

Nuclear imaging with radiolabeled odor molecules in patients with olfactory disorder

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Abstract. – Smell loss originates from peripheral disorders, like intranasal obstruction and olfactory cell injury, as well as central pathway diseases. Information derived from electrophysiological and psychophysical tests are useful for identifying loss of smell, but not for discriminating between central and peripheral deficits. This is because conventional imaging modalities are unable to deliver information about functional olfactory performance. Although functional imaging is able to show abnormal changes in central olfactory pathways, it seems that it is only possible to observe such abnormalities in olfactory cell dysfunction. We hypothesize that the scanning of peripheral olfactory systems by radiolabeled odor molecules may specifically reveal olfactory dysfunction and may be useful for differentiating peripheral from central olfactory disorders.

Key Words:

Olfactory, Nuclear imaging, Radiolabeled odor, SPECT, PET, Electrophysiologic testing, Electro-olfactogram, EOG.

Introduction

Olfactory functions can be disrupted by intranasal obstructions (transport olfactory loss), destruction of receptors or olfactory cell functions (sensory olfactory loss), and pathological processes affecting central pathways¹. A primary objective of assessing the impaired sense of smell is to distinguish an intranasal disorder, including olfactory cell injury, from a central cause. Although, functional imaging such as single photon emission computed tomography (SPECT)², positron-emission tomography (PET)³, functional magnetic resonance imaging

(fMRI)⁴, is helpful for identifying cerebral hypoperfusion in anosmic patient, it seems that it is incapable of differentiating peripheral from central causes⁵.

We hypothesize that radio-labeling volatile odor molecules (like vinyl and camphor) are helpful for the evaluation of olfactory cells and receptors by isotope scan and may differentiate olfactory cell disorders from central olfactory dysfunctions. In addition, radio-labeling volatile odor molecules may be able to evaluate the degree of injury to olfactory cells.

Anatomy

The olfactory receptor cell is a bipolar sensory neuron with a dendritic knob that extends into the mucosal cell layer of the nasal cavity and a thin unmyelinated axon that travels in bundles through the cribriform plate into the olfactory bulb. The dendritic knobs bear cilia where odorant transduction occurs. The axons of the first cranial (olfactory) nerve terminate within the olfactory bulb's glomeruli, where they form synaptic contacts with interneurons that have processes restricted to the bulb, and with output neurons (mitral and internal tufted cells) that contribute axons to the lateral olfactory tract⁶. From the olfactory bulb and tract, fibers pass through the olfactory stria to septal nuclei. From the medial and lateral septal nuclei, fibers extend to the limbic system with branches to the uncus, hippocampus, parahippocampal region, septum pellucidum, fornices, amygdala, and gyrus rectus regions⁶. The nasociliary olfactory nerves, olfactory bulbs, and olfactory tracts are essential for odor detection. Disruption in this pathway results anosmia⁶. The ability to recognize, interpret, and remember odors, is located more classically in the uncus and hippocampus⁷.

Causes

Olfactory dysfunction is clinically categorized under peripheral and central causes. The most common reasons of anosmia are trauma, upper respiratory infections, and smoking¹. Causes of posttraumatic olfactory dysfunction may include: (1) shearing injury of the olfactory nerve axons, (2) brain contusion and hemorrhage in the olfactory regions, and (3) sinonasal tract alternation. It is important to identify the conductive causes of olfactory loss because they are often reversible through medical or surgical correction. In 10% of cases, olfactory function returns, but is reduced (8). The regeneration or recovery of damaged olfactory neurons may be responsible for the improvement of olfaction months after a traumatic injury. Hamsters have demonstrated that transected olfactory receptor cell axons may grow through the cribriform plate and reestablish contact with cells in the olfactory bulb⁹.

Upper respiratory infection is the most commonly identified etiologic cause of anosmia. Although most patients who develop anosmia following upper respiratory infection show no imaging abnormalities, evidence suggests the virus may damage that olfactory epithelium. Because these patients developed anosmia following an upper respiratory infection, the imaging provides evidence that a viral neuritis may damage the olfactory nerves or bulbs^{10,11}. In addition to intracranial abnormalities in congenital anosmia, abnormalities may also exist in the nasal cavity neuroepithelium. Thus, this syndrome may be a central or peripheral cause of anosmia¹².

Occupational and accidental exposure to toxins such as acrylates, methacrylates, phosphorus fire, chlorine gas, oil vapors, solvents, household cleaners, and airborne cadmium have been linked to olfactory dysfunction. Such toxins may affect the peripheral and central toxic central nervous system. However, it is difficult to differentiate the ultimate cause in such cases. Imaging in such cases is frequently used^{12,13}.

Electrophysiologic and Psychophysical Test

Two general types of olfactory testing exist: psychophysical testing (olfactory threshold tests, odor identification tests) and electrophysiologic testing (electro-olfactogram [EOG] or odor event-related potentials [OERPs]). The information derived from these tests does not allow for differentiation between central and peripheral deficits. Most olfactory testing relies on measuring the patient's detection thresholds of a specific odorant, or the ability to identify multiple odorants⁸.

Conventional Imaging

Brain CT and MRI have revealed details of CNS pathology in addition to measurements of olfactory bulb size and other anatomical structures in the CNS olfactory system in normal subjects and in patients with hyposmia and impaired smell of various causes. However, these methods provided no information about functional olfactory performance².

Functional Imaging

Several techniques such as PET³, SPECT², and functional(fMRI)⁴ have been proposed for an objective study of the olfactory pathways. One of the most widely referenced studies, Levy et al¹⁴, found that brain activation to three different olfactory stimuli (pyridine, menthone, amylacetate) was lower in all nine brain sections in anosmic patients compared with normal subjects. This finding was particularly strong in the inferior frontal and cingulate gyral regions of the frontal cortex and in the regions of medial and posterior temporal cortex.

A recent study by Henkin and Levy¹⁵ evaluated the role of fMRI to determine brain activation in response to olfactory stimulation in patients who have never had the ability to recognize odors (congenital hyposmia). Brain activation in response to odors was present in patients with congenital hyposmia, but the activation was significantly lower than in normal subjects and patients with acquired hyposmia. Using quantitative positron emission tomography, the study showed that posttraumatic impaired smell is closely associated with cerebral perfusion abnormalities evident in cerebral PET images¹⁶. We showed that patients with posttraumatic anosmia exhibit decreased brain activation compared to normal subjects who experience olfactory stimulation. This finding was especially strong in the orbitofrontal region^{2,17} which was confirmed by the following research¹⁸.

In Iran, several nuclear medicine centers routinely use brain perfusion SPECT for olfactory assessment. The hypoperfused areas may be due to the loss of olfactory input to these areas because of direct and/or contrecoup injury to these sites⁵. However, these modalities do not have the ability to discriminate between peripheral and central injuries.

Hypothesis

As discussed above, functional imaging in anosmic patients shows hypoperfusion in smell areas. However, it seems that these methods alone reveal the existence of perfusion abnormality with a lack

of high specificity for anosmia and the inability to detect peripheral origins. We hypothesize that isotope labeling of odors molecules, such as camphor or vinyl, and the scanning olfactory receptors in the nasal cavity roof, may be helpful in recognizing olfactory cell disorders in the central olfactory pathway. Furthermore, it may also reveal the severity of the olfactory cell injury by quantitatively measuring the amount of binding that occurs between the isotope label and its receptor. This can improve the specificity for anosmia.

Clinical Implication

Olfactory neurons have the capability for neurogenesis, which allows for new receptor growth. Therefore, it is concluded that the late return of the function may be associated with a peripheral (olfactory nerves/ bulbs/tracts) mechanism, rather than central one. Hamsters have previously displayed this phenomenon¹⁹. If the hypothesis is proven, it may be helpful for identifying causes of olfactory dysfunction, and will thus, lead to better management practices. Moreover, by determining the severity of smell loss, it will provide a clearly prognosis of the disorder.

Despite occupational medicine's interest in vision and hearing, the evaluation of olfaction has not received adequate attention, which may be due to a lack of standardized olfactory tests. The primary olfactory neuron and receptor is the only sensory cell directly in contact with the environment and, thus, potentially exposed to airborne toxicants. The olfactory damage reflects the effect of a toxicant on the CNS¹³. Mascagni et al¹³ showed that delayed olfactory improvement in workers could occur, while the recovery failed in hypersusceptible workers, who continued to perform poorly in olfactory function. Therefore, in occupational medicine, this method may useful to evaluate the toxic effect of environmentally volatile toxicants.

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