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The Role of Olfactory Bulb in Epilepsy: Emphasizing on its Connection with Hippocampus

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Author

Navid Heidari[1]*
Mahmoud Rezaei[1]

1. Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

***Corresponding author:**

Navid Heidari,

Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran, Postal code: 1411713116;

E-mail: navidh25@gmail.com

ABSTRACT

Epilepsy is a neurological disorder characterized by recurrent seizures resulting from abnormal neuronal activity in the brain. The olfactory system is implicated in temporal lobe epilepsy (TLE), and some areas of the olfactory system may serve as sources of seizures. TLE patients often experience olfactory sensations or auras before seizure onset, and olfactory stimulation has been shown to modulate or suppress seizure activity. The connection between the OB and certain brain areas, including the hippocampus, plays a significant role in the spread and propagation of seizure attacks. The document highlights the anatomical and functional relationship between the OB, entorhinal cortex, and hippocampus, suggesting that the olfactory system is involved in the pathogenesis of epilepsy.

Keywords: Epilepsy, Seizure, Olfactory bulb, Hippocampus.

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures due to increased neuronal activity in the brain (1). A seizure is the occurrence of transient signs or symptoms resulting from abnormal and synchronized neuronal activity in the brain (2). This disorder is associated with autonomic, sensory, and motor symptoms based on the brain region involved during the onset or progression of seizures (3). According to the World Health Organization, approximately 70 million people worldwide are affected by this condition, representing 1 to 2 percent of the global population (4). Nowadays, the connection between the olfactory system and temporal lobe epilepsy (TLE) is particularly important. The primary olfactory cortex, known as the piriform cortex (PC), plays a crucial role and may be the source of seizures in TLE (5, 6). Brain regions involved in olfaction, such as the piriform cortex (PC), also play a role in seizures originating from the amygdala. One influential factor in the spread and propagation of seizure attacks in the hippocampal region is the neuronal connections between the hippocampus and certain brain areas, including the olfactory bulb (OB) (7).

Role of Olfactory Circuits in Seizure

Numerous reports have explored the involvement of olfactory structures in TLE (8, 9). Some studies have indicated that olfactory sensations can serve as an indicator of seizure onset in patients with TLE, a phenomenon described as an aura (8, 10). Furthermore, sensory-environmental stimulation with an olfactory stimulus can suppress, inhibit, or modulate these seizures (7, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19). Many TLE patients experience

olfactory sensations or auras (phantosmia, distorted perception of smells) before seizure onset (20). This phenomenon has been recognized since ancient Greek times (130-210 BCE) and was first reported by Penfield and Jasper in 1954. Olfactory auras, which are typically unpleasant and lack an environmental source, are associated with complex partial seizures originating from the mesial temporal lobe (21). The International League Against Epilepsy (ILAE) proposed in 2010 that olfactory auras are related to focal seizures and represent a mental, sensory, or psychic phenomenon (22).

Olfactory auras occur in conjunction with seizure activity in specific regions, following activity in the entorhinal cortex (part of the parahippocampal gyrus), the amygdala, or the anterior insula. Olfactory auras sometimes coexist with other sensory auras, such as gustatory (primarily taste) and auditory or visual auras. It is suggested that the olfactory system may modulate seizure activity but is not necessarily the initiator (10, 23, 24, 25, 26). In a case report, olfactory stimulation was found to prevent seizures in an epilepsy patient, yielding satisfactory results (14). Therefore, olfactory stimulation may contribute to seizure management. Specifically, many TLE patients who experience olfactory sensations before seizure onset can potentially prevent seizures by using olfactory stimuli (7).

Relationship Between OB and Involved Areas in Seizure

The connection between the olfactory system and TLE is crucial, with the primary olfactory cortex being an essential part of the limbic system from which TLE originates (6, 27). The primary olfactory cortex, also known as the piriform cortex, is centrally located within the limbic system. Brain regions involved in olfaction, such as the PC, play a role in seizures originating from the amygdala and have been shown to interfere with continuous seizure activity in the limbic system. The unique tissue morphology, synaptic circuitry, and embryonic development of the OB contribute to its distinctive features. Unlike other sensory systems, the olfactory system does not project directly to the thalamus because the OB, with its granule cell neurons and axon less periglomerular neurons, serves as an intrinsic equivalent of the thalamus. Projection neurons from olfactory regions, including mitral and tufted cells, primarily project to the anterior olfactory nucleus via the anterior commissure, connecting to the amygdala, entorhinal cortex, insular cortex, contralateral OB, septal nuclei (during embryonic development), and hypothalamus (20).

OB is one of the brain structures that has synaptic plasticity (28, 29), but its epileptogenic potential remains unknown as this aspect has been less studied in animals or humans. The primary olfactory neurons, whose cell bodies are located in the nasal epithelium, continuously regenerate and replace through an active reconstruction process. Their unmyelinated axons reach the synaptic glomeruli in the OB via the cribriform plate. Significant intrinsic synaptic remodeling and plasticity have been demonstrated throughout the OB (20). Both the OB and the hippocampus are important reservoirs of precursor stem cells, which are not only involved in synaptic plasticity but may also contribute to seizure activity in the hippocampus and possibly the OB (20).

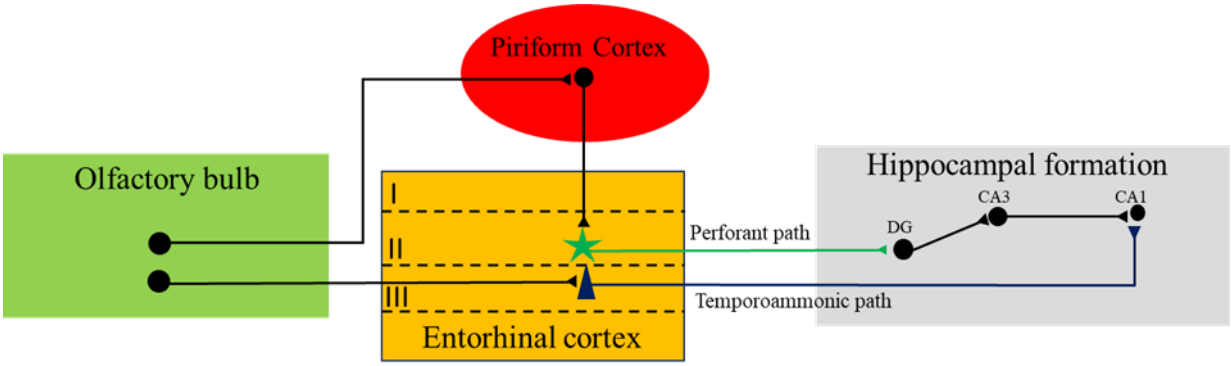

Figure 1. Relationship Between OB and Involved Areas in Seizure

In addition to receiving direct input fibers from the OB, the entorhinal cortex also receives fibers from both the perirhinal and pre-amygdaloid cortices. The entorhinal cortex is the most significant source of input fibers to the hippocampus (30).

Anatomical and electrophysiological findings indicate a functional relationship between the OB and the hippocampus, mediated by the lateral olfactory pathway and the perforant path. Fibers from the lateral OB are sent to the lateral entorhinal cortex, which contains pyramidal and stellate cells, and then proceed to the hippocampus (31). Fibers originating from mitral cells synapse in layer I of the lateral entorhinal cortex with the apical dendrites of layer II stellate cells, layer III pyramidal cells, and non-pyramidal granule cells in layer I. Axons of layer II stellate cells project from the temporoammonic path to the dentate gyrus molecular layer, while axons of layer III pyramidal cells reach the CA1 region via the perforant path (31).

Considering that the entorhinal cortex provides innervation to the PC and, conversely, the entorhinal cortex is the main source of afferents to the hippocampus, observations from this perspective support the old notion that the hippocampus has a close association with the sense of smell (30). The ventral hippocampus is also connected to emotion-related circuits through olfactory input (32). The CA1 region of the hippocampus sends numerous fibers to the anterior olfactory nuclei and the same-side OB (33). In the mouse brain, direct fibers from pyramidal cells in the ventral CA1 hippocampus and the lateral entorhinal cortex were identified as forming a feedback monosynaptic pathway to the granule cell layer of the OB (34). Additionally, the OB has a direct connection to the prefrontal cortex (PFC) and the prelimbic PFC via the anterior olfactory nuclei (35).

Conclusion

In conclusion, the olfactory bulb (OB) and its connection with the hippocampus are crucial in understanding the mechanisms underlying epilepsy, particularly temporal lobe epilepsy (TLE). The piriform cortex (PC) within the OB appears to play a significant role in the initiation and propagation of seizures. Olfactory sensations or auras preceding seizure activity are common in TLE patients, indicating the involvement of the olfactory system in seizure onset. Olfactory stimulation has the potential to modulate or prevent seizures, highlighting its therapeutic value in seizure management. The anatomical and electrophysiological findings suggest a functional relationship between the OB and the hippocampus, mediated by the lateral olfactory pathway and the perforant path. The entorhinal cortex, which receives input from the OB and projects to the hippocampus, further supports the association between the sense of smell and the hippocampus. Understanding the role of the OB and its connections in epilepsy contributes to the broader comprehension of this neurological disorder and may pave the way for novel therapeutic approaches targeting the olfactory system.

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Declaration

Authors have no conflict of interest to declare.

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