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Inositol pyrophosphates: Why so many phosphates?

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A B S T R A C T

The inositol pyrophosphates (PP-InsPs) are a specialized group of "energetic" signaling molecules found in yeasts, plants and animals. PP-InsPs boast the most crowded three dimensional phosphate arrays found in Nature; multiple phosphates and diphosphates are crammed around the six-carbon, inositol ring. Yet, phosphate esters are also a major energy currency in cells. So the synthesis of PP-InsPs, and the maintenance of their levels in the face of a high rate of ongoing turnover, all requires significant bioenergetic input. What are the particular properties of PP-InsPs that repay this investment of cellular energy? Potential answers to that question are discussed here, against the backdrop of a recent hypothesis that signaling by PP-InsPs is evolutionarily ancient. The latter idea is extended herein, with the proposal that the primordial origins of PP-InsPs is reflected in the apparent lack of isomeric specificity of certain of their actions. Nevertheless, there are other aspects of signaling by these polyphosphates that are more selective for a particular PP-InsP isomer. Consideration of the nature of both specific and non-specific effects of PP-InsPs can help rationalize why such molecules possess so many phosphates.
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Introduction and some comments on nomenclature

The phosphate group is a ubiquitous signaling device that establishes specificity in ligand-protein and protein–protein interactions. The phosphate's bulk imposes geometric constraints upon these interactions. The phosphate's negative charge at physiological pH further enhances specificity through ionic and hydrogen bonds with certain amino acid residues at physiological pH. Both proteins and small molecules can offer their phosphorylation and dephosphorylation for cell-signaling purposes. But there is one molecule in particular that belies its basic simplicity by hosting multiple phosphate recognition patterns that have extraordinary functionally versatility. This entity is a six-carbon ring structure that is systematically described as *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol. Most of us know it better as *myo*-inositol, or more frequently just as inositol (Fig. 1). The combinatorial placement of

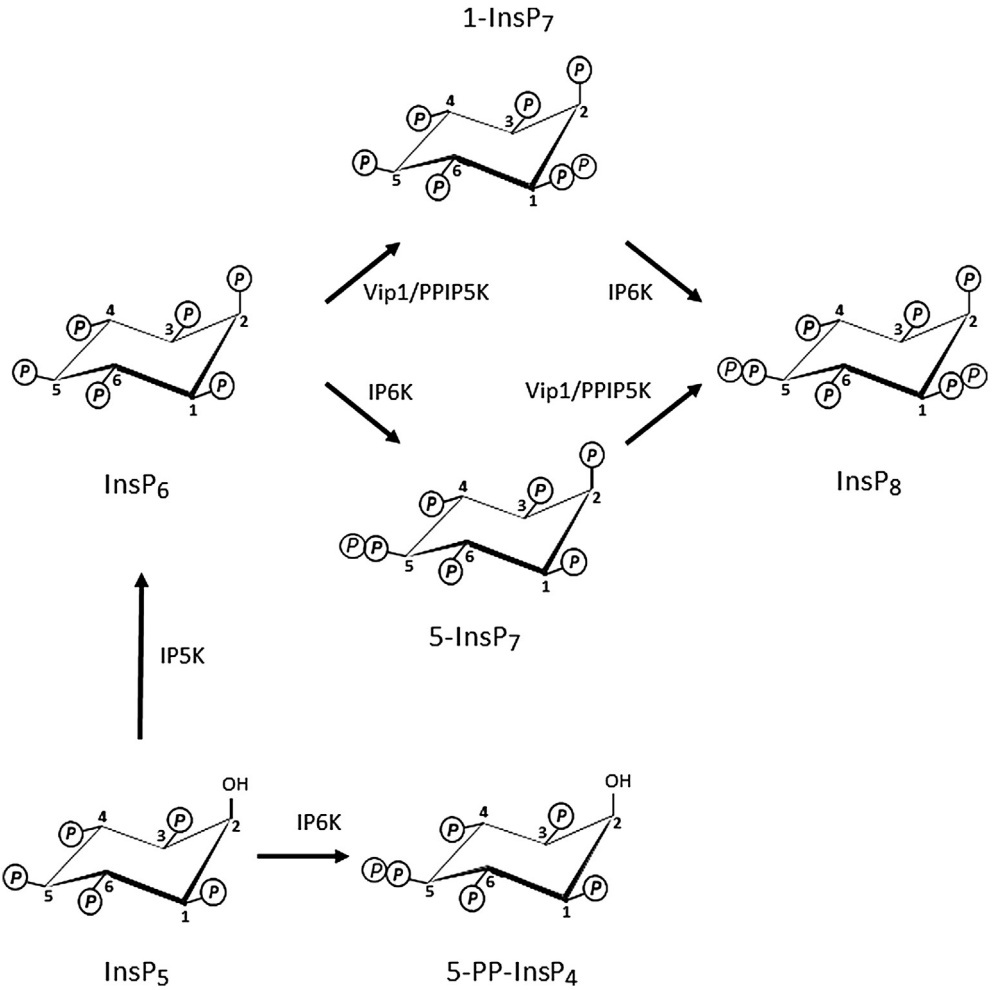

Fig. 1. Synthesis of the PP-InsPs. The figure describes the metabolic reactions that account for the synthesis of the PP-InsPs in both yeasts and mammalian cells. The positions of the diphosphate groups were determined in the following publications: Albert et al. (1997), Draskovic et al. (2008), and Wang et al. (2012). IP5K (E.C. 2.7.1.158), inositol pentakisphosphate kinase; IP6K (E.C.2.7.4.21), inositol hexakisphosphate kinase, PPIP5K (Vip1 in *Saccharomyces cerevisiae*) (E.C.2.7.4.24), diphosphoinositol pentakisphosphate kinase. This figure is adapted from Shears et al. (2013). For the brave-hearted who wish to gain insight into the unassailable logic behind the universal numbering system for the six carbon atoms of Ins, start here: Nomenclature Committee of the International Union of Biochemistry (1989).

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