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Behavioral analysis of sensorimotor control using the zebrafish mutant \textit{belladonna}

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Summary

In my PhD thesis, I have employed mutant and wild type zebrafish as my experimental model for gaining access to the visual system of vertebrates. The optokinetic response (OKR) is a visually-controlled behavior that stabilizes the visual world on the retina. Motion in the whole visual field leads to characteristic slow following and fast resetting eye movements in order to minimize the retinal slip velocity. Since the OKR is essentially a negative feedback loop, it is a suitable paradigm to investigate the impact of visual pathway abnormalities on visual behavior.

The zebrafish mutant belladonna was identified in a genetic screen due to its ipsilateral retinofugal projections, a condition referred to as achiasmia. This mutant also showed abnormal oculomotor behavior such as a reversed OKR and spontaneous eye oscillations (SOs). In addition to a series of optokinetic experiments, I used a mathematical modeling approach to link the oculomotor instabilities to the underlying optic nerve misprojection. It turned out that these behaviors depended on visual input and could be explained by a sign-inverted retinal slip velocity input to the optokinetic system. Furthermore, the SOs in achiasmatic belladonna closely resembled congenital nystagmus (CN) in humans. Therefore, belladonna may be a valuable behavioral animal model for oculomotor diseases, in particular when visual pathway abnormalities are involved.

belladonna also exhibited an abnormal motor response that is characterized by swimming in small circles (circling). It is well established that, among other sensory modalities, postural control relies on visual input. Circling depended on visual input and could be initiated but was not maintained by SOs. It was hypothesized that the transition between SOs and circling was mediated by emerging self-motion perception (vection). It is conceivable that circling is, much like reversed OKR and SOs, a result of the achiasmatic condition in belladonna. Analogously, impaired postural balance seen in some CN patients may be triggered by the unstable visual input due to the nystagmus.

Finally, I aimed to clone a retina-specific receptor, the metabotropic glutamate receptor type 6, in zebrafish. The genomic structure among grm6 orthologues is highly conserved. I have successfully identified two grm6 orthologues, grm6a and grm6b, in zebrafish by phylogenetic analysis based on protein sequence identity. The unique and novel expression pattern (in the retinal ganglion cells) of both paralogues revealed by RNA in situ hybridization has challenged the conventional view that the expression of grm6 is restricted to ON-bipolar cells. Our data not only suggest that gene expression of grm6 is developmentally regulated, but also provide the first histological evidence to support the previous hypothesis that yet undefined components (other than Grm6) may play the main role in the synaptic transmission between cone photoreceptors and cone ON-bipolar cells at the first synapse in the retina, at least in teleost.
Zusammenfassung