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Exploring profilin

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Profilins are regulators of actin polymerization. Profilin 2 is expressed mainly in neurons, but its specific function is unknown. A study by *Boyl et al.* provides evidence that profilin 2 is required for activity-stimulated actin polymerization in the synapse, which controls neurotransmitter release, neuronal excitability and novelty-seeking behaviour in mice.

There are four mammalian profilin isoforms, all of which are G-actin binding proteins. Profilins are implicated in the actin dynamics that control membrane trafficking events such as vesicle endo- and exocytosis. Brain cells express profilin 2, but the role of this protein in brain function is not well understood. The authors therefore used profilin 2-knockout mice (*Pfn2*^{-/-}) to investigate the effects of profilin 2 at anatomical, electrophysiological and behavioural levels.

Surprisingly, they found that *Pfn2*^{-/-} mice displayed normal development and brain anatomy. Learning and memory, long-term potentiation (LTP) and long-term depression (LTD) were not impaired in *Pfn2*^{-/-} mice when compared with control mice. These results suggest that profilin 2 is not required for development, synaptic plasticity or learning and memory.

The authors noticed, however, that the *Pfn2*^{-/-} mice behaved differently to control mice. They were hyperactive, and they showed elevated exploratory and novelty-seeking behaviour when placed into a new environment. This included increased locomotor activity, wall rearings and rearings in the centre of the experimental area. Conversely, in the familiar environment of their home cage, they showed reduced locomotor activity compared with control mice.

Locomotor and exploratory behaviour are known to be mediated by the striatum. Ultrastructural analysis of this brain region showed differences in the organization of synapses when *Pfn2*^{-/-} and wild-type mice were compared. Electrophysiological recordings from striatal spiny neurons showed that the frequency of miniature excitatory postsynaptic currents (mEPSPs) was slightly higher, indicating that more vesicles at striatal *Pfn2*^{-/-} synapses were released. Furthermore, paired-pulse facilitation was decreased in

Pfn2^{-/-} mice, pointing towards a higher vesicle release probability. Immunoprecipitation and EM studies also indicated that the number of docked vesicles is approximately 25% higher in *Pfn2*^{-/-} mice.

How does profilin 2 alter vesicle release? When neurotransmitter secretion was stimulated in cortical synaptosomes from control mice, F-actin levels were significantly increased. This did not occur in synaptosome preparations from *Pfn2*^{-/-} mice. In addition, profilin 2, but not profilin 1, was shown to be tightly associated with the WAVE-complex, a protein complex that is implicated in actin dynamics and is abundant in synaptosomal preparations. The authors therefore suggest that WAVE and profilin 2 might cooperate to restrict synaptic vesicle release.

These results show that profilin 2 is crucial for actin polymerization at the synapse, which might provide a physical barrier to vesicle release. Future studies focussing on the downstream signalling pathways used by profilin 1 and profilin 2 will further contribute to our understanding of neurotransmitter release and the role of actin in this process.

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ORIGINAL RESEARCH PAPER *Boyl, P. P. et al.*
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