

NEI Workshop on Ocular Pain and Sensitivity

Rationale

The NEI Workshop on Ocular Pain and Sensitivity was held on Sept 30 - Oct 1, 2010. Chronic ocular pain is poorly understood. While primarily considered an ocular surface phenomenon, little is known about the biology of its peripheral and central mechanisms. Clinicians have traditionally concluded that patients who report corneal pain and sensitivity exacerbated by moving air as having dry eye syndrome even though many have normal tear flow and lack supporting signs. The disparity between symptoms and signs is typical of neuropathic pain. In the most severe cases, the ocular pain may be associated with emotional fear, anxiety, depression, cognitive impairments and ideations of suicide. Treatments, such as anticonvulsants and tricyclic antidepressants, are characterized by low therapeutic ratios, narrow pharmacological windows and a lack of pharmacological specificity. A better understanding of the mechanisms and appropriate characterization of ocular pain are prerequisites for developing more effective treatments.

Needs, Gaps, and Opportunities in Ocular Pain and Sensitivity

The high priority items in vision research identified at the workshop are described below.

Diagnosis and Treatment

- Unlike headache and other well-defined clinical pain entities, the field of chronic ocular pain and sensitivity lacks a formal taxonomy/nomenclature. A common language is required to facilitate linking symptoms with pathological mechanisms.
- The parameters that delineate inflammatory and neuropathic corneal pain need to be established since their therapeutic strategies may differ.
- A standard clinical protocol for assessing ocular pain and sensitivity is required. Appropriate eye pain questionnaires have yet to be validated. There are no adequate tools to measure its attenuation, receptive field spread, allodynia and temporal summation in patients with chronic ocular pain.
- New drugs and delivery systems are needed to effectively treat peripheral and central mechanisms of ocular pain.
- Clinical endpoints for testing and approval of drugs for ocular pain need to be established.

Peripheral Nervous System

- A better understanding of the primary afferents innervating ocular structures is required, including characterization of the heterogeneity of nerve fibers and function. This should include the anatomy, projections, physiology and neurochemistry of these neurons in health and disease, including their regenerative mechanisms.

- Delineation of the morphometrics of corneal nerves in health and disease requires better automated software for current corneal imaging systems and the development of better imaging technology.
- The molecular and cellular mechanisms responsible for spontaneous (ectopic) corneal pain, hyperalgesia, desensitization, and allodynia of the ocular surface and their spread to receptive fields of non-ophthalmic branches of the trigeminal nerve and more widely, need to be investigated.
- The molecular and cellular changes that occur in primary sensory neurons as a result of disease or trauma need to be further studied.
- There is a lack of understanding of the mechanistic differences between ocular itch, burning, and pain sensations; the neuronal receptors responsible for ocular itch are unknown.

Central Nervous System (CNS)

- Ocular surface neurons project to multiple locations in the brainstem. Their locations and functions need to be identified.
- Ocular pain pathways have been mapped to the thalamus, but cortical representations of ocular sensations and descending modulatory pathways are unknown.
- The central mechanisms responsible for ocular pain sensitization and pain “memory” are unknown.
- The mechanisms responsible for the transition from acute to chronic ocular pain need to be studied.
- Functional changes in the central nervous system that occur in patients with chronic ocular pain have been insufficiently studied using MRI/fMRI/PET.
- There are cases where eye pain and foreign body sensation occur in the absence of ocular surface staining or a foreign body, respectively. The mechanisms and pathways involved are unknown.
- The molecular, cellular and integrative mechanisms responsible for the different forms of photophobia are unknown.

Other Areas of Opportunity

- The role of tears in the pathogenesis and maintenance of chronic inflammatory corneal pain needs to be investigated.
- The roles that neurons play in the health, healing, scarring and immunology of the cornea, and the molecular and cellular mechanisms responsible have yet to be determined.

NEI Planning Workshops

For over thirty years, the NEI has developed a new [strategic plan](#) approximately every 5-7 years to identify current trends, challenges, and opportunities in vision research. These plans represent a snapshot of the landscape of vision research. In the intervening years, advances in biomedical research often reveal new, unanticipated areas or disciplines demanding more immediate attention. The NEI maintains an ongoing workshop development process. Needs, gaps, and opportunities identified by these workshops are considered areas of high importance to vision research and the NEI.

Participants and Agenda

The NEI Office of Program Planning and Analysis organized the meeting, with input from external co-chairs, Drs. Carlos Belmonte and Todd Margolis. Advances in understanding the pathophysiology of pain and sensitivity in other areas such as headache, joint, and dental pain have been more thoroughly investigated than ocular pain and sensitivity. A multidisciplinary workshop was convened that included expertise in ophthalmology as well as clinicians and scientists from non-ocular fields with expertise in pain. [Attendees](#) included 18 clinicians and scientists with expertise in ocular pain, dry eye syndrome, and ocular immunology, as well as pain taxonomy, anatomy, physiology, genetics, pharmacology, neuronal plasticity, perception, and clinical trials using other model tissues.

Prior to the meeting, each participant provided a “white paper” that summarized important recent research both in their own lab as well as by others in the field. Topics ranged from basic to clinical research, and include inflammation and immunology, peripheral and central nervous system, diagnosis, and treatment of ocular pain. A [summary of the white papers](#) was distributed to participants before the workshop.

The program consisted of two days of brief topic overviews with an emphasis on discussion (see [Agenda](#)).