Interaction of Munc18 and Syntaxin in the regulation of insulin secretion

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Syntaxin 1A (Stx1A) and Munc18-1 play essential roles in vesicular trafficking and exocytosis. The molecular mechanism and the functional roles of their interaction remain to be explored. In the present study, we have studied the intracellular localization and interaction of Stx1A and Munc18-1 in insulin secreting INS-1 cells as well as CHO cells by confocal and evanescent field fluorescence imaging. We found that Munc18-1 colocalized with clusters of Stx1A and its open-form mutant, but not the mutant lacking Habc domain, at the plasma membrane in live INS-1 cells, suggesting the interaction of Munc18-1 with the Habc domain of Stx1A is necessary for the translocation of Munc18-1 to the plasma membrane. In CHO cells, where no endogenous Stx1A is reported, Stx1A failed to localize to the plasma membrane even in the presence of coexpressed Munc18-1, suggesting Munc18-1 is not required for the transportation of Stx1A to the plasma membrane. Moreover, in vivo FRET measurement demonstrated the interaction between Munc18-1 and Stx1A, whereas no significant FRET signal was observed for Munc18-1 and the open-form Stx1A mutant despite their colocalization. By overexpression of Munc18-1 in primary cultured pancreatic beta cells, we further showed that Munc18-1 negatively regulated insulin secretion by inhibiting the recruitment of granules to the readily releasable pool. Overexpression of neither the wild type Stx1A nor the open-form Stx1A affects exocytosis, suggesting the availability of Stx1A in its open form is not a rate limiting step in insulin secretion.