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Review

Integration of olfactory and gustatory chemosignals in the insular cortex

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ABSTRACT

Background: Flavor is an integrative sensation comprised of taste, odor, and mouthfeel. The interaction between olfactory cues and taste is particularly important for flavor formation. Because odor information is conveyed to the insular cortex (IC), the integration of olfactory and gustatory chemosignals may be performed in the IC. However, little is known about how these chemosignals converge in the IC. In this review, we explore the mechanisms underlying signal integration in the IC, and we summarize several studies relevant to this issue. Some morphological findings have indicated the presence of bidirectional connections between the piriform cortex (PC) and IC. Clarifying the functional interactions between these cortices, some groups, including ours, have demonstrated the spatiotemporal dynamics of excitatory propagation induced by simultaneously stimulating olfactory and gustatory pathways, using an *in vivo* optical imaging technique with a voltage sensitive dye.
Highlights: In our study, simultaneous stimulation of olfactory and gustatory pathways showed spatially additive responding regions within the PC and IC. Responses of the agranular IC (AI) to simultaneous stimulation showed a synergistic increase in amplitudes, whereas the responses in other areas were of the same order of magnitude as the responses to the single stimulation of either olfactory or gustatory pathway.
Conclusion: Several studies, including fMRI analyses in human and animal studies, suggest that the IC directly integrates olfactory and gustatory chemical signals. In particular, our study raises the possibility that the AI plays an important role in integrating olfactory and gustatory signals.

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1. Introduction

What type of central mechanism underlies our sensation that a particular food is palatable? Why is it that, under different circumstances, the same foods may taste different? This complexity of gustation is due to the fact that we experience the tastes of foods as flavors, which are a compound sensation formed from multimodal information, including taste, odor, and texture (mouthfeel) [1]. The interaction between olfactory cues and taste is particularly important for flavor formation. As described by Shepherd (2006), "Flavor perception is one of the most complex of human behaviors. It involves almost all of the senses, particularly the sense of smell, which is involved through odor images generated in the olfactory pathway" [1].

The importance of olfaction in forming flavors as a compound sense is similar in humans and animals, including rodents. However, it is not yet clear how and where in the brain the odor information is involved in the formation of a flavor. Historically, the brain region integrating the two chemical senses of gustation and olfaction has been considered to be a secondary sensory area within the orbitofrontal cortex (OFC) [2–4], but several lines of evidence regarding the olfactory pathway suggest the possibility that the integration of gustation and olfaction is carried out in a cortical pathway before the OFC [5,6]. One candidate region is the insular cortex (IC), which is known to function in the integration of chemical senses. In this review, we discuss the IC as a region potentially responsible for the integration of disparate types of chemosignals in animals as well as humans, and we introduce our own research pertaining to the possible role of the IC.

2. The gustatory neural pathway

Tastants—water-soluble chemicals in foods—are detected by taste cells in the taste buds distributed in the oropharyngeal epithelia. This taste information is then transmitted to the nucleus of the solitary tract (NST), the first relay station in the medulla oblongata, via the facial, glossopharyngeal, and vagus nerves [7,8]. The gustatory projection from the NST reaches the parabrachial nucleus (PbN) in the pons and then the parvocellular part of the ventral posteromedial thalamic nucleus (VPMpc) in animals other than the primates. In primates, including humans, the taste pathway directly connects to the VPMpc only [9].

From the VPMpc, the gustatory pathway connects to the primary gustatory cortex, a cerebral cortical region located along the border between the anterior IC and the frontal operculum. This afferent pathway is a common route among mammals. In addition to the pathway from the PbN to the IC, the PbN also sends axons to the amygdala, which then projects to the IC. Finally, taste information arrives at the OFC, which is known as the secondary gustatory cortex [7–10].

3. The olfactory neural pathway

Volatile compounds known as odorants are received by olfactory sensory neurons (OSNs) that line the olfactory epithelium. Mammals partially perceive odorants as flavors in the mouth due to the odorants' retronasal passage into the nose during eating [11]. The olfactory information is first transmitted from the OSN to the main olfactory bulb (mOB), the first relay center in the olfactory system [12,13]. The projection from the mOB connects directly or indirectly via the olfactory peduncle areas to the piriform cortex (PC), which is a part of the paleocortex with a relatively simple three-layered structure [14]. After the olfactory information is processed in the PC, odor signals are sent to higher olfactory associative regions such as the amygdala, olfactory tubercle, and the OFC. In general, the odor signal first converges with the taste pathway in the OFC.

4. The insular cortex as a possible flavor center

The IC of rodents is located on the dorsal region of the rhinal fissure and over the middle cerebral artery (MCA) in an anteroposterior direction. This cortical region is divided into three parts: the granular insular cortex (GI), the intermediate dysgranular insular (DI) cortex, and the agranular insular cortex (AI) [15]. The relay neurons in the VPMpc project their axons to the DI and GI (DI/GI), and extracellular recordings have demonstrated that the DI/GI respond to various gustatory stimuli [16]. Some optical imaging studies also revealed that gustatory stimuli in the oral cavity activate optical signals in the DI/GI around the MCA [17–19].

Based on these findings, the IC, particularly the DI/GI, is generally thought to be the gustatory center, although several studies have also suggested that the IC affects olfactory information processing as well [5,6,20–24]. These results are consistent with other imaging studies in rodents.

A morphological study of the neural projections in rodents indicated the presence of bidirectional pathways between the IC and the PC. Through using the intracellular injection of biotinylated dextran amine to trace its projection *in vivo*, Johnson et al. (2000) demonstrated that a single pyramidal cell in layer II of the rat posterior PC extended its axon branches to the entire length of the cerebral hemisphere, including the IC [20]. Conversely, anterograde projections from the posterior AI reach the DI and the PC [21]. Interestingly, some neurons in the rat mOB project their axons directly to the AI [22]. Similar to animal experiments, some reports suggest a role for the IC in the interaction between odor and taste information in humans. Studies using functional magnetic resonance imaging (fMRI) have described the detection of odor-evoked brain activities within the human IC [23,24].

Thus, several studies have suggested that the odor information is processed in the IC, suggesting that the integration of chemosignals, at least in part, may also be carried out in the IC. Considering the neuronal connectivity between the PC and the IC, the AI would be better suited to playing a key role in the integration of olfaction and gustation in the IC. However, it is unclear how the odor signals converge with the taste pathway in the IC.

5. Responses in the AI evoked by simultaneous stimulation of the olfactory and gustatory pathways

To explore the mechanisms by which odor and taste information are integrated to form flavors, we examined the spatiotemporal propagation of the excitatory responses in the rat IC and PC by electrically stimulating either or both of these chemosensory pathways. The responses evoked by the electrical stimulation to the chemosensory pathways were observed by an optical imaging technique using a voltage-sensitive dye (RH1691) [18,19,25,26]. This technique is suitable for revealing the coordinated function of the neural network, because it directly reflects the electrical activities of the neurons at high spatial resolution [27]. Since the IC in rodents is located on the cortical surface and is adjacent to the PC, it is possible to observe the odor- and taste-evoked neuronal responses at the same time within the same field of view (Fig. 1).

We observed that when only the rat VPMpc was electrically stimulated with the use of a concentric microelectrode, the obvious evoked-responses were observed mainly on the rostral gustatory cortex (GC), which is located in the DI. Unlike VPMpc stimulation, electrical stimulation of the rat mOB evoked responses along the PC.