Signal Transduction, a Step Forward in Medicine Regarding Regulators of Cellular Process

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Abstract

Signal transduction is carried out by inositol trisphosphate IP3. Earlier, we supported the signal transduction by synthesis of various compounds such as IP3, and phosphoinositide PIPx. IP3-binding protein was thoroughly investigated, the materials concerning signal transduction are playing a vital role in medicine discovery. During our previous work, DAB was found to be a regulator of Ca2+ release and consequent cellular process. Cathetel ablation of tricuspid valve and insertion of stent wear effective for heart disease.

Keywords: Signal transduction; Inositol; Inositol trisphosphate; Phosphoinositide; Regulator of cellular process; DAB; Atrial fibrillation; Coronary thrombosis

Introduction

First phospholipid was reported from bovine brain Brockenhoff in 1961 [1]. The finding was followed by the hypothesis that the receptor controlled hydrolysis of phosphoinositides could be directly linked to cellular calcium mobilization of Michell in 1975 [2]. The discovery by Berridge found that D—myo-inositol 1,4,5-trisphosphate(IP3) act as a second messenger, and the fundamental cell-signal transduction mechanism has been elucidated. IP3 stimulates the release of Ca2+ from the intracellular stores in the endoplasmic reticulum through IP3 receptor while regulating a wide range of cellular processes [3-27].

Ozaki et al. [28] succeeded in the first total synthesis of optically active myo-inositol trisphosphate involving 13 steps from readily available myo-inositol [28,29]. Later on several IPx and phosphinositide (PIPx) were synthesized by developing different synthetic methods and new reagents.

Inositol is actually a vitamin like compound found in both plants and animals. Plants are known to produce inositol from glucose and make PIx from inositol for signal transduction [25,26]. The synthesis of other important reagents is defined as follow.

Synthetic Competition of Inositol Phosphates

The synthesis of [1,4,5] P3 from inositol orthoformate, Vacca [30], from myo-inositol [31], from arons using Pseudomonas oxidation Ley [32] from Quinic acid, Falck [33] from inositol, Stephanov [34] Phosphothioate analogues Potier [35]

Maracekand Prestwich [36,37] prepared D-myo-[3H]I P3 (1,4,5), essential and most used reagent for the study of signal transduction.

Preparation of IPx, IP3 Derivatives, IP3 Analogues and Assessment of their Activities

Several compounds were synthesized and tested in our laboratory for making advances in signal transduction studies [38-86]. Such efforts included supply of necessary reagents such as IP3, other IPX used to such investigations. Furthermore the finding included the new methods of synthesis and development of reagents described. However, details were described in our earlier review article on transduction [38-41].

Inositol phosphate IPX

Inositol derivatives

4- glucopyranosyl inositol, 1-tartaric acid derivative [42] enzyme aided inositol derivative [43], 1,3,5-tribenzyol-inositol [44]. Inositol monophosphate IP1P(1) [43,45,46]; Inositol bisphosphate IP2 - IP2(5,6) [47], IP2(3,4) [47]; Inositol tris phosphateIP3-IP3(1,4,5) [44,48-50,45,65],IP3(1,4,5) analogue [57-63,65], IP3(1,3,4) [54], IP3(2,4,5) [45,65], IP3(1,4,5) phsphofluoridate [62,63],unsaturated IP3(3,4,5) [66].

2-substituted IP3 (1,4,5) [57-59],3-Substituted IP3 [60,67]

Inositol tetrakis phosphateIP4

IP4(1,3,4,5) [50,58,59,63,68],IP4(1,3,4,6) [47,63],IP4(1,4,5,6) [65], IP4(1,2,5,6) [68,69]

IP4(3,4,5,6) [67,68],IP4(1,3,4,5) analogues [63,70-72]

IP4(1,2,4,5) analogues [72]

Inositol pentakis phosphate IP5

IP5(1,3,4,5,6) analogue [72]
Phosphoinositide PIPx [38]

In addition, many Inositol lipid, Phosphatidyl inositol, PIPx [72-76]. Our efforts also lead to develop phosphonium salt methodology [39,77] and other compounds summarized as follows:

- Phosphatidylinositol 3,4,5-trisphosphate [78]
- Stearoyl-linolenoyl-PI(3,4,5)P3 [79]
- Unsaturated-PI(3,4,5)P3 [80]
- 2,6-Di-O-(D- mannopyranosyl)phosphatidyl-D-myo-inositol [81]

IP3-binding Protein

It is worth mentioning that 2-Substituted IP3 analogues were also synthesized which were used for the preparation of affinity columns. The reaction of 2-aminobenzoyl-inositol1,4,5-trisphosphate with affinity resin gave IP3 affinity column. Using this affinity resin, we could get IP3-binding protein, and such proteins were characterized [82].

- Putative inositol 1,4,5-trisphosphate binding protein in rat brain cytozol [83].
- Partial purification and reconstitution of inositol 1,4,5-trisphosphate receptor/calcium channel of bovine liver microsomes [84].
- Inositol 1,4,5-trisphosphate Affinity Chromatography. Fishing out Ins(1,4,5)P3-recognizable Protein [82].
- Inositol 1,4,5-trisphosphate binding to porcine tracheal smooth muscle aldolase [77].
- A new inositol 1,4,5-trisphosphate binding protein similar to phospholipase C-d 1 [85].
- D-myo-Inositol 1,4,5-trisphosphate-binding proteins in rat brain membranes [79].
- Expression and characterization of an inositol 1,4,5-trisphosphate binding domain of phosphatidylinositol-specific phospholipase CD1 [74].
- D-myo-Inositol 1,4,5-trisphosphate binding domain of phospholipase CD1 [75].
- Platelet-derived growth factor activates protein kinase Ce through redundant and independent signaling pathways involving phospholipase Cg or phosphatidylinositol 3-kinase from porcine skeletal muscle. Cellular Signalling [86].
- The metabolism of D-myo-inositol 1,4,5-trisphosphate and D-myo-inositol 1,3,4,5-tetrakisphosphate by porcine skeletal muscle. Cellular transmembrane signaling involving phospholipids and calcium [87].

Inositol, Inositol-trisphosphate

Inositol is an elegant sweet sugar. The seeds like rice, wheat and corn contain much phytic acid (inositol hexaphosphate) as Ca salt. Plants make glucose by photo synthesis from carbon dioxide and water. Some of the glucose is converted to inositol. Inositol is converted to phospholipids (PIP3) and phytic acid. PIP3 is converted to IP3 and diacylglycerol. These two compounds are essential for signal transduction of plants. It is well established that plant make phytic acid as a storage of phosphorous. Phosphorous is an essential atom as fertilizer because phosphorous is an essential atom to make nucleic acid, DNA. The seed store phosphorous atom as a store, so that seeds might be able to germinate on land lacking phosphorous.

It is well understood by new that inositol is biosynthesized in plant but seldom produced in animal. Therefore it is classified as an essential carbohydrate which is a kind of vitamin. The anti-oxidant and pro-oxidant activity of some B-vitamin and vitamin like compounds [25]. Arachidopain inositol trisphosphate-4 mediates high-affinity H symport of myo-inositol across the plasma membrane [26]. Inositol is called as a king of biologically active compounds. Inositol is active for anti-hyperlipidemia and called as anti hyperlipidea liver vitamin. Inositol is also active for panic disorder [96,97] and depressive disorder [98,99].

Inositol is produced from rice brain at TsunoShokuhinInd (Wakayama, Japan) in large quantities and used as healthy food, diet food, supplement, healthy drink, dog food, fish food and taste improving material, cosmetic, medicine.

Inositol is converted to phosphoinositides (PIPx) while PIP3 is converted to IP3 and diacylglycerol. These two compounds are essential for signal transduction. Therefore inositol is used as medicine, health food and health drink. Berridge and Nishizuka won Albert Lasker Basic Medical Research award and Wolf Prize in Medicine for “their discoveries concerning cellular transmembrane signaling involving phospholipids and calcium.

G-protein

Seeds and Brian K [100-105] were awarded Chemistry Nobel prize in 2012. They cloned the gene first for the β-adrenergic receptor, and then rapidly thereafter, for a total of 8 adrenergic receptors. This led to the seminal discovery that all GPCRs have a very similar molecular structure. Today we know that about 1,000 receptors in the human body belong to this same family.
Discovery of Regulators of Ca^{2+} release and Consequent Cellular Processes
Since 1997, we were studying 2-aminoethyl diphenylborinate (2-APB) analogues to find IP3 receptor inhibitor and regulate IP3-induced calcium release [106-128].

We discovered that Diphenylaminocadionate (O,N) borane. (DAB) adducts of amino acid with diphenyl borinic acid are best compounds [129-132].

We think that 911 Diphenyl-L-lysinate O,N) borane [133], 919 Diphenyl 2,3-diaminopropionate O,N)borane are the best 2 compounds

By choosing the compound we can control the release of Ca^{2+} and regulate many cellular processes such as secretion, cardiac contraction, fertilization, proliferation synaptic plasticity, atrial arrhythmias [115], inhibition of calcium entry channel [116,117], arrhythmogenic action of endothelin-1 on ventricular cardiac myocytes [116-122], dysreguration of neural inhibition of calcium entry channel [116,117], excitation-contraction coupling in the heart [117], Alzheimer disease, including Alzheimer`s disease, Huntington`s disease. We look for more effective transglutaminase inhibitors. We synthesized 5-bromo-2-thienyl-(N-t-butyl-N-benzyl)-aminoethyl ketone. We found that boron compounds also can inhibit transglutaminase (Ca2+-dependent enzyme) [138]. There are many neurodegenerative disease, including Alzheimer`s disease, Huntington`s disease. We looked for more effective transglutaminase inhibitors. We synthesized 250 β-aminoethyl ketones and found that these compounds had strong transglutaminase inhibitory activities [143,144]. A typical compound is 5-bromo-2-thienyl-(N-t-butyl-N-benzyl)-aminoethyl ketone.

The boron compounds were found to be effective as inhibitor of acyl protein thioesterase [144].

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