatomy, function, evolution and history. Relevant and interesting references were cascaded. Theories were identified and are discussed in the following sections.

Results

Mate selection and reproduction

Olfaction has an essential role in the propagation of life and in evolution. It is pheromone-mediated in mate selection,[18] conception and the successful development and nurturing of progeny. The multibillion dollar deodorant and perfume industry uses this concept to mask body odours and market certain aromas that are deemed attractive to potential mates.

Murine studies have shown a number of pheromone-regulated effects, including the Lee–Boot effect where the menstrual cycle of female mice is suppressed in the absence of male mice.[19] The Bruce effect, or pregnancy block, is another pheromone-mediated effect, whereby a pregnant female mouse housed with a male who did not impregnate her will miscarry.[20] There is also evidence that humans respond to pheromones in a similar fashion. McClintock found that women can synchronise their menstrual cycles if cohabiting[21] – a phenomenon mediated by two opposing axillary pheromones.[22] Russell and co-workers found that humans can determine the gender of another via their odour[23] and that newborn babies can recognise the axillary and breast odours of their mothers.[24,25] Olfaction therefore plays a vital role in mate selection and conception, as well as early infant nurture – all essential for the propagation of life.

Survival and safety

The sense of olfaction acts as a safety mechanism alerting us to the presence of harmful or offensive odours and predators, hence influencing survival and the prolongation of life.

The defensive reflex of flight on encountering a predator is mediated by pheromones and has been studied extensively in rodents.[26] Mice also release alarm pheromones under stressful conditions, such as elevated levels of carbon dioxide, that elicit a freezing response in other mice. The detection of dangerous odours, such as gas or smoke, also has an important role in human safety and survival. *Tert*-butylthiol (an organosulphur compound) is added to natural gas, thereby producing the typical odour of *rotten eggs* used to aid the detection of gas leaks. People with anosmia could potentially be offered nasal implants in the future to detect such dangerous odours. Future counter-terrorism technology may be able to detect dangers, such as explosives, by using electronic nose devices.[27] Potential advances in the clinical environment include the detection, using electronic noses, of airborne odours produced by organisms such as methicillin-resistant *Staphylococcus aureus*, which could potentially protect patients and equipment from contamination, hence reducing patient mortality and morbidity.

Degeneration and disease

Deficiencies in olfaction can be congenital in the instance of Kallmann's syndrome,[28] due to age-related decline[29] or the result of disease, including sinonasal, neurodegenerative or neoplastic conditions. Aberration of olfaction is common, with over two million people in the USA being affected.[30] Irrespective of the cause of a declining sense of olfaction – congenital, ageing or disease-related – there is a subsequent decline in a patient's quality of life that needs to be addressed when selecting treatment.

A temporary decline in olfaction, attributed to rhinitis and nasal obstruction, has been seen over a one year period in up to 15 per cent of the adult female population.[31] However, the most common causes for chronic anosmia are following viral upper respiratory

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tract infection (40 per cent), after head trauma (39 per cent) and due to sinonasal disease, including nasal polyposis (6 per cent).[32,33] Treatments for chronic sinonasal disease, including steroids and endoscopic sinus surgery, have shown an improvement in olfaction, albeit on a temporary basis.[34]

Neurodegenerative conditions, such as Alzheimer's and Parkinson's disease, may present with parosmia or anosmia.[35] The post-mortem histological examination of Alzheimer's patients has shown changes in the olfactory areas.[36] This decline in olfaction may be measured using olfactometry, a possible screening tool for such conditions that are increasing in incidence in a population with an ageing demographic. Olfactory dysfunction has also been described as an early sign in schizophrenic patients[37] and may therefore be used as a test for predisposition and onset of this psychiatric condition. The association of olfactory aberration with neurodegenerative and psychiatric conditions suggests that olfaction influences cognition and social functioning – important components of daily human life.

- **Phylogenetically, olfaction is one of the oldest senses, with a basic understanding dating as far back as Socrates**
- **Olfaction has a role in mate selection, conception and early infant nurture**
- **Safety and survival are mediated by olfaction, protecting us from predators and harmful substances**
- **The most common causes of chronic anosmia are following viral upper respiratory tract infection (40 per cent), after head trauma (39 per cent) and due to sinonasal disease, including nasal polyposis (6 per cent)**
- **The European position paper emphasises the need for increased research to reduce morbidity from anosmia post-resection of sinonasal and skull base tumours**
- **Olfaction can be used as a diagnostic tool in neoplastic processes to detect bladder carcinoma and mesothelioma**

Head and neck malignancies, including sinonasal ones, may present with the emission of unpleasant odours or as symptoms of altered olfaction. As olfaction contributes greatly to our sense of taste,[38] patients with anosmia also experience gustatory dysfunction. The impact on quality of life caused by abnormalities in taste and odour perception is seldom addressed in cancer patients post-surgery or post-chemoradiotherapy, but can lead to significant morbidity, including malnutrition.[39] This can have a negative impact on prognosis and hence overall patient survival. To highlight this problem, the European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base recommended increased research in this field to reduce morbidity post-resection of sinonasal and skull base tumours.[40]

In addition, olfaction can be used as a diagnostic tool in neoplastic processes. Recent work with dogs trained to detect urine samples from patients with bladder cancer has shown a success rate of 41 per cent.[41] In the respiratory setting, electronic noses have also been used to detect malignant mesothelioma using a breath test to analyse volatile organic compounds.[42] These new techniques open the future possibility of using olfaction to detect disease processes and can therefore have a positive impact on patient survival – another influence of olfaction on life.

Conclusion

From the cradle to the grave, the role of olfaction pervades all aspects of life, influencing mate selection, conception, infant nurture, life prolongation and disease. In addition, an individual's quality of life is influenced by olfaction and considerable debilitation is associated with dysfunction or absence of the sense of smell. Although phylogenetically one of the oldest senses, the importance of olfaction is being appreciated only relatively recently and should be considered as a key ingredient to human evolution, survival and the enjoyment of life.

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