

The roles of dystrophin and dystrobrevin : in synaptic signaling in drosophila

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Citation

Potikanond, S. (2012, January 19). The roles of dystrophin and dystrobrevin : in synaptic signaling in drosophila. Retrieved from https://hdl.handle.net/1887/18388

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Propositions

Belonging to the dissertation



The Roles of Dystrophin and Dystrobrevin in Synaptic Signaling in Drosophila

- 1. The Rho-GAP Crossveinless-c, a negative regulator of Rho-GTPase signaling pathways, genetically interacts with Dystrophin and Dystrobrevin (this thesis)
- 2. Loss of Dystrophin results in the delocalization of Dystrobrevin from the postsynaptic region of the NMJ. This, in turn, causes a reduction in the activity of the Rho-GAP Crossveinless-c leading to an increased activity of the Rho-GTPase CDC42 (this thesis)
- 3. The Ca²⁺/calmodulin-dependent kinase II (CaMKII) is a postsynaptic target of Dystrophin, acting downstream of CDC42 (this thesis)
- 4. Dystrobrevin acts via the regulatory subunit of protein kinase-A (PKA-R). Expression of constitutively-active PKA, either pre- or postsynaptically, rescues the *Dystrobrevin* mutant increased neurotransmitter release phenotype (this thesis)
- 5. The CNS-specific Dystrophin isoform, Dp186, is required to maintain wild type synaptic transmission in the olfactory system (this thesis)
- 6. CaMKII activity controls retrograde signaling and presynaptic BMP receptor *wishful thinking (wit)* is required for this retrograde signaling to function (Haghighi et al. Neuron. 2003;39(2):255). *wit* also is required for the increased neurotransmitter release in the Dystrophin DLP2 null mutant (van der Plas et al. J. Neurosci. 2006;26(1):333). These results suggest that CaMKII and Dystrophin may use the same retrograde signaling pathway controlling the synaptic homeostasis.
- 7. The Schizophrenia susceptibility gene, *dysbindin* or Dystrobrevin-binding protein 1, is required presynaptically for the homeostatic modulation of neurotransmission at the Drosophila NMJ (Dickman & Davis, Science. 2009;326(5956):1127). It is conceivable that this protein interacts with Dystrobrevin at this site.
- Ephexin, the Rho-type guanine nucleotide exchange factor (Rho-GEF), and Cdc42 couple synaptic Eph signaling to the modulation of presynaptic Ca_v2.1 channels during the homeostatic enhancement of presynaptic release at the Drosophila NMJ (Frank et al. Neuron. 2009;61(4):556). It is possible that a presynaptic role of Dystrobrevin is required in this pathway.
- 9. The murine Dystrophin isoform Dp71 plays a role in glutamatergic synapse organization and function in the brain. Dp71-null mice show stronger learning impairments than mdx mice supporting the hypothesis that Dp71-deficiency contributes to the cognitive deficits in Duchenne muscular dystrophy patients (Daoud et al. PLoS One. 2008;4(8):e6574).
- 10. "After climbing a great hill, one only finds that there are many more hills to climb." (Nelson Mandela)
- 11. "When another person makes you suffer, it is because he suffers deeply within himself, and his suffering is spilling over. He does not need punishment; he needs help. That's the message he is sending." (Thich Nhat Hanh)
- 12. "One of the things I learned when I was negotiating was that until I changed myself, I could not change others." (Nelson Mandela)
- 13. "There are only two mistakes one can make along the road to success; not going all the way, and not starting" (Buddha)