Better knowledge of the normal control mechanisms involving disparity feedback, vergence tonus, and muscle length adaptation will be critical in our understanding of the causes of strabismus and its evolution over time.

Commercial Relationships: David L. Guyton, None

Program Number: 1827
Presentation Time: 11:23 AM–11:41 AM

Neural Mechanisms for Binocular Oculomotor Signaling in Strabismus
Michael J. Mustari. University of Washington, Seattle, WA.

Presentation Description: High acuity vision in primates depends on the fovea of each eye. The oculomotor system controls eye alignment and movement so that the foveae are directed at an object of interest. Full visual function in primates requires coordinated binocular experience in early life. If this experience is disrupted, permanent loss of normal eye alignment (strabismus) and deficits in visual function (amblyopia) can occur. Improving treatment for various forms of strabismus requires understanding neural mechanisms for binocular oculomotor control.

Human and nonhuman primates have similar visual and oculomotor systems, and dependence on early visual experience. Establishment of nonhuman primate models for developmental strabismus facilitates discovery of neural mechanisms for normal and strabismic eye alignment and eye movements. Recent studies have discovered a loss of normal binocular visual sensitivity in primary visual cortex and extrastriate visual areas (MT, MST) that could lead to visual suppression and alterations in the calibration of distal oculomotor centers. For example, horizontal medial rectus and vertical lateral rectus motoneurons have been shown to encode cross-axis smooth pursuit movements in pattern strabismus. Recently, we found abnormalities in the paramedian pontine reticular formation (PPRF), which carries signals related to instantaneous, horizontal saccadic velocity. Microstimulation (MS) of the PPRF of normal animals evokes conjugate horizontal ramp eye movements. In contrast, MS of PPRF of strabismic animals evokes disconjugate movements with each eye moving at different velocities and in different directions. Neurons in PPRF of these animals showed an abnormally broad distribution of preferred directions and 12/60 even preferring vertical saccades. These findings suggest that a neural mechanism, acting alone, could explain disconjugacies in some forms of strabismus. This does not rule out abnormalities in orbital tissues, eye muscle pulleys, or eye muscles themselves in different forms of strabismus.

Taken together, these studies suggest that interference with coordinated binocular visual-oculomotor experience during an early sensitive period disrupts the calibration and normal tuning of brain areas from visual cortex reaching to oculomotor neurons that are essential for maintaining eye alignment and eye movements.

Commercial Relationships: Michael J. Mustari, None

Program Number: 1828
Presentation Time: 11:41 AM–11:59 AM

Palisade Endings in Strabismus
Anja Horn-Bochtler. Institute of Anatomy and Cell Biology I, Ludwig Maximilians University, Munich, Germany.

Presentation Description: Specialized nerve endings at the myotendinous junction of extraocular muscles - the palisade endings – are thought to contribute to the fine adjustment of the eye muscles in binocular vision, by transmitting proprioceptive signals to the brain. A malfunction of this system could theoretically cause strabismus. This talk will summarize recent findings on the anatomy of palisade endings in primates, including humans. It will
also address the following questions: Do palisade endings differ in number or histochemical properties between extraocular muscles? Are there changes of palisade endings during aging? Do palisade endings in specimens of extraocular muscles resected during strabismus surgery exhibit abnormalities?

**Commercial Relationships:** Anja Horn-Bochtler, None

**Program Number:** 1829
**Presentation Time:** 11:59 AM–12:17 PM

**Strabismus: Alterations in the Periphery and Brain-Muscle Communication**

*Linda K. McLoon.* Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis, MN.

**Presentation Description:** Recent studies have demonstrated that the oculomotor control system is responsible for driving the eye misalignment in some forms of strabismus. Skeletal muscles are extremely sensitive to changes in their innervational status and environmental milieu, and the extraocular muscles are similarly adaptable. Examination of the extraocular muscles (EOM) from human subjects with various forms of childhood onset strabismus can provide us with a “window” into possible etiologies for eye misalignment in an otherwise apparently normal oculomotor system. The EOM from these subjects show alteration in fiber size, neuromuscular junction size and density, and differences in connective tissue elements, such as collagen and elastin. While it is difficult to determine whether these changes are primary or secondary, surgical interventions do modify these structural and biochemical elements to more closely mimic the EOM of age-matched controls. While the surgery had been insufficient to completely correct the misalignment, hence the subjects required a second surgery, the adaptation towards normalcy supports the view that there is significant two-way communication between the EOM and the oculomotor system in the brain. Recent work in infant non-human primates shows that sustained release of specific neurotrophic factors not only modifies myofiber size and patterns of innervation but also can produce strabismus in these infants. What is particularly important about these studies is that treatment of a single extraocular muscle with a continuous supply of a specific neurotrophic factor can produce bilateral changes in patterns of EOM innervation. This suggests that there is an active adjustment between the oculomotor system and the structure of the EOM. Collectively these studies suggest that modifications in specific neurotrophic signaling pathways may be involved in the development of some forms of childhood onset strabismus. These results also suggest that one potential treatment for strabismus would be manipulation at the periphery with one or more neurotrophic factors. Such treatment would have direct effects on EOM and their retrograde transport to the brain could result in permanent improvement of eye alignment.

**Commercial Relationships:** Linda K. McLoon, None

**Program Number:** 1830
**Presentation Time:** 12:17 PM–12:35 PM

**Novel therapies for strabismus**

*Stephen P. Christiansen.* Boston Univ School of Medicine, Boston, MA.

**Presentation Description:** Strabismus surgery, at its essence, is an operation that either strengthens or weakens the effect of an extraocular muscle (EOM) by adjusting its mechanical advantage at its insertion. This results in a change in the rotational position of the globe, but it also creates permanent changes in the ocular motor plant that may be advantageous or deleterious in the long term. Because resting tonus across an agonist-antagonist pair changes with time, recurrent or consecutive strabismus is common. Ideally, strabismus treatment should adjust EOM strength without altering the ocular motor construct, thereby preserving normal EOM-globe and EOM-orbit relationships as long as possible so that future interventions, if required, may be as successful as possible.

The use of botulinum toxin (BTX-A) has shown the clinical utility of a pharmacologic approach where EOM strength can be modulated without the need for incisional surgery. Newer agents can augment and extend the effectiveness of BTX-A, and investigational drugs hold promise for an armamentarium of agents that can be dosed and combined in such a way that ensures satisfactory short-term and long-term alignment can be achieved. If, at a future date, alignment deteriorates, pharmacological enhancement can be applied, all without the long-term alteration of EOM insertional biomechanics. Growth factors, toxins, and local anesthetics may all have their place in the future treatment of strabismus. Incumbent on current investigators is the need to not only demonstrate efficacy, but safety, especially in the use of these agents in infants and small children. We are at the dawn of a new era in the treatment of strabismus.

**Commercial Relationships:** Stephen P. Christiansen, None

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