Small molecules demonstrate that dynamin is a bi-directional modulator of the exocytosis fusion pore

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Signaling molecules are released from excitable cells through a process called exocytosis. Exocytosis requires vesicles to fuse with the plasma membrane and a fusion pore to be created to enable release of vesicle contents into the extracellular environment. Dynamin is widely known for its role mediating endocytosis, but has an independent role in regulating fusion pore expansion in exocytosis. Dynamin acts primarily by its oligomerisation-stimulated GTPase activity and can self-assemble to rings or helical complexes. The mechanisms behind its role in fusion pore expansion are unclear, but its GTPase activity appears to be involved.

We have utilized a palette of small molecules targeted at dynamin function to reveal dynamin is a bidirectional regulator of fusion pore expansion and vesicle release in chromaffin cells. Using single cell amperometry we find that small molecule dynamin inhibitors or activators significantly reduce or increase, respectively, the amount of catecholamine released from single vesicles during an exocytosis event. TIRF microscopy analysis of NPY release from single vesicles demonstrates that activation of dynamin reduces the number of kiss and run events and slows the kinetics of release only during full fusion exocytosis. Inhibitors of actin polymerisation or myosin II can block this effect of dynamin activation on release kinetics. Thus we illustrate that small molecule dynamin effectors represent a novel suite of compounds that control the fusion pore during exocytosis and demonstrate that dynamin regulates the fusion pore and vesicle release *via* interactions with the actomyosin complex.