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

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Abstract

Signal transduction is carried out by inositol trisphophate IP3Earlier, 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 fiblillation; Coronary thrombosic

Introduction

First phospholipid was reported from bovine brain Brockenhoff in 1961 [1]. The findingwas 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(IP_3) act as a second messenger, and the fundamental cell-signal transduction mechanism has been elucidated. IP_3 stimulates the release of Ca^{2+} from the intracellular stores in the endoplasmic reticulum through IP_3 receptor while regulating a wide range of cellular processes [3-27].

Ozaki et al. [28] succeeded in the first total synthesis of optically active my-inositol trisphosphate involving 13 stepsi from readily available myo-inositol [28,29]. Later on several IPx and phosphinositide (PIPx) were synthesized by developing differentsynthetic 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 PIPx 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 I (1,4,5) P_3 from inositol orthoformate, Vacca [30], from myo-inositol [31], from arens using Pseudomonus oxidation Ley [32] from Quinic acid, Falck [33] from inositol, Stephanov [34] Phosphothioate analogues Potter [35]

Maracekand Prestwich [36,37] prepared D-myo-(^{3}H)I P_3 (1,4,5), essential and most used reagent for the study of signal transduction.

Preparation of IPx, IP_3 Derivatives, IP_3 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 transdution [38-41].

Inositol phosphate IP_X

Inositol derivatives

4- glucopyranosyl inositol, 1-tartaric acid derivative [42] enzyme aided inositol derivative [43], 1,3,5-tribenboyl-inositol [44], Inositol monophosphate IPIP(1) [43,45,46]; Inositol bisphophate 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 [57-63,64], IP3(1,3,4) [54], IP3(2,4,5) [45,65], IP3 (3,4,5) [58,66,67] IP3(2,4,5) [51,55],IP3(1,4,6) [44]IP3(1,4,6) [60], IP3(1,3,4) [60], IP3(1,2-cyclic 4,5 [47,54], 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], PI4(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:

- Phosphatidyinositol 3,4,5-trisphosphate [78]
- Stearoyl-linolenoyl-PI(3,4,5)P3 [79]
- Unsaturatedl-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-inosl1,4,5-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-triphosphate 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 CD 1 [75].
- Platelet-derived growth factor activates protein kinase Ce through redundant and independent signaling pathways involving phospholipase Cg or phosphatidylinositol 3-kinase [76].
- Detection and partial purification of inositol 1,4,5-trisphosphate 3-kinase from porcine skeletal muscle. Cellular Signallimg [86].
- The metabolism of D-myo-inositol 1,4,5-trisphosphate and D-myo-inositol 1,3,4,5-tetrakisphosphate by porcine skeletal muscle [87].
- Isolation of the active form of RAC-protein kinase (PKB/Akt) from transfected COS-7 cells treated with heat shock stress and effects of phosphatidylinositol 3,4,5-trisphosphate and phosphatidylinositol 4,5-bisphosphate on its enzyme activity [88].
- Expression and characterization of an inositol 1,4,5-trisphosphate binding domain of phosphatidylinositol-specific phospholipase CD-1 [89].
- A novel A-isoform-like inositol 1,4,5-trisphosphate 3-kinase from chicken erythrocytes exhibits alternative splicing and conservation of intron positions between vertebrates and invertebrates [90].

Discovery of Medicine

During of research work, I could discover Carmofur, which is an orally active antitumor agent. HCFU, 1-hexylcarbamoyl-5-fluorouracil [91-94]. This compound was obtained from 5-fluorouracil and hexyl isocyanate [95]. However in the current communication, I wish to describe our successful attempts in developing the compounds related with signal transduction. An ionization property of phosphatydylinositol polyphosphate in mixed model membranes was also reported.

The materials concerning signal transduction are inositol, inositol trisphosphate and G-protein. These compounds are playing very important role for the discovery of new medicines. This is clear from the facts that many investigators working on these materials are highly cited researchers and they were honored with Nobel prizes and Lasker awards.

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 (PIP_2) and phytic acid. PIP_2 is converted to IP_3 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]. Adrabidopain inositol trisphosporter-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 PIP_2 is converted to IP_3 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

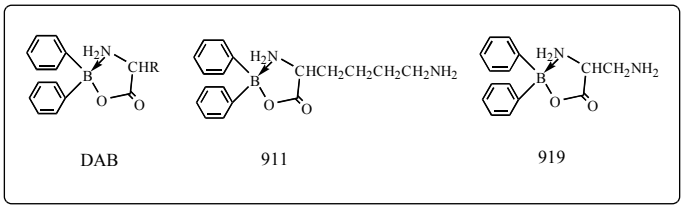
Seeds and Brian K [100-105] were awarded Chemistry Nobel prize in 2012. They cloned the gene first for the β-adrenergic receptor, and then rapidly thereafter, for a total of 8 adrenergic receptors. This led to the seminal discovery that all GPCRs have a very similar molecular structure. Today we know 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 Diphenylaminoacidonate (O,N) borane. (DAB) adducts of amino acid with diphenyl borinic acid are best compounds [129-132].

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



911 IC50 0.2

919 IC50 0.2

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 arryhythmiss [115], inhibition of calcium entry channel [116,117], excitation-contraction coupling in the heart [117], arrhythmogenic action of endothelin-1 on ventricular cardiac myocytes [116-122], dysreguration of neural calcium signaling in heart disorders [120-122]. Alzheimer disease [133-139], Huntington aggregation [140-144] and protein cross- link by transglutaminase [140-144].

Recently we found that DAB inhibited Huntington cell aggregation proportionally at SOCE inhibition activity of compounds and Huntington cell aggregation inhibition degree. This is a clear example that DAB regulated the cell response [144].

The 2-APB analogues presented in this study could be proven to be excellent lead compounds for many human diseases including heart diseases [120,122], Alzheimer`s [136-139] and Huntington`s disease [140-144].

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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