Sensory systems
Editorial overview
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Abbreviations

CNG channel	cyclic-nucleotide-gated channel
fMRI	functional magnetic resonance imaging
NT3	neurotrophin 3
RM	raphe magnus and nucleus reticularis magnocellularis

Introduction

The reviews in this issue reflect the extraordinary breadth and vitality of contemporary research in sensory systems. The reader will find reviews of all stages of sensory processing, from the molecular events underlying transduction in receptor cells to the neural circuits underlying the formation of perceptual decisions. Reviews focusing on the sensory periphery occupy the first half of the issue; reviews concerning the central nervous system are grouped in the second half. This organization reflects a natural division in research approach. For the investigator using biophysical methods on sensory receptor cells, the goal may be to understand how conformational changes in channel molecules contribute to such fundamental properties of sensation as adaptation or sensitivity. For the investigator imaging human visual cortex, the challenge may be to identify the neural systems that are active and the computations that take place during visual perception. Yet, there is a common theme to sensory neurobiology: to characterize the biological basis of sensation. Even developmental work in sensory systems seeks to determine how molecules, cells and circuits are assembled so as to produce normal sensation and sensorimotor performance.

Mechanosensors

Analogies can be drawn on several levels between insect chordotonal organs and vertebrate inner ear organs. Both comprise ciliated mechanoreceptive cells and various accessory or supporting cells. Chordotonal organs and inner ear organs both come in sets, with each organ in the set differentiated according to the kind of mechanical input transduced or the location or direction in space of the mechanical input. In both insects and vertebrates, the afferent nerves from these organs project to neighboring parts of the brain. In addition to these analogies, there may be homologies. Recent work highlighted in the reviews by Eberl (pp 389–393) and Kollmar (pp 394–398) suggests that homologous genes control the development of mechanosensors in both insect chordotonal organs and vertebrate inner ear organs.

The molecular mechanism of transduction in insect ciliated mechanoreceptors is unknown, but it is presumed that the cilium plays a central role and that the mechanosensitive channels, which have not yet been precisely localized, sense ciliary deflection by sound or other mechanical input. Kernan [1] has proposed that all ciliated mechanoreceptors share a common transduction machinery. Indeed, as Eberl notes in his review, most mechanosensation mutants that have been identified in *Drosophila* have defects in all ciliated mechanoreceptors (i.e. both bristle and chordotonal organs).

Vertebrate hair cells are also ciliated, but the cilium is not an essential part of the transduction apparatus, as has been shown experimentally [2] and evolutionarily: the cilium atrophies during the maturation of mammalian and avian cochleas. In vertebrate hair cells, the mechanotransducing elements are specialized microvilli, misnamed stereocilia, that are organized in an array called a hair bundle. The stereocilia house actin rather than the microtubules that are characteristic of true cilia. The dimensions, number and pattern of stereocilia vary with beautiful precision within and across hair-cell epithelia. This variation has important functional consequences for the sensitivity and tuning of the receptor potential. Hair bundles are therefore ideal model systems in which to examine developmental regulation of form and, more specifically, of actin arrays. Whereas the morphological steps involved in the development of hair bundles are known in some detail [3], how it is achieved is a mystery. In his review, Kollmar takes a fresh look at this process, drawing on research in other systems — including *Drosophila* — that shows that small guanosine triphosphatases, the Rho GTPases, regulate the actin cytoskeleton.

The vertebrate hair cell is a metabolically active and exquisitely mechanosensitive cell that is unsurprisingly vulnerable to insult by noise, trauma, disease and various drugs. Endogenous repair mechanisms exist for hair cells in many organs but are conspicuously missing from mammalian cochleas. The only remedy for profound deafness resulting from hair cell loss is a cochlear implant. These implants exploit the fact that cochlear afferent neurons persist long after hair cells die; they deliver sound-evoked electrical stimulation to the residual afferent neurons. Their use has risen dramatically in the past decade; however, many aspects of their performance remain unpredictable or unexpected, despite the fact that they were designed along engineering and physiological principles. In some respects, implants perform better than

expected given the clear differences between the patterns of activity that they evoke and those evoked by sounds in normal auditory nerves. Rubinstein and Miller (pp 399–404) describe recent advances in understanding how cochlear implants work. One practical and important development is that it is now possible to predict with reasonable confidence the success of an implant simply from the duration of deafness and the residual speech comprehension with a hearing aid.

In the final review on mechanotransducers, Chen and Frank (pp 405–409) describe how recent work on transcription factors, neurotrophins and their receptors has taken our understanding of the normal development of muscle spindle (Ia) afferents and their connections to a new level. Because of the spatial segregation of the spindle afferent's cell body from its peripheral and central terminals, these neurons have long been an attractive system for studying the sources of signals that promote survival and establish synaptic connectivity. Recent genetic and molecular tools have made it possible to ask such questions with great specificity: individual genes can be 'knocked out', as has been done to great effect with *neurotrophin 3* (*NT3*). Moreover, the concentrations of individual neurotrophins can be manipulated locally and at specific times during development by overexpressing them or by injecting antibodies. These experiments have led to new insights, but also to new puzzles to challenge investigators. For example, some experimental evidence supports the hypothesis that NT3 released by motoneurons in the ventral spinal cord causes ingrowing Ia afferents to 'stop and arborize', a prelude to forming connections. Yet, the central projections of Ia afferents appear normal in NT3 mutant mice. Chen and Frank suggest an explanation for these conflicting results and experiments to test their proposal.

Sensory adaptation and calcium signaling in vertebrate photoreceptors and olfactory neurons

The stimulus-gated transduction channels of sensory receptor cells are frequently permeable to most small inorganic cations. This appears to be a design feature, as it allows the influx of both the dominant monovalent ion — permitting large currents — and calcium — which, with its potent and diverse capabilities as a second messenger, is then available to provide feedback, negative or positive, on the transduction process. Two reviews consider the roles of calcium in transduction and adaptation in vertebrate photoreceptors and olfactory neurons, which have broadly analogous biochemical cascades of transduction. The transduction machinery in both cases is confined to specialized cilia. Light or odorants activate receptors that, in turn, activate G–protein cascades that culminate in changes in the concentration of cyclic nucleotides. These changes modulate the open probability of cyclic-nucleotide-gated (CNG) transduction channels in the plasma membrane of the cilia. A key difference is that in photoreceptors, light leads to closure of the channels, thereby reducing calcium influx, whereas in olfactory neurons, odorants lead to opening of the channels, thereby increasing calcium influx.

The extended cascades of phototransduction and odorant transduction offer abundant opportunities for feedback. The review of rod adaptation mechanisms by Pugh, Nikonov and Lamb (pp 410–418) discusses eight distinct mechanisms with diverse effects on two principal functional characteristics of rods, their operating range for steady lights and their sensitivity to dim flashes. The diversity of mechanisms should not surprise anyone who has tried to absorb the large and complex literature in this field. What may surprise some, though, is that a major factor in rod adaptation is an ineluctable consequence of the forward transduction process and does not depend on calcium feedback. The final enzyme in the forward cascade is a phosphodiesterase, which hydrolyzes cGMP, thereby reducing the concentration of cGMP and closing the CNG channels. Pugh *et al.* find that the rise in steady phosphodiesterase activity produced by background light can account with elegant simplicity for much of the background-induced attenuation of the dim-flash response.

One form of calcium-mediated adaptive feedback common to photoreceptors and olfactory neurons is a change in the affinity of CNG channels for cyclic nucleotides. In photoreceptors, the photoinduced reduction in calcium influx produces an increased affinity, which would tend to reopen channels. This mechanism contributes, at most, modestly to rod adaptation, but is profoundly important in olfactory adaptation, where the odorant-induced enhancement of calcium influx decreases the channel affinity for cAMP. In her review of calcium signalling in olfactory neurons, Menini (pp 419–426) describes recent work showing that the decrement in the response of an isolated olfactory neuron to the second of two odorant pulses is fully explained by the decreased affinity of the CNG channels for cAMP. However, these are early days in olfactory adaptation, and the history of the more mature field of phototransduction, summarized by Pugh *et al.*, suggests that other negative feedback mechanisms may emerge in different experimental paradigms.

In addition to its negative feedback on cAMP affinity, calcium influx through the CNG channels of olfactory neurons activates a chloride current that dramatically enhances the receptor potential, a form of positive feedback that has not been found in other sensory cells. As Menini's review makes clear, information is rapidly emerging about other aspects of calcium signaling and homeostasis in olfactory neurons, from the effects of CNG channel structure on calcium permeation to mechanisms of calcium extrusion from the sensory cilia.

Taste coding

Research on the molecules of olfactory transduction has had a surprising payoff in understanding the organization of the olfactory system: the receptor proteins that bind the

odorants also define how afferent input segregates in the olfactory bulb. Olfactory neurons express just one receptor protein and project to olfactory bulb glomeruli specific for that receptor protein (see [4] for a review).

The review by Smith and St John (pp 427–435) argues that similar insights are unlikely to emerge from information about taste transduction mechanisms. They emphasize that taste coding is a complex process with important differences from the encoding of sound, light, and even odorants. To begin with, the stimulus domain is discontinuous and transduction mechanisms are correspondingly diverse. Mechanisms for detecting saltiness or acidity differ in fundamental ways from those for detecting sweet or bitter compounds. The diversity of transduction mechanisms naturally leads to notions of labeled lines: might each type of tastant activate its own private set of afferents? Most taste neurons, however, are broadly tuned for taste, and central taste neurons frequently also respond to touch and changes in temperature. These observations pose challenges for taste coding that are less readily accommodated by labeled lines than by schemes involving across-fiber patterns of activity.

Pain modulation

In rats, pain transmission in the spinal cord is modulated by neurons in the midbrain periaqueductal gray area and the pontomedullary RM (raphe magnus and nucleus reticularis magnocellularis). Mason's review (pp 436–441) discusses several recent challenges to the consensus view of RM-mediated analgesia. Considerable evidence exists showing that ON and OFF cells in RM facilitate and inhibit nociception, respectively, and are reciprocally active. Recent findings with inflammatory damage, however, show that ON and OFF cells can be active simultaneously. Pain modulatory neurons in RM have receptive fields that frequently cover the whole body and so have been assumed to have general, not local, action. However, recent experiments on humans reveal opioid-mediated pain modulation that is restricted to a particular body site. As an indicator of pain modulation, experimenters commonly look for altered latency of limb or tail withdrawal to noxious stimuli. Mason points out that motor withdrawal is not tightly linked to ON and OFF cell activity and that other potential targets of pain modulation are largely unexplored.

Spike timing

The significance of spike timing for coding and transmitting information within the central nervous system has been intensely controversial in recent years. The review by Bair (pp 447–453) focuses on the phenomenon of spike synchrony across populations of neurons in the mammalian visual system and the various functions that have been proposed for synchronous spikes. This phenomenon has produced a torrent of papers — both theoretical and experimental — during the past two years. At present, however, there is little agreement about the functional significance of synchrony. Any proposal concerning function must come to grips with the issue of how the putative function can be reconciled with the well-known role of spike timing in representing time *per se* within the nervous system (i.e. in coding the timing of external events). Perhaps the most spectacular examples of this function take place in the auditory system, in which binaural neurons can respond differentially to sounds presented asynchronously to the two ears at intervals as short as a few tens of microseconds. Carney (pp 442–446) provides an overview of recent developments in our understanding of the temporal response properties of neurons in the auditory nerve and brainstem of mammals.

Visual motion

The study of visual motion has been a particularly fecund area of systems neuroscience; new developments in this area are summarized in a group of three reviews. Egelhaaf and Warzecha (pp 454–460) review recent advances in our understanding of how motion is encoded in real time by the visual system of the fly — a motion processing system *par excellence*. Important new advances have been made at several levels in this system, from beautiful experiments on the processing of motion signals by individual dendrites to technical innovations that permit measurement of the motion signals that enter the fly's visual system during free flight. The latter information is being used in an insect flight simulator in which electrophysiological recordings can be obtained while the animal's visual system is confronted with an actual 'fly's eye' view of the world.

Baker (pp 461–466) provides a lucid account of the phenomenon of second-order motion, a topic of substantial interest to psychophysicists and physiologists in recent years. Neurons at the initial stage of motion processing in the visual cortex — so-called 'first-order' mechanisms —respond to the motion of visual patterns defined by luminance variations. Yet, it can be demonstrated psychophysically that humans can easily see the motion of visual texture patterns defined by variations of other image properties, such as contrast or texture differences. Baker reviews recent psychophysical, electrophysiological, and computational work that elucidates the mechanisms underlying this fascinating ability to perceive 'second-order' motion.

Finally, Kawano (pp 467–473) summarizes recent behavioral and electrophysiological investigations of ocular tracking, which refers to a reflexive visuomotor response in which sudden motion of the visual world elicits remarkably short-latency following movements of the eyes. This tracking response is independent of motivation and is not under volitional control, yet recent investigations show compellingly that this 'reflexive' behavioral response is sensitive to complex aspects of the visual scene and is mediated, in part, by high-level motion-processing circuits within the visual cortex.

Neuroimaging of the human visual system

Functional magnetic resonance imaging (fMRI) using blood oxygenation level dependent (BOLD) contrast, which was

invented by Seiji Ogawa and colleagues at Bell Labs [5], has added a powerful new technique to the armamentarium of sensory science. For the first time in history, activity within the human central nervous system can be studied systematically at spatial scales that permit mapping of sensory topography and at temporal scales approximating the time course of single trials in sensory discrimination tasks. Neuroimaging techniques are being employed creatively by a rapidly growing community of sensory neuroscientists. Heeger (pp 474–479) reviews recent fMRI studies of the human visual system. As depicted on the cover of this volume, substantial progress has been made in identifying distinct areas of the human visual cortex. More importantly, perhaps, Heeger describes new work in which fMRI is being used to ask questions about the neural computations being performed within the visual cortex. Like all techniques, fMRI is limited in the kinds of questions it can address. Yet, the field is developing with remarkable rapidity — interesting new fMRI papers appear each month — and the power of the technique is only beginning to be exploited.

Amblyopia

Amblyopia is an impairment of vision that results from abnormal visual experience early in life. It is a widespread clinical problem, affecting 2–4% of the population at large. As described in the review by Kiorpes and McKee (pp 480–486), amblyopia is of neural rather than optical origin, yet the initial stages of neural processing in the retina and thalamus appear entirely normal in amblyopic animals. Thus, the primary deficit in amblyopia is almost certainly cortical. Kiorpes and McKee describe current notions concerning the mechanistic basis of amblyopia and evaluate the experimental evidence for and against each hypothesis. Future studies of human amplyopes using fMRI techniques may provide considerable impetus to this field.

Somatosensory perception

The study of somatosensation has played a pivotal role in the history of sensory physiology. Some of the earliest and most incisive attempts to establish quantitative links between neural activity and perceptual performance were made by Vernon Mountcastle and colleagues at Johns Hopkins University (see [6]). As reviewed by Romo and Salinas (pp 487–493), the study of somatosensation continues to contribute insights concerning the neural mechanisms underlying higher perceptual functions. Some of the most exciting studies of the past two years have come from Romo's laboratory. After training monkeys on a variation of the classical frequency discrimination task developed by Mountcastle (see [6]), Romo and colleagues used electrical microstimulation techniques to explore the role of primary somatosensory cortex in mediating the sensation of flutter vibration. More recently, these investigators have discovered neural activity in prefrontal cortex that appears to reflect the memory of the initial vibration frequency experienced by the monkey in a two-interval frequency discrimination task. In a pleasing symmetry, the somatosensory frequency discrimination paradigm, which played such a pivotal role at the beginning of the modern era of inquiry into physiological–psychophysical relations, remains one of the most promising paradigms for analyzing the highest levels of perceptual decision-making in the primate brain.

Neurolab

Neuroscience research was highlighted in the recent space shuttle flight dubbed 'Neurolab'. The experiments explored the effects of perturbing gravity on the normal development and performance of various aspects of nervous system function. One underlying goal is to understand which of these effects pose a challenge to space exploration. Highstein and Cohen (pp 495–499) comment on preliminary results discussed at a recent meeting of the investigators involved in Neurolab. Many technical firsts were achieved and interesting results noted, such as the changes in the structure and physiology of vestibular organs in space.

Concluding remarks

The reviews in this issue demonstrate that the frontiers of sensory neuroscience are expanding rapidly at diverse levels, from molecules to brain circuitry, and in diverse settings, from the basic laboratory to the clinic and outer space. A critical goal is to integrate newly acquired knowledge across levels. Progress in this direction is evident in this issue. Pugh *et al.* synthesize a bewildering array of biochemical and biophysical data from photoreceptors into a cogent description of the fundamental consequences for sensory adaptation. Moreover, the reviews on cochlear prostheses and amblyopia illustrate achievements in our efforts to understand clinical phenomena in terms of the underlying neuroscience. Yet, embarrassing gaps remain. For example, fMRI has become a major tool for physiological analysis of the human brain, but the relation between the blood flow signal detected by fMRI and nerve cell electrophysiology is largely unknown. In another arena, sensory physiologists are relating the electrical activity of individual nerve cells to the behavioral performance of alert animals ranging from flies to monkeys, yet fundamental questions remain about the nature of the neural code and the aspects of neural activity that we should be analyzing. Research that forges new links between the levels of analysis will increasingly drive progress in our understanding of sensory systems.

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