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Childhood Onset Strabismus: A Neurotrophic Factor Hypothesis

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Abstract

Strabismus is a genetically heterogeneous disorder with complex molecular and neurophysiological causes. Evidence in the literature suggests a strong role for motor innervation in the etiology of strabismus, which connects central neural processes to the peripheral extraocular muscles. Current treatments of strabismus through surgery show that an inherent sensorimotor plasticity in the ocular motor system decreases the effectiveness of treatment, often driving eye alignment back toward its misaligned pre-surgical state by altering extraocular muscle tonus. There is recent interest in capitalizing on existing biological processes in extraocular muscles to overcome these compensatory mechanisms. Neurotrophins are trophic factors that regulate survival and development in neurons and muscle, including extraocular muscles. Local administration of neurotrophins on extraocular muscles partially reversed strabismus in an animal model of strabismus. The hypothesis is that sustained release of neurotrophins gives more time to the ocular motor system to adapt to a slow change in alignment in the desired direction. The effect of neurotrophins on extraocular muscles is complex, as different neurotrophic factors have diverse effects on extraocular muscle contraction profiles, patterns of innervation, and density of extraocular muscle precursor cells. Neurotrophic factors show promise as a therapeutic option for strabismus, which may help to improve treatment outcomes and offset devastating amblyopia and psychosocial effects of disease in strabismus patients.

Keywords

neurotrophic factor; strabismus; extraocular muscles; insulin-like growth factor; glial derived neurotrophic factor

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Childhood onset strabismus is a common disorder, affecting 3–5% of children,[1,2] but there is increasing evidence that the underlying molecular and neurophysiological basis of eye misalignment are extremely complex and heterogeneous. While the clinical manifestations of strabismus can be similar between children with childhood onset strabismus - in the absence of associated known genetic mutations, anisometropia, or known precipitating injury – a similar deviation and clinical presentation of eye misalignment is likely to have dissimilar underlying causes. This is an important point, and most likely plays a role in why responses to similar treatments vary significantly.[3–6] The response variability underscores the fact that surgical treatment does not address the underlying cause of strabismus in many individuals. There is significant evidence that strabismic misalignment is driven by the ocular motor system, both at the motor neuron level and in supranuclear areas that project onto the motor neurons.[7–14] These studies strongly suggest that the goal of future treatment development should include discovering ways to change the inherent motor drive from the brain.

Additional evidence that the main contributor to the development of childhood onset strabismus originates from the central nervous system comes from study of the rarest forms of strabismus, the congenital cranial dysinnervation disorders (CCDD). The CCDDs are often called “congenital fibrosis of the extraocular muscles” or CFEOM. The majority of these rare genetic CCDDs result in strabismus due to abnormal axon growth in the motor nerves from one or more nuclei of the ocular motor complex.[15,16] Mutations in the *KIF21A* gene causes CFEOM1 and CFEOM3,[17] and *KIF21A* is a kinesin that is responsible for cargo delivery through retrograde and anterograde axonal transport and the mutation results in oculomotor nerve loss and muscle atrophy. Similarly, CFEOM2 is caused by mutations in the *ARIX/PHOX2A* gene, which is critically important for the development and routing of cranial nerves III (oculomotor) and IV (trochlear).[18] Interestingly, Ret, a glial cell line-derived neurotrophic factor (GDNF) receptor subunit, also is regulated in part by the PHOX2A gene[19], implicating down-stream neurotrophic factor alterations that would be the sequelae of these motor nerve abnormalities. The absence of the abducens nerve in Duane retraction syndrome can be caused by mutations in *SALL4*, *ROBO3*, *HOXA1*, and the *CHN1* gene, which results in mutations in the α2-chimaerin protein which alters normal cytoskeletal dynamics and abducens nerve formation.[16,20,21] While rare, these CCDDs demonstrate that some forms of strabismus can result from primary ocular motor nerve maldevelopment.

Recording from motor neurons in monkeys with strabismus showed that neuronal activity from the oculomotor or abducens nuclei, as well as upstream ocular motor areas, drive the misalignment of the eyes, regardless of the method by which the monkeys were made strabismic.[7–10] In an elegant series of studies in a primate model of strabismus, motor neurons were recorded prior to and after surgical treatment.[22,23] In the first month after surgical correction, the neural drive was either selectively decreased or selectively increased, both in the direction that reduced the effectiveness of the treatment – by weakening the neural drive to the surgically strengthened muscle in one monkey or increasing the neural drive to the surgically weakened muscle in a second monkey. Despite treatment, they demonstrated an inherent drive in the ocular motor system to return the muscles, and thus eye misalignment, back to thepre-surgical misaligned strabismic state. It is interesting to

note that the strabismic angles were about 20% improved over the pre-surgical levels. These adaptive neurophysiological changes were also seen in the untreated eye on the contralateral side, an adaptive phenomenon seen after similar types of strabismus surgery in cats and rabbits, with coordinated changes in muscle tension, muscle fiber size, and muscle.[24–26] These studies illustrate three important points about the development and potential treatment of strabismus. First, as is likely to be true in children with naturally occurring strabismus, the use of prism rearing to produce strabismus does not always result in the same outcome; the animals can develop exotropia or esotropia with significantly variable angles of deviation.[27,28] Second, the response to treatment, whether surgical or using botulinum toxin, [29] is also heterogeneous. Finally, perturbations of the periphery – specifically the extraocular muscles – trigger a cascade of changes at the neuronal level. These changes are driven to reestablish and maintain baseline pre-surgical eye misalignment. Perturbations of the periphery alone, without any concomitant intervention to modify the cascade of neuronal events that it triggered, are unlikely to lead to a successful outcome. The logical question based on these data is what might implement this type of neuronal plasticity? Even in adult strabismic animals, the ocular motor system has significant plasticity both at the muscle and motor neuron levels.[23,20] One hypothesis for altering communication between the ocular motor neurons and extraocular muscles would be to use the normal biology of the system, including the normally active retrograde and anterograde transport of neurotrophins, whose levels are regulated in development and in response to injury and regeneration. Neurotrophins are a family of proteins that play a critical role in regulating survival, development, and response to injury in both neurons and muscle fibers.[31] Neurotrophic factors are produced by the motor neurons as well as the muscle fibers, and can be transported either from the motor neurons to the muscle by anterograde transport or from the muscle to the motor neurons by retrograde transport to provide trophic support. A number of neurotrophic factors have been identified in the oculomotor and abducens motor neurons and/or extraocular muscles specifically. GDNF, brain derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGFI), cardiotrophin-1, neurotrophin-3, and neurotrophin-4 were shown to be retrogradely transported from the extraocular muscles to the ocular motor neurons[32–34] where they play a critical trophic role during development.[35] The myogenic precursor cells, which are plentiful in the extraocular muscles, also express higher levels of neurotrophic factors than those isolated from limb skeletal muscle.[36] The expression levels of IGF-I, IGF-II, transforming growth factor β1, and fibroblast growth factor 2 are significantly increased in extraocular muscles after strabismus surgery,[37] demonstrating that these factors modulate their levels based on the conditions within muscles and nerves. These neurotrophic factors are maintained in both the adult ocular motor neurons and the extraocular muscles, and studies have implicated their retention in the adult muscles as critical in the sparing of eye movements in neurodegenerative conditions like amyotrophic lateral sclerosis.[38–40] A recent series of studies from the Pastor laboratory showed that neurotropic factors play an important role in synaptic maintenance and synaptic plasticity in the adult brain.[41] After axotomy of the abducens nerve in adult cats, exogenously applied BDNF, neurotrophin-3, or nerve growth factor not only restored afferent synapses on the injured motor neurons but also differentially regulated firing patterns from these neurons. [42,43] BDNF restored the tonic firing of motor neurons, neurotrophin-3 restored the phasic firing pattern, and nerve growth factor restored both burst and tonic signals.[42,43] These

studies all demonstrate a significant but varied impact specific neurotrophic factors have on ocular motor neuronal function both in development and in maintenance and plasticity of the adult ocular motor system.

Strong support for the role of altered neurotrophic signaling in strabismus development and/or maintenance comes from gene expression analyses of extraocular muscle from individuals with strabismus compared to age-matched controls.[44,45] Amongst the down-regulated genes I strabismic extraocular muscles were three neurotrophic factors: ciliary neurotrophic factor, GDNF, and neuregulin 1. Two IGF binding proteins (IGFBP), IGFBP5 and IGFBP7, were significantly up-regulated in the extraocular muscles removed during strabismus surgery. These would be predicted to alter muscle satellite cell proliferation,[46] which has been reported in the extraocular muscles from patients with strabismus.[47–49] These changes would alter the normal process of myofiber remodeling in these muscles,[50,51] with resultant changes in muscle structure and function.

Our laboratories and others have tested the ability of various neurotrophic factors, using a number of animal models, as a potential method to alter eye alignment in a way that we hypothesize would allow the plasticity inherent in the ocular motor system to adapt to the changes in the perceived visual world over time. The rationale for these studies is based on the concept that in order to change eye alignment, there needs to be changes in the neural input to the extraocular muscles that allows the inherent plasticity of the system to maintain clear vision over time. It is hypothesized that these neurotrophic factors would be carried retrogradely to the innervating motor neurons, alter motor drive over the duration of treatment, and maintain the “new” eye alignment even after treatment has ended.

Initial studies showed significant alterations on force generation and contractile characteristics of direct muscle injections of IGFI or IGFII in adult rabbit extraocular muscle[52,53] and retrobulbar injections of IGFI, cardiotrophin 1, GDNF, or BDNF in juvenile chickens in the treated extraocular muscles.[54–56] Some of these neurotrophic factors increased the force-generating capacity of the treated extraocular muscles, such as after IGF-1, IGF-II, or cardiotrophin 1,[52–55] and inactivation of IGF-1 or cardiotrophin-1 with antibodies similarly reduced muscle force generation and contraction time.[54,56] Other neurotrophic factors reduced muscle force generation or slowed contraction time, including such factors as transforming growth factor β1 or bone morphogenetic protein-4.[57,58] These studies were important “proof of concept” data showing that exogenously applied neurotrophic factors had the ability to alter the functional properties of the treated extraocular muscles effectively. How these changes would manifest clinically is intriguing but unknown.

One of the critical parameters of this approach as a potential strabismus treatment is that these treatments needed to provide sustained exposure to the neurotrophic agent for eye misalignment to improve but also to be maintained after treatment ended. Using sustained release pellet implanted on the surface of a single extraocular muscle, we demonstrated that IGF-I significantly increased muscle force generation as well as muscle cross-sectional areas.[59] When single rabbit extraocular muscles were treated with 3 months of sustained bone morphogenetic protein-4, muscle force and myofiber cross-sectional areas decreased.[58]

These studies demonstrated that we could safely administer neurotrophic factors in a sustained manner and alter both structure and function of the treated extraocular muscles.

Using a non-human primate model, the next series of experiments demonstrated that sustained exposure of a single extraocular muscle in the infant non-human primate to IGF-1 for 3 months was able to alter eye alignment and produced a strabismus of greater than 10°.[60] As predicted from the skeletal muscle literature, the IGF-1 treated muscles had larger cross-sectional areas than control muscle fibers. Sustained treatment was produced by implantation of a slow release pellet containing the IGF1. In a similar experiment, using BDNF, no change in eye alignment was seen; however, there was a significant increase in myofiber size only in the slow myosin heavy chain expressing fibers.[61] This result was particularly intriguing in light of the study from the Pastor laboratory demonstrating that prolonged BDNF treatment of the abducens nerve in adult cat resulted in selective return of tonic firing patterns of the neurons when stimulated.[42] A similar experiment using sustained treatment with GDNF in normal infant monkeys produced an eye misalignment of 10°, which was maintained at about 8° up to 3 months after the end of treatment.[62] This study demonstrated that slow and continuous treatment with a neurotrophic factor had the potential to correct eye alignment in a sustained manner, which may have longer lasting treatment effects and be more likely to override compensatory mechanisms in the ocular motor system.

A recent study examined the effect of treatment of one medial rectus muscle in two adult strabismic monkeys with slow release of 2μg IGF-1 per day over the course of 3 months using a sustained release method.[30] Both monkeys had been made strabismic at birth using the alternating monocular occlusion method[63] and had exotropia. The alternating monocular occlusion method induces strabismus by disrupting binocular pathways in the visual system[63,64] with subsequent exotropia. Monkey one, whose pellet placement was verified with an MRI at two months into treatment, ultimately showed a reduction in strabismus angle by about 11–14°. This was a 40% reduction in its misalignment. The pellet placement could not be verified as directly on the medial rectus muscle in monkey two, but it still showed a 15% improvement in its strabismus angle. There were a number of concomitant changes within the treated muscles that we hypothesize play a role in improving eye alignment in strabismic monkeys. In addition to larger muscle fiber size, there was also a significant increase in the nerve density within these muscles. IGF-1 is a neurotrophic factor that is retrogradely transported to the motor neurons.[33,34] The next question to be addressed is whether prolonged treatment of an extraocular muscle with IGF-1 or other neurotrophic factor will alter the neuronal drive to the muscles, and whether this alteration in neuronal drive, if present, will be maintained when treatment ends. These studies are on-going.

The improvement of misalignment in these adult strabismic monkeys, who were well past any “sensitive period” for the development of binocularity[65] strongly supports this approach for the potential treatment of strabismus. This study showed that even the adult ocular motor system has inherent plasticity when treated in a sustained manner with a neurotrophic factor, in this case IGF-1. The question remains whether this approach will work in children with childhood-onset strabismus. Considering how common eye misalignment is in children, and that in the absence of correct alignment and binocular vision, a large number of children develop amblyopia with its associated loss in visual acuity,[66] it is important to understand

the potential foundational bases for the development of strabismus in the first place. Once we understand the underlying cause, we can then begin to develop targeted approaches that have the potential to treat and correct eye misalignment permanently. Prevention of vision loss is the ultimate goal.

Slow release of growth factors could be an alternative approach to provide enough time for the visuo-oculomotor system to adapt to the new eye alignment. This is envisioned as a replacement or an adjuvant for surgery using the same basic principles for treatment as would be applied to surgery, with the use of strengthening neurotrophic factors for an underacting muscle and the use of weakening neurotrophic factors for an overacting muscle. Surgical interventions lead to an abrupt change in eye alignment and muscle conditions. This abrupt change in eye alignment subsequently leads to an abrupt change in the visual inputs the system is used to receiving, such that the eye alignment could be perceived as "incorrect". In monkey studies, the visuo-motor system changed the neuronal drives from the motor neurons after surgical correction to retrieve a pre-surgical eye misalignment.[23] These changes appear to be due to both neuronal and muscle plasticity, and further studies are needed to improve our understanding of these changes. Balancing the influence of growth factors at the muscle level on extraocular muscle tonus could lead to new treatments for strabismus.

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