

Vesicle-associated membrane protein 8 (VAMP 8) is a SNARE selectively required for sequential granule-to-granule fusion

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Pancreatic acinar cells secrete digestive enzymes. The regulation of enzyme secretion is complex and poorly understood. It has to be tightly regulated to prevent inappropriate release of enzymes into the body which is one of the characteristics of acute pancreatitis. Here we use live-cell methods to determine the importance of a protein, VAMP8, in secretory control.

Digestive enzymes are contained within zymogen granules. When cells are stimulated zymogen granules fuse with the cell membrane and release their enzymes into the pancreatic duct. Zymogen granules can also fuse with each other in a process called compound exocytosis. Compound exocytosis is important in many cell types. We understand little about its regulation but recent work has suggested involvement of vesicle associated membrane protein 8 (VAMP8).

VAMP8 is a soluble NSF attachment protein receptor (SNARE) found on intracellular membranes and suggested as important for exocytosis in exocrine and blood cells. Previous work has shown that either inhibiting VAMP8 function or in VAMP8^{-/-} knockout mice, there is a reduction in secretion and a reduction in granule-granule fusion observed with electron microscopy. This work predicts that in VAMP8^{-/-} knockout mice deficits should be seen in the extent and/or kinetics of single granule fusion. Here we have tested this prediction using a new assay that identifies both primary fusion events (fusion with the cell membrane) and secondary fusion events (granule-granule fusion) during compound exocytosis. Our data show that fusion events in pancreatic acinar cells of VAMP8^{-/-} knockout animals have a reduction both in the extent and the kinetics of secondary granule fusion with little effect on primary granule fusion.

We conclude VAMP8 is an important SNARE engaged in secondary fusion. Previous evidence suggests VAMP8 is present on a subset of granules which, with our new data, indicates some granules might be specialized for compound exocytosis.