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Review article

The role of sleep in the plasticity of the olfactory system

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ABSTRACT

The central olfactory system mediates a variety of odor-guided behaviors crucial for maintenance of animal life. The olfactory neural circuit must be highly plastic to ensure that it responds appropriately to changing odor circumstances. Recent studies have revealed that the processing of odor information changes drastically during waking and sleep and that neural activity during sleep plays pivotal roles in the structural reorganization and functional plasticity of the olfactory system. While olfactory information from the external world is efficiently transferred to the olfactory cortex (OC) via the olfactory bulb (OB) during waking, this information flow is attenuated during slow-wave sleep: during slow-wave sleep, the OC neurons exhibit synchronous discharges without odor input under the entrainment of sharp waves in the local field potential recording. Top-down transfer of sharp-wave activity to the OB during slow-wave sleep promotes structural reorganization of the OB neural circuit. Further, the activity of the OC during sleep is affected by the olfactory experience during prior waking period, and perturbation of the sleep activity disrupts proper olfactory memory. Thus, as is seen also in the hippocampus and neocortex, the neural activities of the olfactory system during sleep likely play essential roles in circuit reorganization and memory consolidation.

Contents

1. Introduction

It is now widely accepted that sleep plays an active role in neural plasticity, including memory consolidation and synaptic downscaling (Buzsaki, 1989; Rasch and Born, 2013; Tononi and Cirelli, 2014). Sleep is essential for many aspects of brain function, including olfaction. A few human studies have shown that sleep deprivation for 1–2 days impairs the ability to identify odors (Killgore and McBride 2006; Shanahan and Gottfried, 2014).

The central olfactory system mediates a vast variety of odor-guided behavioral responses, including approaches to the odor of foods or to the odor (or pheromone) of partners, and flight from the odors of predators (Doty, 1986). Such responses are essential behaviors for animals to survive. Although some basic odor-induced behaviors are mediated by innately determined neuronal circuits, most such behaviors develop based on previous experience with the object or environment emitting the odor. It is therefore likely that the neuronal circuits of the central olfactory system are highly plastic, being reorganized daily to update and improve behavioral responses to the ever-changing external odor world. It is very likely that odor experiences during waking

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are appropriately processed during subsequent sleep, improving the nature of olfactory responses during the next round of waking, allowing the animal to behave more appropriately in any particular odor environment.

An important neural feature underlying the direct link between odor information and essential behavior is that the olfactory system is phylogenetically old. The olfactory cortex (OC), the central cortical structure of the olfactory system, is a paleocortex rather than a neocortex. The OC is a component of the limbic system and forms massive reciprocal connections with various brain areas, including the amygdala and prefrontal cortex (Shipley and Ennis, 1996; Haberly, 2001; Illig, 2005; Mori, 2014). The OC is thus regarded as an association cortex integrating odor inputs with other intrinsic brain activities such as emotion, valence, motivation, and behavior. The OC is an intriguing target of research examining how sleep contributes to the association of the various kinds of information and the expression of suitable odor-guided behaviors during the subsequent waking period.

Recent studies have revealed the adaptive role played by sleep in the olfactory system and indicate that this tends to parallel our understanding of how the hippocampus and neocortex operate. In this review, I first introduce the neural circuit of the olfactory system and explain how olfactory information is processed in the olfactory neural circuit during both waking and sleep. I then introduce recent evidence that sleep plays important roles in both structural reorganization and the functional plasticity of the olfactory system.

2. The neuronal circuitry of the olfactory system

Hundreds of thousands or millions of distinct odor molecules are estimated to exist in the external world. In rodents, these huge numbers of odor molecules are first received by approximately 1000 types of odorant receptors (ORs), each encoded by a distinct gene (Buck and Axel, 1991). ORs are expressed in the olfactory sensory neurons (OSNs) of the olfactory epithelium (OE), and individual odor molecules are received by specific combinations of ORs (Malnic et al., 1999).

Individual OSNs in the OE express a single type of OR (Chess et al., 1994). OSNs expressing a given OR project their axons to converge on a few topographically fixed glomeruli in the olfactory bulb (OB); this is the first relay center of the central olfactory system (Fig. 1). The glomeruli are formed of neurophils covering the entire surface of the OB, and, in the mouse, each OB contains about 1800 glomeruli. Because of the axonal convergence of OSNs, each individual glomerulus represents a single type of OR. Accordingly, the spatial arrangement of glomeruli in the OB forms a sensory map that spatially represents the activities of numerous types of OR (Mori et al., 2006; Mori and Sakano, 2011). Within the glomeruli, the OSN axons engage in excitatory synaptic connections to the primary dendrites of mitral and tufted cells; these are the glutamatergic projection neurons of the OBs (Mori, 1987; Shepherd et al., 2004). Each mitral/tufted cell projects a single primary dendrite to a single glomerulus and, thus, essentially, receives information from a single OR.

The mitral and tufted cells project their axons to the OC to form excitatory synapses with the apical dendrites of the pyramidal cells of the OC (Fig. 1), which is divided into several areas (Neville and Haberly, 2004). The largest of these is the piriform cortex (PC), which is further subdivided into the anterior piriform cortex (APC) and posterior piriform cortex. The OC also includes the anterior olfactory nucleus, the tenia tecta, the olfactory tubercle, the cortical amygdala, and the lateral entorhinal cortex.

The OC is a component of the paleocortex; in contrast to the six-layered structure of the neocortex, each area of the OC exhibits a pyramidal cell-based cortical structure with three distinct layers (Fig. 1). Pyramidal cells in layers II and III of the OC extend apical dendrites superficially into layer I and receive glutamatergic excitatory synaptic inputs from the mitral/tufted cell axons in the most superficial domain of the apical dendrite (layer Ia). Pyramidal cells exhibit association fibers that terminate in layers Ib, II, and III of the same or another area of the OC. The pyramidal cells of the OC also project axons outside the OC, to the ventral agranular insular cortex, the orbitofrontal cortex, the amygdaloid complex, the thalamus, and the hypothalamus (Shipley and Ennis, 1996).

Additionally, the pyramidal cells of the OC, especially those of the anterior OC (the anterior olfactory nucleus and the APC) project enormous numbers of collateral axons back to the OB (Fig. 1). The top-down centrifugal axons of OC pyramidal cells project principally to the deep layer of the OB (the granule cell layer [GCL]) to terminate on inhibitory interneurons such as granule cells (GCs) and short-axon cells (Luskin and Price, 1983; Boyd et al., 2012; Markopoulos et al., 2012).

Such an elaborate neuronal framework indicates that olfactory information reaches the OC via a very small number of synaptic transfers. Indeed, the pyramidal cells of the OC are located only two synapses distant from the external world; odor information is received by OSNs of the OE, transferred to the mitral/tufted cells of the OB, and then transferred to the pyramidal cells of the OC. Notably, odor information reaches the OC without relay through the thalamus. The olfactory system is, in fact, the only sensory system that sends information directly to the primary cortex without thalamic relay. Thus, odor information from the external world directly enters an association cortex, the OC, wherein it is integrated with the intrinsic activities of higher cortical functions. Further, the OB, which is located just one synapse distant from the external world, receives massive top-down inputs from the OC. This allows the neural circuit of the OB to be regulated by higher cortical activities. Thus, as will be discussed in the following sections, the neural circuits of the OB and OC are strongly influenced by intrinsic brain activities and are plastically modulated in this manner during sleep.

3. Behavioral state-dependent neural activities of the olfactory system

As is also true of many other brain regions, the neural activities of the olfactory system change drastically from waking to sleep. The olfactory neural circuit is highly active not only during the waking period for detecting odors but also during the subsequent sleep period for further processing odor information obtained during waking (Yamaguchi et al., 2013; Barnes and Wilson, 2014a; Shanahan and Gottfried, 2014).

During the waking period, odor inhalation induces spike responses of mitral/tufted cells of the OB. These cells then activate pyramidal cells of the OC via axons that terminate in layer Ia of the OC. The initially activated OC pyramidal cells further activate other OC pyramidal cells via association fibers that terminate in layers Ib, II, and III. During the waking state, therefore, odor information is conveyed by the pathway consisting of OSNs–mitral/tufted cells–OC pyramidal cells (Fig. 1, red arrows). Local field potential (LFP) recordings from the OB and OC indicate that odor stimulation evokes a high frequency (gamma and beta) range of oscillation that is coherent between the OB and OC (Manabe and Mori, 2013; Mori et al., 2013; Kay, 2014).

During sleep, the neural activities of the OC change in line with alterations in the global state of the brain, including the hippocampus and neocortex. During slow-wave sleep, LFP recordings of the OC are characterized by large, irregular slow-wave activity (0.5–4 Hz in rats) (Fig. 2A). Such activity ceases during REM sleep and is replaced by smaller and faster fluctuation of LFP (Manabe