REVIEW ARTICLE

OLFACTORY DYSFUNCTION IN NEURODEGENERATIVE DISEASES

M. Hakan Özdener, Nancy E. Rawson

Monell Chemical Senses Center, University City Science Center

Interest in olfactory dysfunction has increased tremendously in the past decade, in part due to observations that chemosensory impairment is an early symptom of many neurodegenerative diseases. Several features of the olfactory system make it particularly relevant to understanding neurodegeneration/regeneration. First, while being vulnerable to environmental and infectious exposure, the olfactory system has the unique property of ongoing replacement of the olfactory sensory neurons under physiological conditions and following injury. Second, the receptor neurons residing in the periphery are developmentally related to the central nervous system, yet are accessible relatively noninvasively via biopsy from living subjects. Third, olfactory performance can easily be tested in a variety of ways that provide insight into the function of brain areas involved in detection, identification and memory. In addition to providing insights into the etiology or diagnosis of disease, a better understanding of olfactory neurobiology is needed to develop ways to treat olfactory dysfunction, which affects both quality of life and personal safety. At least 3,000,000 Americans suffer from chemosensory disorders and that is likely to grow as the aging segment of the population increases. Olfactory impairment represents a danger to the individuals resulting from inability to detect hazards as natural gas and spoiled food and threatens quality of life through the loss of enjoyment of foods and fragrances.

The neurological systems responsible for olfactory function represent perhaps the most diverse, complex and adaptable components of the nervous system. Losses in olfaction result from changes at both the anatomical and molecular level. This loss can result from aging, toxins, infectious agents, environmental factors and a variety of diseases. Understanding the neurobiology of this sensory system may help us to develop new diagnostic measures and treatments for neurodegenerative disease as well as improving the quality of life for millions of people who are handicapped by the inability to detect the flavors and fragrances around them.

Key words: Olfactory dysfunction, neurodegenerative diseases

INTRODUCTION

Olfactory impairment is a common occurrence in aging and may be an early signal of neurodegenerative diseases. Olfactory loss caused by aging and diseases affects both quality of life and personal safety. Aging, as well as viral infections, neurodegenerative diseases, head injuries, chronic sinusitis infections and nasal obstructions are the most common causes of olfactory disorders (73). In addition, at least one third of older people report dissatisfaction with their sense of taste or smell (1, 70). The impact of sensory loss on elders is not only physiological but also emotional. The sense of smell and its capacity is critical for most mammals in terms of identification and evaluation of food, mates and territories, and in general for the maintenance of a good quality of life.

The susceptibility of elderly people to aging and diseases, particularly neurodegenerative diseases, is varied. Therefore, complaints about sensory functions should be considered seriously as possible indicators of neurodegenerative diseases or other underlying conditions. The population of elderly is increasing as a result of improved health care throughout the world, and the attention of the medical and scientific community has focused on prevention and treatment of age-related diseases and dysfunctions. Olfactory dysfunction can lead to changes of dietary habits that may in turn exacerbate disease states or contribute to nutritional deficiencies (72, 73). Although diagnosis of taste and smell disorders has improved considerably over the last two decades, treatment of these disorders is still

Correspondence: M. Hakan Ozdener and Nancy Rawson Monell Chemical Senses Center, 3500 Market St. Philadelphia, PA 19104 USA E-mail:hozdener@monell.org, rawson@monell.org

limited to conditions with discernible and reversible causes (71, 72).

Taste and smell are fundamental sensory systems responsible for the perception of aroma and flavor. Olfactory function is commonly measured based on either detection sensitivity (threshold), identification or discrimination of odors. These tests can be performed fairly easy and may be useful tools to improve diagnosis of conditions in which olfactory loss is an early symptom, such as Alzheimer's dementia, Parkinson's disease and other neurodegenerative disorders.

Unlike the central nervous system (CNS) neurons and other sensory neurons, olfactory neurons are unique in their ability to be replaced after injury. These primary receptor neurons are developmentally related to the central nervous system, yet are accessible for study from living patients. Studies of the cellular processes underlying the regenerative capacity of the peripheral and central components of the olfactory system are leading to new therapeutic approaches in the treatment of spinal cord injury (90, 91), and stroke (92, 93) and may also contribute to the treatment or prevention of neurodegenerative diseases. In this review, we will review recent progress made in understanding olfactory function and olfactory dysfunction in neurodegenerative diseases and aging.

Anatomy and cellular features of olfactory system

This sensory system is able to detect and discriminate an enormous variety of volatile molecules with great sensitivity and specificity. Tens of thousands of chemicals can be detected, many at concentrations as low as a few parts per trillion (94, 95). This feat is accomplished through anatomical, cellular and molecular features that are designed to amplify, encode and integrate a vast array of incoming olfactory information.

The olfactory epithelium is localized to the interior surface of the nasal cavity and consists primarily of three basic cell types: olfactory receptor neurons (ORNs), supporting cells, and basal cells (2). Post mortem biopsies, anatomical studies and explant cultures of olfactory neurons from different parts of the nasal cavity show that sensory epithelium extends from the olfactory cleft down to varying degrees onto the superior aspect of the medial turbinate (3, 4, 5). The turbinate structures are cartilaginous ridges covered with respiratory epithelium, a non-sensory ciliated columnar epithelial tissue also populated with mucus secreting goblet cells. This structure

increases the surface area available for both warming and humidifying incoming air, as well as funneling volatile chemicals up into the sensory epithelium. Human olfactory receptor neurons have a generally similar morphology to those of other vertebrates, although there is variation among species (6). The receptor cell is comprised of a cell body with an apical dendrite terminating in a knob containing multiple nonmotile cilia. The cilia project into the mucus overlying the nasal epithelium where they have direct contact with volatile chemicals in the air. Basally, an axon projects through the cribriform plate to synapse with the dendrites of mitral cells in the olfactory bulb. The mitral cells project via the olfactory nerve (cranial nerve I) to the entorhinal cortex, as well as regions involved in emotion and memory, such as the amygdala and hippocampus. Several types of interneurons modulate mitral cell activity, including periglomerular cells, tufted cells and granule cells. Granule cells are dopaminergic/GABAergic interneurons that are involved in signal processing and modulation (105, 106).

Transduction Mechanisms

During the past decade, tremendous advances in our understanding of the initial events in olfactory transduction have been made. The discovery of a large family of genes encoding for seven transmembrane domain, G-protein-coupled receptors that apparently represent odorant receptors is a cornerstone in this progress. Each olfactory receptor is responsive to a range of stimuli. Odorant binding leads to a depolarizing current within the cilia of the bipolar receptor cells that ultimately triggers the action potentials that collectively provide the neural code that is deciphered by higher brain centers (83). Most of the olfactory receptor proteins are linked to the stimulatory guanine nucleotide-binding protein (G_{olf}). When stimulated, it activates the enzyme adenylate cyclase to produce the second messenger adenosine monophosphate (cAMP) (96). cAMP diffuses through the cell and activates cellular depolarization via the opening of cyclic-nucleotide-gated ionic channels (83). Another possible mechanism is that some odorants also activate cyclic guanosine monophosphate (cGMP), which is believed to play a role in the modulation of the sensitivity of olfactory receptor neurons, such as during adaptation (83). In addition, recent evidence indicates that some odorants may activate phospholipase C to produce the second messenger inositol trisphosphate

(IP_3), which may also modulate the activity of the cAMP pathway via the activity of phosphoinositol-3 kinase (85). Medications, diseases or disorders that interfere with or alter the ability of these transduction pathways to operate can influence olfactory performance. Also, as this tissue is available via biopsy from live subjects, functional studies may suggest specific genetic or pathologic alterations related to early symptoms or causes of neurodegenerative disease (21).

Neuroregeneration in the olfactory system

The exposure of ORNs to the external environment makes these primary sensory neurons vulnerable to injury from environmental insults such toxins, infectious agents and trauma. However, unlike the central nervous system (CNS) neurons and other sensory neurons, ORNs are able to be replaced after injury. The average lifecycle of an ORN is approximately 30-120 days (8). This replacement process begins with a population of multi-potent basal neuroepithelial precursor cells which undergo successive stages of differentiation to a fully mature ORN. It is also thought that these cells may differentiate along a non-neuronal pathway, although there may be separate populations of precursor cells as well (107-110). Following olfactory nerve injury or toxic exposure, reconstitution of neuroepithelial cells and establishment of connections within the olfactory bulb can be enhanced by growth factors including retinoic acid, IGF-1, TGF-α, TGF-β and FGF2 (9-12, 49). Apoptotic cell death has been observed in cells representing all stages of neurogenesis (e.g. in proliferating neuronal precursors, immature olfactory receptor neurons, and mature olfactory receptor neurons), implying that apoptotic regulation of neuronal numbers may occur at multiple stages of the neuronal lineage (83, 84). Remarkably, central components of the olfactory system may also be replaced. A population of proliferating stem cells arising in the subventricular zone migrate into the olfactory bulb where they differentiate into granule cells (50, 51). This process appears to continue throughout life, although the impact on olfaction and the mechanisms controlling proliferation and differentiation of these cells are unknown.

Age associated olfactory loss

Detailed information about the prevalence of chemosensory disorders has been limited. Initial report covering late 1970s done by National Institutes of Health indicating that more than 2 million adults in the United States had a disorder of smell or taste. Another survey conducted by the National Geographic Society in 1987 showed that 1% of their 1.2 million respondents could not smell 3 or more of 6 odorants using a 'scratch and sniff' test. This study indicated that age was an important factor, with a decline beginning in the second decade of life (20). A recent study conducted by the NIH collaborating with the National Center for Health Statistics (NCHS) in 1993 to acquire information on the prevalence of smell/taste problems showed a prevalence of 2.7 million (1.4%) U.S. adults with olfactory problems. The prevalence rates increased exponentially with age. Almost 40% of respondents with a chemosensory problem (1.5 million) were 65 years of age or greater (71, 74). The ability to detect, discriminate and identify odors are most sensitive to age and disease related dysfunction (19, 20). In spite of the widespread age-related prevalence of olfactory loss, remarkably little is known about the specific mechanisms responsible and no treatments are currently available.

Several features of olfactory system are particularly susceptible to age and disease associated changes that may lead to functional deficits. Changes at both the anatomical and molecular level may contribute to this loss. Local injury from physical or chemical causes, damage to neural projections, disturbance of the cycle of neurogenesis resulting from general malnutrition, infectious diseases, metabolic disturbances, drugs, or radiation, or alteration of the composition of the mucus due to medication are possible major causative reasons to be determined in the pathogenesis of olfactory dysfunction (73). The composition of mucus is critical to proper ORN function, and may change with hydration, which is often reduced in the elderly, as well as from age-related diseases or associated medications. Reduction and/or alteration in olfactory function may also be due to changes at the level of the receptor cell. For instance, a age-related loss of selectivity was observed in a study of odorant response characteristics of ORNs dissociated from biopsies (114), and age-related changes in ion channel distribution (111, 112), or other components of the intracellular signaling cascades (113) could result in receptor cell

dysfunction. Although the extent of olfactory epithelium is reduced with aging (21, 98), it remains unclear whether this accounts for age-related olfactory loss, as studies indicate that olfactory function is not affected even with substantial reduction of olfactory epithelial area (21, 22). Other anatomical changes, such as altered vascular and mucosal composition and peptidergic innervation could lead to reduced sensitivity through indirect mechanisms or changes in the transport and clearance of odorants (97). Sensory dysfunction may be a consequence of chronic diseases such as diabetes, cancer, radiation, surgery and dentures. However, in most cases, the cause of olfactory loss is unknown and the development of treatments will require a better understanding of the mechanisms underlying this sensory impairment.

Olfactory impairment and neurodegenerative diseases

Scientists and physicians have paid increasing attention to the olfactory system and its function during the last decade, largely because of: (a) advances in our understanding of the histocompatibility basis for the receptor mechanisms, (b) evidence that the receptor cells undergo neurogenesis and both programmed and induced cell death, and (c) important technical and practical developments in psychophysical measurement, and (d) the accessibility of these cells relatively noninvasively from living subjects (14-18). These developments have led to the development of standardized olfactory testing that can assess detection sensitivity (threshold) and ability to identify odors. These tests can be easy to perform and may be useful in improving diagnosis (80). Since the first observation of olfactory function impairment in Parkinson disease (23) and senile dementia (24), olfactory function testing has revealed compromised olfactory function in a number of neurodegenerative diseases such Alzheimer's disease (25-28), Parkinson disease (29, 30), Huntington's disease (31), HIV associated dementia (32, 33) and amyotrophic lateral sclerosis (57).

Alzheimer's Disease and Down's Syndrome

Olfactory impairment and neuroanatomical changes in the central portions of the olfactory system occur early in the development of Alzheimers' disease, and olfactory testing has been explored as a diagnostic aide (79, 81, 98). Patients with AD perform more poorly on tests of odor identification (99, 100) and

exhibit altered olfactory evoked response potentials compared to age-matched controls (101). Olfactory tests alone, however, are insufficient to discriminate AD from Parkinson's disease and careful consideration of cognitive function is required to insure reliable results (102).

It is generally accepted that the classic AD neuropathology occurs in the entorhinal cortex very early in the development of the disease (103) and this observation led some to speculate that a causative agent might enter the brain via the nasal epithelium, and to investigate whether histological studies of biopsies of the olfactory neuroepithelium might be useful as an early diagnostic tool. However, more comprehensive studies indicate that the density of plaques and tangles in the olfactory bulb is less severe, and studies of the peripheral olfactory epithelium have been inconsistent. In general, phosphorylated tau and neurofilament proteins are not observed in the perikarya of the olfactory neurons, but are evident within the axons and dendrites of these cells (13, 104). Several studies have reported AD-specific neuropathology within the olfactory epithelium (7, 34, 81) but others using different markers, have noted similar features in non-AD and healthy olfactory tissue from elderly controls. In addition, studies that have included tissue from patients with other types of dementia or neurological disease have failed to identify any marker present in the olfactory epithelium that would serve to reliably distinguish AD from other conditions such as Parkinson's disease or vascular dementia (35, 36). Consistent with these findings, while we have observed some functional differences in preliminary studies of ORNs obtained via biopsy from patients with early stage AD, these neurons appeared normal morphologically and were able to respond to odorants (21, 82). Further studies of olfactory neuronal cell function may prove more useful than histology alone in understanding the alteration in cellular metabolism or signaling that herald the onset of this type of disease.

Patients with Down's syndrome display neuropathologic features similar in some respects to those seen in AD. Likewise, individuals with Down's syndrome had significant deficits in olfactory functioning compared to the control groups (78). The Alcohol Sniff Test (AST), a rapid screen for olfactory function, revealed olfactory deficits in children with Down's syndrome (43). Another study also indicated that olfactory

deficits may provide a sensitive and early indicator of the deterioration and progression of the brain in older patients with Down's syndrome (44).

Parkinson's Disease

Impairment in olfactory function is a well documented abnormality in patients with Parkinson's disease (PD) (64). The cellular and molecular mechanisms for this deficit are unknown, but likely relate to impairment at several levels of the olfactory system. Olfactory impairment in PD was not related to degree of motor dysfunction, or the disease duration, but was related to disease severity (30, 58, 59, 60, 65). Interestingly, Hawkes et al. proposed that idiopathic Parkinson's disease may start in the olfactory system prior to damage in the basal ganglia (61). Another study indicated that olfactory testing may be useful for differential diagnosis between PD and progressive supranuclear palsy (PSP) (63). Both PD and PSP have similar motor symptoms and PSP is commonly misdiagnosed as PD, although they are distinct neuropathologic entities (21, 63). In one study, olfactory dysfunction was seen in patients with an abnormal reduction in striatal dopamine transporter binding who subsequently developed clinical parkinsonism. None of 23 normosmic relatives of these patients developed signs or symptoms of parkinsonism (86). These observations indicate that olfactory deficits may precede clinical motor signs in PD, and support a practical clinical application in the early diagnosis/prognosis of the disease.

PD-related olfactory dysfunction may relate to the function of dopamine receptors in both central (105, 115-117) and peripheral components of the system (37-40). Centrally, dopamine modulates synaptic activity in the olfactory bulb and entorhinal cortex, influences the activity of several ion channels and enzymes involved in olfactory transduction, and has been reported to induce apoptosis and modulate differentiation of olfactory neurons in vitro (86-88). These effects are mediated via D2 receptors in the periphery (88), and D1 and D2 receptors on mitral/tufted and juxtaglomerular cells in the olfactory bulb (66). The dopaminergic granule cells in the olfactory bulb derive from stem cells that migrate throughout life from the subventricular zone. These stem cells are being studied as a potential source for dopaminergic replacement cells via transplant (62).

Human Immunodeficiency Virus infection and AIDS

HIV-associated dementia is a leading cause of neurodegenerative disorders among individuals under 30 years (89). The human immunodeficiency virus (HIV-1) infection infects the central nervous system (CNS) and 7-25 percent of patients with CNS infection develop dementia and at least 50% of them develop mild neurocognitive impairment. Several studies have shown that patients with neurocognitive impairment caused by HIV infection had diminished odor sensitivity (52-54). Impaired olfactory function may serve as early marker of HIV associated neurological impairment (55) and could be helpful to evaluate the impact of therapeutic agents. Schiffman also reported that HIV positive patients had significantly impaired menthol detection compared to controls. It is likely that the chemosensory losses found in HIV patients reflect both central and peripheral deficits (56). It was reported that out of 207 HIV-infected patients, 70% of them (n=144) reported that chemosensory complaints were associated with a poor quality of life (75). Wasting with reduced caloric intake is an increasingly common clinical manifestation of AIDS. The perceptions of taste and smell play an important role in stimulating caloric intake and flavor enhancement of food can have a significant positive impact on nutritional status in hospitalized patients (56). Significant taste and smell losses in HIV infected subjects may be of clinical significance in the development or progression of HIV associated wasting, and are thus worthy of clinical consideration and treatment (76).

Creutzfeldt-Jacob disease

Taste and smell loss was reported as an early sign of Creutzfeldt-Jacob disease (67). The pathologic prion protein (PrPSc) was found in the neuroepithelium of the olfactory mucosa in patients with sporadic Creutzfeldt-Jacob disease (68). This result indicates that olfactory biopsy may provide diagnostic information, and further studies are warranted.

Huntington's disease and Multiple Sclerosis

Patients with Huntington's disease exhibit significant deficits in odor identification, but odor recognition memory was not found to be affected (69, 79). In an animal model of the disease, the olfactory system exhibited early and significant accumulation of huntingtin-containing aggregates, which may account for

the early olfactory impairment (77).

Olfactory dysfunction may also be an early indicator of disease progression in multiple sclerosis. The Cross Cultural Smell Identification test utilized in patients with multiple sclerosis indicated that these patients scored significantly worse than control groups. They also found a significant correlation between smell alteration and symptoms of anxiety and depression and the severity of neurological impairments (47).

In several studies, neuropathology based on plaque numbers were directly related to olfactory function (41, 42). As plaque numbers declined or increased in the inferior frontal and temporal lobes, olfactory function declined or improved in correlation (45, 46, 48). While these reports are suggestive of olfactory involvement and potential utility in diagnostic approaches for these diseases, no studies have been done to directly investigate the neuropathology or cell/molecular basis for the olfactory impairment.

Summary and future direction

The olfactory system is a fundamental sensory system responsible for the perception of flavor and fragrance. Olfaction is critical for most mammals for the maintenance of a good quality of life. Although diagnosis of smell disorders caused by aging and neurodegenerative diseases, has improved considerably over the last two decades, treatment of these disorders is still limited to conditions with discernible and reversible causes. Sensory complaints are often overlooked by the medical community. Understanding the biological bases for olfactory system disorders can help us to develop new approaches to improve the quality of flavor experience for those with impaired ability. In addition, studies of olfaction and ORN function may lend new insight into the etiology of neurodegenerative disease. Future research is needed for a better understanding of chemosensory mechanisms, establishing improved diagnostic procedures, and disseminating knowledge about chemosensory disorders among practitioners and the general public (71, 72).

REFERENCES

1- Pelchat ML. You can teach an old dog new tricks: olfaction and responses to novel foods by the elderly. Appetite 2000; 35(2):153-60

2- Graziadei PP. Cell dynamics in the olfactory mucosa. Tissue Cell 1973;5(1): 113-31

3- Rawson NE, Gomez G, Cowart B et al. Selectivity and response characteristics of human olfactory neurons. J Neurophysiol 1997;77(3):1606-13

4- Nibu K, Li G, Zhang X et al. Olfactory neuron-specific expression of NeuroD in mouse and human nasal mucosa. Cell Tissue Res 1999;298(3):405-14

5- Gomez G, Rawson NE, Hahn CG, Michaels R, Restrepo D. Characteristics of odorant elicited calcium changes in cultured human olfactory neurons. J Neurosci Res 2000;62(5):737-49

6- Schild D, Restrepo D. Transduction mechanisms in vertebrate olfactory receptor cells. Physiol Rev 1998;78(2): 429-66

7- Yamagishi M, Ishizuka Y, Seki K. Pathology of olfactory mucosa in patients with Alzheimer's disease. Ann Otol Rhinol Laryngol 1994 Jun;103(6):421-7

8- Astic L, Saucier D. Neuronal plasticity and regeneration in the olfactory system of mammals: morphological and functional recovery following olfactory bulb deafferentation. Cell Mol Life Sci 2001;58(4):538-45

9- Costanzo RM. Regeneration of olfactory receptor cells. Ciba Found Symp 1991;160:233-42

10- Schwob JE. Neural regeneration and the peripheral olfactory system. Anat Rec 2002;269(1):33-49

11- Federico G, Maremmani C, Cinquanta L, Baroncelli GI, Fattori B, Saggese G. Mucus of the human olfactory epithelium contains the insulin-like growth factor-I system which is altered in some neurodegenerative diseases. Brain Res 1999;835(2):306-14

12- Amoore JE. Specific anosmia: a clue to the olfactory code. Nature 1967;214(93): 1095-8

13- Talamo BR, Rudel R, Kosik KS et al. Pathological changes in olfactory neurons in patients with Alzheimer's disease. Nature 1989;337(6209):736-9

14- Rawson NE. Gomez G Cell and molecular biology of human olfaction. Microsc Res Tech 2002;58(3):142-51

15- Amoore JE. Evidence for the chemical olfactory code in man.Ann N Y Acad Sci 1974;237(0):137-43

16- Menashe I, Man O, Lancet D, Gilad Y. Different noses for different people. Nat Genet 2003;34(2):143-4

17- Wysocki CJ, Dorries KM. Beauchamp GK Ability to perceive androstenone can be acquired by ostensibly anosmic people. Proc Natl Acad Sci U S A 1989;86(20): 7976-8

18- Beauchamp GK, Yamazaki K. Chemical signalling in mice. Biochem Soc Trans 2003;31(Pt 1):147-51

19- Deems DA, and Doty RL. Age-related changes in the phenyl ethyl alcohol odor detection threshold. Trans Pa Acad Ophthalmol Otolaryngol 1987;39(1):646-50

20- Wysocki CH, Gilbert AN. National Geographic Smell Survey. Effects of age are heterogenous. Ann N Y Acad Sci 1989;561:12-28

21- Rawson NE, Gomez G, Cowart B, Restrepo D. The use of olfactory receptor neurons (ORNs) from biopsies to study changes in aging and neurodegenerative diseases.Ann N Y Acad Sci 1998;855: 701-7

22- Loo AT, Youngentob SL, Kent PF, Schwob JE. The aging olfactory epithelium: neurogenesis, response to damage, and odorant-induced activity. Int J Dev Neurosci 1996;14(7-8):881-900

23- Ansari KA, Johnson A. Olfactory function in patients with Parkinson's disease. J Chronic Dis 1975;28(9):493-7

24- Waldton S. Clinical observations of impaired cranial nerve function in senile dementia. Acta Psychiatr Scand 1974;50(5):539-47

25- Koss E, Weiffenbach JM, Haxby JV, Friedland RP. Olfactory detection and identification performance are dissociated in early Alzheimer's disease. Neurology 1988;38(8):1228-32

26- Morgan CD, Nordin S, Murphy C. Odor identification as an early marker for Alzheimer's disease: impact of lexical functioning and detection sensitivity. J Clin Exp Neuropsychol 1995;17(5):793-803

27- Murphy C, Gilmore MM, Seery CS, Salmon DP, Lasker BR. Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. Neurobiol Aging 1990 Jul-Aug;11(4):465-9

28- Rezek DL. Olfactory deficits as a neurologic sign in dementia of the Alzheimer type. Arch Neurol 1987 Oct;44(10):1030-2

29- Korten JJ, Meulstee J. Olfactory disturbances in Parkinsonism. Clin Neurol Neurosurg 1980;82(2):113-8

30- Doty RL, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 1988;38(8):1237-44

31- Moberg PJ, Pearlson GD, Speedie LJ, Lipsey JR, Strauss ME, Folstein SE. Olfactory recognition: differential impairments in early and late Huntington's and Alzheimer's diseases. J Clin Exp Neuropsychol 1987;9(6):650-64

32- Razani J, Murphy C, Davidson TM, Grant I, McCutchan A. Odor sensitivity is impaired in HIV-positive cognitively impaired patients. Physiol Behav 1996 ;59(4-5):877-81

33- Hornung DE, Kurtz DB, Bradshaw CB et. The olfactory loss that accompanies an HIV infection. Physiol Behav 1998;64(4): 549-56

34- Lee JH, Goedert M, Hill WD, Lee VM, Trojanowski JQ. Tau proteins are abnormally expressed in olfactory epithelium of Alzheimer patients and developmentally regulated in human fetal spinal cord. Exp Neurol 1993;121(1):93-105

35- Crino PB, Martin JA, Hill WD, Greenberg B, Lee VM, Trojanowski JQ. Beta-Amyloid peptide and amyloid precursor proteins in olfactory mucosa of patients with Alzheimer's disease, Parkinson's disease, and Down syndrome. Ann Otol Rhinol Laryngol 1995;104(8):655-61

36- Yamagishi M, Ishizuka Y, Seki K. Definitive diagnosis of Alzheimer's disease using olfactory mucosal biopsy. Nippon Jibiinkoka Gakkai Kaiho 1994 ;97(1):51-60

37- Herve D, Levi-Strauss M, Marey-Semper I et al. G(olf) and Gs in rat basal ganglia: possible involvement of G(olf) in the coupling of dopamine D1 receptor with adenylyl cyclase. J Neurosci 1993;13(5): 2237-48

38- Berkowicz DA, Trombley PQ. Dopaminergic modulation at the olfactory nerve synapse. Brain Res 2000;855(1):90-9

39- Trombley PQ, Shepherd GM. Synaptic transmission and modulation in the olfactory bulb. Curr Opin Neurobiol 1993;3(4):540-7

40- Vargas G, Lucero MT. Dopamine modulates inwardly rectifying hyperpolarization-activated current (Ih) in cultured rat olfactory receptor neurons. J Neurophysiol 1999;81(1):149-58

41- Zivadinov R, Zorzon M, Monti Bragadin L, Pagliaro G, Cazzato G. Olfactory loss in multiple sclerosis. J Neurol Sci 1999;168(2):127-30

42- Zorzon M, Ukmar M, Bragadin LM et al. Olfactory dysfunction and extent of white matter abnormalities in multiple sclerosis: a clinical and MR study. Mult Scler 2000;6(6):386-90

43- Davidson TM, Freed C, Healy MP, Murphy C. Rapid clinical evaluation of anosmia in children: the Alcohol Sniff Test. Ann N Y Acad Sci 1998;855:787-92

44- Murphy C and Jinich S Olfactory dysfunction in Down's Syndrome. Neurobiol Aging 1996;17(4):631-7

45- Doty RL, Li C, Mannon LJ, Yousem DM Olfactory dysfunction in multiple sclerosis.N Engl J Med 1997;336(26): 1918-9

46- Doty RL, Li C, Mannon LJ, Yousem DM., Olfactory dysfunction in multiple sclerosis: relation to longitudinal changes in plaque numbers in central olfactory structures. Neurology 1999;53(4):880-2

47- Zivadinov R, Zorzon M, Monti Bragadin L, Pagliaro G, Cazzato G. Olfactory loss in multiple sclerosis. J Neurol Sci 1999 ;168(2):127-30

48- Doty RL, Li C, Mannon LJ, Yousem DM. Olfactory dysfunction in multiple sclerosis. Relation to plaque load in inferior frontal and temporal lobes. Ann N Y Acad Sci 1998;855:781-6

49- Yee KK, Rawson NE. Retinoic acid enhances the rate of olfactory recovery after olfactory nerve transsection. Brain Res Dev Brain Res 2000;124:129-32

50- Englund U, Bjorklund A, Wictorin K.Migration patterns and phenotypic differentiation of long-term expanded human neural progenitor cells after transplantation into the adult rat brain. Brain Res Dev Brain Res 2002;134(1-2): 123-41

51- Fricker RA, Carpenter MK, Winkler C, Greco C, Gates MA, Bjorklund A. Site-specific migration and neuronal differentiation of human neural progenitor cells after transplantation in the adult rat brain. J Neurosci 1999;19(14):5990-6005

52- Brody D, Adler LA, Kim T, Angrist B, Rotrosen J. Effects of buspirone in seven schizophrenic subjects. J Clin Psychopharmacol 1990;10(1):68-9

53- Hornung DE, Kurtz DB, Bradshaw CB et al. The olfactory loss that accompanies an HIV infection. Physiol Behav 1998;64(4): 549-56

54- Razani J, Murphy C, Davidson TM, Grant I, McCutchan A. Odor sensitivity is impaired in HIV-positive cognitively impaired patients. Physiol Behav 1996 ;59(4-5):877-81

55- Serby MJ, Larson PM, Kalkstein D. Olfaction and neuropsychiatry In: Serby, MJ. Chobor KL eds. Science of Olfaction. New York: Springer-Verlag; 1992:559-584

56- Heald AE, Schiffman SS. Taste and smell. Neglected senses that contribute to the malnutrition of AIDS. N C Med J 1997 ;58(2):100-4

57- Ahlskog JE, Waring SC, Petersen RC et al. Olfactory dysfunction in Guamanian ALS, parkinsonism, and dementia. Neurology 1998;51(6):1672-7

58- Adler CH, Gwinn KA, Newman S. Olfactory function in restless legs syndrome. Mov Disord 1998;13(3):563-5

59- Doty RL, Bromley SM, Stern MB. Olfactory testing as an aid in the diagnosis of Parkinson's disease: development of optimal discrimination criteria. Neurodegeneration 1995;4(1):93-7

60- Wszolek ZK, Markopoulou K. Olfactory dysfunction in Parkinson's disease. Clin Neurosci 1998;5(2):94-101

61- Hawkes CH, Shephard BC, Daniel SE. Is Parkinson's disease a primary olfactory disorder? QJM 1999;92(8):473-80

62- Parati EA, Bez A, Ponti D, Sala S, Pozzi S, Pagano SF. Neural stem cells. Biological features and therapeutic potential in Parkinson's disease. J Neurosurg Sci 2003 ;47(1):8-17

63- Doty RL, Golbe LI, McKeown DA, Stern MB, Lehrach CM, Crawford D. Olfactory testing differentiates between progressive supranuclear palsy and idiopathic Parkinson's disease. Neurology 1993 ;43(5):962-5

64- Sobel N, Thomason ME, Stappen I et al. An impairment in sniffing contributes to the olfactory impairment in Parkinson's disease. Proc Natl Acad Sci U S A 2001 ;98(7):4154-9

65- Tissingh G, Berendse HW, Bergmans P et al. Loss of olfaction in de novo and treated Parkinson's disease: possible implications for early diagnosis. Mov Disord 2001;16(1):41-6

66- Wilson DA, Sullivan RM. The D2 antagonist spiperone mimics the effects of olfactory deprivation on mitral/tufted cell odor response patterns. J Neurosci 1995; 15:5574-81

67- Reuber M, Al-Din AS, Baborie A, Chakrabarty A. New variant Creutzfeldt-Jakob disease presenting with loss of taste and smell. J Neurol Neurosurg Psychiatry 2001;71(3):412-3

68- Zanusso G, Ferrari S, Cardone F et al. Detection of pathologic prion protein in the olfactory epithelium in sporadic Creutzfeldt-Jakob disease .N Engl J Med 2003;348(8):711-9

69- Nordin S, Paulsen JS, Murphy C. Sensory- and memory-mediated olfactory dysfunction in Huntington's disease.J Int Neuropsychol Soc 1995;1(3):281-90

70- Winkler S, Garg AK. Mekayarajjananonth T, Bakaeen LG, Khan E. Depressed taste and smell in geriatric patients. J Am Dent Assoc 1999;130(12):1759-65

71- Spielman AI. Chemosensory function and dysfunction Crit Rev Oral Biol Med 1998;9(3):267-91

72- Bromley SM. Smell and taste disorders: a primary care approach. Am Fam Physician 2000;61(2):427-36

73- Schiffman SS. Taste and smell in disease (second of two parts). N Engl J Med 1983 ;308(22):1337-43

74- Hoffman HJ, Ishii EK, MacTurk RH. Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS). Ann N Y Acad Sci 1998;855:716-22

75- Heald AE, Pieper CF, Schiffman SS. Taste and smell complaints in HIV-infected patients 1998;12(13):1667-74

76- Graham CS, Graham BG, Bartlett JA, Heald AE. Schiffman SS. Taste and smell losses in HIV infected patients. Physiol Behav 1995;58(2):287-93

77- Menalled LB, Sison JD, Dragatsis I, Zeitlin S, Chesselet MF. Time course of early motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. J Comp Neurol 2003;465(1):11-26

78- Nijjar RK, Murphy C. Olfactory impairment increases as a function of age in persons with Down syndrome Neurobiol Aging 2002;23(1):65-73

79- Bacon Moore AS, Paulsen JS, Murphy C. A test of odor fluency in patients with Alzheimer's and Huntington's disease. J Clin Exp Neuropsychol 1999;21(3):341-51

80- Murphy C. Loss of olfactory function in dementing disease. Physiol Behav 1999 ;66(2):177-82

81- Arnold SE, Smutzer GS, Trojanowski JQ, Moberg PJ. Cellular and molecular neuropathology of the olfactory epithelium and central olfactory pathways in Alzheimer's disease and schizophrenia. Ann N Y Acad Sci 1998;855:762-75

82- Rawson NE, and et al unpublished data

83- Doty RL Olfaction. Annual Review of Psychology 2001;52: 423-52

84- Holcomb JD, Mumm JS, Calof AL. Apoptosis in the neuronal lineage of the mouse olfactory epithelium: regulation in vivo and in vitro. Dev Biol 1995;172(1): 307-23

85- Zhainazarov AB, Doolin R, Herlihy JD, Ache BW. Odor-stimulated phosphatidylinositol 3-kinase in lobster olfactory receptor cells. J Neurophysiol 2001;85(6):2537-44

86- Berendse HW, Booij J, Francot CM et al. Subclinical dopaminergic dysfunction in asymptomatic Parkinson's disease patients' relatives with a decreased sense of smell. Ann Neurol 2001;50(1):34-41

87- Coronas V, Feron F, Hen R, Sicard G, Jourdan F. Moyse E- In vitro induction of apoptosis or differentiation by dopamine in an immortalized olfactory neuronal cell line. J Neurochem 1997;69(5):1870-81

88- Koster NL, Norman AB, Richtand NM et al. Olfactory receptor neurons express D2 dopamine receptors. J Comp Neurol 1999 ;411(4):666-73

89- Wilkie FL, Goodkin K, Khamis I et al. Cognitive Functioning in Younger and Older HIV-1-Infected Adults. J Acquir Immune Defic Syndr 2003;33(2):S93-S105

90- Huang H, Chen L, Wang H et al. Influence of patients' age on functional recovery after transplantation of olfactory ensheathing cells into injured spinal cord injury. Chin Med J (Engl) 2003;116(10): 1488-91

91- Resnick DK, Cechvala CF, Yan Y, Witwer BP, Sun D, Zhang S. Adult olfactory ensheathing cell transplantation for acute spinal cord injury. J Neurotrauma 2003 ;20(3):279-85

92- Parent JM. Injury-induced neurogenesis in the adult mammalian brain. Neuroscientist 2003;9(4):261-72

93- Arlotta P, Magavi SS, Macklis JD. Induction of adult neurogenesis: molecular manipulation of neural precursors in situ. Ann N Y Acad Sci 2003;991:229-36

94- Walker JC, Hall SB, Walker DB, Kendal-Reed MS, Hood AF, Niu XF. Human odor detectability: new methodology used to determine threshold and variation. Chem Senses 2003;28(9):817-26

95- Angioy AM, Desogus A, Barbarossa IT, Anderson P, Hansson BS. Extreme sensitivity in an olfactory system. Chem Senses 2003;28(4):279-84

96- Lowe G, Nakamura T, Gold GH. Adenylate cyclase mediates olfactory transduction for a wide variety of odorants. Proc Natl Acad Sci U S A 1989;86(14):5641-5

97- Ohta Y, Ichimura K. Changes in epidermal growth factor receptors in olfactory epithelium associated with aging. Ann Otol Rhinol Laryngol 2000;109(1):95-8

98- Loo AT, Youngentob SL, Kent PF, Schwob JE. The aging olfactory epithelium: neurogenesis, response to damage, and odorant-induced activity. Int J Dev Neurosci 1996;14(7-8):881-900

99- McCaffrey RJ, Duff K, Solomon GS. Olfactory dysfunction discriminates probable Alzheimer's dementia from major depression: a cross-validation and extension. J Neuropsychiatry Clin Neurosci 2000;12(1):29-33

100-Rezek DL. Olfactory deficits as a neurologic sign in dementia of the Alzheimer type. Arch Neurol 1987 ;44(10):1030-2

101-Warner MD, Peabody CA, Flattery JJ, Tinklenberg JR. Olfactory deficits and Alzheimer's disease. Biol Psychiatry 1986 ;21(1):116-8

102-Thesen T, Murphy C. Age-related changes in olfactory processing detected with olfactory event-related brain potentials using velopharyngeal closure and natural breathing. Int J Psychophysiol 2001;40(2):119-27

103-Mesholam RI, Moberg PJ, Mahr RN, Doty RL. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases.Arch Neurol 1998;55(1):84-90

104-Reyes PF, Deems DA, Suarez MG. Olfactory-related changes in Alzheimer's disease: a quantitative neuropathologic study. Brain Res Bull 1993;32(1):1-5

105-Trombley PQ, Shepherd GM. Synaptic transmission and modulation in the olfactory bulb. Curr Opin Neurobiol 1993; 3:540-7

106-Brunig I, Sommer M, Hatt H et al. Dopamine receptor subtypes modulate olfactory bulb gamma-aminobutyric acid type A receptors. Proc Natl Acad Sci U S A 1999;96:2456-60

107-DeHamer MK, Guevara JL, Hannon K et al. Genesis of olfactory receptor neurons in vitro: regulation of progenitor cell divisions by fibroblast growth factors. Neuron 1994;13:1083-97

108-Calof AL, Mumm JS, Rim PC et al. The neuronal stem cell of the olfactory epithelium. J Neurobiol 1998;36:190-205

109-Calof AL, Bonnin A, Crocker C et al. Progenitor cells of the olfactory receptor neuron lineage. Microsc Res Tech 2002; 58:176-88

110-Huard JM, Youngentob SL, Goldstein BJ et al. Adult olfactory epithelium contains multipotent progenitors that give rise to neurons and non-neural cells. J Comp Neurol 1998;400:469-86

111-Thibault O, Hadley R, Landfield PW Elevated postsynaptic Ca2+ i and L-type calcium channel activity in aged hippocampal neurons: relationship to impaired synaptic plasticity. J Neurosci 2001;21(24):9744-56

112- Tanaka Y, Ando S. Age-related changes in the subtypes of voltage-dependent calcium channels in rat brain cortical synapses. Neurosci Res 2001;39(2):213-20

113-Palego L, Giromella A, Mazzoni MR et al. Gender and age-related variation in adenylyl cyclase activity in the human prefrontal cortex, hippocampus and dorsal

raphe nuclei. Neurosci Lett 2000;279(1): 53-6

114-Rawson NE, Gomez G, Cowart B et al. The use of olfactory receptor neurons (ORNs) from biopsies to study changes in aging and neurodegenerative diseases. Ann N Y Acad Sci 1998;855:701-7

115-Church AC, Bunney BS, Krieger NR. Neuronal localization of dopamine-sensitive adenylate cyclase within the rat olfactory tubercle. Brain Res 1982;234: 369-76

116-Baker H, Farbman AI. Olfactory afferent regulation of the dopamine phenotype in the fetal rat olfactory system. Neuroscience 1993;52:115-34

117-Mijnster MJ, Isovich E, Flugge G et al. Localization of dopamine receptors in the tree shrew brain using 3H -SCH23390 and 125I -epidepride. Brain Res 1999;841: 101-13