Inositol – Clinical Applications for Exogenous Use

Lisa Colodny, Pharm D. and Ronald L. Hoffman, M.D.

Abstract

Recent advances in nutritional and biochemical research have documented inositol as an important dietary and cellular constituent. The processes involved in inositol metabolism and its derivatives in the tissues of mammals have been characterized *in vivo* as well as at the enzymatic level. Biochemical functions defined for phosphatidylinositol in biological membranes include the regulation of cellular responses to external stimuli and/or nerve transmission as well as the mediation of enzyme activity through interactions with various specific proteins. Altered production of inositol has been documented in patients with diabetes mellitus, chronic renal failure, galactosemia, and multiple sclerosis. Inositol has been reported to be effective in treating central nervous system disorders such as depression, Alzheimer's disease, panic disorder, and obsessive-compulsive disorder. It has documented benefit for use in pediatric respiratory depression syndrome. In addition, recent studies have evaluated its usefulness as an analgesic. Inositol has been studied extensively as potential treatment to alleviate some negative effects associated with lithium therapy. The use of inositol in pregnant women remains controversial. Although its benefit in preventing neural tube defects in embryonic mice is documented, the risk of inducing uterine contractions limits its usefulness in pregnancy.
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Introduction

Inositol has been identified as an important dietary and cellular constituent. Biochemical functions of phosphoinositol (PI) in cell membranes include regulation of cellular responses to external stimuli as well as mediation of enzyme activity.
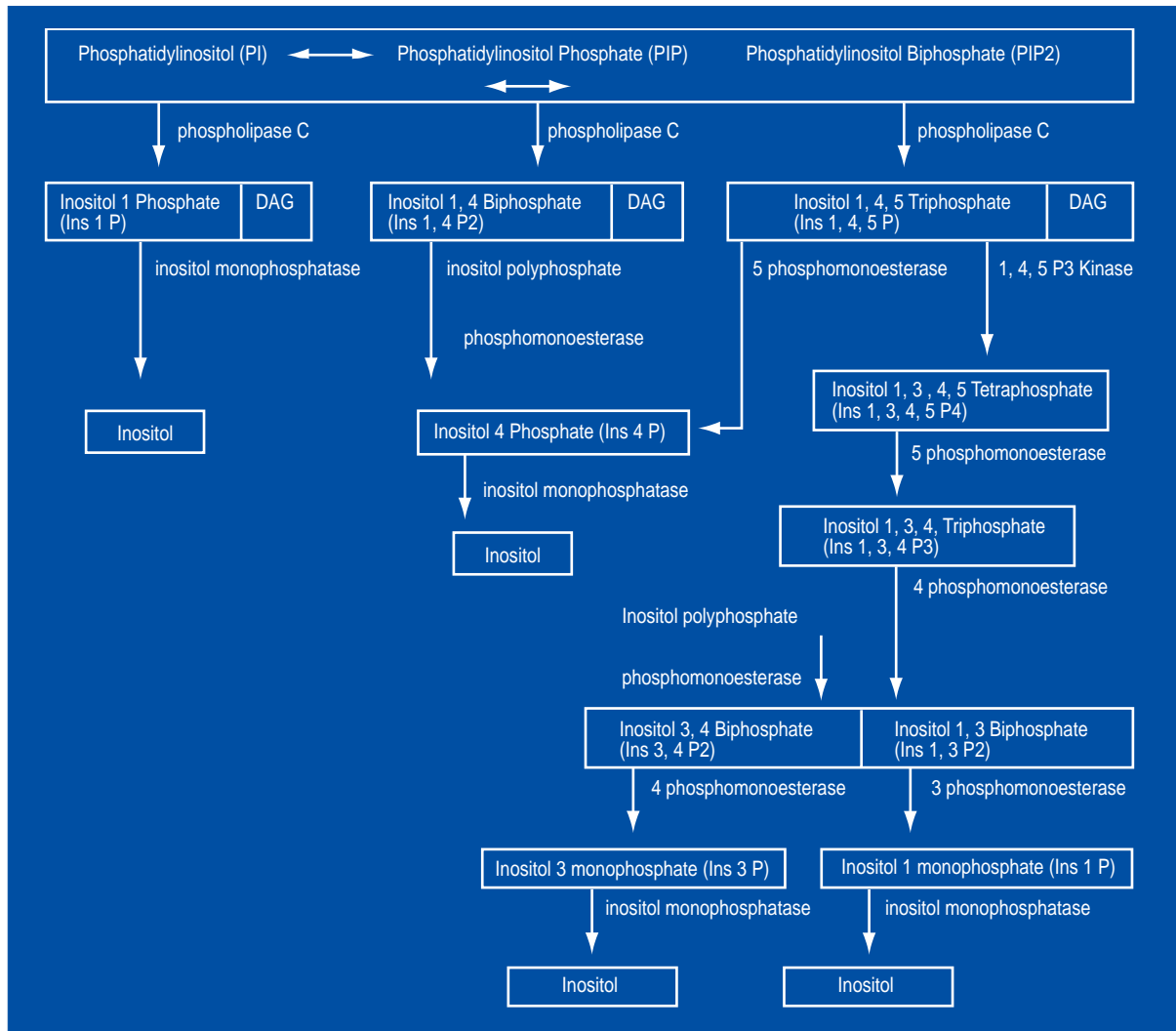
In mammals, inositol exists as phosphorylated derivatives, various phosphoinositides, and in its free form. These membranous bound phosphatidylinositols are cleaved by phospholipase C to form diacylglycerol (DAG) and the inositol phosphates. Subsequent enzymatic processes produce a variety of mono-, bi-, tri-, and tetraphosphate inositols depending on specific substrate and the enzyme as described in the diagram that follows. For example, the Ins-1,4,5-P3 kinase is stimulated by calcium. Therefore, the conversion of Ins-1,4,5-P3 to the Ins-1,3,4,5-P4 is facilitated when cytosolic concentrations are increased due to any agonistic action at the

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Lisa Colodny, Pharm D. is Clinical Coordinator of Pharmacy Services at Broward General Medical Center
Correspondence address: 1600 S. Andrews Ave., Ft. Lauderdale, FL 33316
Ronald L. Hoffman, M.D. is Chief Practicing Physician at the Hoffman Medical Center in New York and Vice President of the American College for Advancement in Medicine (ACAM)

Figure 1. Biosynthesis of inositol.

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Phosphatidylinositol (PI) ←——→ Phosphatidylinositol Phosphate (PIP)   Phosphatidylinositol Biphosphate (PIP2)
                                          ←——→

        │ phospholipase C                  │ phospholipase C                    │ phospholipase C
        ↓                                  ↓                                    ↓

  Inositol 1 Phosphate │ DAG      Inositol 1, 4 Biphosphate │ DAG      Inositol 1, 4, 5 Triphosphate │ DAG
  (Ins 1 P)                       (Ins 1, 4 P2)                        (Ins 1, 4, 5 P)

        │ inositol monophosphatase     │ inositol polyphosphate       5 phosphomonoesterase │   │ 1, 4, 5 P3 Kinase
        ↓                              │                                                        ↓
                                       │ phosphomonoesterase               Inositol 1, 3 , 4, 5 Tetraphosphate
  Inositol                             ↓                                   (Ins 1, 3, 4, 5 P4)
                              Inositol 4 Phosphate (Ins 4 P) ←——                 │ 5 phosphomonoesterase
                                       │ inositol monophosphatase               ↓
                                       ↓                                  Inositol 1, 3, 4, Triphosphate
                                  Inositol                               (Ins 1, 3, 4 P3)
                                                                               │ 4 phosphomonoesterase
                      Inositol polyphosphate                                   ↓

                      phosphomonoesterase
                                       │                                        │
                                       ↓                                        ↓
                         Inositol 3, 4 Biphosphate       Inositol 1, 3 Biphosphate
                         (Ins 3, 4 P2)                   (Ins 1, 3 P2)
                              │ 4 phosphomonoesterase         │ 3 phosphomonoesterase
                              ↓                               ↓
                 Inositol 3 monophosphate (Ins 3 P)   Inositol 1 monophosphate (Ins 1 P)
                              │ inositol monophosphatase      │ inositol monophosphatase
                              ↓                               ↓
                         Inositol                        Inositol
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cell membrane site. Likewise, the action of the enzyme, polyphosphate 1-phosphomonoesterase is inhibited by lithium and also by calcium in the physiologic range (Figure 1).[1]

The end product of each pathway eventually is inositol, which is recycled back as a component of the original PI precursor. In addition, this parent compound, phosphatidylinositol, can moderate the activity of numerous membrane enzymes.

Glycosyl-phosphatidylinositol (GPI) structures covalently anchor several enzymes (acetylcholinesterase, alkaline phosphatase, membrane dipeptidase, and 5-nucleotidase) to the outer surface of the plasma membrane.[2] In addition, these GPI anchors may provide the

protein with other properties, such as phospholipase cleavage susceptibility and the ability to cluster in detergent insoluble domains. These anchors can also act as signalers both intracellularly and transmembranously to regulate metabolic processes of the cells. This allows for enzymes to be activated when agonist activity is high, thereby decreasing further mobilization of calcium. Inactive enzymes remain attached to the membrane and allow agonist stimulation when calcium demand is decreased.

The inositols are ubiquitous, cyclic carbohydrates with a basic 6-carbon ring structure. There are actually nine isomers of inositol, of which myo-inositol is the most

Figure 2. The chemical structure of myo-inositol.[1]
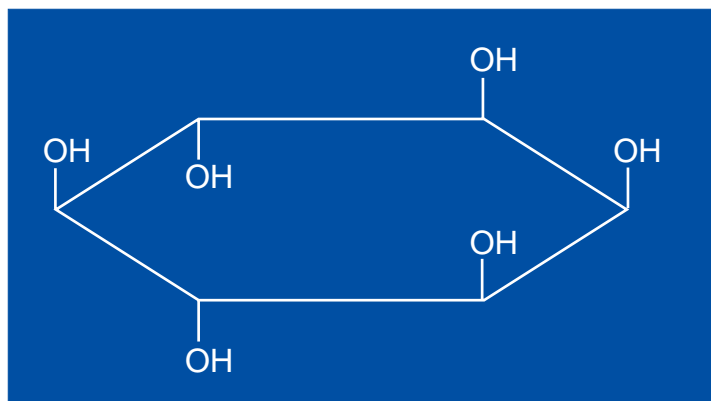
abundant isomer in the central nervous system of mammals (Figure 2). Myo-inositol is unique in that it has a single axial hydroxyl group at the number 2 carbon.[1]

Physiology

Because amines, polypeptides, and glycoproteins cannot penetrate the lipid layer of target cell membranes, an alternative activator is required. It is known that most hor-

Figure 3. Signaling system where cAMP activates a kinase to promote the agonistic intent.

mones act as a "second messenger" by binding to these cell membrane receptors and beginning a cascade of reactions that produces a "messenger" to actually potentiate the intended action.[3]

This "second messenger" concept is not unique to hormones. The original "second messenger" to be discovered was cyclic adenosine monophosphate (cAMP). For this reason, cAMP is also the best understood. For example, the hormonal effects of epinephrine and norepinephrine are regulated by cAMP. The neurotransmitters released at nerve endings are also regulated by cAMP.

When the agonist binds to the cell membrane receptor, ATP is converted to cAMP which in turn activates a kinase enzyme. The kinase becomes the "second messenger" as it continues in the cycle to promote the original agonistic effect (Figure 3).

Phosphoinositide composition of the central nervous system cell membranes are fatty-acid enriched and consist primarily of phosphatidylinositol (PI), phosphatidylinositol-4-phosphate (PIP), and phosphatidylinositol-4,5-biphosphate (PIP2).

Once the membrane is stimulated, phospholipase C is activated and consequently inositol triphosphate along with diacylglycerol is produced. PI is used as a precursor for phosphatidylinositol-3-phosphate [PI(3)P] and 3,4,5-triphosphate (Figure 4).[1]

Cytoplasmic calcium concentration is kept very low by active transport carriers, calcium pumps in the cell membrane itself, and in the endoplasmic reticulum. Usually the calcium concentration inside the cytoplasm is 5,000-10,000 times less than the concentration in the extracellular fluid.

This endoplasmic store of calcium can be accessed upon stimulation by inositol. Inositol triphosphate is released from the cell membrane and travels through the cytoplasm until it reaches the

endoplasmic reticulum. This inositol then releases the sequestered calcium, which can go on to mediate the release of neurotransmitters in response to depolarization (Figure 5).[4]

In addition to releasing endoplasmic reticulum calcium, myo-inositol functions as the major central nervous system non-nitrogenous osmoregulator. Modulation of this inositol pool is regulated in response to states of high or low osmolalities. The inositol pool is supplied via a sodium/inositol transporter, a sodium dependent active transport system, and a passive low affinity transporter.

Hypo- or hyperfunctioning occurs in different areas of the brain depending on the concentration of a specific myo-inositol pool.[1] Regulation of the brain inositol system is maintained exclusively by the production of intrinsic myo-inositol. Levels of intrinsic myo-inositol must be closely regulated, as an increase or decrease in the concentration can directly affect cellular signaling. IMPase, a magnesium dependent enzyme that hydrolyzes myo-inositol monophosphate into intracellular myo-inositol, accomplishes this regulation.[5]

Using rats as models, Kitamura et al proposed modulation of osmolality by inositol occurs in the renal medulla, especially the ascending limb of Henle.[6] During this study, acute renal failure was induced by injection of MMI (2-0, C methylene-myo-inositol), a sodium transport inhibitor, producing a significant increase in serum creatinine and urea nitrogen 12 hours after the dose was administered. The subsequent administration of myo-inositol prevented acute renal failure and improved tubular injury after MMI injection.[6] This may suggest a future role for inositol

supplementation to improve renal function in compromised patient populations.

The specificity of the IP3 receptors as well as the identification of other inositol receptors may play an important role in the development of newer inositol agents that can be directed to a specific receptor or enzyme. Recently, the work of Monkawa et al identified three different types of inositol-1,4,5-

**Figure 4.** Inositol signaling system with inositol triphosphate acting as the second messenger.
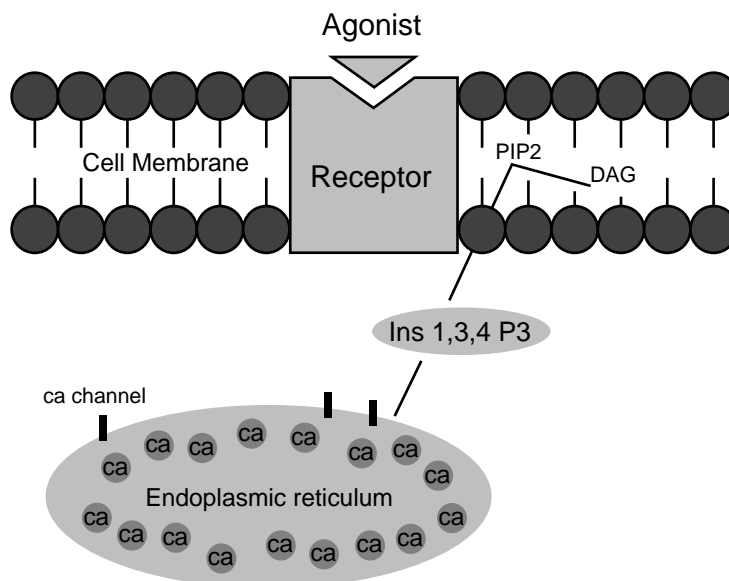
DAG = diacylglycerol, PIP2 = phosphatidylinositol-4,5-biphosphate.

triphosphate receptors in the rat kidney.[7] Type 1 inositol triphosphate receptors were most commonly located in the glomerular mesangial cells and in vascular smooth muscle cells. Receptors of type 2 specificity were located in the collecting ducts from the cortex to the inner medulla. Type 3 inositol triphosphate receptors can be found at all sites.[6]

Although receptor differences in the human model are not as clearly understood, calcium may have the potential to inhibit IP3

Figure 5. Inositol mediates the release of calcium from the endoplasmic reticulum. Calcium then augments the neurotransmitter release into the synapse.
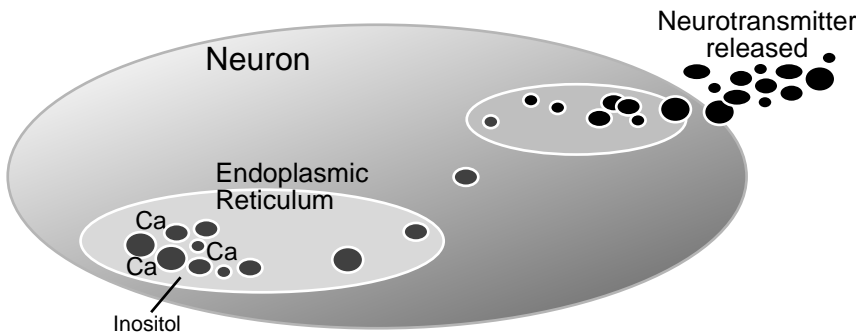
system. The receptors listed in Table 1 are linked to the G proteins and produce DAG and inositol-1,4,5-triphosphate as second messengers.[1] The receptors listed can be found in nearly every human organ system. The potential interactions between these receptors and their agonists are responsible for regulation of the body on a day-to-day basis. In view of the intricacy of these systems and their actions, a perfect balance is required for regulation of the signaling systems.

Theoretically, an imbalance of inositol concentration could potentially affect the development and function of one or all of these receptors. Therefore, any organ system that houses these receptors could also be potentially affected. Cholinergic receptors are located in the liver, heart, stomach, and lungs. Serotonin and glutamine receptors are found mostly in the CNS tissues. Adrenergic receptors are present in various tissues including CNS, vascular tissues, and heart. Histaminergic receptors are predominantly found in the lungs and stomach. Given the omnipresence of inositol or inositol related entities, maintaining a state of euinositolism may be a promising objective for regulation of functions required for development and/or maintenance of organ systems.

Under normal conditions the average dietary intake of inositol is only about one gram per day. Fortunately, oral intake of inositol accounts for only one of three pathways

binding to types 1 and 3 triphosphate receptors. Calcium binding to type 3 receptors may be stimulated at intermediate concentrations of calcium. As a result of these differences, type 3 receptors are more sensitive to IP3 than type 1 receptors when the cytosolic calcium

Table 1. Receptors identified in the inositol signaling system.

Receptor System	Types
Cholinergic	M1, M2, M3
Serotonergic	5HT2a & 5HT2c
Adrenergic	alpha 1a, alpha 1b, & alpha 1d
Glutaminergic	mGlu1 & mGlu5
Histaminergic	H1
Tachykinins	Nk1, Nk2, & Nk3
Cholecystokinin	CCKa & CCKb
Bombesin	BB1 & BB2
Bradykinin	B1 & B2
Platelet activating factor	PAF

concentration is within normal range.[8] However, as the cytosolic calcium concentrations increase, type 1 receptors become more sensitive to IP3 compared to type 3 receptors.

In addition to the IP3 receptors, numerous non-inositol receptors have been identified in the central nervous system that can potentially interact with the inositol signaling

for inositol production. Inositol monophosphate can be produced as a result of a receptor mediated salvage system and from glucose-6-phosphate. Inositol from either of these two pathways is metabolized by a lithium sensitive enzyme, polyphosphate-1-phosphomonoesterase. These two pathways account for the majority of inositol produced (Figure 6). Inositol accumulation from the third pathway, attained as a result of dietary uptake, is considered a minor pathway.

Potential Clinical Applications

A change in CNS availability of inositol may produce altered brain signaling and eventually lead to the development of neurological disorders. Studies evaluating the effectiveness of inositol indicate it may be effective in the treatment of depression, Alzheimer's disease, panic disorder, obsessive compulsive disorder, autism, post-traumatic stress disorder, and pain control.

Depression: The prevalence of depression in the United States is not definitively known. Depressive symptoms occur in 13-20 percent of the U.S. population. Depression is twice as likely to occur in females, average age of onset being 35-45; whereas it is 55 years of age for men.

The biological etiology for depression is believed to be linked to a deficiency of neurotransmitters at postsynaptic receptor sites. In the catecholamine theory the deficiency is norepinephrine; in the indolamine theory the deficiency is serotonin. Receptors linked to the inositol signaling system include serotonin (5HT2a and 5HT2b) and norepinephrine (alpha 1a, 1b, and 1d). Therefore, inositol may be an important participant in this neurological arena.

Presently, serotonin reuptake inhibitors (SSRIs) are the primary class of agents utilized for depressed patients. Kavoussi et al reported bupropion (a semi-serotonin agent) and sertraline (an SSRI) equally effective for the treatment of depression.[9] However, orgasm dysfunction, nausea, vomiting, somnolence, and sweating were frequently reported side-effects in the sertraline group.[10] Lydiard et al reported amitriptyline not superior to placebo for several subjective assessments of depression.[11] Van Houdenhave et al reported 23 percent of study patients experienced mild to moderate gastrointestinal effects for sertraline treated patients and a withdrawal rate of eight percent.[12] Venlafaxine was evaluated by Dunner et al and a dropout rate of 11.5 percent due to side-effects associated with

Figure 6. Two major productive pathways for inositol.

Pathway 1:
- PIP2
- Inositol 1, 4, 5 phosphate (Ins 1, 4, 5 P3)
- Inositol 1, 4 phosphate (Ins 1, 4 P2)
- inositol

Pathway 2:
- PIP2
- Inositol 1, 4, 5 phosphate (Ins 1, 4, 5 P3)
- Inositol 1, 3, 4, 5 tetrakisphosphate (Ins 1, 3, 4, 5, P4)
- inositol
- inositol
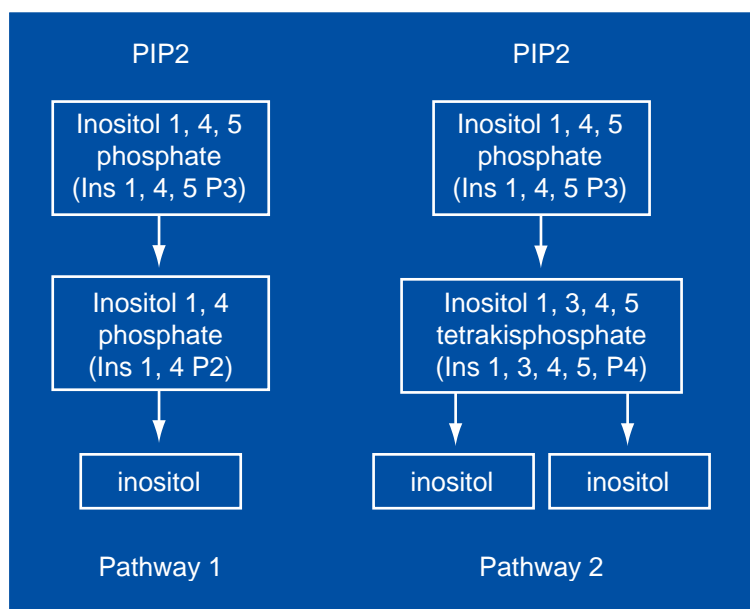
therapy was reported.[13] Presently, the SSRIs as a class are probably the best tolerated antidepressants currently available for use in patients with depression. They are commonly selected over the anticholinergic agents due to their effectiveness and lack of anticholinergic side-effects.

Anticholinergic effects of antidepressants include dry mouth, blurred vision, constipation, and urinary hesitancy. Autonomic effects include sweating, impotence and ejaculation dysfunction. At normal doses cardiac adverse effects include tachycardia and EKG changes. Other effects include: orthostatic hypotension, sedation, restlessness, insomnia, weight gain, anorexia, nausea, vomiting, tremor, and confusion.

In 1978, Barkai et al demonstrated depressed patients had significantly decreased CSF levels of inositol as compared to healthy patients.[14] In 1993 this theory was expanded to conclude that administration of high-dose inositol could increase CSF levels by as much as 70 percent.[15] This led to the study of inositol for treatment of depression.[16,17]

In 1995 Levine et al completed a, double-blind study for treatment of depression using inositol at a dose of 12 grams daily compared to placebo.[18] Patients receiving inositol showed significant improvement in depression as ranked by the Hamilton Depression Rating Scale (33.4 +/- 6 versups 21.6 +/- 10). Side-effects experienced by the inositol group were nausea and flatus. There were no hematological abnormalities in laboratory parameters. A few patients experienced mild elevations in fasting serum glucose concentrations. The researchers concluded that twelve grams daily was well tolerated. Another important observation was the absence of manic episodes in the bipolar patients treated with inositol. This lack of manic episodes may suggest that when the signaling system is not overactive, addition of inositol will not increase the signaling system's activity.[18]

Another study reported in 1995 by Levine et al evaluated the potential for relapse of depression once inositol therapy was discontinued. In this study, patients treated with 12 grams inositol daily experienced significant antidepressant effects. Half of the patients who responded to therapy relapsed rapidly on discontinuation of inositol.[19]

It can be concluded that inositol at a dose of 12 grams daily may be effective in treating the clinical manifestations of depression and should be considered a treatment alternative. In addition to the possible clinical responses relative to symptom resolution, therapy with inositol may be advantageous since potential side-effects of the more conventional therapy can be avoided.

Panic Disorder: Panic disorder begins as an acute or spontaneous attack of anxiety that involves an intense, terrifying fear. The attack seems to peak in about ten minutes and lasts approximately 20-30 minutes. The disorder is usually progressive and patients may develop anticipatory anxiety as a result. Most patients will eventually develop symptoms of avoidance behavior or agoraphobia.

Several drugs for the treatment of panic disorders are available, although response is often unpredictable. Conventional therapy includes SSRIs, the serotonergic agent clomipramine, tricyclic antidepressants such as imipramine or desipramine, MAOIs (especially phenelzine), alprazolam, and clonazepam. However, treatment with these medications continues to produce a significant number of adverse reactions.

Papp et al concluded clomipramine at therapeutic doses produced a significant number of adverse drug reactions and a high drop rate.[20] Paroxetine for panic disorder was evaluated by Ballenger et al who reported adverse drug reactions consistent with those most commonly reported for the class as a whole.[21] The most compelling adverse drug reaction information was reported by Cowly et al, who found 27 percent of the clinical trials reporting intolerable side-effects as the most common reason for treatment failures, especially with tricyclic antidepressants.[22] Rosenbaum et al concluded clonazepam in higher doses was more likely to cause somnolence and ataxia, while normal maintenance doses were more likely to be associated with depression, dizziness, fatigue, and irritability.[23]

Benjamin et al expanded the clinical use of inositol by evaluating its effectiveness in panic disorder.[24] This was an eight week double-blind, crossover study whereby patients were treated with 12 grams inositol daily for four weeks and then crossed over to the other study arm. Improvement was assessed using patient diaries, the Marks-Matthews Phobia Scale, the Hamilton Anxiety Rating Scale, and the Hamilton Depression Scale. The frequency and severity of panic attacks and the severity of agoraphobia declined significantly more after inositol than after placebo (a decrease from 10 attacks per week to 3 per week in the treated group compared to a decrease from 10 to 6 in the placebo group.) The authors conclude inositol's efficacy and safety, and the fact that inositol is a natural component of the human diet make it a potentially attractive therapeutic agent for panic disorder.

Obsessive Compulsive Disorder (OCD): OCD is the fourth most common psychiatric disorder. It is estimated 2.5 percent of adults and one percent of children meet the DSM-IV classification for OCD. It usually first appears late in adolescence or early adulthood. OCD incidence is higher in females than in males. The age of onset is usually earlier in males than in females, 6-15 years compared to 20-29 years, respectively.[25]

Although OCD can occur following a brain injury, there is usually no neurological precipitant. Most compelling for the evidence suggesting a biological cause is the successful treatment using SSRIs. Currently the medication of choice for treating OCD is the benzodiazepine agent, clomipramine. Flament et al reported a 26-percent discontinuation rate for OCD treated with clomipramine and 11 percent for those treated with the serotonin agent, sertraline. In addition, there is poor tolerance for long-term use of clomipramine.[26] Nausea, vomiting, and decreased sleep were the most commonly reported side-effects in a study of citalopram for OCD.[27] Patients also reported decreased sexual desire and orgasmic dysfunction.

Since the phosphatidylinositol cycle as a second messenger is known to affect several neurotransmitters, including serotonin receptors, inositol at 18 grams daily was studied for treatment in OCD in a double-blind, placebo controlled, crossover trial. Thirteen patients were treated for six weeks. There was a significant improvement at week six during the inositol period when compared to placebo period. There were no side-effects reported during the study period.[28] The improvement noted with inositol in this study was comparable to that reported for fluvoxamine and fluoxetine.[28] Longer periods of inositol therapy may produce even more significant results.

Alzheimer's Disease: Alzheimer's Disease (AD) is a degenerative brain disorder that affects approximately four million people in the United States.[29] This number is anticipated to increase to nearly nine million by the year 2040. It is estimated that currently more than 10 percent of the U.S. population aged 65 or older and 48 percent of those aged 85 or older have AD.[30]

Annually, the national cost of AD is estimated at 110 billion dollars. This includes the direct costs of medical care and social services, informal costs, and costs due to lost productivity. First characterized in 1907 by Alois Alzheimer, AD is a dementia of insidious onset, with deterioration of intellectual ability occurring gradually. Clinically, it is a progressive brain failure that results from neuronal dysfunction and ultimately cell death. Multiple neuronal pathways are destroyed in AD. This destruction is believed to be caused by accumulation of neuritic plaques and neurofibrillary tangles (NFT).

NFTs are located intracellularly within the cytoplasm of neurons. The neuritic plaques are extracellularly located (brain and cerebral vasculature). Both the plaques and NFTs significantly interfere with neuronal transmission.

Table 2. Agents approved and in clinical trial for the treatment of AD.

Medication	Class	Side Effects	FDA Status
Tacrine	Cholinesterase Inhibitor	Nausea, vomiting, Increased LFT	Approved
Donepezil	Cholinesterase Inhibitor	++ Nausea	Approved
Rivastigmin	Cholinesterase Inhibitor		In study
Metrifonate	Organophosphate derivative	Decrease blood cholinesterase headache, vertigo	In study
CX516		Unknown	In study
Calcium channel blockers	Block NMDA receptor	Bradycardia, headache, hypotension	In study
NSAIDS	anti inflammation	Gastrointestinal	In study
Nicotine	Nicotinergic	Tachycardia, headache, insomnia, dizziness	Controversial
Nerve growth factor	Stimulate nerve growth	Undisclosed	In study
Estrogen	+ cholinergic function	Nausea, vomiting, spotting	In study
Xanomelin	Muscarinic agonist	Gastrointestinal	In study
Linopiridine	Acetylcholine releaser	Undisclosed	In study
Sabeluzole	Benzothiazole derivative	Nausea, headache, dizziness	In study
Huperzine	Cholinesterase Inhibitor	Undisclosed	In study

Although the role of aluminum in AD is still speculative at best, the presence of aluminosilicates at the core of senile plaques in diseased neurons is a consistent feature found in the CNS of AD patients during autopsy.[31] It is known that aluminum inhibits the incorporation of inositol into phospholipids and the hydrolysis of the phosphoinositides by binding to one of two specific phosphate groups. This copulation of phosphate and aluminum affects the calcium releasing effects of the cell. The resulting profound disturbance of the phosphatidylinositol second messenger system may account for neuronal malfunction and eventual cell death.[31]

Currently all medications for AD are palliative. Even with newer agents like tacrine, the prognosis for AD is not improved. The newer agents do not affect the underlying disease processes, although progression of the disease may be retarded. Table 2 lists the currently approved agents and those currently being studied for Alzheimer's disease.[30,32-39]

Since the potential role of aluminum as a causative agent for cell death may be affected by the deregulation of calcium concentration, possibly due to inositol depletion, supplementation with inositol may produce positive CNS effects. Recent data suggests the loss of PI second messenger system target sites and IP3 receptors may add to cognitive impairment and the failure of conventional therapies in AD. Therefore, supplementation of inositol to replenish the diminished PI system may be beneficial in the treatment of AD.

In 1996 Barak et al completed a double-blind, controlled, crossover study of six grams inositol daily compared to placebo for 30 days in 11 Alzheimer's patients.[40] Patients in the study were diagnosed with dementia of the AD type as classified by DSM - IIIR and aged 65 years or older. The Cambridge Mental Disorder of the Elderly Examination (CAMDEX) was used as the basic assessment parameter and was administered upon admission into the study. Included in CAMDEX is part A: patient's present physical and mental state, part B: Cognitive Subscale of CAMDEX (CAMCOG), part C: interviewers observations, and part D: physical examination. CAMCOG was repeated at two, four, six, and eight weeks. Participants scored 80 or less on the CAMCOG examination and their symptoms of depression were not severe.

Patients were excluded from the study if they had a history of psychiatric, alcohol, and/or drug addiction disorders, or abnormalities in baseline laboratory values (blood count, electrolytes, liver or kidney functions, VDRL,

or CT scan) not consistent with AD. Patients with additional neurologic, metabolic, endocrinologic disorders, or presence of internal disease that grossly impaired brain functioning were also excluded.

Subjects were given either three grams inositol or placebo in the morning and again in the evening. After four weeks patients were crossed over into the other arm (inositol or placebo) for an additional four weeks. Only benzodiazepines were allowed during the study period (15 mg of oxazepam or equivalent), provided the patient was receiving it on study entry.

Analysis of the improvement scores of all patients who completed the study showed inositol increased the total CAMCOG score from a baseline of 31.36 +/- 20.90 to 40.09 +/- 24.54, while the placebo group increased from baseline of 35.9 +/- 25.96 to 39.27 +/- 25.10. The authors concluded only two of the eight subscales (language and orientation) showed significant improvement with inositol. Adverse effects of the inositol treated group were considered mild and transient (insomnia and flatus).

Further studies targeting orientation and/or improvement in language skills are warranted. The relatively small number of patients enrolled in the study may have lacked the statistical power to identify other significant differences that may have existed. It is also questionable why the researchers decided to use inositol at a dose of six grams when it is known relatively larger doses (12 grams or more) are generally required. Thirdly, the length of time inositol was administered may have been too short since studies in which patients were treated for three to five months produced more favorable results.

Recent advances in AD neurobiology have provided evidence for development of more effective and less toxic strategies for disease management. Of most significance is the realization that muscarinic receptors (M1)

post-synaptically are relatively preserved in AD patients, whereas the number of pre-synaptic receptors (M2) are reduced (Figure 7).[41] Therefore, stimulation of intact post-synaptic membranes by M1 receptor agonists may theoretically be more efficacious in treatment of AD than treatment with conventional therapies like acetylcholinesterase inhibitors that predominantly act on dysfunctional pre-synaptic membrane receptors.

Inositol's proposed mechanism of action in the CNS does not include direct manipulation with either pre- or post-receptors.

Figure 7. Muscarinic 1 receptors are believed to be intact in AD, whereas M2 receptors may be decreased or dysfunctional
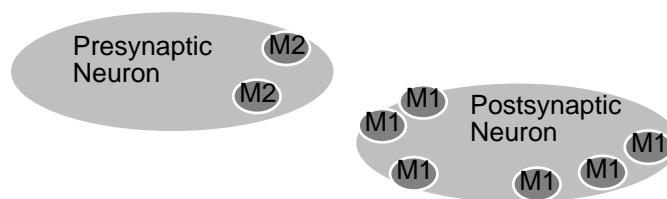
However, it may indirectly affect the relationship between receptor and agonist. By mediating the physiochemical characteristics of the M1 pre-synaptic receptor (solubility, osmolality, etc.), inositol may alter the binding site and influence the signaling that occurs as a result.

The development of a diagnostic test to confirm the existence of an "Alzheimer's protein" may also provide beneficial early therapy for patients predisposed to AD. In December 1997 the discovery of a protein called AD7c-NTP in nerve cells that may cause Alzheimer-like changes, including cell death, was announced.[42] This might enable physicians to identify patients with the AD protein and begin appropriate therapy, which can include inositol given its benign adverse

reaction profile. Presently, the debilitating neurological signs on presentation are often the initial prognosticators of AD. By this time, however, the damage that has occurred is usually severe and untreatable. Physicians may opt to include inositol in addition to one of the other agents for AD before neurological deterioration is severe.

Post Traumatic Stress Disorder (PTSD): PTSD is a pathological reaction to a psychologically traumatic experience. Symptoms may be acute or delayed, and are characterized by nightmares and flashbacks where the event is re-experienced.

Resistance to drug therapy may best be explained by Adamac who reported the traumatic event may actually produce a "photograph" of the occurrence in the CNS. This permanent emotional memory may be triggered exogenously and the event is relived continually upon exposure to agonists.[43]

Only about 50 percent of PSTD patients reported significant improvement in depressive symptoms at one month when compliant with medications. SSRIs produced better outcomes than norepinephrine inhibitors.

In 1996 the effects of inositol in patients suffering from PSTD were evaluated by Kaplan et al. Patients were given 12 grams daily or placebo for four weeks, then crossed over into the other study group for an additional four weeks. There were no significant differences in improvement between the treated group as compared to the placebo group.[44]

Autism: The use of inositol at 200 mg/kg was evaluated in nine children for the treatment of autism.[45] The investigators concluded there was benefit for its use in this patient population. Studies on a larger population seem warranted.

Respiratory Distress Syndrome Disorder (RDSD): One of the oldest documented uses of inositol is for use in neonatal RDSD.[46] It is known that inositol administration to im-

mature animals increases pulmonary surfactant levels. Administration of inositol at 80 mg/kg parenterally to premature infants may decrease the likelihood of respiratory distress syndrome. Hallman et al concluded parenteral inositol therapy during the early neonatal period may also decrease the incidence of severe, chronic injury of the retina.[47]

Analgesia: Given the success of inositol for some central nervous system disorders, its use for pain control was recently evaluated. Tarnow et al reported an analgesic effect for inositol-1,2,6-triphosphate in a double-blind, randomized study of 24 patients undergoing cholecystectomy.[48] Opioid analgesia requirements were significantly reduced when patients received a bolus inositol dose of 240 mg followed by 90 mg/hr for 24 hours. There were no side-effects reported with the bolus or maintenance infusions.

The analgesic relationship between inositol and pain was also investigated by Raffa et al who reported the phosphoinositide pathway may play an important role in opioid efficacy and in the development of morphine tolerance.[49]

The recent work of Ferrara et al proposed an anti-edematous action of alpha-trinositol when used to treat canine scald injuries, reportedly through a decrease of the transmembrane flux.[50]

Lithium-Induced Adverse Reactions: It is believed lithium inhibits inositol monophosphatase which in turn depletes brain stores of inositol. In fact, this may be the mechanism for lithium's effectiveness in treating manic-depressive disorder.

Concern is therefore warranted over the concept of treating lithium induced side-effects with inositol, since administration of inositol may cause the concentration of inositol to rise and subsequently reintroduce manic or depressive episodes. However, the exogenous administration of inositol does not appear to alter the manic-depressive control at all.

It is theorized inositol derived from inositol phosphate breakdown is recycled for use in membranous phosphatidylinositol. Hyperactivated systems would be affected by lithium's depletion of the recyclable inositol pool, whereas isosystems would not be affected.[51] A similar finding was reported by Berridge et al who concluded lithium inhibits phosphoinositide derived second messengers of activated systems only.[52]

Johnson et al concluded inositol depletion induced by lithium can be bypassed by introduction of exogenous inositol.[53] They administered inositol at 1500 mg daily (500 mg three times daily) to 11 patients who experienced polyuria-polydipsia as a result of lithium treatment. Forty-five percent of the patients experienced dramatic improvement in polyuria-polydipsia complaints; another 36 percent reported mild improvement. This improvement may be more related to the osmoregulatory effect of inositol than its function as a second messenger. Improvement was also noted in lithium-induced psoriasis.

Possible Clinical Contraindications for Inositol Supplementation

Attention Deficit Hyperactivity Disorder (ADHD): ADHD is a disorder of early childhood which can be symptomatic well into adulthood. These patients are inattentive, impulsive, quick-tempered, unable to tolerate stress, and are restless since childhood. ADHD is most commonly treated with methylphenidate, but propranolol and tricyclic antidepressants are also alternatives.

Evaluation of inositol in 11 children with attention deficit hyperactivity disorder was reported in 1995 by Levine et al in a double-blind, crossover study.[54] There were no therapeutic advantages observed in the inositol group. In fact, there was a trend toward the worsening of the disorder in the inositol treated group. Therefore, inositol appears to have no clinical advantages for the treatment of ADHD and may even antagonize the condition.

Schizophrenia: Schizophrenia accounts for 7-20 percent of all psychiatric hospital admissions. It is estimated that 0.5-1.0 percent of the worldwide population will experience a schizophrenic episode at some point in life. Schizophrenia usually begins in adolescence and early childhood, only rarely beginning before adolescence or after the age of 40. It affects the sexes equally and usually becomes more pronounced at approximately age 20. Males tend to have an earlier onset than females (15-24 years versus 25-34 years, respectively).

The most accepted and well-supported biochemical etiology for the development of schizophrenia involves the neurotransmitter, dopamine. It is believed excessive concentrations of dopamine may induce psychotic/schizophrenic episodes.

Although anti-psychotics drugs are effective in treating the disorder, the adverse reactions associated with them can be severe. The side-effects can range from Parkinsonian-like symptoms to anticholinergic effects (dry mouth, constipation, urinary retention, drowsiness, etc) depending on the pharmacological class of the agent. Therefore, noncompliance with anti-psychotic medications is a pivotal problem for patients and caregivers.

In 1993, Levine et al performed the first study utilizing inositol as an agent for schizophrenia. This study found no significant benefit of inositol supplementation.[55,56] However, the authors concluded the dose of six grams daily was probably not sufficient to produce a significant clinical effect. Large exogenous doses are usually required since inositol absorption from the periphery into the CNS is poor. In addition, losses of seven to eight grams daily can result from degradation by renal enzymes.[57]

Another theory for the lack of efficacy of inositol may be explained by the recent work

of Jope et al who reported schizophrenia may be associated with an increased, rather than decreased, activity of the phosphoinositol signaling system.[58] Therefore, it may be contraindicated in schizophrenia.

Pregnancy: Inositol may stimulate uterine contractions. Oxytocin is a potent uterine stimulator whose clinical use in labor and delivery is well documented. Phaneuf et al reported oxytocin's clinical effectiveness is due to the activation of phospholipase C to produce inositol-1,4,5-triphosphate which releases calcium from intracellular stores and stimulates uterine contractions.[59] The activation of the phosphatidylinositol signaling system by calcium agonists is also supported by the work of Chien et al who noted dose-related myometrial contractions when laboratory mice were injected with a calcium agonist.[60]

Reece et al reported inositol supplementation of 0.08 mg/kg/day significantly decreased embryonic neural tube defects from 20.4 percent to 9.5 percent in diabetic rats. They concluded the incidence of diabetic embryopathy and congenital malformations may be reduced by supplementation with inositol.[61] Similarly, Greene et al stated about 30 percent of all neural tube defects are resistant to supplementation with folic acid alone. However, addition of inositol significantly decreased the incidence of spinal neural tube defects in mice by increasing protein kinase activity and delaying the closure of the neuropore. They concluded that combination therapy of folic acid and inositol may prevent neural tube defects like spina bifida in humans.[62] Therefore, while inositol may prevent neural tube defects, its use during pregnancy may be contraindicated due to the potential for uterine stimulation.

Conclusion

Propelled by incredible advances in the understanding of the pathological etiologies and characteristics of psychiatric disorders, prospects for treatment have brightened considerably in the last 10 years. It is known that a change in the CNS concentration of inositol may lead to modified brain cell signaling pathways, and possibly to the development of a psychiatric disorder. Recent evidence indicates inositol has psychoactive effects by interacting with the second messenger system and ultimately regulating the cytosolic concentration of calcium.

The signaling by calcium is known to mediate an array of cellular functions (secretion, contraction, and conduction). Due to the role calcium plays, its regulation intracellularly is known to be a complex phenomenon involving a number of active and passive transport systems. Inositol is now established as a significant mediator of calcium mobilization in the endoplasmic reticulum. Modifying this mobilization of calcium may be effective in treating some CNS disorders like Alzheimer's disease, depression, panic disorder, obsessive compulsive disorder, and as an analgesic for pain control. Likewise, its use to alleviate lithium-induced adverse reactions is also promising.

The benefit of inositol therapy in post traumatic stress disorder and autism has yet to be established. To date most studies have been characteristically small in number. In addition, studies have not consistently approached realistic doses of inositol for therapeutic effect to be evaluated. There is a need for additional studies to be performed utilizing large numbers of patients and increased supplemental doses of inositol.

At this time inositol supplementation for the treatment of schizophrenia and attention deficit hyperactivity disorder is not believed to be effective. In fact, it may be contraindicated as it might exacerbate these conditions. The risk of premature labor induction versus benefit for prevention of embryonic defects should be considered thoroughly before initiation of inositol therapy during pregnancy.

As new clinical studies involving inositol are concluded and the research is evaluated, the understanding of inositol's role in intracellular and extracellular signaling may provide even better insight into the therapeutic applications of inositol and inositol-based products.

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