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MEETING REPORT

The 15th International Symposium on Olfaction and Taste

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Introduction

The 15th International Symposium on Olfaction and Taste (ISOT) meeting marked the 30th anniversary of the host organization, the Association for Chemoreception Sciences, and the 100th anniversary of the scientific description of the umami taste modality. The meeting featured 23 symposia, 177 platform presentations, and more than 500 posters. These numbers reflect the continued maturation and appeal of the chemical senses as a field of research. Reports of significant, even surprising, findings abounded. Advances on some long-standing problems were described and new problems were revealed.

Olfaction

In olfaction, our understanding of the encoding of odor signals continues to improve. Several presentations reported the identification of odor agonists for odorant receptors (ORs), the largest effort being described in reports by Joel Mainland and Hiroaki Matsunami (Duke University). They matched 62 mouse and human receptors with at least one odorant agonist, more than doubling the number of mammalian ORs with known agonists. The diversity of receptor sequence and odorant structure represented was sufficient to allow a degree of predictability in the relationship between receptor and odorant. The problem of membrane trafficking of ORs that has hindered functional expression of mammalian ORs was further resolved with Matsunami's much anticipated report that mice lacking the OR accessory proteins RTP1 and RTP2 have deficits in odor detection. Other proteins that regulate ORs were also reported. Sabrina Baumgart (Ruhr University) described the interaction of ORs with MUPP1, a multi-PDZ domain protein and Sebastian Rasche (Ruhr University) reported further evidence of internalization of ORs by β-arrestin2.

Insect ORs, which are ligand-gated ion channels rather than the G-protein coupled receptors used by vertebrates, may also have distinct activation mechanisms. Several groups provided evidence implicating odorant-binding proteins (OBPs) and pheromone-binding proteins (PBPs) in the activation of insect ORs. The long-standing idea that OBPs and related proteins can be essential for activation of ORs, even becoming agonists themselves when stabilized in an active conformation by a bound odorant, was best supported by John Laughlin's (University of Colorado) report of a constitutively active mutant of LUSH, an OBP necessary for the detection of 11-cis-vaccenyl acetate by fruit flies. The report by Takao Nakagawa (Rockefeller University) of several compounds with greater antagonism of multiple insect ORs than the only commercial repellent (DEET) brings hope for future advances in our ability to reduce the impact of insects as pests.

While the primary mechanisms of vertebrate olfactory transduction are largely understood, much remains to be learned about the events that establish, maintain, and modulate the encoding of odor signals. Paul Jenkins and Dyke McEwen (University of Michigan) reported discoveries important to olfactory cilia. Respectively, they found that phosphofurin acidic cluster sorting protein 1 (PACS-1) is involved in the trafficking of cyclic-nucleotide gated channels into mammalian olfactory cilia via interaction with the CNGB1b subunit of the channel, and that retinitis pigmentosa GTPase regulator (RPGR), whose isoforms locate to dendritic knobs or olfactory cilia, is necessary for odorant responses. Daniela Brunert (Ruhr University) reported that odorants stimulate production of nitric oxide by olfactory sensory neurons and that the dynamics of electro-olfactograms were altered in mice lacking endothelial nitric oxide synthase (eNOS). Agnes Savigner (Lyon, France) reported that leptin and insulin increase the excitability of rat olfactory sensory neurons, strengthening links between satiety and the sense of smell. This agrees with the report by David Marks (Florida State University) that the daily regimen of intranasal insulin now

used by some diabetics improves object memory and odor discrimination in mice.

Once encoded odor signals are passed into the central nervous system where the signal processing events that contribute to odor identification and discrimination are complex and often difficult to investigate. However, progress is being made. The most numerous cell type within the olfactory bulb is the granule cell, an axonless, GABAergic interneuron that forms reciprocal dendrodendritic synapses with the olfactory bulb output neurons, mitral and tufted cells. Granule cells and their dendrodendritic synapses are hypothesized to underlie feedback, feedforward and/or lateral inhibition of mitral cells, but are also the target of descending input from olfactory cortical areas. A symposium on ''Dendrodendritic synapses: 40 Years of progress'' organized by Charles Greer, Laura Lopez-Mascaraque and Fernando de Castro Soubriet reviewed recent work on this unusual component of the olfactory bulb circuitry. The talks in this symposium ranged from intricate dissection of granule cell-mitral cell interactions and dynamic regulation of inhibitory control based on ongoing firing patterns (Matt Ennis, University of Tennessee; Nathan Urban, Carnegie Mellon University) to larger circuit analyses, development and plasticity (Pierre-Marie Lledo, Pasteur Institute; Ben Strowbridge, Case Western Reserve University; Kensaku Mori, University of Tokyo). One issue of particular note that has gone understudied is analysis of the descending control of granule cells by cortical feedback. Both Lledo and Strowbridge reported distinct differences between the synaptic physiology of mitral cell glutamatergic dendrodendritic synapses on granule cells and the physiology of glutamatergic synapses onto granule cell somata, presumed to be from olfactory cortex. These descending synapses were more plastic than the dendrodendritic synapses, particularly in immature granule cells. This feedback and plasticity may be important in regulating granule cell survival. Granule cells are also the target of modulatory inputs to the olfactory bulb, regulating circuit excitability in a state-dependent manner (Mori). This symposium was followed by a special lecture where Gordon Shepherd (Yale University) described the discovery and history of dendrodendritic synapses, providing wonderful personal insights into his involvements in the original anatomical and physiological description of this unusual neural connection.

A series of symposia funded by the National Institute of Aging highlighted recent advances on both normal and pathological aging of the chemical senses. These symposia included talks ranging from molecular biology to psychophysics, from *Caenorhabditis elegans* to humans. The symposium, ''Chemical senses and other aging sensory and motor systems,'' chaired by Wen Chen (National Institute on Aging), included a report by Robert Wilson (Rush University Medical Center) that further advanced the potential of olfactory psychophysical testing for identifying patients with incipient Alzheimer's disease. Performance on smell identification tests in pre-symptomatic subjects was a strong predictor of subsequent Alzheimer's onset and rate of cognitive decline. A poster by James Howard (Northwestern University) echoed the same theme, showing that early stage Alzheimer's disease patients had less odor-evoked activity in piriform cortex than normal. Another pathology for which olfaction appears to be a ready indicator (in this case, hypersensitivity to odors) is Fragile X syndrome, a neural development disorder caused by trinucleotide repeat expansion near the Fmr1 gene on the X chromosome. Michael Akins (Brown University) reported that the RNA binding protein FMR1, which is not expressed in severe Fragile X syndrome, locates to presynaptic terminals of olfactory sensory neurons and may be critical for developmental regulation of synapse formation in several regions of the nervous system, consistent with the symptoms of Fragile X syndrome.

Taste

The study of the peripheral gustatory system was transformed with the discoveries of the T1R and T2R families of G-protein coupled receptors (GPCRs) and the properties of these receptors continue to be a focus of taste research. Researchers from Senomyx, Inc. described important new studies of both of these receptor families, which play critical roles in the detection of sweet-, umami- and bitter-tasting stimuli. Hong Xu reported ligands for 22 of the 25 human T2Rs, finding that most of these bitter receptors are broadly tuned. Alexey Pronin's identification of antagonists for human T2R8 signals hope for the development of additives that will reduce the bitter taste of some foods and medicines. Responses of the umami receptor, composed of T1R1 and T1R3, to glutamate are enhanced by monophosphorylated nucleotides. Xiaodong Li reported that inosine monophosphate stabilizes the closed state of T1R1 by binding near the mouth of the venus flytrap module that binds glutamate, providing a putative structural mechanism for enhanced responsivity. Similarly, Guy Servant and Feng Zhang reported the discovery of sweet enhancers that appear to bind alongside sucralose in the venus flytrap module of T1R2.

In addition to driving seminal advances in our understanding of basic taste transduction mechanisms, the discovery of T1Rs and T2Rs has catalyzed other unexpected advances. For example, T1R/T2R expression occurs in taste receptor cells that lacked morphological synapses with nerve fibers in the taste bud, raising the question of how sweet, umami, and bitter responses are communicated to the central nervous system. The answer may be purinergic signaling within the taste bud. Sweet and bitter stimuli release ATP within taste buds, suggesting that taste receptor cells lacking synapses (Type II cells) could communicate directly with afferent nerve fibers. Ruibiao Yang (University of Denver) reported

that immunoreactivity for the P2X2 purinergic receptor is present on virtually all nerve fibers in the taste bud and is in close association with the Type II cells that express T1R/T2R receptors. Stephen Roper (University of Miami) reported the finding that taste buds from double knockout mice lacking both P2X2 and P2X3 purinergic receptors did not release ATP in response to taste stimuli. This finding is surprising since the previously reported behavioral and electrophysiological taste deficiencies in these mice were thought to originate from their lack of post-synaptic receptors. Other studies presented new evidence regarding transmitter co-release and peptide neuromodulators in the taste bud. In response to sour stimuli, Leslie Stone (Colorado State University) and Robert Stimac (University of Miami) demonstrated ATP and 5HT release, respectively, suggesting that taste cells may co-release neurotransmitters. Further, Yijen Huang (University of Miami) detected norepinephrine release, presumably from the same set of taste cells known to release serotonin, in response to a mixture of tastants. Yu-Kyong Shin (National Institute on Aging) reported that glucagon-like peptide 1 was expressed by subtypes of taste bud cells, that its receptor is present on nerve fibers in the taste bud, and that mice lacking this receptor had reduced behavioral responses to sweet compounds. These observations underscore the large number and emerging complexity of neurotransmitters and neuromodulators within the taste bud.

GPCRs may also provide a mechanism for rodents to detect divalent cations, allowing them to appropriately modify their intake of calcium when homeostasis is challenged. Michael Tordoff (Monell Chemical Senses Center) reported analysis of mice congenic between the calcium-preferring strain PWK/Phj (PWK) and a non-preferring strain (C57Bl/6). The analysis revealed that calcium preferences were linked to differences in the Tas1r3 allele, which codes for the T1R3 receptor necessary for sweet and umami taste. Furthermore, chorda tympani responses to calcium were lower in Tas1r3 null than wild type mice. A second mechanism for sensing oral calcium was implicated by Ana San Gabriel (Ajinomoto Corporation), who reported that the calcium sensing receptor (CaSR), a GPCR that can bind both calcium and amino acids, was expressed in taste bud cells. Together, these studies suggest that umami and calcium taste might depend upon the same set of receptors, although utilized in different ways.

Another developing story in taste research is the investigation of how fat is sensed in the mouth. That fat detection, which was traditionally attributed to texture detection by the trigeminal system, might also directly involve taste has long been suspected but difficult to prove. The notion that the taste system could sense fat gained credence when sectioning of the chorda tympani nerve was found to impair fat detection. However, elevated fatty acid thresholds could indirectly result from the denervation of salivary glands that occurs when this nerve is cut. In a creative approach, Jennifer Stratford (Florida State University) found that rats with denervated salivary glands and intact chorda tympani nerves had increased fat detection thresholds, but less than rats with sectioned chorda tympani nerves, thereby leaving open the possibility that taste receptor cells do respond to fat. What, then, is the fat detector in these cells - inhibition of potassium channels, a fat transporter (e.g., CD36), or GPCRs? Shigenobu Matsumura and Ai Eguchi (Kyoto University) provided evidence in support of the latter. GPR120 was found in taste receptor cells and when heterologously expressed in HEK cells, GPR120 conferred responses to unsaturated fatty acids with chain lengths of 14 – 22 carbons – responses that closely parallel the preference behavior for fats displayed by mice. In addition, Pin Liu (Utah State University) reported that fatty acids directly evoked increased intracellular calcium and depolarization in taste receptor cells. These reports help build the case that fat is not only a texture, but also a taste.

The central processing of taste signals has been more difficult to study than peripheral taste mechanisms, but hard-won advances in this field were also reported. Systemic benzodiazepine administration has long been known to induce hyperphagia of palatable stimuli but to what extent this effect is due to enhanced palatability as opposed to an increase in perceived intensity was unclear. David Pittman (Wofford College) and John-Paul Baird (Amherst College) reported that the benzodiazepine agonist chlordiazepoxide (CDP) increased licking to both ingestive and aversive stimuli in brief-access taste tests, indicating a general increase in palatability. Licking to water was unaffected by the drug. Electrophysiological analysis of neurons in the parabrachial nucleus revealed both an increase in the proportion of sucrose-best cells and a decrease in sour and bitter activity with CDP, suggesting a possible neural correlate of changes in palatability. Similarly, Andras Hajnal (Pennsylvania State University) found that hyperphagic Otsuka Long-Evans Tokushima fatty (OLETF) rats work harder for sucrose in a progressive ratio task and show a rightward shift in the concentration-response function for this stimulus in parabrachial neurons compared to lean counterparts. Neural correlates of palatability were further demonstrated by Alan Carleton (Swiss Federal School of Technology) who reported that sweet and bitter stimuli activate overlapping but distinct areas of gustatory cortex in naïve rats but after forming a conditioned taste aversion to a sweet stimulus show a topographical shift in its representation so that it more closely resembles that of an aversive bitter stimulus.

Conclusions

The 15th ISOT meeting celebrated worldwide growth of the chemical senses as a field of research. Studies of the olfactory and taste periphery emphasized the great diversity of cellular

and molecular mechanisms brought to bear for the recognition and encoding of odors and tastes. Understanding the interactions between stimulus and receptor remains a high priority for investigation, but important advances were made in many other areas as well. Characterization of less studied chemosensory subsystems, including those linked to somatic and nociceptive afferents and those utilizing non-canonical transduction mechanisms, emphasized the diversity of cell types that are used to detect chemosensory stimuli. The continued growth in conceptual and technical approaches to the study of chemosensory processing within the central nervous system was also notable, and offers promise for further understanding how chemical cues are perceived in the context of other stimuli, experience and motivational state of the organism. New insights into the interactions between hormonal and chemosensory systems suggest a link between chemosensory functions, chemosensory-influenced behaviors such as ingestion, and metabolism. Furthermore, additional evidence linking chemosensation with human disease emphasizes the important role the chemical senses will play in advancing human health as the field moves forward from the 15th ISOT meeting.