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cGMP signaling and bifurcation of sensory axons at the dorsal root entry zone of the spinal cord

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Background

The function of the nervous system depends on precise and selective connections of neurons. Various guidance cues instruct axons in choosing their pathway, polarity of growth, termination of growth and also branching. In vitro studies demonstrated that signaling cascades activated by axonal guidance receptors could be modulated by cyclic nucleotides. Previous analyses of cGKI (cGMP dependent protein kinase I) deficient mice in our lab showed that cGMP signaling via cGKI is important in axonal pathfinding and connectivity of sensory neurons. Sensory axons bifurcate upon arrival at the dorsal root entry zone (DREZ) of the spinal cord. Embryonic cGKI knock-out mice lack the bifurcation of sensory axons at the DREZ, i.e. the ingrowing axon either turns rostrally or caudally. Here, we present results of the detailed analysis of axonal pathfinding errors in cGKI deficient mice and of the search for other components of cGMP signaling in dorsal root ganglions (DRG).

Results

DiI tracing studies carried out before, were limited to the visualization of bundles of axons, which did not allow to quantify errors of single axons. Therefore, we extended our DiI tracing studies to the single axon level. Thereby, we could confirm statistically significant deviations (absence of T-shaped bifurcations) in the pattern of ingrowing sensory axons of cGKI knock-out mice as compared to the wild-type.

Screens for a role of guanylyl cyclases in sensory axon bifurcation carried out in our lab suggest that the natriuretic peptide receptor 2 (Npr2) might serve such a function in DRG neurons. We studied embryos of mice lacking functional Npr2 using DiI labelling and observed axonal bifurcation errors identical to that in cGKI knock-out mice.

Cross-breeding experiments with the transgenic mouse line GFP-M expressing GFP in a small proportion of DRG neurons provide further evidence for the bifurcation errors in cGKI deficient mice and Npr2 mutant mice. The resulting offspring was analyzed at postnatal day 21 indicating that bifurcation errors remain in adult animals.

Interestingly, whereas sensory axons in the spinal cord of cGKI mutant animals do not bifurcate other types of sensory axon branching seem not to be affected: we could detect collaterals formed by interstitial branching from the longitudinal arms of sensory axons both in wild-type and mutant mice.

We show that the vasodilator-stimulated phosphoprotein (VASP) is phosphorylated in dorsal root ganglions upon

stimulation of cGKI. Since VASP has a role in cytoskeletal organisation we considered that VASP might be a downstream target of cGKI involved in axonal pathfinding. However, the examination of VASP knock-out mice revealed no pathfinding errors of sensory axons.

Conclusion

We could show that cGMP acting via cGKI triggers bifurcation of sensory axons at the DREZ of the spinal cord. The absence of functional Npr2 results in a phenotype identical to that observed in cGKI knock-out mice suggesting that both Npr2 and cGKI are part of a cGMP signaling pathway important for sensory axon bifurcation. Currently, we aim to extend our insight into the mechanism of sensory axon bifurcation by identification of downstream target(s) of cGKI in sensory axons.