Chapter 11

Inositol Phosphates and Phosphoinositides in Health and Disease

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1. INTRODUCTION

Inositol is an essential molecule found ubiquitously in biological systems. Phosphorylation of the cyclic inositol ring produces two related families of molecules, inositol phosphates and phosphoinositides. Research into the roles of inositol and its derivatives has been hampered by the complex and multitudinous interactions of these molecules in multiple cellular pathways. However, the potential rewards of such studies are immense, as inositol phosphates and phosphoinositides (PIs) play a role in numerous human diseases. This review addresses current knowledge of the role of inositol phosphates and PIs in human health and disease.

Part one of this review focuses on the role of inositol phosphates in cellular signaling pathways. Specifically, we focus on inositol 1,4,5-triphosphate (InsP$_3$) and inositol hexaphosphate (InsP$_6$) because these are the most highly studied inositol phosphates in relation to human disease. InsP$_3$ plays an essential role as a secondary messenger in the InsP$_3$/Ca$^{2+}$ signal transduction pathway, which is responsible for modulating the activity of numerous cellular processes. Perturbation of this pathway has been implicated in a variety of disorders including bipolar affective disorder, Alzheimer’s disease (AD), Parkinson’s disease, and malignant hyperthermia (MH). InsP$_6$ may be the most abundant inositol phosphate and is found ubiquitously in mammalian cells. Recently, InsP$_6$ has been identified as a potential antineoplastic therapy due to

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its antioxidant properties. As a result of the important functions of these molecules, increasing interest in examining the roles of other inositol phosphates has led to identification of novel functions. We briefly discuss the significance of recent findings regarding a variety of other inositol phosphates that provide promising avenues for future research.

In part two, we review the role of PIs in human disease. Although PIs are not abundant in biological systems, they have displayed numerous important functions in multiple signal transduction pathways. A number of human diseases are characterized by dysfunctional PI pathways, including cancer, type 2 diabetes, Lowe syndrome, myotubular myopathy, and Charcot-Marie-Tooth disease.

2. INOSITOL PHOSPHATES

The existence of inositol phosphates has been known for over 80 years (Posternak, 1919). Inositol, a six-carbon cyclitol found ubiquitously in all biological systems (Bachhawat and Mande, 1999; Chen et al., 2000; Majumder et al., 2003), exists in eight possible isomeric forms (myo, chiro, scyllo, neo, cis, epi, allo, and muco), of which myo is physiologically the most common and important stereoisomer. Phosphorylation of the inositol ring at one or more positions generates numerous PIs and inositol phosphates. The study of and interest in inositol phosphates is complicated by three major factors (Irvine and Schell, 2001): (1) there are many of them (63 possible isomers for inositol monophosphates alone), a potential that can be expanded further by attaching more than one phosphate on the same position, as in inositol pyrophosphates; (2) the multiplicity of metabolic pathways makes it hard to understand how their levels are regulated in cells; and (3) inositol phosphates are suspected to play a role in multiple signaling pathways (especially due to their involvement in Ca^{2+} metabolism), and, therefore, it is difficult to “bring them together” in one place.

Although the cellular roles of these molecules are not fully understood, inositol phosphates have been shown to convey signals for a variety of hormones, growth factors, and neurotransmitters (Berridge, 1993; Berridge and Irvine, 1989). As mentioned, cells contain a large array of inositol phosphates, some of which respond to receptor stimulation, providing the basis for multiple and complex responses. Among the inositol phosphates, we focus on InsP_{3} and InsP_{6}, the most widely studied in relation to human health and disease.

2.1 Inositol 1,4,5-triphosphate (InsP_{3}) – A major role in neurological disorders

Streb and coworkers (1983) discovered that InsP_{3} is a Ca^{2+}-mobilizing second messenger. Since then, a huge body of data has accumulated regarding its pivotal roles in the regulation of multiple cellular pathways, and its possible association with multiple illnesses, mainly neurological disorders.