

Regulatory action of inositol pyrophosphate metabolism in the control of synaptic vesicle membrane cycling

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Abstract

Inositol is a naturally occurring glucose isomer and a key nutrient of the human diet. When levels of inositol are extremely low, disturbances such as diabetic changes, anxiety disorders, and hypercholesterolemia ensue. Inositol-derived metabolites (e.g., phosphoinositides and inositol polyphosphates) are key second messengers that are essential for controlling a wide range of cellular events such as growth and metabolic homeostasis. Inositol pyrophosphates such as 5-IP₇ (5-diphosphoinositol pentakisphosphate) are highly energetic inositol polyphosphates harboring phosphoanhydride bonds. While inositol pyrophosphates are known to regulate various physiologic events, including growth, the detailed modes of actions in cellular signaling networks have remained unclear. I will discuss our recent work demonstrating that 5-IP₇ acts through Synaptotagmin-1 (Syt1) binding to interfere with the fusogenic activity of Ca²⁺ in the control of vesicle membrane fusion. The data reveal a role of 5-IP₇ as a potent inhibitor of Syt1 in regulating the synaptic exocytotic pathway and expand our view on the signaling mechanisms of neuronal inositol pyrophosphates.