Insights about the Olfactory Bulb Structural Organization and Dysfunction

Review Article

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ABSTRACT

Background: The olfactory bulb (OB) is a critical structure for the sense of olfaction, processing olfactory information from the nose to the brain. The OB's is characterized by layered organization that facilitates olfactory processing. Key neuronal populations within the OB—including juxtaglomerular, tufted, and mitral cells—play specialized roles in odor detection, signal modulation, and transmission to the olfactory cortex. The OB possess a regenerative capacity throughout life, primarily in the granular cell layer, permitting recovery from olfactory dysfunction. Olfactory dysfunction can significantly influence the quality of life and has been associated with a range of conditions such as COVID-19, cardiovascular diseases, and neurodegenerative disorders. Emerging research on intranasal delivery of therapeutic agents, including stem cells, extracellular vesicles (EVs) and nanoparticles (NPs), highlights its potential in treating neurological conditions and improving olfactory function.

Conclusion: The OB plays a pivotal role in olfaction and broader neurological function. Advances in the intranasal route of delivery, particularly involving EVs and stem cells, may revolutionize treatment strategies for olfactory and neurodegenerative disorders. Overall, understanding the OB's functional and structural complexities and its associated pathways is vital for developing effective treatments for these conditions.

Key Words: Central nervous system (CNS), exosomes, intranasal (IN) delivery.

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INTRODUCTION

The olfactory bulb (OB) is a specialized part in the brain that plays an essential role for in the sense of olfaction. It serves as a main element of the olfactory system, it is positioned between the olfactory neuroepithelium of the nasal cavity and the brain[1]. The main role of the OB is to process and relay olfactory input, enabling the detection and discrimination of different aromas[2].

Olfactory dysfunction has been identified as a potential early marker for cognitive impairment and mood disorders, particularly depression, and has been strongly associated with neurodegenerative diseases—often preceding the onset of clinical symptoms by several years[3]. Additionally, the OB is susceptible to pathological changes in cardiovascular diseases[4] and has been shown to accumulate elevated levels of environmental metals and toxins, including manganese[5], iron and zinc[6], and lead[7].

Emerging therapeutic modalities have focused on the use of extracellular vesicles (EVs), which are nanosized, membrane-bound particles involved in intercellular communication. Among these, exosomes—a subtype of EVs defined by their size and endosomal origin—have shown promise in preclinical models as a potential treatment for neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis, and Parkinson's disease[8,9]. These vesicles facilitate a range of neural functions, including synaptic transmission, axonal maintenance, and myelination, particularly within the central nervous system (CNS)[10].

Recent research has increasingly explored the intranasal (IN) route as a non-invasive method for delivering therapeutic cells, molecules, and drugs directly to the CNS. This approach exploits the unique nose-to-brain pathway, enabling substances to bypass the blood–brain barrier (BBB). Delivery occurs primarily through the olfactory and trigeminal nerve pathways, allowing targeted distribution to intracerebral regions while minimizing systemic exposure[11,12].

ANATOMY OF THE OLFACTORY BULB

The OB consists of a pair of independent, ovoid structures with smooth margins[13]. In humans, it is situated inferior to the frontal lobe, superior to the cribriform plate of the ethmoid bone (Diagram 1a)[14]. Both bulbs receive axons from the olfactory receptor neurons (ORNs), which reside in the respiratory epithelium of nasal cavity. These axons pass through the cribriform plate of the ethmoid bone

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and continue as olfactory nerves. The nerves are encircled by neuroglial cells —primarily olfactory ensheathing cells and astrocytes— and project directly to the ipsilateral OB[2].

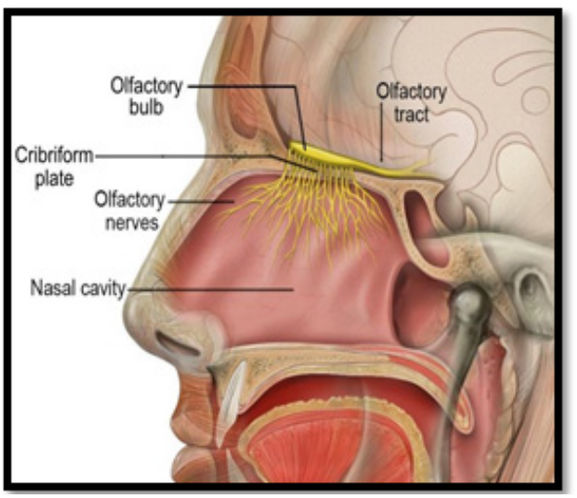

Diagram (1a): Showing the location of olfactory bulb in human[14].

In rats, the OB's anatomical location differs slightly from that in humans. It is located ventro-cranially to the frontal lobe, at the most ventral aspect of each cerebral hemisphere, adjacent to the orbital portion of the frontal bone (Diagram 1b)[15].

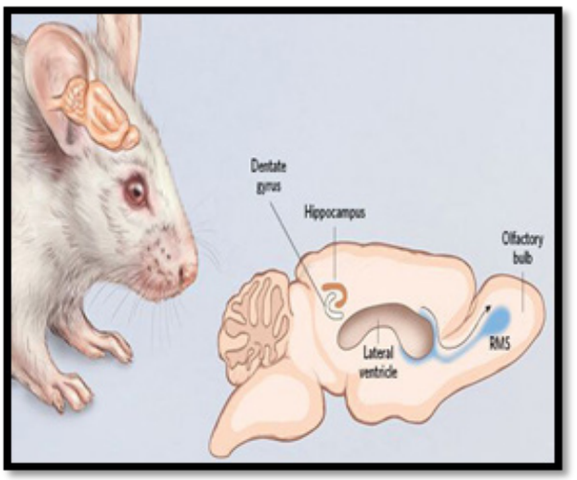

Diagram (1b): Showing the location of olfactory bulb in rats[15].

HISTOLOGICAL ORGANIZATION OF THE OLFACTORY BULB

Each OB is arranged into six consecutive layers (Diagram 2). Superficially inwards, these layers are: (1) Olfactory nerve layer, (2) Glomerular layer, (3) External plexiform layer, (4) Mitral cell layer, (5) internal plexiform layer and (6) Granular cell layer[16]. This precise laminar arrangement is essential for the processing, integration, and coding of olfactory information[1].

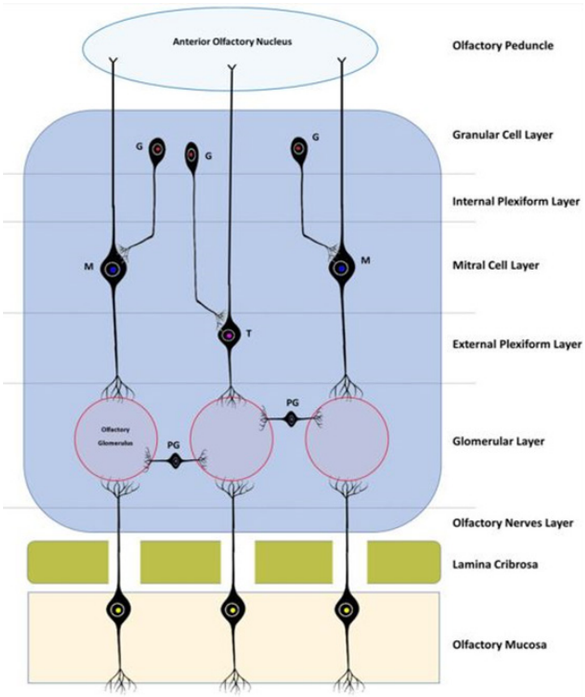

Diagram (2): Showing the OB layers and their relation to the olfactory mucosa[1].

The OB shares certain structural similarities with the retina, as both exhibit a layered (laminar) architecture. This organization supports three key stages of sensory information processing: input reception, synaptic integration, and output modulation[17]. Such an arrangement allows the OB to refine sensory signals received from the peripheral nervous system before transmitting them to higher brain centers[13].

HISTOLOGICAL LAYERS OF THE OLFACTORY BULB

The outermost layer of the OB, Olfactory nerve layer (ONL) is formed of axons from ORNs. These axons pass through the lamina cribrosa, traverse the subarachnoid space to reach the OB[1]. Within the ONL, axons branch extensively into several divisions of horizontal and oblique fibers which intermingle with the second order neurons in adjacent glomeruli. Ovoid-shaped ensheathing glial cells are dispersed throughout this layer, encasing the nerve fibers[13].

Just beneath the ONL lies the glomerular layer (GL), where several olfactory nerve axons gather to form multiple circular or ovoid olfactory glomeruli[1]. These glomeruli are distributed circumferentially around the OB and may occur singly, in pairs, or in clusters[13]. Each glomerulus exhibits a complex synaptic connection between the olfactory nerve axons, mitral cells, and tufted cells. Glomeruli are surrounded by various types of juxtaglomerular cells[1], and astrocyte cell bodies often located within the shell of

these surrounding cells[18]. Structurally, each glomerulus consists of two functional compartments: the olfactory neuron zone (ON zone), which contains ORN axons, and the non-olfactory neuron zone (non-ON zone), which contains processes from OB neurons[19].

The external plexiform layer (EPL) lies beneath the glomerular layer and is subdivided—though without clear demarcation—into superficial EPL, intermediate EPL, and deep EPL[20]. It is a relatively thick layer containing moderate number of sparsely distributed tufted cells, as well as dendritic processes from both dendrites of the mitral and tufted cells. The EPL also comprises branched secondary dendrites from granule cells[1].

The mitral cell layer (MCL) is a very thin layer comprising a single row of relatively large mitral neurons with prominent, rounded central nuclei[1]. Scattered granule cells may also be observed interspersed among the mitral cells in this layer[19].

Beneath the MCL is the Internal plexiform layer (IPL), which is thinner compared to its external counterpart. It is a non-cellular layer that contains axons from mitral and tufted cells[1].

The innermost and broadest layer of the OB is the granular cell layer (GCL). It consists primarily of granule cell bodies[1], along with deep short-axon (dSA) cells. Notably, the outer portion of this layer contains long, parallel cellular bands formed predominantly by granule cell clusters[13].

OLFACTORY BULB NEURONS (DIAGRAM 3)

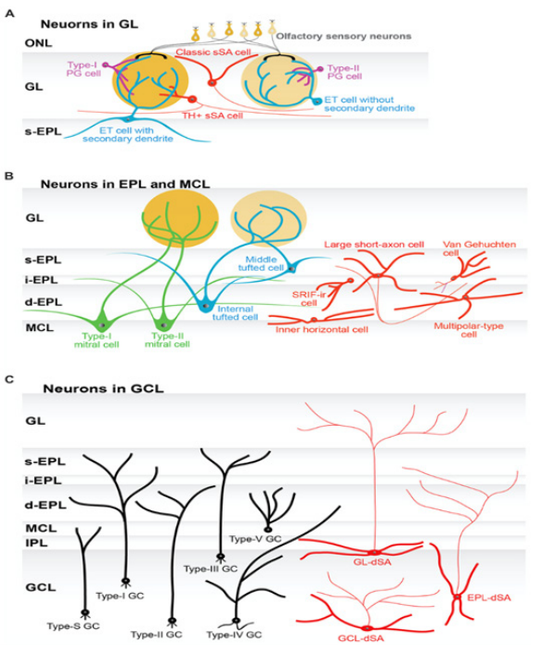

Diagram (3): Showing different types of OB neurons[19]

The Juxtaglomerular cells (JG cells):

Juxtaglomerular (JG) cells are located in the glomerular layer of the OB and consist primarily of inhibitory GABAergic interneurons, although a subset of excitatory interneurons is also present. These cells are restricted to the OB and do not project beyond it. While often discussed collectively, JG cells can be classified into three morphologically and functionally distinct types: periglomerular cells (PG cells), superficial short axon cells (sSA cells), and external tufted cells (ET cells)[21].

The most abundant among JG cells are the periglomerular (PG) cells, which are characterized by small cell bodies and typically form limited, single-glomerular connections. They extend their dendrites into a single glomerulus and are often considered axon-less, though some possess axons that project laterally across several glomeruli before terminating in the interglomerular space[21]. PG cells are further subdivided into two types:

- Type I PG cells, which send dendrites into both the olfactory neuron (ON) and non-olfactory neuron (non-ON) zones of the glomerulus.
- Type II PG cells, which extend dendrites solely into the non-ON zone and thus do not receive direct input from olfactory ORNs[19].
- The second type of JG cells is the superficial short axon (sSA) cells, which have larger cell bodies than PG cells. These are classified into two subtypes:
- Classic sSA cells, whose dendrites arborize exclusively within the interglomerular space.
- TH+ GAD+ sSA cells, which express both tyrosine hydroxylase (TH) and glutamic acid decarboxylase (GAD). Their dendrites may contact up to 50 glomeruli, and their axons can extend several hundred micrometers, reaching glomeruli up to one millimeter away[18,19].

The third type of JG cells is the external tufted (ET) cells, which have the largest cell bodies among the JG population. These cells project mono- or di-glomerular dendrites that often occupy a substantial portion of the glomerular volume[22]. Their axons traverse the external plexiform layer but remain confined within the OB[18].

Two major subtypes of ET cells have been described based on dendritic and axonal architecture:

- The first subtype has cell bodies located exclusively within the glomerular layer, lacks secondary (basal) dendrites, and possesses axons restricted to the OB.
- The second subtype has cell bodies located in the deep third of the glomerular layer or at its boundary with the internal plexiform layer (IPL),

and typically exhibits more complex dendritic and axonal structures[19].

All ET cells are excitatory interneurons that play a crucial role in glomerular signal processing and interglomerular coordination[22].

The Tufted cells

Tufted cells are excitatory projection neurons within the OB and are classified into three distinct subtypes based on their anatomical location: external tufted (ET) cells, middle tufted (MT) cells, and internal tufted (IT) cells. ET cells are situated at the interface between the glomerular layer (GL) and the external plexiform layer (EPL), while MT and IT cells are located within the superficial and deep regions of the EPL, respectively[19].

MT cells possess medium-sized cell bodies, whereas IT cells have relatively larger cell bodies. Due to their structural and functional similarities with mitral cells, IT cells are sometimes referred to as "displaced mitral cells"[19]. Despite their anatomical differences, all tufted cell subtypes are predominantly glutamatergic excitatory neurons. Each cell typically extends a single primary dendrite into one glomerulus, forming precise and glomerulus-specific synaptic connections[22].

The Mitral cells (M cells)

Mitral cells are the largest projection neurons in the OB, with somatic diameters exceeding 20 μm[1]. Their cell bodies reside within the MCL, while their dendritic processes extend entirely into the EPL.

Based on the depth of their secondary dendrites within the EPL, mitral cells are typically classified into two main types:

- Type I mitral cells, which have long secondary dendrites projecting into the deep EPL
- Type II mitral cells, whose secondary dendrites extend into the intermediate EPL.
- A third subtype has also been identified, with secondary dendrites extending into the superficial EPL. These cells are subject to strong inhibitory control by granule cells—either through dendro-dendritic inhibition within the EPL or somatic inhibition in the MCL[19].

Morphologically, mitral cells exhibit a variety of cell body shapes, including triangular, rounded, and fusiform forms[19]. Their axons project to several key regions involved in olfactory processing, including the medial and posteromedial cortical amygdala, the nucleus of the accessory olfactory tract, and the nucleus of the stria terminalis. From there, olfactory signals are further transmitted to hypothalamic nuclei[23].

Only the primary dendrites of mitral and tufted cells extend into the olfactory glomeruli, with each neuron typically innervating a single glomerulus—reflecting the “single-cell, single-receptor” principle. Within the glomerulus, mitral and tufted cells form synapses with olfactory bulb interneurons, including PG cells. Outside the glomeruli, their secondary dendrites interact primarily with dendrites of granule cells via dendro-dendritic synapses.

Mitral and tufted cells serve as the main efferent neurons of the OB, relaying processed olfactory information to the olfactory cortex. While they share several structural, functional, and molecular characteristics, they differ in soma size, dendritic and axonal projection patterns, and their responsiveness to odorant stimuli[22].

Granule cells (G cells)

Granule cells are cells with small-bodies having inhibitory interneurons located primarily within the GCL of the OB, typically measuring less than 6–8 μm in diameter. These cells transmit information exclusively via dendro-dendritic synapses[24]. Their dendrites extend into the EPL, where they form reciprocal synaptic connections with the secondary dendrites of both mitral and tufted cells. Although G cells are most abundant in the GCL, some are also found scattered within the MCL and the IPL[24].

Deep short axon cells (dSA)

Deep short axon (dSA) cells are GABAergic interneurons located primarily in the IPL and GCL of the OB. This heterogeneous population includes several morphologically distinct cell types, such as Golgi cells, Cajal cells, horizontal cells, and Blanes cells[25].

Among these, Blanes cells—characterized by their large cell bodies and spiny dendrites—are the most frequently encountered. In contrast, Cajal cells (small), Golgi cells (sparsely spiny), and horizontal cells (medium-sized) are observed less commonly. Most dSA cells have dendritic arborizations confined to the IPL and GCL. Their axons, however, may project to the GL, EPL, or GCL, contributing to local inhibitory circuits within the olfactory bulb[25].

OLFACTORY TRANSDUCTION TO THE OLFACTORY BULB

Olfactory transduction is the process by which odorant molecules—acting as chemical stimuli—are converted into electrical signals that can be interpreted by the brain. This process begins when an odorant binds to G protein-coupled receptors (GPCRs) located on the cilia of ORNs. This binding activates a G protein, which in turn initiates an intracellular signaling cascade that catalyzes the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP)[26].

The generated cAMP binds to ion channels on the

neuronal membrane, causing them to open. This allows the influx of sodium (Na^+) and calcium (Ca^{2+}) ions, accompanied by the efflux of chloride (Cl^-) ions. As ion exchange continues, the membrane potential rises until it reaches a threshold, triggering an action potential. This electrical signal is then propagated along the axons of the ORNs, which pass through the cribriform plate and terminate in the glomeruli of the OB.

Each glomerulus serves as a functional unit for odor representation, receiving input from ORNs that express the same type of odorant receptor[27]. This convergence provides the OB with a highly organized map for initial odor processing before signals are transmitted to higher olfactory centers.

Olfactory pathway (Diagram 4)[28]

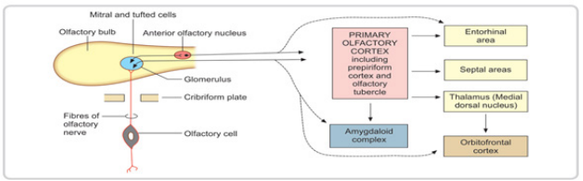

Diagram (4): Showing the olfactory pathway and connections[28]

The axons from ORNs project to the glomeruli of the OB, where they synapse with the dendrites of mitral and tufted cells. The axons of these projection neurons form the olfactory tract, which also sends collateral fibers to the anterior olfactory nucleus (AON)—a small group of neurons located between the OB and the tract. Notably, the AON and OB also exchange commissural fibers with their counterparts on the contralateral side, contributing to bilateral integration of olfactory signals.

Posteriorly, the olfactory tract divides into two main branches: the medial olfactory stria and the lateral olfactory stria. These striae ultimately converge on the olfactory tubercle, a prominent elevation of the anterior perforated substance.

Direct projections from the OB reach the primary olfactory cortex, which includes the piriform cortex and the gyrus semilunaris. Additional fibers also terminate in the anterior olfactory nucleus and the olfactory tubercle.

From the primary olfactory cortex, secondary projections extend to regions involved in higher-order processing of olfactory information, including the entorhinal cortex, septal area, and medial dorsal nucleus of the thalamus. From the thalamus, olfactory signals are further relayed to the orbitofrontal cortex, where conscious perception and discrimination of odors occur.

REGENERATION OF OLFACTORY BULB NEURONS

Olfactory bulb neurons, including both GABAergic and glutamatergic types, are continuously regenerated throughout life across all OB layers. The highest rate of neurogenesis occurs in the GCL[20]. This regenerative process begins in the subventricular zone of the lateral ventricles and the sub-granular zone of the dentate gyrus in the hippocampus. Neuroblasts generated in these regions migrate toward the OB along the rostral migratory stream, where they differentiate into mature neurons.

However, not all neuronal subtypes appear to be regenerated during adulthood. For example, tyrosine hydroxylase (TH) and glutamic acid decarboxylase (GAD) co-expressing sSA cells may not undergo adult neurogenesis[20].

Subventricular neurogenesis has also been implicated in the spontaneous recovery of olfactory function following head trauma. This is thought to result from the increased generation of dopaminergic neurons within the OB glomeruli, contributing to functional restoration[28].

OLFACTORY BULB DYSFUNCTION

Olfactory dysfunction (OD) can significantly impair various aspects of an individual's life. Affected individuals often experience reduced appetite, leading to inadequate nutritional intake and a sense of insecurity, which together can diminish overall quality of life[29,30].

Olfactory dysfunction in Covid-19

Olfactory and gustatory dysfunctions have been hallmark symptoms of coronavirus disease 2019 (COVID-19). However, their prevalence and underlying mechanisms have varied across different viral strains due to rapid mutations in the virus. The angiotensin-converting enzyme 2 (ACE2) receptor, which binds the spike protein of SARS-CoV-2 in the olfactory epithelium, plays a central role in the development of OD.

While most cases of COVID-19–related OD resolve within a few weeks, some individuals experience prolonged symptoms, including parosmia (distorted odor perception) or phantosmia (perception of odors without stimuli), which can have long-term effects on mental and emotional well-being. Evidence suggests that SARS-CoV-2 may cause sensorineural olfactory damage by affecting olfactory nerve cells and disrupting synaptic glomeruli within the OB[31].

Olfactory dysfunction in cardiovascular diseases

Olfactory dysfunction has been increasingly associated with various forms of cardiovascular disease. In particular, studies have shown a higher prevalence of olfactory impairment in individuals with coronary artery disease, especially among males[32]. A significant correlation has also been observed between reduced olfactory function and the severity of ischemic heart failure[33].

Moreover, poor olfaction has been identified as a potential predictor of long-term congestive heart failure risk, particularly in older adults who subjectively rate their health as "very good" or "excellent"[4]. The consequences of OD in this population extend beyond physical health; it has also been linked to increased risk of depression, social isolation, and physical inactivity, all of which can further compound cardiovascular morbidity[34].

Olfactory dysfunction in emotion and memory disturbance, depression and neurodegenerative diseases

Accumulating evidence indicates that olfactory impairment often represents one of the earliest clinical manifestations in neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease. In neurology, OD may serve as an early biomarker for the onset of these conditions, although the precise pathophysiological mechanisms remain unclear. Anosmia is frequently recognized not only as an initial symptom but also as an indicator of disease progression and cognitive decline[3].

The olfactory system plays a pivotal role in various aspects of human behavior, with olfactory stimuli intricately linked to emotions and memories through direct connections to the limbic system and cerebral cortex. Olfaction significantly influences behavioral responses and social communication in animals as well[35]. Notably, human emotional states are strongly modulated by the sense of smell; loss of olfaction (anosmia) is associated with increased symptoms of depression and anxiety. The presence of olfactory impairments in psychiatric disorders such as schizophrenia and depression further supports the relationship between olfaction and mood regulation. These conditions affect neurotransmitter systems—including dopamine, acetylcholine, and noradrenaline—which are known to modulate olfactory pathways at the level of the OB[36].

Pollution and toxins-induced olfactory dysfunction

Exposure to air pollutants, such as particulate matter (PM) with a diameter of 2.5 μm and nitrogen oxide (NO), has been associated with a decline in olfactory function, particularly in elderly populations. Individuals exposed to higher levels of NO and PM ≥ 2.5 μm exhibited a faster rate of olfactory decline compared to those with lower exposure, suggesting a cumulative detrimental effect of airborne contaminants on sensory function during aging. These findings underscore the critical importance of maintaining good air quality to preserve olfactory health[37].

Occupational exposure to toxic substances—including cadmium, chromium, nickel, and formaldehyde—can also result in OD. Direct exposure of olfactory neurons to these environmental toxins can damage the olfactory epithelium and related central structures such as the OB, highlighting the need for vigilant monitoring and mitigation of occupational olfactory hazards[38].

Additionally, exposure to various chemicals, such as ammonia, hairdressing chemicals, chemotherapy agents, gasoline, and intranasal zinc, can induce diverse forms of chemosensory dysfunction. Most affected individuals primarily exhibit olfactory impairment, while some also experience taste disturbances. A minority report experiencing parosmias. Olfactory testing in these patients reveals a spectrum of dysfunction ranging from normal olfactory function (normosmia) to severe hyposmia and complete anosmia, whereas taste abnormalities often manifest as hypogeusia[39].

Intranasal route of delivery to the olfactory bulb and brain areas (Diagram 5):

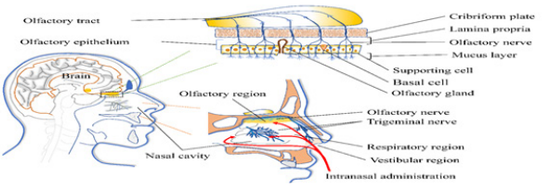

Diagram (5): Showing the intranasal route to the olfactory system[40].

The nasal cavity represents a unique direct pathway from the external environment to the brain[11]. This route has been utilized for delivering various compounds, including intranasal (IN) insulin, one of the first peptides administered to the central nervous system via this method[41]. Similarly, IN delivery of oxytocin to the brain has been demonstrated successfully[42].

The presence of rat bone marrow-derived mesenchymal stem cells (BM-MSCs) in various brain regions following IN administration was first reported in 2009[43]. After IN delivery in mice, these cells reached the OB, thalamus, hippocampus, and cerebral cortex. Later studies showed that neural stem progenitor cells administered intranasally could target intracerebral glioma in mice, appearing in the OB within six hours post-administration[11].

Therapeutic effects of intranasally administered rat MSCs were observed in neonatal focal stroke models, specifically after 72 hours in a middle cerebral artery ischemia rat model[44]. Moreover, the first-in-human study administering IN BM-MSCs at doses of 45–50 × 106 cells in mature neonates with perinatal arterial ischemic stroke demonstrated safety and therapeutic potential without adverse effects[45].

Research over the past decade has also explored IN delivery of conditioned media from stem cells. Conditioned media derived from human exfoliated deciduous teeth, administered daily for 13 days post-ischemia, improved motor function, reduced infarct size, and enhanced migration of neuronal progenitor cells near the infarct area[46]. Similarly, conditioned medium from human umbilical cord-derived MSCs, given intranasally in a rat cerebral ischemia model, improved neurological function, although it did not reduce infarct volume[47].

Intranasal delivery of nanoparticles (NPs) and nano formulations is an emerging field. For example, valproic acid-loaded lipid NPs delivered intranasally achieved high brain concentrations and prevented seizures in a maximal electroshock seizure model, showing efficacy comparable to intraperitoneal phenytoin[48]. A breakthrough was the IN delivery of nucleic acids encapsulated in chitosan nanoparticles[49]. Additionally, Solanum tuberosum lectin conjugated with polyethylene glycol–poly(lactic-co-glycolic acid) (PLGA-PEG) NPs carrying basic fibroblast growth factor improved cognition in an Alzheimer's disease mouse model[50]. IN administration of chitosan-coated resveratrol lipid microparticles enhanced brain delivery sixfold without systemic exposure in rats[51].

Importantly, IN delivery enhances drug bioavailability in the brain by bypassing gastrointestinal absorption and hepatic metabolism[52]. For instance, IN suspension of lead oxide (PbO) NPs readily penetrates brain structures, dispersing widely and depositing within the OB[53,54].

CONCLUSION

The OB is a sophisticated neural structure that form intricate synaptic networks essential for odor detection and processing. Olfactory dysfunction is a significant clinical indicator linked to neurodegenerative, cardiovascular, infectious, and environmental conditions, affecting quality of life and cognitive health. However, its continuous neurogenesis not only supports olfactory function and recovery from injury but also provides hope for developing novel regenerative treatments.

Leveraging the unique anatomy and microstructure of the olfactory system, intranasal delivery of therapeutics offers a promising, non-invasive strategy for treating neurological disorders by directly targeting brain regions while bypassing systemic barriers. Continued exploration of the OB anatomy, structure, function, and regenerative capacity combined with advances in intranasal delivery holds significant promise for the development of novel diagnostic and therapeutic modalities in neuroscience and clinical medicine.

AUTHORS' CONTRIBUTIONS

NB conceptualized the study. NB, SK and LA designed the study. NB, SK and LA designed the data collection tool. MA carried out data collection. MA wrote the original draft. NB, SK and LA revised the article before submission.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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