The Role of Glucose in the Pathogenesis of Alzheimer's Disease Revisited: What Tells us the Therapeutic use of Lithium?

A. Strunecká[1,*] and P. Grof[2]

[1]*Department of Physiology and Developmental Physiology, Faculty of Science, Charles University in Prague, Czech Republic;* [2]*Mood Disorders Center of Ottawa and Department of Psychiatry, University of Toronto, Canada*

Abstract: The ultimate aim of many researchers is to design a drug, which could arrest or delay specifically the clinical evolution of symptoms of Alzheimer's disease (AD). The association of increased activity of glycogen synthase kinase-3 (GSK-3) with neuronal apoptosis, amyloid metabolism, and hyperphosphorylation of protein tau makes this kinase an attractive target for the therapy of neurodegenerative diseases. Lithium has been shown to be an important inhibitor of GSK-3 activity and therefore recently suggested as one of the treatment of AD. For some time, the most widely accepted mechanism of action of lithium was its inhibitory effect on inositol monophosphatase, resulting in depletion of inositol with profound effects on phosphoinositide signaling system. Although much evidence has not supported the inositol depletion hypothesis subsequently, the important role of inositol and inositides in the CNS, in addition to their role in phosphoinositide signaling pathways, has been discussed. A new perspective on the role of glucose in neurodegenerative changes in the CNS has been emerging from several lines of evidence. These accumulated observations may improve our understanding of the links between deficient glucose metabolism in the aging brain and the events leading to the onset of AD. The impairment of glucose utilization might act as the common denominator for the development of pathological hallmarks of AD.

Keywords: Alzheimer´s disease, acetylcholinesterase, beta amyloid, protein tau, glycogen synthase kinase–3, inositol monophosphatase, inositides, lithium.

INTRODUCTION

Effective therapies for Alzheimer's disease (AD) are desperately needed since millions people worldwide suffer from this devastating disease. The current therapeutic strategy for AD is based on the cholinergic theory, which suggests that the degeneration and alteration of the cholinergic central neurotransmission explains the cognitive deficit in AD [1,2]. The inhibition of the enzyme acetylcholinesterase (AChE) is expected to increase the levels of the acetylcholine in the brain [3]. Numerous research projects are aimed at developing drugs focused on preventing the neurodegenerative processes that take place in the brain early at the onset of AD [4,5]. The intensive fundamental research supported by rapid technological advances of both biochemistry and molecular biology reveals complicated network of interactions among molecules, enzymes, and signaling systems underlying pathological changes in brains of patients with AD. Intense efforts are underway to find an underlying metabolic disorder, which could be targeted by therapy. The ultimate dream of many researchers and clinicians is to design a drug, which could arrest or delay the clinical evolution of symptoms of this illness – the most frequent obstacle to healthy aging. The discovery of the pluripotent role of glycogen synthase kinase-3 (GSK-3) led to the suggestion of tackling the main brain lesions in AD with lithium [6-8].

*Address correspondence to this author at the Department of Physiology and Developmental Physiology, Faculty of Science, Charles University, Vinicna 7, 128 00, Prague 2, Czech Republic; Tel: +420 221 951 769; E-mail: strun@natur.cuni.cz

The theoretical base for such speculation emerged from the knowledge of interactions among amyloid precursor protein (APP) processing [9], phosphorylation of protein tau, presenilin genes, and GSK-3 sensitivity to lithium [10,11,6]. The idea of the therapeutic use of lithium in AD has recently attracted interest of many researchers and clinicians. Lithium is mainly known from psychiatry, because of its use for the treatment and prophylaxis of bipolar disorder (BD) [12,13]. The effects of lithium on a number of enzymes and biological processes have been studied over the last three decades [14-17]. It has been demonstrated that lithium administration regulates multiple GSK-3 targets *in vivo* supporting the hypothesis that inhibition of GSK-3 may represent a mechanism of lithium´s mood stabilizing properties. For some time, the most widely accepted mechanism of action of lithium was its inhibitory effect on inositol monophosphatase (IMPase), resulting in the depletion of inositol and the inhibition of phosphoinositide signaling pathway. The study of mechanisms of lithium therapeutic effects on various levels reveals its potential new roles in the therapy of AD [6]. The evidence of neuroprotective effects of lithium supports its use as novel therapeutics against neurodegenerative diseases [15,18].

Some authors concluded that the cholinergic deficit, nerve cell atrophy, amyloid plaques, and neurofibrillary tangles (NT) in the brains of AD patients are secondary to the decline of glucose metabolism [19,20]. A new perspective on the role of glucose in neurodegenerative changes in the CNS has been emerging from several lines of evidence. These accumulated observations may improve our understanding of

1871-5249/06 $50.00+.00

the links between deficient glucose metabolism in the aging brain and the events leading to the onset of AD.

In this review we therefore first explore the evidence of the role of glucose in neurodegenerative changes in the CNS. We then proceed to discussing the potential of lithium in the treatment of AD and the links of its therapeutic effects to inositide metabolism and alterations in glucose utilization. The new perspectives suggest that the impairment of glucose utilization might act as the common denominator in the pathogenesis of AD.

DISTURBANCES OF CEREBRAL GLUCOSE METABOLISM IN AD PATIENTS

Many studies have documented a close relation between the regional impairment of cerebral glucose metabolism and impaired cognitive functions in patients with AD [21-29] (Table **1**). It has been suggested that a disturbance in the insulin signal transduction pathway and decreased glucose metabolism may be the central and early pathophysiological events in development of pathological hallmarks of AD with sporadic origin [30].

Neuroimaging Measures

It is well established that regional cerebral metabolic rates for glucose assessed by [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) in patients with AD provide a sensitive, *in vivo* metabolic index of AD [20,26,31,32]. Sensitivity of PET for distinguishing patients with dementia with Lewy bodies from AD, however, is higher than that of clinical evaluation.

This technique also allows the recognition of patients who are prone to develop AD [33]. In a multicenter study comprising 10 PET centers (Network for Efficiency and Standardisation of Dementia Diagnosis - NEST-DD) that employed an automated voxel-based analysis of FDG-PET images, the distinction between controls and AD patients was 93% sensitive and 93% specific, and even in very mild dementia (at MMSE 24 or higher) sensitivity was still 84% at 93% specificity. Significantly abnormal metabolism in mild cognitive impairment (MCI) indicates a high risk to develop dementia within the next two years. Reduced neocortical glucose metabolism can probably be detected with FDG-PET in AD on average one year before onset of subjective cognitive impairment [20].

Jelic and Nordberg [34] followed 25 MCI patients with PET scans and cognitive tests. Six patients converted to AD during 2 years of follow-up, and all had showed a significant lower glucose metabolic index at inclusion in the study compared to the MCI patients that did not convert to AD during the 2 years followup. Alexander *et al.* [26] compared the group of 14 AD patients with 34 age-matched healthy subjects using FDG-PET scans. One year later, the AD patients had significant declines in glucose metabolism. These findings also support the feasibility of using FDG-PET as an outcome measure to test the ability of treatments to attenuate the progression of AD.

The MMSE scores and full-scale IQ show significant correlations with the regional cerebral glucose metabolic rates (rCMRglc) in the temporal and parietal lobes on both sides and in the left frontal lobe, which were significantly reduced in patients with clinically diagnosed AD in compari-

Table 1. Deficient Glucose Metabolism in Brains of AD Patients (Using FDG-PET Neuroimaging)

Diagnosis	No of patients	Parts of the brain	Reference
MCI	25	temporoparietal association areas, posterior cingulate and hippocampus	[34]
MCI	Analysis from refs	temporoparietal association areas, posterior cingulate and hippocampus	[33]
mild to moderate dementia	17	right hippocampus, right middle and inferior frontal gyri, right middle temporal gyrus, prefrontal cortex and left middle frontal gyrus	[32]
Probable AD	8	neocortical, subcortical, and paralimbic regions	[21]
AD	8	temporal cortex	[22]
Probable AD	25	whole brain, temporoparietal, frontal and occipital association cortex	[23]
Probable AD	66	posterior cingulate cortex	[24]
AD	26	temporal and parietal lobes on both sides and the left frontal lobe	[25]
mild + moderate AD	14	parietal, temporal, occipital, frontal, and posterior cingulate cortices	[26]
AD	10 PET centers	neocortex	[20]
AD	7 twin pairs	hippocampus and lateral temporal cortex	[27]
AD	86	frontal and anterior cingulate areas	[28]
early onset late onset	74 46	parietal, frontal and subcortical (basal ganglia and thalamus) areas	[29]

son to those in the normal controls [25]. In the demented twins, the reduction of rCMRglc was detected in the hippocampus and lateral temporal cortex, i.e. the brain areas, which show early changes in pathological and imaging studies in AD. Their non-demented co-twins showed milder reductions, which may be an indication of genetic susceptibility for dementia, and an early sign of a dementing illness in them [27].

Kim *et al.* [29] compared the overall glucose metabolism between early onset and late onset of AD in a large sample of patients. They suggested that greater hypometabolism in early onset than in late onset patients is required to reach the same severity of dementia, probably reflecting greater functional reserve in younger than in older subjects. Alternatively, the metabolic decline curve suggests that the early onset patients may take a more rapid course in the reduction of glucose metabolism than the late onset patients.

Mosconi *et al.* [28] investigated whether there is evidence that a genetic predisposition to AD contributes to accelerate declines in brain glucose metabolism. Their FDG-PET study showed different metabolic phenotypes related to the ApoE genotype in clinical AD patients, as revealed with voxel based statistical methods. The results suggested a generalized disorder in E4 carriers impairing metabolism globally, in addition to the more localized changes typical of AD patients. In both human and animal models, peripheral control of glycemia is reduced with aging (for review see [35]). Aging also reduces the ability to enhance glucose supply for cognitive functions. The effects of additional glucose supply can be seen in the presence of cognitive impairments in AD [36].

The Parallels between Diabetes Mellitus (DM) and AD

Epidemiologic evidence has suggested that DM significantly increases risk for the development of AD [30,37-39]. Recently, Convit [40] suggested an explanatory model on links between cognitive impairment and abnormalities in peripheral glucose regulation. In some 25 studies, DM has been associated with cognitive deficits, including learning and memory, intelligence, and executive functions. Deficits in learning and memory have also been described among non-diabetic individuals with insulin resistance.

Mosconi *et al.* [28] suggest that in people that have both DM and an ApoE4 allele, the risk of developing AD is more than double the risk of people with an ApoE4 allele without DM. Although DM does not produce any of the usual brain pathology associated with AD, their study shown that DM dramatically increases the amyloid deposition and NT in people with the ApoE4 genotype. The generalized metabolic disorder in ApoE4 carriers of clinical AD patients was found using FDG-PET [28,38,41].

Ubeda *et al.* [42] reported that the deposition of amyloid within the insulin-producing islets of Langerhans in the pancreas is a common pathological finding in patients with diabetes mellitus type-2 (DM2). Its relationship with age and the progression of the disease resembles the pathological deposition of β-amyloid (Aβ) in the brains of AD patients. An increased prevalence of islet amyloid in patients with AD and increased prevalence of cerebral Aβ in patients with DM2 was studied in a community-based controlled study, the Mayo Clinic AD Patient Registry [43]. Pancreas and brain were examined from autopsy specimens obtained from 105 humans (first, 28 cases of AD vs. 21 non-AD control subjects and, second, 35 subjects with DM2 vs. 21 non-DM2 control subjects) for the presence of islet and brain amyloid. Both DM2 (35% vs. 18%; $P < 0.05$) and impaired fasting glucose (IFG) (46% vs. 24%; $P < 0.01$) were more prevalent in AD versus control subjects, so 81% of cases of AD had either DM2 or IFG. Islet amyloid was more frequent and extensive in patients with AD than in control subjects. However, diffuse and neuritic plaques were not more common in DM2 than in control subjects. These data support the hypothesis that patients with AD are more vulnerable to DM2.

It is not without interest, that the utility of lithium or other GSK-3 inhibitors is currently studied for intervention in DM2 [44,45]. DM2 is associated with an increased risk of cognitive dysfunction and AD. Although some uncertainty remains about the exact pathogenesis, the role of insulin resistance of the brain and/or insulin–induced amyloid pathology has been identified in several studies [46]. Insulin stimulation led to a transient increase in tau phosphorylation, before becoming inhibitory over the long term [47].

The interpretation of paralles between DM, decline of cognitive deficit, and the onset of AD is a complex one. With regard to glycemic control, the impact of DM is to create a deficit similar to that observed in aging but more marked. Persistent hyperglycemia can markedly down-regulate glucose transport across the brain blood barrier (BBB). The treatment with intensive insulin therapy has the common side effect of producing periodic hypoglycemic episodes (for review see [35]). Repeated hypoglycemia appears to improve the supply of glucose to the brain. The finding that periodic hypoglycemic episodes can attenuate age-related cognitive decline is consistent with the findings from studies of calorie restrictions [48].

Aging is associated not only with impaired glucose regulation but also with impaired insulin sensitivity. Insulin receptors are expressed in the brain regions that support the formation of memory [49]. Craft *et al.* [50] reported that adults with AD showed memory enhancement when plasma insulin levels were raised to 85 μU/ml, whereas normal adults' memory was unchanged. Some AD patients have improved cognitive function following intranasal insulin administration [51].

Steen *et al.* [52] demonstrated extensive abnormalities in insulin and insulin-like growth factor type I and II (IGF-I and IGF-II) signaling mechanisms in brains with AD, and showed that while each of the corresponding growth factors is normally made in CNS neurons, the expression levels are markedly reduced in AD. These abnormalities were associated with reduced levels of insulin receptor substrate (IRS) mRNA, tau mRNA, IRS-associated PI 3-kinase, phospho-Akt, increased GSK-3β activity, and APP mRNA expression. The strikingly reduced CNS expression of genes encoding insulin, IGF-I, and IGF-II, as well as the insulin and IGF-I receptors, suggests that AD may include neuroendocrine dysfunction that resembles yet is distinct from DM.

The Effect of Impaired Glucose Metabolism on Cholinergic Deficit and Aβ Formation

The cholinergic hypothesis suggests that the reduction of cholinergic neurotransmission could explain the most important cognitive deficit in AD (for review see [2]). The basal forebrain nuclei that give rise to cholinergic fibers show cell degeneration in brains of AD patients. The 60-70% depletion of AChE and choline acetyltransferase in the cortex and in the limbic structures of patients with AD is one of the most consistent and profound changes as early as one year after onset of the disease [53]. Cortical AChE activity was found to be significantly lower in patients with AD than in age-matched normal controls [20,54]. These authors examined AChE activity *in vivo* in the nucleus basalis of Meynert (nbM), the amygdala, and cerebral neocortex. Measurements were performed in normal controls and in patients with mild to moderate AD with PET and [^{11}C]-labeled N-methyl-4-piperidyl-acetate, which is a specific substrate of AChE. AChE activity was reduced significantly in amygdala and cerebral cortex. In contrast, AChE activity and glucose metabolism appeared preserved or even increased in the nbM. The authors concluded that neocortical and amygdaloid functional changes of the cholinergic system are an early and leading event in AD, rather than the consequence of neurodegeneration of basal nuclei.

The actual development of a cognitive deficit is a threshold phenomenon that occurs if glucose turnover in the hippocampus or temporoparietal cortex drops below a critical level of about 40% of the level of age-matched controls [19]. Meier-Ruge *et al.* [55] suggested that the low glucose turnover in AD causes a cholinergic deficit by decreasing the synthesis of acetyl coenzym A (AcCoA), which is used by choline acetyltransferase in the acetylation of choline to acetylcholine. This becomes obvious by the fact that AcCoA, the key substrate of acetylcholine synthesis, is exclusively synthesized in the glycolytic pathway in the brain.

The basic principle of current cholinergic therapy for AD is aimed at attenuating cognitive deficits by inhibiting the enzyme AChE and increasing the levels of the acetylcholine. Evaluation of the treatment effects of cholinesterase inhibitors by PET and SPECT indicates that the drugs improve cerebral glucose metabolism, cerebral blood flow, and nicotinic neurotransmission [4]. A linkage has been suggested between the cholinergic deficits in AD and the secretion of APP.

The therapeutical use of AChE inhibitors directed the research of AD to the study of the catalytic function of this enzyme [3]. Nevertheless, in connection with the pathogenesis of AD the noncatalytic and nonspecific role of AChE has been discussed. AChE colocalizes with Aβ deposits of AD brains [56]. AChE accelerates Aβ formation and it may therefore act as a pathological chaperone inducing a conformational transition of Aβ. This action of AChE was not affected by edrophonium, an active site inhibitor, but it was affected by propidium, a peripheral anionic binding site ligand. AChE associated with plaques, tangles, and Aβ angiopathies possess different enzymatic properties, and, quite possibly, is of different source as compared with the enzyme associated with normal neurons and axons [3]. Most disturbing is the fact that the currently available AChE inhibitors are designed to inhibit normal AChEs in the brain and throughout the body, but not the abnormal ones [57]. The association of Aβ deposition with decreased hippocampal glucose metabolism and spatial memory impairment in APP/PS1 mice has been recently reported [58].

The results of intensive research of AChE as a target of AD therapy lead us to pose further questions. Is the degeneration of cholinergic neurons and the reduction of acetylcholine the primary change or is it evoked by impaired glucose metabolism? Why there are so many forms of AChE? Investigations of lithium effects on Wnt signaling pathways during the last few years provide new insight into the potential links between AChE and Aβ-neurotoxicity.

The Effect of Decreased Glucose Metabolism on Hyperphosphorylation of Protein Tau

Microtubule-associated protein tau is abnormally hyperphosphorylated and aggregated into NT in brains of AD patients [59]. The hypothesis that the decreased glucose metabolism and the resulting decrease in ATP triggers the hyperphosphorylation of protein tau by activating protein kinase 40erk was suggested [55]. Assuming that reduced glucose metabolism might cause abnormal tau hyperphosphorylation, Planel *et al.* [60] induced *in vivo* alterations of glucose metabolism in mice by starvation or intraperitoneal injections of either insulin or deoxyglucose. They found that the treatments led to abnormal tau hyperphosphorylation with patterns resembling those in early AD brains.

Liu *et al.* [61] demonstrated that human brain tau was modified by O-GlcNAcylation, a type of protein O-glycosylation by which the monosaccharide beta-N-acetylglucosamine (GlcNAc) attaches to serine/threonine residues *via* an O-linked glycosidic bond. O-GlcNAcylation negatively regulated tau phosphorylation at most of the phosphorylation sites. In an animal model of starved mice, low glucose uptake/metabolism that mimicked those observed in AD brain produced a decrease in O-GlcNAcylation and consequent hyperphosphorylation of tau at the majority of the phosphorylation sites. The O-GlcNAcylation level in AD brain extracts was decreased as compared to that in controls. These results suggest that abnormal hyperphosphorylation of tau could result from decreased tau O-GlcNAcylation, which probably is induced by deficient brain glucose uptake/metabolism in AD.

THE EFFECTS OF LITHIUM ON GLUCOSE METABOLISM AND GSK-3 ACTIVITY

Several researchers reported that lithium exerts some systemic effects, such as increased glucose uptake, glucose tolerance and weight gain in humans (e.g. [62]). In patients with BD who were given lithium prophylactically in single daily doses, glucose tolerance was increased for some hours after each lithium administration [63]. Furthermore, patients with BD treated with lithium experienced hypoglycemic symptoms coinciding with low serum glucose concentration [64]. A plot of the lithium dose required to increase the lithium plasma therapeutic concentration versus the blood glucose concentration simply shows linear correlation between lithium dose and glucose level [65].

Lithium effects on brain energy metabolism have been attributed to its effects on some enzymes of glucose metabolism [66,67]. The investigations of lithium effects on glucose metabolism generated the finding that lithium is the important inhibitor of GSK-3 [66-70]. The observation that lithium also mimics insulin's ability to stimulate glucose transport has led to the suggestion that GSK-3 may coordinate glucose transport and glycogen synthesis [71].

Enzymes of Glucose Metabolism

Lithium influences the enzymatic activity of enzymes involved in glycolysis, gluconeogenesis, and glycogenesis (Table **2**) through the competition for magnesium [72-74]. However, the investigations *in vivo* indicate, that only a few enzymes are significantly inhibited in the brain at therapeutic serum lithium concentrations (0.6–1.2 mM) [75]. At similar therapeutic serum levels, intracellular lithium concentrations in brain tissues can be much lower, even as low as 0.1 mM [76].

To illustrate the lack of effect, lithium proved to be a noncompetitive inhibitor of enolase in rabbit muscle [77] and pig brain [78]; enolase is directly adhering with anaerobic production of energy in glycolysis. Yet, there is no evidence that during lithium administration enolase is significantly inhibited in the mammalian brain and that lithium acts as a metabolic inhibitor. It is also unclear whether the inhibition of pyruvate kinase (PK) by lithium [79,80] is of significance for the therapeutic effects in BD [73]. The inhibition of PK impairs glycolysis and the glycolytic production of ATP. Considering AD, inhibition of PK would decrease the level of pyruvate. This could, in consequence, reduce the formation of AcCoA. Lithium inhibition of PK would thus cause a cholinergic deficit [81]. The *in vivo* observations are not consistent with lithium inhibition of PK. Lithium treatment increases acetylcholine content in rat brain and choline concentration in the human red blood cells to more than ten-times control levels [82,83]. Guerri [84] found an increase of AChE of rat brain synaptosomes after 7 days of lithium administration. The mechanism of lithium effect on AChE activity may take place either through directly changing the configuration of AChE molecules and/or correcting the impaired metabolism of glucose.

Lithium also inhibits the key enzyme in glycogenolysis - phosphoglucomutase (PGM) [85,86]. PGM has an important role in preparing glycogen and fructose derivatives for glycolysis or release into the bloodstream. Lithium-dependent inhibition of this enzyme has not received much attention. A protein family of related magnesium-dependent phosphomonoesterases that are inhibited by lithium seems to identify candidate enzymes to account for the observed therapeutic effects of lithium [74,75]. This family includes IMPase and fructose 1,6-bisphosphatase (FBPase). Regarding the regulation of glucose metabolism, FBPase is the key enzyme for controlling the gluconeogenesis.

The effects of lithium on brain energy metabolites were investigated in rats [66,67]. Administration of LiCl to rats in food was found to increase the concentrations of brain glucose, brain lactate and brain glycogen. The incorporation of ^{14}C from [U-^{14}C] D-glucose, administered intraperitoneally to the rats, was increased in brain glucose and brain lactate. The results were explained by a lithium-induced increase in brain glucose uptake and an increased rate of glycolysis. Lithium has also been shown to be an effective stimulator of glucose transport [87]. Stimulation by lithium ions of the incorporation of [U-^{14}C] glucose into glycogen in rat brain slices was reported.

Rodriguez-Gil *et al.* [88] presented a thorough study of lithium´s effects on rat liver glucose metabolism. Administration of lithium to fed-healthy rats activated glycogen synthase and inactivated glycogen phosphorylase but liver glycogen content strongly decreased. The authors attributed this effect to a decrease in glucose 6-phosphate level, which

Table 2. The Effects of Lithium on Activities of Enzymes of Glucose Metabolism *In Vitro*

Enzyme	Role	The effects of lithium
glycogen synthase	conversion of glucose-6P to glycogen	↑
phosphorylase	breakdown of glycogen to glucose 1-phosphate	↓
GSK-3	inhibits glycogen synthase activates glycogen phosphorylase	↓
phosphoglucomutase	glucose 1-phosphate ↔ glucose 6-phosphate	↓↑
hexokinase	glucose + ATP → glucose 6-phosphate	↓↑
phosphofructokinase	fru-6-phosphate + ATP →fru-1,6-bisphosphate	↓
fru-1,6-phosphatase	fru-1,6-bisphosphate → fru-6-phosphate	↓
6-phosphofructo-2-kinase	fru-6-phosphate ↔ fru-2,6-bisphosphate	↓↑
enolase	2-phosphoglycerate to phosphoenolpyruvate	↓
pyruvate kinase	phosphoenolpyruvate + ADP→ pyruvate + ATP	↓↑
lactate dehydrogenase	pyruvate↔ lactate	↓

was caused by the decrease in glucokinase activity after lithium administration (see Table **2**). Liver PK and 6-phosphofructo-2-kinase were also decreased in the liver. Lithium administration to starved-healthy and fed-streptozocin-diabetic rats caused increases of liver glycogen, glucose 6-phosphate, and fructose 2,6-phosphate. Glucokinase, 6-phosphofructo-2-kinase and PK activities were also increased. Lithium treatment activated glycogen synthase and inactivated phosphorylase in a manner similar to that observed in fed-healthy rats. The resulting response to lithium treatment might therefore differ in various tissues and might be dependent on the physiological state.

Lithium has been shown to inhibit key enzymes of glycolysis – hexokinase, phosphofructokinase, and PK in several tissues. Together with the inhibition of enolase the chronic administration of lithium would inevitably lead to the reduction of the rate of glycolysis and act as a metabolic poison. However, it seems that the mechanism of how therapeutic concentrations of lithium regulate carbohydrate metabolism *in vivo* is much more complex.

Regulation of GSK-3 Activity

Some 20 years ago, GSK-3 was categorized as a serine/threonine kinase that could phosphorylate glycogen synthase and regulate the glucose metabolism pathway [89,90]. Later, this enzyme was discovered as a participant in Wnt/wingless signaling. Wnt signaling (Fig. **1**) has been implicated in developmental processes as diverse as elaboration of embryonic polarity, formation of germ layers, neural patterning, spindle orientation, and gap junction communication [91]. Wnt signalization plays an important role in axonal remodeling in developing neurons, cytoskeletal organization, apoptotic processes, and neuronal plasticity [17,70,92]. GSK-3 exhibits significant activity, even in resting, unstimulated cells. This constitutively active protein kinase is inhibited in response to extracellular signals, such as insulin, polypeptide growth factors, and neurotrophic factors [16,93] (Fig. **1**).

In mammals, two closely related isoforms GSK-3α and GSK-3β are present that have similar biological effect and 97% sequence homology in their catalytic domains [94-96].

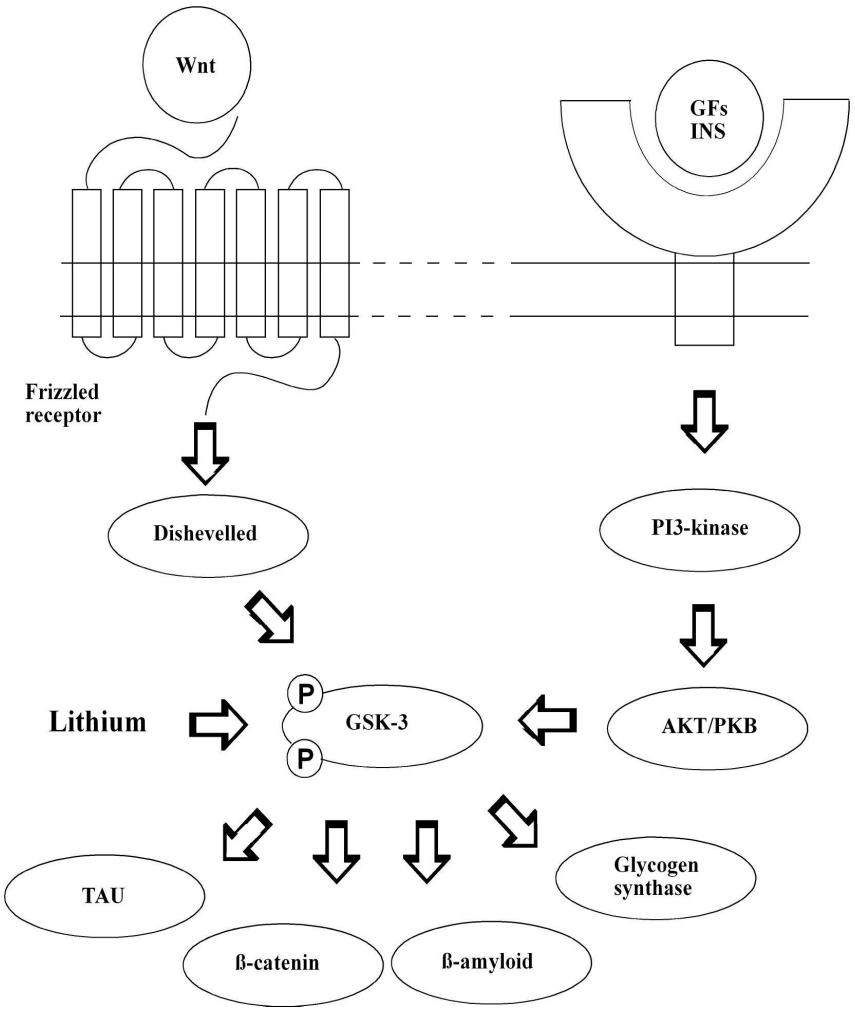

Fig. (1). GSK-3 is a component of diverse signaling pathways. Active GSK-3 mediates formation of Aβ, phosphorylation of protein tau, degradation of β-catenin, and activation of glycogen synthase. In the Wnt signaling pathway, secreted Wnt glycoproteins interact with the frizzled family of receptors and through disheveled mediated signaling inhibit GSK-3. Insulin and insulin-like growth factor (IGF-1) through tyrosine receptor kinase activate PI3-kinase-mediated signaling, resulting in inhibition of GSK-3.

The constitutive activity of GSK-3 arises from phosphorylation of tyrosines 279 (for α) or 216 (for β) [97]. The primary mechanism of regulation of GSK-3 activity has been attributed to inhibitory phosphorylation of N-terminal serine 21(α) and 9(β) [10,90,92,98,99]. A curious feature observed in vertebrate systems is that GSK-3 activity is required for its own inhibition. The enzyme prefers substrates that are specifically prephosphorylated by other kinases at C-terminal serine, which acts as a primer allowing GSK-3 to phosphorylate its N-terminal serine. Determining the kinases most responsible for GSK-3 phosphorylation seems to be very difficult task considering diverse biological targets [100,101]. Serine/threonine protein phosphatase-1 (PP-1) has been proposed to activate GSK-3 in rat forebrain and sympathetic neurons [102,103].

GSK-3 is highly abundant in brain tissue and is regulated by inhibition through numerous signal transduction systems [16,104]. For example, insulin increases the activity of protein kinase Akt/PKB that inhibits both isoforms of GSK-3 [89,105]. As GSK-3 inhibits glycogen synthase by phosphorylation, inhibitory phosphorylation of GSK-3 should promote glycogen synthesis and lower glucose levels. However, under normal conditions, GSK-3 inhibition may not be sufficient to cause hypoglycemia [106]. In contrast, in DM2, GSK-3 activity inversely correlates with glycogen synthase activity [107]. GSK-3 phosphorylates and inactivates insulin receptor substrate, thereby making cells resistant to insulin [108]. Under these conditions of elevated glucose, the inhibition of GSK-3 would be expected to decrease glucose levels [106]. Clodfelder-Miller *et al.* [109] demonstrated that the Akt-GSK-3 signaling pathway is regulated in mouse brain *in vivo* in response to physiological and pathological changes in insulin and glucose. Akt and GSK-3 are sensitive to glucose, as fasting decreased and glucose administration increased by several-fold the phosphorylation of Akt and GSK-3 in the cerebral cortex and hippocampus of non-diabetic mice.

While noting GSK-3's many associated functions, this review will focus on GSK-3 involvement in development of pathological hallmarks of AD and the link to alterations of glucose metabolism. The utility of lithium as GSK-3 inhibitor for intervention and control of neurodegenerative diseases will be discussed.

The Effects of Lithium on GSK-3 Activity

Inhibition of GSK-3 by lithium *in vitro* has been demonstrated in a number of systems [16]. It was initially recognized that therapeutic concentrations of lithium inhibit the activity of GSK-3 by competition with magnesium [110,111]. Several groups have reported that lithium causes increased phosphorylation of GSK-3β on serine 9 and GSK-3α on serine 21 [10,98,112], which accelerates the conversion of GSK-3 to an inactive state. The reports on lithium activation of glycogen synthase and inhibition of phosphorylase [88,113,114] are in concordance with the observed effects of lithium on GSK-3 activity. The dance of phosphate groups proceeds during these regulatory processes (Table **3**).

Although the *in vitro* inhibition of GSK-3 by lithium occurs at therapeutically relevant concentrations with a K(i) of 1-2 mM, the degree of inhibition of this enzyme in the mammalian brain *in vivo* has not been fully established. It is not excluded that only a small fraction of GSK-3 activity is inhibited under therapeutic conditions. The intriguing observation that GSK-3 phosphorylation is increased in the brains of lithium-treated mice [115] provides the support for direct inhibition of GSK-3 by lithium *in vivo*. O'Brien *et al.* [116] found that lithium therapy activates Wnt signaling mice brains *in vivo*, as measured by increased Wnt-dependent gene expression in the amygdala, hippocampus, and hypothalamus. Remarkably, the lithium-sensitive behaviors were also observed in mice lacking one copy of the gene encoding GSK-3β. However, authors concluded that their observations support a central role for GSK-3β in mediating behavioral responses to lithium.

Inestrosa *et al.* [117] identified the AChE motif that promotes Aβ formation and presented evidence that lithium blocked AChE-Aβ toxicity on hippocampal cultures. These authors suggested that AChE-Aβ dependent neurotoxicity may result in the loss of function of Wnt signaling components. This observation supported the view that lithium, an activator of the Wnt cascade, may be considered as a candidate for therapeutic intervention in the processes of brain plaque formation.

Phiel *et al.* [6] demonstrated that therapeutic concentrations of lithium inhibited the production of Aβ40 and Aβ42 in the Chinese hamster ovary cells that stably expressed APP

Table 3. Transfer of Phosphate Groups During GSK-3-Lithium Interactions Involved in Regulation of Glycogen Formation (1 without Lithium, 2 with Lithium)

Step No.	Event	Enzyme activity
1A	GSK-3 phosphorylates glycogen synthase	inactive
1B	GSK-3 phosphorylates phosphorylase	active
	glycogen → glu-1-P → glu-6-P	
2A	Li phosphorylates GSK-3	inactive
2B	glycogen synthase is not phosphorylated	active
2C	phosphorylase is not phosphorylated	inactive
	glu-6-P → glu-1-P → glycogen	

by interfering with APP cleavage at the γ-secretase step. Their detailed experiments documented that the target of lithium is GSK-3α, which is required for maximal processing of APP. Li also blocked the accumulation of Aβ peptides in cultured neurons and in the brains of mice overproducing Aβ. Since GSK-3 also phosphorylates protein tau, Phiel and Klein [118] suggested GSK-3α as an attractive target in the treatment of AD.

The involvement of GSK-3β in phosphorylation of protein tau [119] and lithium inhibition of tau phosphorylation has been documented by many authors [10,120-122]. Hartigan and Johnson [123] found that a transient rise in cytosolic calcium level ($[Ca^{2+}]_i$) led to an increase in tau phosphorylation through elevation of GSK-3 activity. This was accompanied by increased tyrosine phosphorylation of GSK-3. The recently initiated clinical study (http://www.clinicaltrials.gov/ct/show/NCT00088387) has investigated the effect of lithium administration to AD patients on the level of protein tau in the cerebrospinal fluid.

The extensive research of mechanisms of lithium therapeutical effects has revealed the links between impairment of glucose metabolism, phosphoinositide signaling and inositol phosphates in the brain.

THE EFFECTS OF LITHIUM ON INOSITIDE METABOLISM IN THE BRAIN

For some time, the most widely accepted mechanism of action of lithium was its inhibitory effect on IMPase, resulting in the depletion of inositol with profound effects on neuronal signal transduction pathways. It has become increasingly clear that multiple interactions and overlapping systems are involved in regulating CNS function. There is no doubt that the chronic administration of therapeutic doses of lithium affects the function of second messenger generating systems in the brain [15,124-126]. Important initial observations indicated that the administration of therapeutically used doses of lithium to rats resulted in the increase of the concentration of inositol 1-phosphate (Ins(1)P) and the decrease of inositol levels in their brains [127-129].

Berridge *et al.* [130,131] brought evidence that the inhibitory effect of lithium on IMPase is a general phenomenon that can be observed in numerous tissues stimulated with various agonists. The basic premise was that the depletion of inositol will desensitize phosphoinositide signaling by slowing down the resynthesis of the phosphatidylinositol 4,5-bisphosphate (PIP_2). This hypothesis has been accepted by many researchers in psychiatry and brain research, widely discussed and tested during the last decade [15,118,126,132,133]. However, several misunderstandings considering the regulation of phosphoinositide signaling system and misinterpretation of results have appeared. Considering a reduced glucose metabolic rate in brains of AD patients, we could speculate that metabolism of brain phosphoinositides may be influenced by energy state of a cell. Let´s therefore attempt to re-evaluate a widespread inositol depletion hypothesis in the light of new knowledge about the metabolic fate of myo-inositol moiety generated from glucose 6-phosphate.

De Novo Biosynthesis of Inositol

The biosynthesis of inositol has been known as an evolutionary conserved pathway over all eucaryotic organisms [134,135]. Myo-inositol is physiologically the most common stereoisomer among the eight possible geometric isomers of inositol – the hexahydrocyclohexan [136]. The name inositol will be therefore used for myo-inositol. Inositol can be generated in the CNS by three routes: i) *de novo* synthesis from glucose 6-phosphate, ii) breakdown of inositides, and iii) transport across the (BBB). In the *de novo* synthesis of inositol, D-glucose 6-phosphate is converted of to L-Ins(1)P in reaction catalyzed by MIP synthase. This is an NAD^+ dependent internal oxidoreduction and aldol cyclization reaction.

$$\textit{D-glucose 6-phosphate} + NAD^+ \xrightarrow{\textit{MIPsynthase}} \textit{L-Ins(1)P} + NADH + H^+$$

MIP synthase is present throughout evolutionarily diverse organisms and is considered an ancient protein/gene [134]. A comparative study shows that the rat brain contains MIP synthase activity of the same order of magnitude as liver, lung, and spleen. Little is known about mammalian MIP synthase and nothing is known about its regulation [137, 138]. The second step in inositol biosynthesis is the conversion of Ins(1)P to inositol by IMPase.

$$\textit{L-Ins(1)P} \xrightarrow{\textit{IMPase}} \textit{inositol}$$

This is a common step to inositol production *via* the *de novo* pathway and its recycling from inositol phosphates derived from phosphoinositide signaling pathways. IMPase is completely dependent on Mg^{2+}, which has a K_m of 1 mM. The mechanism of how lithium competes for a Mg^{2+} binding site has been clarified by X-ray crystallographic studies on IMPase [132,139]. Two IMPase genes have been localized on chromosome 18p11.2 and on chromosome 8q21.13-21.3 [140-142].

Lithium Affects the levels of Ins(1)P and Inositol in the Rat Brain

An important initial observation was that treatment of rats with therapeutically used doses of lithium increased 40 times the concentration of Ins(1)P in their brains [127,143]. The administration of LiCl (3.6 mequiv/kg/day) to adult male rats in the food for 9 days resulted in an increase in the cerebral cortex level of Ins(1)P to 4.43 ± 0.52 mmol/kg (dry weight) compared with a control level of 0.24 ± 0.02 mmol/kg [129]. Larger doses of LiCl over a 3-5 day period resulted in even larger increases in Ins(1)P and a 35% decrease in inositol. The molecular basis of the increased level of Ins(1)P was the inhibition of IMPase. Hallcher and Sherman [128] reported that lithium chloride inhibits the hydrolysis of both D- and L-Ins(1)P to the extent of 50% at a concentration of 0.8 mM. These authors also determined that 90% of the increase of Ins(1)P is due to the D-enantiomer, evidence that lithium is largely producing this effect *via* agonist-stimulated phospholipase C (PLC)-breakdown of phosphatidylinositol (PI). The explanation of physiological meaning of lithium effect on Ins(1)P was based on the knowledge about the role of PI at that time.

Origin of Inositol Depletion Hypothesis

The Hokins demonstrated that the activation of muscarinic cholinergic or α_1 adrenergic receptors results in a net loss of PI in the guinea-pig brain [144,145]. This observation was explained by the initial phosphodiesteratic breakdown of PI, liberating diacylglycerol (DAG), which was in turn rapidly rephosphorylated in the presence of ATP to yield phosphatidic acid (PA). Ins(1)P needs to be hydrolyzed by IMPase, since the resynthesis of PI from CMP-PA requires free inositol as a substrate (Fig. **2**).

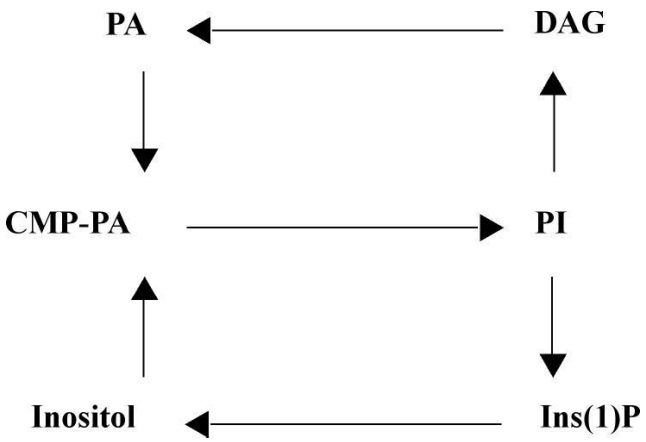

Fig. (2). PI-PLC hydrolysis after receptor stimulation and resynthesis of PI. **PI cycle** according to suggestion of Lowell and Mabel Hokin [145].

Berridge *et al.* [131] demonstrated that lithium amplifies agonist-dependent PI responses in the brain. Later it has been demonstrated in several design systems that the target of PLC activated after receptor stimulation is particularly PIP_2 [146,147]. $Ins(1,4,5)P_3$ was discovered as a new second messenger molecule and a novel phosphoinositide signaling system has been postulated (Fig. **3**) [130,148,149]. Phosphoinositides were shown to participate in many processes in the brain [125,150,151].

Lithium has been widely used as a tool for amplifying the response after agonist-dependent stimulation of PLC [152,153]. Berridge ´s famous inositol depletion hypothesis was based on three presumptions: i) higher turnover of PIP_2 reflects the increased receptor activation in pathogenic neurons, ii) in parts of the brain, where receptors are overstimulated and PIP_2 hydrolysis occurs, lithium inhibits the dephosphorylation of Ins(1)P, and iii) BBB is essentialy unpermeable for inositol. The decrease of the pool of free inositol would be expected to limit the amount of newly synthesized PI and consequently PIP_2. The therapeutic effect of lithium has been thus explained as inhibition of PIP_2 resynthesis and reduction of signal transduction from pathogenic neurons.

The Effect of Lithium Administration on Inositol Levels in the Human Brain

The levels of inositol were investigated in 12 adult depressed patients with BD [154] by means of quantitative proton magnetic resonance spectroscopy ($[^1H]$-MRS). Significant decreases (approximately 30%) in myo-inositol levels were observed in the right frontal lobe after a short-term administration of lithium, and these decreases persisted with chronic treatment. However, the acute inositol reduction occurred at a time when the patient's clinical state was clearly unchanged. The authors thus concluded that the short-term reduction of inositol per se is not associated with therapeutic response and does not support the inositol depletion hypothesis as originally posited.

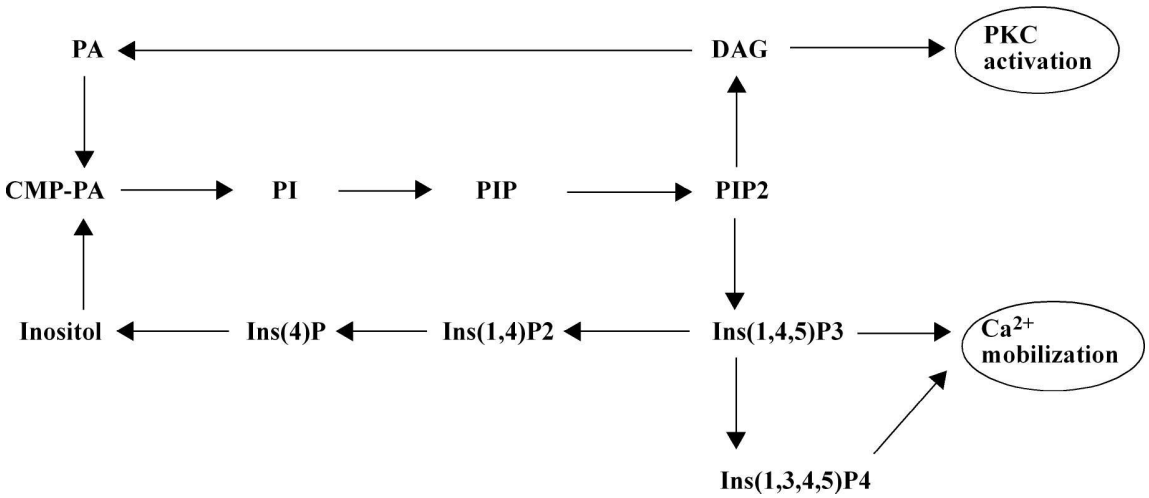

Fig. (3). Phosphoinositide signaling system. A great amount of experimental evidence supports the general concept that PIP_2 from the plasma membrane is hydrolyzed and yields $Ins(1,4,5)P_3$ and DAG upon receptor stimulation. Both products of this hydrolysis catalyzed by PLC have second messenger role. $Ins(1,4,5)P_3$ binds to a receptor in membranes of endoplasmic reticulum, which results in a release of Ca^{2+} into the cytosol. The $Ins(1,4,5)P_3$ receptor composes an $Ins(1,4,5)P_3$-gated Ca^{2+}-channel. DAG activates protein kinase C (PKC). The coupling between the receptor and PLC is mediated by G-proteins. In this "dual" second messenger hypothesis, $Ins(1,4,5)P_3$ is the link between PIP_2 and Ca^{2+}.

Silverstone *et al.* [155] examined 16 patients with BD taking lithium using both [^{1}H]-MRS and [^{31}P]-MRS and compared these with age and sex-matched healthy controls. In BD patients who were manic or depressed there were abnormalities in brain inositol concentrations, with changes in frontal and temporal lobes, as well as the cingulate gyrus and basal ganglia. These abnormalities were not seen in either euthymic patients or healthy controls.

Inositol Depletion Hypothesis Revisited

Although some studies report a reduction in agonist-stimulated PIP_2 hydrolysis in rat brain slices following chronic lithium treatment, these findings have often been small and inconsistent [16]. This is conceivable, since it is very difficult to measure the levels of very labile PIP_2 *post mortem*. It seems that the overwhelming experimental evidence has not supported the widespread hypothesis [126, 132, 133,151]. The simple calculation can demonstrate that the inositol depletion hypothesis was derived as an oversimplification from experiments *in vitro*. The level of PI – the parent phospholipid for the synthesis of PIP_2 – is at least 10 times higher compared to PIP_2 level in the brain. Moreover, there is also a pool of phosphatidylinositol 4-phosphate (PIP), which can be phosphorylated by PIP 5-kinase. The breakdown of approximately 0.5% of the entire amount of PIP_2 is enough for doubling the Ins(1,4,5)P_3 cytosolic level. Neither the increased production of Ins(1)P can be explained by the degradation of Ins(1,4,5)P_3, since its level is about 30 times lower than that of Ins(1)P. Moreover, the flurry of activities in 1980´s revealed that Ins(1)P is not the product of Ins(1,4,5)P_3 dephosphorylation. Instead of this, Ins(4)P is formed [156].

The inositol depletion hypothesis could be valid under the condition when biosynthesis of Ins(1)P *de novo* by MIP synthase is impaired, IMPase is completely blocked, and BBB is essentialy unpermeable for inositol. The interesting finding that lithium treatment upregulates both MIP synthase and IMPase mRNA levels in mouse hippocampus has been explained as a compensatory response of both genes to inositol depletion [135]. Various species might also differ markedly in the requirement of inositol levels. For example, Lee *et al.* [157] demonstrated that lithium-induced accumulation of Ins(1,4,5)P_3 require inositol supplementation in mouse and rat but not in guinea pig.

Spector [158] demonstrated that inositol was transported across the BBB in the rat brain by a low capacity, saturable system with a one-half saturation concentration of approximately 0.1 mM. An active transport system also maintains inositol in the human brain at a much higher concentration than in the blood [159]. Inositol levels in the range of 2-15 mM have been reported in the brain [160]. Chengappa *et al.* [161] provided evidence that inositol crosses the BBB in pharmacological doses, and had shown efficacy in a small double-blind study of patients with DSM-IV diagnosed BD. Inositol was well tolerated with minimal side effects.

A high affinity Na^+-inositol cotransporter (SMIT1) has been studied in the murine brain. The SMIT1 gene is highly expressed prenatally in the central nervous system and placenta [160]. Cellular concentration gradients of this magnitude indicate a dependence on active inositol transport, especially at the time of growth and differentiation. Berry *et al.* [160,162] generated mice with a homozygous targeted deletion of this gene. Newborn SMIT1(-/-) animals have no evidence of SMIT1 mRNA, a 92% reduction in the level of brain inositol, and an 84% reduction in whole body inositol. They expire shortly after birth. These authors found surprisingly that the brain PI levels do not decrease and concluded that PI deficiency due to "inositol depletion" is not a mechanism of lithium action in the brain. It has been demonstrated earlier that micromolar concentrations of inositol may be sufficient for *de novo* synthesis of PI as the K_m of MIP synthase has been reported to be in the micromolar range [163,164]. Neurons might also take inositol up from the extracellular milieu *via* H^+/myo-inositol symporter [165]. MIP synthase was found in the walls of all vascular elements including cerebral capillaries in bovine brain [166].

It is therefore unlikely that the reduction of PIP_2 synthesis due to the decreased level of inositol could be the regulatory mechanism in the brain [151]. However, it remains clear, that lithium affects the levels of inositol and Ins(1)P in mammalian brains. The earlier experiments of Sherman´s group were recently confirmed by a high-resolution nuclear magnetic resonance spectroscopy [167]. As predicted, lithium-treated rats exhibited a significant increase in the concentration of Ins(1)P and a significant decrease in inositol concentration compared to saline-treated controls. Nevertheless, the question of the regulatory role of such changes remains unanswered.

Does Lithium Affect PI cycle or PIP_2 cycle?

It is interesting to recall the original suggestion of Hokin [125] that there are two separate physiologically active cycles - the phosphoinositide cycle and the PI cycle. Under physiological conditions of ionic strength and pH, the Ca^{2+} concentration required for the breakdown of PIP_2 is at the resting cytosolic Ca^{2+} level ($[Ca^{2+}]_i$). The hydrolysis of PIP_2 is therefore Ca^{2+} non-dependent. On the other hand, hydrolysis of PI is Ca^{2+} dependent. The sustained increase of $[Ca^{2+}]_i$ induced by pathological agents might thus led to the increased PI breakdown by agonist-stimulated PLC. In earlier experiments, the depletion of PIP_2 could be detected under extreme conditions only, with high doses of lithium and pilocarpine [168,129]. It is also possible that more active cells and brain regions may be affected by lithium in different ways. In pathologically overstimulated neurons, where PLC-stimulated PIP_2 breakdown proceeds, lithium inhibition of IMPase would result in accumulation of Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4 [157]. These two second messenger molecules evoke the state of sustained increase of $[Ca^{2+}]_i$, which could potentiate the breakdown of PI. It therefore seems that lithium stimulation of PI cycle may be more significant in therapeutic situations presumably dealing with overstimulated neurons than in the usual experimental circumstances.

The Effects of Reduced Energy Metabolism on Inositide Metabolism

Metabolism of brain inositides may be influenced by a reduced glucose metabolic rate in brains of AD patients. Healthy cell maintains its content of ATP, Ca^{2+} homeostasis, and keeps the ability to maintain the equilibrium between the

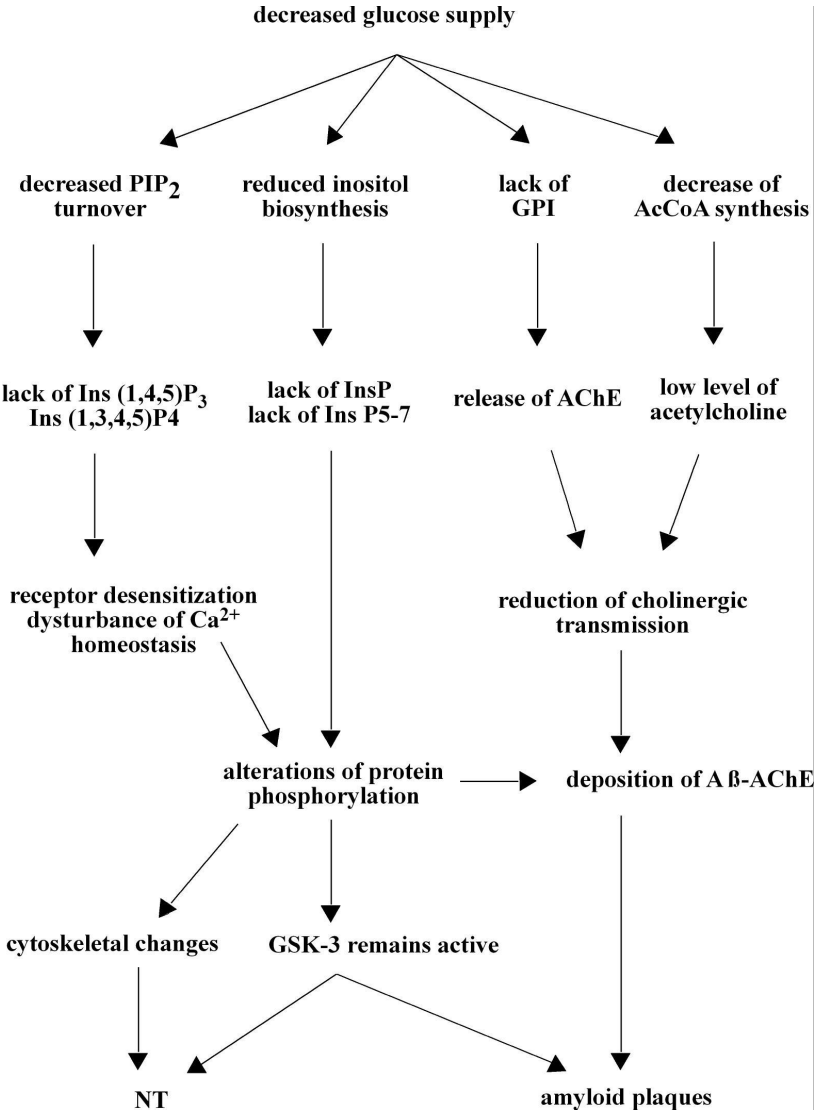

Fig. (4). Consequence of changes leading to the development of pathological hallmarks of AD after the reduced glucose supply

breakdown of PIP_2 and its resynthesis *via* phosphorylation of PI. Calcium mobilization proceeds as a transient peak or as a short wave oscillation. Physiological functional response proceeds and second messengers molecules – $Ins(1,4,5)P_3$ and DAG - undergo metabolic transformation. We assume that the generation and degradation of second messengers is regulated by the mechanism of a negative feedback in healthy cells.

Pathological agents might induce the state of sustained activation characterized by the increased levels of $Ins(1,4,5)P_3$, DAG, and $[Ca^{2+}]_i$. Disturbance of Ca^{2+} homeostasis or sustained G-protein activation might induce amplification cascade regulated by a positive feedback. In such a case the breakdown of PIP_2 increases, DAG increases the activity of PKC, phosphorylation of numerous proteins including cytoskeletal proteins is enhanced, $Ins(1,4,5)P_3$ releases Ca^{2+} from intracellular pools and Ca^{2+} channels are opened. Such state of sustained activation consumes great amounts of energy. If the cell does not produce enough energy to cover such an increased demand, the content of PIP_2 in the plasma membrane declines. We can thus expect that the level of PIP_2 will have a tendency to decrease as the consequence of reduced glucose metabolism. Chronically impaired glucose metabolism in the brain can also lead to a decrease of synthesis of PI.

The effect of brain aging and AD pathology on inositide metabolism has been studied both in animal models and in the human brain. Stokes *et al.* [159] reported a decrease in free and total lipid inositol with age in human anterior temporal cortex. At age 20 the concentration of inositol was 60 μmols/g protein and it fell steadily to half that concentration at age 90. There was a similar fall with age in the PI concentration. The reduced PI content in frontal cortex of AD brain, by about 40% was reported [169]. The decrease of PI level, reduction of PI kinase activity and decreased PIP_2 formation were observed during aging and in AD brains by many authors [170, 171]. Zambrzycka [172] investigated PIP and PIP_2 formation in cortical synaptic plasma membranes of adult (4-months-old) and aged (24-months-old) rats. Her

results showed that aging decreases incorporation of [^{32}P] from γ[^{32}P] ATP into endogenous PIP_2 by 40%.

Shimohama´s group studied aberrant phosphoinositide metabolism in AD brains [173]. Their initial observation that the PI-specific PLC activity as a function of $[Ca^{2+}]_i$ showed no difference between control and AD brains was modified in connection with discovery of several families of PI-specific PLC. These authors found that the activity of isozyme PLC δ1 is decreased in AD brains. The accumulation of PLC δ1 in the paired helical filaments suggests that its inactivation may reflect the association between PI metabolism and cytoskeletal components.

The Role of Inositol Phosphates in the Brain

Large number of molecules results from the ability of cells to place phosphate groups in combinatorial manner around the six-carbon inositol ring. The recent flood of discoveries has revealed that many of the cellular inositol phosphates participate in an amazing variety of stereoselective interactions with diverse target proteins. Scientists are perplexed by so multifarious functions of inositol polyphosphates in cells. It seems therefore, that inositol might play another unidentified role in the mammalian brain.

Certain inositol phosphate kinases do have versatile catalytic domains that can metabolize a range of inositol phosphate substrates *in vivo* [174]. The thorough studies of Batty and Nahorski [175] of the effect of lithium in rat cerebral cortex brought surprising observations. Carbachol produced a rapid and sustained (> 40 min) increase in Ins(1,3,4,5)P_4. In the presence of lithium, the increase was sustained only for 10 minutes before falling rapidly. Similarly, in the mouse, Ins(1,3,4,5)P_4 increased over a 5-minute period in the presence of lithium with simultaneous noradrenergic, histaminergic, or serotonergic stimulation [176]. The family of inositol phosphate kinases that specifically phosphorylate the 3-position of Ins(1,4,5)P_3 was later confirmed. Their physiological role is to phosphorylate Ins(1,4,5)P_3 to Ins(1,3,4,5)P_4. This reaction serves to control Ca^{2+} mobilization (for a review see [174,177,178]). Ins(1,3,4,5)P_4 can activate Ca^{2+} channels in the plasma membrane and has ability to synergize with Ins(1,4,5)P_3 to mobilize Ca^{2+}. Ins(1,4,5)P_3 3-kinase is the most active inositol phosphate kinase. Ins(1,3,4,5)P_4 is hydrolyzed by the same 5-phosphatase that hydrolyzes Ins(1,4,5)P_3, but the enzyme has a 10-fold higher affinity and 100-fold lower V_{max} for Ins(1,3,4,5)P_4 than it does for Ins(1,4,5)P_3 [179]. So, Ins(1,3,4,5)P_4 can protect Ins(1,4,5)P_3 against hydrolysis and therefore increase its effectiveness. Moreover, Irvine [178] suggested that Ins(1,3,4,5)P_4 level might persist as a memory of an earlier stimulation. Dendritic spines of neurons are probably the most active sites of Ins(1,3,4,5)P_4 synthesis in the whole body. Lee *et al.* [157] demonstrated that lithium increases accumulation of Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4 in cholinergically stimulated brain cortex slices in guinea pig, mouse and rat.

The synthesis of $InsP_5$ and $InsP_6$ has been reported in the rat brain after labelling with [^{3}H]inositol [180]. Both ^{3}H-labelled $InsP_5$ and $InsP_6$ were found in about the same proportions in the midbrain and hypothalamus. $InsP_5$ was more abundant that $InsP_6$ in the medulla oblongata, whereas the opposite was seen in the hippocampus – the region with the greatest overall concentration of $InsP_6$. The formation of Ins(3)P directly from glucose 6-phosphate could lead to sequential phosphorylation up to $InsP_6$ [177]. Surprisingly, there is evidence that rats derive most of their $InsP_6$ (also known as phytic acid) from their diet by a direct supply to the body tissue without its dephosphorylation in the gut to inositol and then absorbed and reconverted to $InsP_6$ [181]. When rats were fed on a purified diet, in which $InsP_6$ was undetectable, the levels of $InsP_6$ in brain were 3.35 ± 0.57 $\mu mol.kg^{-1}$ and in plasma 0.023 ± 0.008 μmol . L^{-1}. The presence of $InsP_6$ in diet dramatically influenced its levels in brain and in plasma. When rats were given an $InsP_6$-sufficient diet, the levels of $InsP_6$ were about 100-fold higher in brain tissues (36.8 ± 1.8) than in plasma (0.29 ± 0.02); $InsP_6$ concentrations were 8.5-fold higher than total $InsP_3$ concentrations in either plasma or brain.

$InsP_6$ is a most abundant inositol phosphate that elevates simultaneously with Ins(1,4,5)P_3 in activated brain neurons and is lowered by inhibition of neuronal activity. In hippocampal neurons $InsP_6$ increases L-type Ca^{2+} channel activity [182]. In insulin-secreting pancreatic β cells $InsP_6$ inhibits serine-threonine protein phosphatases, modulates Ca^{2+} influx over the plasma membrane and serves as a signal in the pancreatic β cells stimulus-secretion coupling [183]. On the other hand, the possibility remains that the reduced glucose supply and active GSK-3 could reduce the synthesis of Ins(3)P with subsequent reduction of $InsP_6$ formation in the brain. Under such circumstances, the supply of $InsP_6$ from a diet has significant medical and physiological relevance.

The renewed interest on the high-energy concept of higher inositol phosphates is probably the most exciting at present. It has been suggested that a considerable free-energy change accompanies their dephosphorylation due to the relief of severe electrostatic and steric constraints within these molecules [174]. The high-energy concept of phosphoinositides appeared already in 1978 [184]. Kiselev estimated a contribution of free conformational energy into standard free energy of splitting PIP_2 phosphates depending on pH value and concluded that low energy phosphate bond becomes high energy bond due to the free electrostatic interaction of dianionic phosphate group with other negatively charged group in sin-clynal conformation. It has been proposed recently that the phosphorylated inositols containing one or more pyrophosphate moieties on the inositol ring might participate in protein phosphorylation [174,185]. $InsP_6$ is the precursor of diphosphoinositol polyphosphates. The pyrophosphate moieties of diphosphoinositol-pentakisphosphate ($InsP_7$) and bis-diphosphoinositol-tetrakisphosphate ($InsP_8$) contain energetic bonds that turn over rapidly, possibly indicating a molecular switching role. The $InsP_6$ kinases have the capacity to be reversible under *in vitro* assay conditions that are physiologically relevant (for review see [174]). Recently, the Snyder´s group showed that $InsP_7$ physiologically transfers the phosphate of the pyrophosphate moiety to several target proteins [185]. They demonstrated the involvement of inositol pyrophosphates in signaling cascades that mediate cell death.

Neuroprotective and Neurotrophic Effects of Lithium and Inositol

Lithium interesting properties as a neuroprotective agent have been reviewed by several authors [18,186]. The neuroprotective effects of lithium involve multiple mechanisms including changes in the expression of genes and signaling pathways involved in apoptosis. To investigate the potential neurotrophic effects of lithium in humans, a longitudinal clinical study was undertaken using [^{1}H] MRS to measure *N*-acetylaspartate (NAA, a putative marker of neuronal viability) levels [187]. Four weeks of lithium treatment produced a significant increase in NAA levels, effects that were localized almost exclusively to gray matter [154]. These findings provide intriguing indirect support for the contention that chronic lithium increases neuronal viability and function in the human brain.

Lithium treatment also enhances cell proliferation in neuronal cultures and in the brain near the site of the injury [186]. The discovery of neurogenesis in the adult brain [188] also demonstrates the links of inositides and neurotrophic and neuroprotective effects of lithium [15,189]. Newly formed neurons possess functional morphological and electrophysiological interactions with the surrounding cells. Lithium can alone stimulate cerebellar granule cell proliferation and enhance proliferation induced by insulin-like growth factor I (IGF-I) [190]. Even a subtle change in axonal branching or growth cone chemotaxis could have impact on the connectivity of the neural network. Williams *et al*. [191] observed that lithium caused a large increase in the number of collateral axon branches that formed proximal to the growth cones in cultured explants of sensory neurons from newborn rat dorsal root ganglia. The addition of inositol had no effect on the lithium-induced changes. According to our opinion, these observations also argue against the inositol depletion hypothesis. The recent data suggest that PIP_3 is involved in axon specification, possibly by stimulating neurite outgrowth [192,193]. The finding that inositol levels in murine brain tissue are more than 6-fold higher (7.80 *versus* 1.16 μmol/grams of wet weight) than whole body inositol levels at the time of birth [160] may indicate a special role of inositol in brain neurogenesis.

IMPAIRMENT OF GLUCOSE METABOLIC RATE MIGHT BE THE COMMON DENOMINATOR

The pathogenesis of AD involves many alterations at molecular and cellular levels. At present there is no conceptual framework, which could integrate all available information. Various discussions therefore focus on the role of one particular element in the pathogenesis of all other abnormalities. Several candidates for the trigger of AD pathology were suggested such as Aβ [9,194], dysregulation of Ca^{2+} homeostasis [195-199], and decline of glucose metabolism [20,55]. However, the principal question as to what the primary event leading to the onset of AD is unanswered. Recent suggestion of treatment of AD with lithium has led us to evaluate knowledge accumulated during the last three decade of extensive research searching the convincing mechanism of lithium therapeutic effects. This research reveals connections not only with the role of GSK-3 but also with the potential role of lithium in regulation of glucose metabolism and the links with inositol lipids and inositol phosphates. We suggest that the common denominator that can trigger the development of the main AD pathological hallmarks might be the impairment of glucose metabolic rate (Table **4**).

It is evident that the pathological changes of AD develop for a long time before the manifestation of clinical symptoms. The impairment of glucose metabolism might be induced for example by DM or DM2, by hidden metabolic poisons, such as fluoride plus aluminum overload [151], by impairment of the BBB, by chronic fatigue syndrome (CFS), by some viral infections, by aging, etc. DM2 and insulin resistance are associated with micro-vascular dysfunction and the decreased transport of glucose across the BBB [40]. This might evoke several changes in composition of neuronal plasma membrane, where phosphoinositides are the most sensitive compounds.

The decreased turnover of PIP_2 inevitably leads to a desensitization of numerous receptors and ion channels, reduction of activity of protein kinases and intracellular Ca^{2+} mobilization. Moreover, lowering of PIP_2 might evoke various changes in the structure of cytoskeletal proteins [200]. The decline of biosynthesis of PI might also lead to the reduction of PI glycosylation and release of various proteins, which require glycosylated PI (GPI) to be anchored in the plasma membrane. Regarding AD, AChE is one of them [201]. Interesting evidence also emerged recently from the study of the pathogenesis of prion (PrP) diseases, where the PrP-GPI anchor may play a role [202]. In scrapie-infected transgenic mice expressing PrP lacking the GPI-membrane anchor, abnormal protease-resistant PrPres was deposited as amyloid plaques, rather than the usual nonamyloid form of PrPres. Although PrPres amyloid plaques induced brain damage reminiscent of AD, clinical manifestations were minimal. There is overhelming evidence that AChE accelerates Aβ formation and forms neurotoxic Aβ-AChE complex. The

Table 4. Comparison of the Effects of Lithium Administration and Reduced Glucose Metabolism on Pathological Hallmarks of AD

	Patients with AD	Reduced glucose metabolism	Active GSK-3	Effect of lithium
Acetylcholine level	↓	↓	↓	↑ **10x**
Aβ42 deposits	↑	↑	↑	↓
NT – tau hyperP	↑	↑	↑	↓
apoptosis	↑	↑	↑	↓

decreased availability of AcCoA due to the reduced glucose metabolic rate might be one of the trigger of changes in cholinergic transmission [20,81]. PDH, which converts pyruvate to AcCoA is inactivated by GSK-3β *in vitro* and also in Aβ - treated hippocampal cultures. In cholinergic neurons, Aβ impaired acetylcholine synthesis. Inositol-Aβ interactions result in a complex that is non-toxic to nerve growth factor-differentiated PC-12 cells and primary human neuronal cultures [203]. The ability of inositol to induce non-fibrillar β-structure in Aβ42 is a striking phenomenon, which warrants further study.

There is clear evidence that Aβ triggers neurodegeneration [9] and contributes to Ca^{2+} dysregulation. Some authors suggest that alterations in Aβ formation precede the changes in $[Ca^{2+}]_i$ [194]. However, the mechanisms of Ca^{2+} homeostasis are very complex and subtle and there is no doubt that changes in inositide metabolism are the primary regulatory factors. Exciting findings that inositol polyphosphates might participate in protein phosphorylation open a new line of research for understanding the role of Ins(1)P, Ins(3)P, and Ins $(1,4,5)P_3$ in cell physiology. Shears [174] suggests that the catalytic promiscuity of versatile catalytic domains of inositol phosphate kinases towards different inositol phosphates be sometimes exploited to facilitate tight regulation of physiological processes. The alteration of glucose metabolism and impairment of glycolytic ATP production in the brain can markedly influence such tightly regulatory processes. The slow incorporation of labelled inositol into $InsP_5$ and $InsP_6$ indicates that the major source of Ins(3)P for the pathway to $InsP_6$ would be glucose 6-phosphate rather than inositol [178].

Increased levels of total GSK-3 have not been consistently observed in patients with AD, however, active GSK-3 localizes to pretangle neurones, dystrophic neurites and NT in AD brains [204]. Neurons undergoing granulovascular degeneration also contain active GSK-3 [205]. The importance of PI 3-kinase activity has been established for the transduction of insulin signaling. It is conceivable to assume that the recurrent hypoglycemia might result in decrease of PIP_2, the only substrate for PI 3-kinase. If this enzyme is inhibited, GSK-3 remains active, stimulating amyloid plaques and NT formation. GSK-3 is also activated by the action of PP-1 in rat brain slices [102]. Despite some peculiar features in the regulation of PP-1 activity, the addition of lithium prevented GSK-$3\beta^{ser9}$ dephosphorylation. Zhang *et al.* [98] suggested an unusual „feedback"mechanism, which amplifies an inhibitory signal and accelerates the conversion of GSK-3 to an inactive state. Lithium is pointing out PP-1 as potential target for novel therapeutics against neurodegenerative diseases [18]. Remarkably, it has been reported that $InsP_6$ also inhibits PP-1 [182].

CONCLUDING REMARKS

The preceding review provides much evidence for rich interconnections between a reduced ability to provide and regulate glucose supply to the brain and altered insulin action on the one hand and aging, AD, DM, and BD on the other hand. Based on the tremendous amount of very detailed studies, a conclusion can be reached that the impairment of glucose utilization may act as one of the common denominators promoting the decline of cognitive functions and neurodegeneration, and facilitates the onset of disease states such as AD. A treatment that could prevent a decline in brain glucose transport and glycemic control, without deleterious side-effects, may attenuate or prevent the onset of AD. This line of thinking can lead to the development of new, more natural and safer treatment interventions for AD, utilizing for example inositol, $InsP_6$, lithium, and possibly other GSK-3 inhibitors. Some aspects of this approach may be also applicable to BD and T2DM.

Looking specifically at the available options, lithium has already been shown to be an effective stimulator of glucose transport in 1978 [87]. The tolerability and the 'natural substance' aspect of inositol may also be particularly appealing. New discoveries of the role of GSK-3 as the key regulator of the Wnt signaling pathway opened a new avenue in searching for therapeutic approaches to chronic degenerative disorders of the CNS. Of necessity, any therapeutic use of lithium or other GSK-3 inhibitors does require monitoring relevant biological markers to ensure safety as well as efficacy.

The integration of the findings detailed in this review may also shed more light on the mode of action of lithium. The effects of lithium on the metabolism of glucose and the inhibition of GSK-3 have been well documented. Furthermore, rather than working through the inhibition of IMPase and depletion of PIP_2, lithium might offer Ins(3)P and $Ins(1,4,5)P_3$ as substrates for further phosphorylations and facilitate the roles of inositol polyphosphates in tight regulations of various biological processes. In addition, the demonstration of neurotrophic and neuroprotective effects of lithium and of neurogenetic properties of inositol suggests that both old and new psychiatric treatments may have considerable utility in the treatment of neurodegenerative disorders as well.

More than one hundred years were needed to overcome the doctrine that new neurons are not added to the adult mammalian brain. Numerous extensive investigations in the areas of cerebral glucose metabolism, lithium, inositides, and GSK-3 were needed to close the circle with the earliest and generally accepted observation that the essential brain functions depends on a continuous supply of glucose.

ACKNOWLEDGEMENT

The financial support of the Grant Agency of the Charles University in Prague (Grant No. 13/2005) Czech Republic is highly appreciated.

ABBREVIATIONS

$[^1H]$-MRS	=	Proton magnetic resonance spectroscopy
$[Ca^{2+}]_i$	=	Cytosolic calcium level
1ns(1)P	=	Inositol 1-phosphate
Aβ	=	β-amyloid
AcCoA	=	Acetyl coenzym A
AchE	=	Acetylcholinesterase
AD	=	Alzheimer´s disease

ApoE = Apolipoprotein E
APP = Amyloid-precursor protein
ATP = Adenosine triphosphate
BBB = Blood-brain barrier
BD = Bipolar disorder
CNS = Central nervous system
DAG = 1,2 - diacylglycerol
DM = Diabetes mellitus
DM2 = Diabetes mellitus type-2
FBPase = Fructose 1, 6-bisphosphatase
FDG-PET = [^{18}F]-2-fluoro-2-deoxy-D-glucose - positron emission tomography
GlcNAc = Monosaccharide beta-N-acetylglucosamine
GPI = Glycosylated inositol glycerophospholipid
GSK-3 = Glycogen synthase kinase-3
IFG = Impaired fasting glucose
IGF-I and IGF-II = Insulin and insulin-like growth factor type I and II
IMPase = Inositol monophosphatase
Ins(1,4,5)P_3 = Inositol 1,4,5-trisphosphate
IRS = Insulin receptor substrate
MCI = Mild cognitive impairment
MIP synthase = Myo-inositol monophosphate synthase
MMSE = Mini-Mental State Examination
NAA = *N*-acetylaspartate
NT = Neurofibrillary tangles
PA = Phosphatidic acid
PGM = Phosphoglucomutase
PI = Inositol glycerophospholipid (phosphatidylinositol)
PIP = Phosphatidylinositol 4-phosphate
PIP_2 = Phosphatidylinositol 4,5-bisphosphate
PIP_3 = Phosphatidylinositol 3,4,5-trisphosphate
PK = Pyruvate kinase
PKC = Protein kinase C
PLC = Phospholipase C
PP-1 = Serine/threonine protein phosphatase-1
PrP = Prion
rCMRglc = Regional cerebral glucose metabolic rates
SMIT1 = Sodium-myo-inositol cotransporter
SPECT = Single photon emission computer tomography

REFERENCES

[1] Saragovi, H.U. Curr. Med. Chem. - Central Nervous System Agents, **2005**, 5, 1.
[2] Suh, W.H.; Suslick,K.S.; Suh, Y.H. *Curr. Med. Chem. - Central Nervous System Agents*, **2005**, *5*, 259.
[3] Tougu, V. Curr. Med. Chem. - Central Nervous System Agents, **2001**, 1, 155.
[4] Nordberg, A. Curr. Med. Chem. - Central Nervous System Agents, **2001**, 1, 239.
[5] Monczor, M. Curr. Med. Chem. - Central Nervous System Agents, **2005**, 5, 5.
[6] Phiel, C.J.; Wilson, C.A.; Lee, V.M.; Klein, P.S. *Nature*, **2003**, *423*, 435.
[7] Van Wauwe, J.; Haefner, B. *Drug News Perspect.*, **2003**, *16*, 557.
[8] Alonso, M.; Martinez, A. *Curr. Med. Chem.*, **2004**, *11*, 755.
[9] Toro, D.D.; Coma, M.; Uribesalgo, I.; Guix, F.X.; Munoz, F.J. *Curr. Med. Chem. - Central Nervous System Agents*, **2005**, *5*, 271.
[10] Stambolic, V.; Ruel, L.; Woodgett, J.R. *Curr. Biol.*,, **1996**, *6*, 1664.
[11] Lovestone, S.; Davis, D.R.; Webster, M.T. *Biol., Psychiatry*, **1999**, *45*, 995.
[12] Grof, P. *J. Clin. Psychiatry*, **2003**, *64*, 53.
[13] Lithium in neuroPsychiatry: The Comprehensive Guide. Taylor Francis: London, UK.**2005**
[14] Bunney, W.E.J.; Pert, A.; Rosenblatt, J.; Pert, C.B.; Gallaper, D. *Arch. Gen. Psychiatry*, **1979**, *36*, 898.
[15] Quiroz, J.A.; Gould, T.D.; Manji, H.K. *Mol. Interv.*, **2004**, *4*, 259.
[16] Gould, T.D.; Manji, H.K. *Neuropsychopharmacology*, **2005**, *30*, 1223.
[17] Strunecká, A.; Pato_ka, J.; _árek, M. *J. Appl. Biomed.*, **2005**, *3*, 25.
[18] Mora, A.; Sabio, G.; Centeno, F. *Curr. Med. Chem. - Central Nervous System Agents*, **2003**, *3*, 335.
[19] Meier-Ruge, W.; Bertoni-Freddari, C.; Iwangoff, P. *Gerontology*, **1994**, *40*, 246.
[20] Herholz, K. *Ann. Nucl. Med.*, **2003**, *17*, 79.
[21] Kumar, A.; Newberg, A.; Alavi, A.; Berlin, J.; Smith, R.; Reivich, M. *Proc. Natl. Acad. Sci. U. S. A.*, **1993**, *90*, 7019.
[22] Swerdlow, R.; Marcus, D.L.; Landman, J.; Kooby, D.; Frey, W., 2nd; Freedman, M.L. *Am. J. Med. Sci.*, **1994**, *308*, 141.
[23] Mielke, R.; Herholz, K.; Grond, M.; Kessler, J.; Heiss, W.D. *Dementia*, **1994**, *5*, 36.
[24] Minoshima, S.; Giordani, B.; Berent, S.; Frey, K.A.; Foster, N.L.; Kuhl, D.E. *Ann. Neurol.*, **1997**, *42*, 85.
[25] Kawano, M.; Ichimiya, A.; Ogomori, K.; Kuwabara, Y.; Sasaki, M.; Yoshida, T.; Tashiro, N. *Dement. Geriatr. Cogn. Disord.*, **2001**, *12*, 171.
[26] Alexander, G.E.; Chen, K.; Pietrini, P.; Rapoport, S.I.; Reiman, E.M. *Am. J. Psychiatry*, **2002**, *159*, 738.
[27] Jarvenpaa, T.; Raiha, I.; Kaprio, J.; Koskenvuo, M.; Laine, M.; Kurki, T.; Vahlberg, T.; Viljanen, T.; Ahonen, K.; Rinne, J.O. *Dement. Geriatr. Cogn. Disord.*, **2003**, *16*, 245.
[28] Mosconi, L.; Nacmias, B.; Sorbi, S.; De Cristofaro, M.T.; Fayazz, M.; Tedde, A.; Bracco, L.; Herholz, K.; Pupi, A. *J. Neurol. Neurosurg. Psychiatry*, **2004**, *75*, 370.
[29] Kim, E.J.; Cho, S.S.; Jeong, Y.; Park, K.C.; Kang, S.J.; Kang, E.; Kim, S.E.; Lee, K.H.; Na, D.L. *Brain*, **2005**, *128*, 1790.
[30] Hoyer, S. *Adv. Exp. Med. Biol.*, **2004**, *541*, 135.
[31] Azari, N.P.; Pettigrew, K.D.; Schapiro, M.B.; Haxby, J.V.; Grady, C.L.; Pietrini, P.; Salerno, J.A.; Heston, L.L.; Rapoport, S.I.; Horwitz, B. *J. Cereb. Blood Flow Metab.*, **1993**, *13*, 438.
[32] Eustache, F.; Piolino, P.; Giffard, B.; Viader, F.; De La Sayette, V.; Baron, J.C.; Desgranges, B. *Brain*, **2004**, *127*, 1549.
[33] Wolf, H.; Jelic, V.; Gertz, H.J.; Nordberg, A.; Julin, P.; Wahlund, L.O. *Acta Neurol. Scand.*, **2003**, *179*, 52.
[34] Jelic, V.; Nordberg, A. *Alzheimer Dis. Assoc. Disord.*, **2000**, *14 Suppl 1*, S109.
[35] McNay, E.C. *Neurobiol. Aging*, **2005**, *26 Suppl 1*, 76.

[36] Manning, C.A.; Parsons, M.W.; Gold, P.E. *Behav. Neural. Biol.*, **1992**, *58*, 125.
[37] Grossman, H. *CNS Spectr.*, **2003**, *8*, 815.
[38] Messier, C. *Exp. Gerontol.*, **2003**, *38*, 941.
[39] Rasgon, N.; Jarvik, L. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2004**, *59*, 178.
[40] Convit, A. Neurobiol. Aging, **2005**, 26 Suppl 1, 31.
[41] Small, G.W. *J. Mol. Neurosci.*, **2002**, *19*, 17.
[42] Ubeda, M.; Kemp, D.M.; Habener, J.F. *Endocrinology*, **2004**, *145*, 3023.
[43] Janson, J.; Laedtke, T.; Parisi, J.E.; O'Brien, P.; Petersen, R.C.; Butler, P.C. *Diabetes*, **2004**, *53*, 474.
[44] Eldar-Finkelman, H.; Ilouz, R. *Expert Opin. Investig. Drugs*, **2003**, *12*, 1511.
[45] Wagman, A.S.; Johnson, K.W.; Bussiere, D.E. *Curr. Pharm. Des.*, **2004**, *10*, 1105.
[46] Biessels, G.J.; Kappelle, L.J. *Biochem. Soc. Trans.*, **2005**, *33*, 1041.
[47] Lesort, M.; Johnson, G.V. *Neuroscience*, **2000**, *99*, 305.
[48] Patel, N.V.; Finch, C.E. *Neurobiol. Aging*, **2002**, *23*, 707.
[49] Ewing, F.M.; Deary, I.J.; McCrimmon, R.J.; Strachan, M.W.; Frier, B.M. *Physiol. Behav.*, **1998**, *64*, 653.
[50] Craft, S.; Asthana, S.; Cook, D.G.; Baker, L.D.; Cherrier, M.; Purganan, K.; Wait, C.; Petrova, A.; Latendresse, S.; Watson, G.S.; Newcomer, J.W.; Schellenberg, G.D.; Krohn, A.J. *Psychoneuroendocrinology*, **2003**, *28*, 809.
[51] Watson, G.S.; Craft, S. *Eur. J. Pharmacol.*, **2004**, *490*, 97.
[52] Steen, E.; Terry, B.M.; Rivera, E.J.; Cannon, J.L.; Neely, T.R.; Tavares, R.; Xu, X.J.; Wands, J.R.; de la Monte, S.M. *J. Alzheimers Dis.*, **2005**, *7*, 63.
[53] Price, D.L.; Whitehouse, P.J.; Struble, R.G.; Price, D.L.; Cork, l., C,; Hedreen, J.C.; Kitt, C.A., Eds. *Basal forebrain cholinergic neurons and neuritic plaques in primate brain. Biological aspects of Alzheimer´s disease,* Cold Spring Harbor Laboratory, Cold Spring Harbor: New York, **1983**.
[54] Herholz, K.; Weisenbach, S.; Zundorf, G.; Lenz, O.; Schroder, H.; Bauer, B.; Kalbe, E.; Heiss, W.D. *Neuroimage*, **2004**, *21*, 136.
[55] Meier-Ruge, W.; Bertoni-Freddari, C. *Rev. Neurosci.*, **1996**, *7*, 1.
[56] Inestrosa, N.C.; Alvarez, A.; Perez, C.A.; Moreno, R.D.; Vicente, M.; Linker, C.; Casanueva, O.I.; Soto, C.; Garrido, J. *Neuron*, **1996**, *16*, 881.
[57] Shen, Z.X. *Med. Hypotheses*, **2004**, *63*, 298.
[58] Sadowski, M.; Pankiewicz, J.; Scholtzova, H.; Ji, Y.; Quartermain, D.; Jensen, C.H.; Duff, K.; Nixon, R.A.; Gruen, R.J.; Wisniewski, T. *J. Neuropathol. Exp. Neurol.*, **2004**, *63*, 418.
[59] Gomez-Ramos, A.; Smith, M.A.; Perry, G.; Avila, J. *Acta Neurobiol. Exp. (Wars)*, **2004**, *64*, 33.
[60] Planel, E.; Miyasaka, T.; Launey, T.; Chui, D.H.; Tanemura, K.; Sato, S.; Murayama, O.; Ishiguro, K.; Tatebayashi, Y.; Takashima, A. *J. Neurosci.*, **2004**, *24*, 2401.
[61] Liu, F.; Iqbal, K.; Grundke-Iqbal, I.; Hart, G.W.; Gong, C.X. *Proc. Natl. Acad. Sci. U. S. A.*, **2004**, *101*, 10804.
[62] Davis, J.; Fann, W.E. *Ann. Rev. Pharmacol.*, **1971**, *11*, 285.
[63] Vendsborg, P.B. *Acta Psychiatr. Scand.*, **1979**, *59*, 306.
[64] Shah, J.H.; DeLeon-Jones, F.A.; Schickler, R.; Nasr, S.; Mayer, M.; Hurks, C. *Metabolism*, **1986**, *35*, 634.
[65] Cyr, M.; Guia, M.A.; Laizure, S.C. *Ann. Pharmacother.*, **2002**, *36*, 427.
[66] Plenge, P. *Psychopharmacology*, **1978**, *58*, 317.
[67] Plenge, P. *Psychopharmacology*, **1982**, *77*, 348.
[68] Klein, P.S.; Melton, D.A. *Proc. Natl. Acad. Sci. U. S. A.*, **1996**, *93*, 8455.
[69] Hedgepeth, C.M.; Conrad, L.J.; Zhang, J.; Huang, H.C.; Lee, V.M.; Klein, P.S. *Dev. Biol.*, **1997**, *185*, 82.
[70] Harwood, A.J. *Curr. Biol.*, **2000**, *10*, R116.
[71] MacAulay, K.; Hajduch, E.; Blair, A.S.; Coghlan, M.P.; Smith, S.A.; Hundal, H.S. *Eur. J. Biochem.*, **2003**, *270*, 3829.
[72] Plenge, P. Lithium Effects on Brain Energy Metabolism. Metal Ions in Neurology and Psychiatry, Alan R. Liss, Inc: New York, **1985.**
[73] Geisler, A.; Mork, A. In *Lithium and Cell Physiology*, Bach, R.O; Gallicchio, V.S., Eds.; Springer-Verlag: New York, Berlin, Heidelberg, **1990**; pp. 125-136.
[74] York, J.D.; Ponder, J.W.; Majerus, P.W. *Proc. Natl. Acad. Sci. U. S. A.*, **1995**, *92*, 5149.
[75] Quiroz, J.A.; Singh, J.; Gould, T.D.; Denicoff, K.D.; Zarate, C.A.; Manji, H.K. *Mol. Psychiatry*, **2004**, *9*, 756.
[76] Bach, R.O; Gallicchio, V.S. *Lithium and Cell Physiology*, Springer-Verlag: New York, Berlin, Heidelberg, **1990.**
[77] Kornblatt, M.J. *Arch. Biochem. Biophys.*, **1996**, *330*, 12.
[78] Gorsich, S.W.; Barrows, V.; Halbert, J.; Farrar, W.W. *J. Protein Chem.*, **1999**, *18*, 103.
[79] Kajda, P.K.; Birch, N.J.; O'Brien, M.J.; Hullin, R.P. *J. Inorg. Biochem.*, **1979**, *11*, 361.
[80] Birch, N.J.; Hughes, M.S.; Thomas, G.M.H.; Partriges, S. *Magnesium Bull.*, **1986**, *8*, 145.
[81] Hoshi, M.; Takashima, A.; Noguchi, K.; Murayama, M.; Sato, M.; Kondo, S.; Saitoh, Y.; Ishiguro, K.; Hoshino, T.; Imahori, K. *Proc. Natl. Acad. Sci. U. S. A.*, **1996**, *93*, 2719.
[82] Jope, R.S.; Simonato, M.; Lally, K. *J. Neurochem.*, **1987**, *49*, 944.
[83] Jope, R.S.; Wright, S.M.; Walter-Ryan, W.G.; Alarcon, R.D. *J. Psychiatr. Res.*, **1986**, *20*, 9.
[84] Guerri, C. *Biochem. Pharmacol.*, **1982**, *31*, 449.
[85] Ray, W.J., Jr.; Szymanki, E.S.; Ng, L. *Biochim. Biophys. Acta*, **1978**, *522*, 434.
[86] Nordenberg, J.; Kaplansky, M.; Beery, E.; Klein, S.; Beitner, R. *Biochem. Pharmacol.*, **1982**, *31*, 1025.
[87] Mickel, R.A.; Hallidy, L.; Haugaard, N.; Haugaard, E.S. *Biochem. Pharmacol.*, **1978**, *27*, 799.
[88] Rodriguez-Gil, J.E.; Fernandez-Novell, J.M.; Barbera, A.; Guinovart, J.J. *Arch. Biochem. Biophys.*, **2000**, *375*, 377.
[89] Frame, S.; Cohen, P. *Biochem. J.*, **2001**, *359*, 1.
[90] Frame, S.; Cohen, P.; Biondi, R.M. *Mol. Cell*, **2001**, *7*, 1321.
[91] Wikramanayake, A.H.; Hong, M.; Lee, P.N.; Pang, K.; Byrum, C.A.; Bince, J.M.; Xu, R.; Martindale, M.Q. *Nature*, **2003**, *426*, 446.
[92] Dajani, R.; Fraser, E.; Roe, S.M.; Young, N.; Good, V.; Dale, T.C.; Pearl, L.H. *Cell*, **2001**, *105*, 721.
[93] Jope, R.S.; Johnson, G.V. *Trends Biochem. Sci.*, **2004**, *29*, 95.
[94] Woodgett, J.R. *EMBO J.*, **1990**, *9*, 2431.
[95] Lau, K.F.; Miller, C.C.; Anderton, B.H.; Shaw, P.C. *Genomics*, **1999,** *60*, 121.
[96] Hansen, L.; Arden, K.C.; Rasmussen, S.B.; Viars, C.S.; Vestergaard, H.; Hansen, T.; Moller, A.M.; Woodgett, J.R.; Pedersen, O. *Diabetologia*, **1997**, *40*, 940.
[97] Bhat, R.V.; Shanley, J.; Correll, M.P.; Fieles, W.E.; Keith, R.A.; Scott, C.W.; Lee, C.M. *Proc. Natl. Acad. Sci. U. S. A.*, **2000**, *97*, 11074.
[98] Zhang, F.; Phiel, C.J.; Spece, L.; Gurvich, N.; Klein, P.S. *J. Biol. Chem.*, **2003**, *278*, 33067.
[99] Manoukian, A.S.; Woodgett, J.R. *Adv. Cancer. Res.*, **2002**, *84*, 203.
[100] Kirshenboim, N.; Plotkin, B.; Shlomo, S.B.; Kaidanovich-Beilin, O.; Eldar-Finkelman, H. *J. Mol. Neurosci.*, **2004**, *24*, 237.
[101] Tanji, C.; Yamamoto, H.; Yorioka, N.; Kohno, N.; Kikuchi, K.; Kikuchi, A. *J. Biol. Chem.*, **2002**, *277*, 36955.
[102] Bennecib, M.; Gong, C.X.; Grundke-Iqbal, I.; Iqbal, K. *FEBS Lett.*, **2000**, *485*, 87.
[103] Plummer, G.; Perreault, K.R.; Holmes, C.F.; Posse De Chaves, E.I. *Biochem. J.*, **2005**, *385*, 685.
[104] Grimes, C.A.; Jope, R.S. *Prog. Neurobiol.*, **2001**, *65*, 391.
[105] Cross, D.A.; Alessi, D.R.; Cohen, P.; Andjelkovich, M.; Hemmings, B.A. *Nature*, **1995**, *378*, 785.
[106] Bhat, R.V.; Budd Haeberlein, S.L.; Avila, J. *J. Neurochem.*, **2004**, *89*, 1313.
[107] Nikoulina, S.E.; Ciaraldi, T.P.; Mudaliar, S.; Mohideen, P.; Carter, L.; Henry, R.R. *Diabetes*, **2000**, *49*, 263.
[108] Eldar-Finkelman, H.; Krebs, E.G. *Proc. Natl. Acad. Sci. U. S. A.*, **1997**, *94*, 9660.
[109] Clodfelder-Miller, B.; De Sarno, P.; Zmijewska, A.A.; Song, L.; Jope, R.S. *J. Biol. Chem.*, **2005**, *280*, 39723.
[110] Ryves, W.J.; Dajani, R.; Pearl, L.; Harwood, A.J. *Biochem. Biophys. Res. Commun.*, **2002**, *290*, 967.
[111] Ryves, W.J.; Harwood, A.J. *Biochem. Biophys. Res. Commun.*, **2001**, *280*, 720.

[112] Chalecka-Franaszek, E.; Chuang, D.M. *Proc. Natl. Acad. Sci. U. S. A.*, **1999**, *96*, 8745.
[113] Pugazhenthi, S.; Khandelwal, R.L. *Mol. Cell Biochem.,* **1995**, *149-150*, 95.
[114] Lawrence, J.C., Jr.; Roach, P.J. *Diabetes*, **1997**, *46*, 541.
[115] De Sarno, P.; Li, X.; Jope, R.S. *Neuropharmacology*, **2002**, *43*, 1158.
[116] O'Brien, W.T.; Harper, A.D.; Jove, F.; Woodgett, J.R.; Maretto, S.; Piccolo, S.; Klein, P.S. *J. Neurosci.*, **2004**, *24*, 6791.
[117] Inestrosa, N.C.; Alvarez, A.; Godoy, J.; Reyes, A.; De Ferrari, G.V. *Acta Neurol. Scand.*, **2000**, *176*, 53.
[118] Phiel, C.J.; Klein, P.S. *Annu. Rev. Pharmacol. Toxicol.,* **2001**, *41*, 789.
[119] Sperber, B.R.; Leight, S.; Goedert, M.; Lee, V.M. *Neurosci. Lett.,* **1995**, *197*, 149.
[120] Hong, M.; Chen, D.C.; Klein, P.S.; Lee, V.M. *J. Biol. Chem.*, **1997**, *272*, 25326.
[121] Munoz-Montano, J.R.; Moreno, F.J.; Avila, J.; Diaz-Nido, J. *FEBS Lett.*, **1997**, *411*, 183.
[122] Lovestone, S.; Davis, D.R.; Webster, M.T.; Kaech, S.; Brion, J.P.; Matus, A.; Anderton, B.H. *Biol. Psychiatry*, **1999**, *45*, 995.
[123] Hartigan, J.A.; Johnson, G.V. *J. Biol. Chem.*, **1999**, *274*, 21395.
[124] Drummond, A.H. *Nature*, **1988**, *331*, 388.
[125] Rana, R.S.; Hokin, L.E. *Physiol. Rev.*, **1990**, *70*, 115.
[126] Manji, H.K.; Potter, W.Z.; Lenox, R.H. *Arch. Gen. Psychiatry*, **1995**, *52*, 531.
[127] Allison, J.H.; Stewart, M.A. *Nat. New Biol.*, **1971**, *233*, 267.
[128] Hallcher, L.M.; Sherman, W.R. *J. Biol. Chem.*, **1980**, *255*, 10896.
[129] Sherman, W.R.; Munsell, L.Y.; Gish, B.G.; Honchar, M.P. *J. Neurochem.*, **1985**, *44*, 798.
[130] Berridge, M.J. *Nature*, **1993**, *361*, 315.
[131] Berridge, M.J.; Downes, C.P.; Hanley, M.R. *Biochem. J.*, **1982**, *206*, 587.
[132] Atack, J.R. *Biol. Psychiatry*, **1995**, *37*, 761.
[133] Shaldubina, A.; Agam, G.; Belmaker, R.H. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2001**, *25*, 855.
[134] Majumder, A.L.; Chatterjee, A.; Ghosh Dastidar, K.; Majee, M. *FEBS Lett.*, **2003**, *553*, 3.
[135] Shamir, A.; Shaltiel, G.; Greenberg, M.L.; Belmaker, R.H.; Agam, G. *Brain Res. Mol. Brain Res.*, **2003**, *115*, 104.
[136] Agranoff, B.W. *Fed. Proc.*, **1986**, *45*, 2629.
[137] Hirsch, J.P.; Henry, S.A. *Mol. Cell Biol.*, **1986**, *6*, 3320.
[138] Vaden, D.L.; Ding, D.; Peterson, B.; Greenberg, M.L. *J. Biol. Chem.*, **2001**, *276*, 15466.
[139] York, J.D.; Odom, A.R.; Murphy, R.; Ives, E.B.; Wente, S.R. *Science*, **1999**, *285*, 96.
[140] Yoshikawa, T.; Padigaru, M.; Karkera, J.D.; Sharma, M.; Berrettini, W.H.; Esterling, L.E.; Detera-Wadleigh, S.D. *Mol. Psychiatry*, **2000**, *5*, 165.
[141] Yoshikawa, T.; Turner, G.; Esterling, L.E.; Sanders, A.R.; Detera-Wadleigh, S.D. *Mol. Psychiatry*, **1997**, *2*, 393.
[142] Sjoholt, G.; Guldbransen, A.K.; Lovlie, R.; Berle, J.O.; Molven, A.; Steen, V.M. *Mol. Psychiatry*, **2000**, *5*, 172.
[143] Allison, J.H.; Blisner, M.E.; Holland, W.H.; Hipps, P.P.; Sherman, W.R. *Biochem. Biophys. Res. Commun.*,**1976**, *71*, 664.
[144] Hokin, L.E.; Hokin, M.R. *J. Biol. Chem.*, **1958**, *233*, 818.
[145] Hokin, L.E.; Hokin, M.R. *Biochim. Biophys. Acta*, **1964**, *84*, 563.
[146] Michell, R.H.; Kirk, C.J.; Jones, L.M.; Downes, C.P.; Creba, J.A. *Philos. Trans. R. Soc. London B Biol. Sci.*, **1981**, *296*, 123.
[147] Creba, J.A.; Downes, C.P.; Hawkins, P.T.; Brewster, G.; Michell, R.H.; Kirk, C.J. *Biochem. J.*, **1983**, *212*, 733.
[148] Berridge, M.J. *Ann. Rev. Physiol.*, **2005**, *67*, 1.
[149] Berridge, M.J.; Irvine, R.F. *Nature*, **1984**, *312*, 315.
[150] Hawthorne, J.N. *J. Lipid Res.*, **1960**, *1*, 255.
[151] Strunecka, A.; Patocka, J. *Structure and Bonding*, **2003,** *104*, 139.
[152] Downes, C.P.; Mussat, M.C.; Michell, R.H. *Biochem. J.*, **1982**, *203*, 169.
[153] Ragan, C.I.; Watling, K.J.; Gee, N.S.; Aspley, S.; Jackson, R.G.; Reid, G.G.; Baker, R.; Billington, D.C.; Barnaby, R.J.; Leeson, P.D. *Biochem. J.*, **1988**, *249*, 143.
[154] Moore, G.J.; Bebchuk, J.M.; Hasanat, K.; Chen, G.; Seraji-Bozorgzad, N.; Wilds, I.B.; Faulk, M.W.; Koch, S.; Glitz, D.A.; Jolkovsky, L.; Manji, H.K. *Biol. Psychiatry*, **2000**, *48*, 1.
[155] Silverstone, P.H.; Wu, R.H.; O'Donnell, T.; Ulrich, M.; Asghar, S.J.; Hanstock, C.C. *Hum. Psychopharmacol.*, **2002**, *17*, 321.
[156] Ragan, C.I. In *Lithium and Cell Physiology;* Bach, R.O.; Gallicchio, V.S., Eds.; Springer-Verlag: New York, Berlin, Heidelberg, **1990;** pp. **102-124.**
[157] Lee, C.H.; Dixon, J.F.; Reichman, M.; Moummi, C.; Los, G.; Hokin, L.E. *Biochem. J.*, **1992**, *282*, 377.
[158] Spector, R. *Neurochem. Res.*, **1988**, *13*, 785.
[159] Stokes, C.E.; Gillon, K.R.; Hawthorne, J.N. *Biochim. Biophys. Acta*, **1983**, *753*, 136.
[160] Berry, G.T.; Wu, S.; Buccafusca, R.; Ren, J.; Gonzales, L.W.; Ballard, P.L.; Golden, J.A.; Stevens, M.J.; Greer, J.J. *J. Biol. Chem.*, **2003**, *278*, 18297.
[161] Chengappa, K.N.; Levine, J.; Gershon, S.; Mallinger, A.G.; Hardan, A.; Vagnucci, A.; Pollock, B.; Luther, J.; Buttenfield, J.; Verfaille, S.; Kupfer, D.J. *Bipolar Disord.*, **2000**, *2*, 47.
[162] Berry, G.T.; Buccafusca, R.; Greer, J.J.; Eccleston, E. *Mol. Genet. Metab.*, **2004**, *82*, 87.
[163] Bleasdale, J.E.; Tyler, N.E.; Busch, F.N.; Quirk, J.G. *Biochem. J.*, **1983**, *212*, 811.
[164] Bleasdale, J.E.; Wallis, P.; MacDonald, P.C.; Johnston, J.M. *Biochim. Biophys. Acta*, **1979**, *575*, 135.
[165] Uldry, M.; Steiner, P.; Zurich, M.G.; Beguin, P.; Hirling, H.; Dolci, W.; Thorens, B. *Embo J.*, **2004**, *23*, 531.
[166] Wong, Y.H.; Kalmbach, S.J.; Hartman, B.K.; Sherman, W.R. *J. Neurochem.*, **1987**, *48*, 1434.
[167] O'Donnell, T.; Rotzinger, S.; Nakashima, T.T.; Hanstock, C.C.; Ulrich, M.; Silverstone, P.H. *Eur. Neuropsychopharmacol.*, **2003**, *13*, 199.
[168] Sherman, W.R.; Gish, B.G.; Honchar, M.P.; Munsell, L.Y. *Fed. Proc.*, **1986**, *45*, 2639.
[169] Jellinger, K.A. *Acta Neuropathol.*, **1993**, *85*, 682.
[170] Bothmer, J.; Jolles, J. *Biochim. Biophys. Acta*, **1994**, *1225*, 111.
[171] Zubenko, G.S.; Stiffler, J.S.; Hughes, H.B.; Martinez, A.J. *Biol. Psychiatry*, **1999**, *45*, 731.
[172] Zambrzycka, A. *Pol. J. Pharmacol.*, **2004**, *56*, 651.
[173] Shimohama, S.; Fujimoto, S.; Matsushima, H.; Takenawa, T.; Taniguchi, T.; Perry, G.; Whitehouse, P.J.; Kimura, J. *J. Neurochem.*, **1995**, *64*, 2629.
[174] Shears, S.B. *Biochem. J.*, **2004**, *377*, 265.
[175] Batty, I.; Nahorski, S.R. *Biochem. J.*, **1987**, *247*, 797.
[176] Whitworth, P.; Kendall, D.A. *J. Neurochem.*, **1988**, *51*, 258.
[177] Irvine, R.F. *J. Physiol.*, **2005**, *566*, 295.
[178] Irvine, R.F.; Schell, M.J. *Nature Rev. Mol. Cell Biol.*, **2001**, *2*, 327.
[179] Connolly, T.M.; Bansal, V.S.; Bross, T.E.; Irvine, R.F.; Majerus, P.W. *J. Biol. Chem.*, **1987**, *262*, 2146.
[180] Vallejo, M.; Jackson, T.; Lightman, S.; Hanley, M.R. *Nature*, **1987**, *330*, 656.
[181] Grases, F.; Simonet, B.M.; Vucenik, I.; Perello, J.; Prieto, R.M.; Shamsuddin, A.M. *Life Sci.*, **2002**, *71*, 1535.
[182] Yang, S.N.; Yu, J.; Mayr, G.W.; Hofmann, F.; Larsson, O.; Berggren, P.O. *Faseb J.*, **2001**, *15*, 1753.
[183] Larsson, O.; Barker, C.J.; Sjoholm, A.; Carlqvist, H.; Michell, R.H.; Bertorello, A.; Nilsson, T.; Honkanen, R.E.; Mayr, G.W.; Zwiller, J.; Berggren, P.O. *Science*, **1997**, *278*, 471.
[184] Kiselev, G.V. *Biokhimiia*, **1978**, *43*, 1328.
[185] Saiardi, A.; Resnick, A.C.; Snowman, A.M.; Wendland, B.; Snyder, S.H. *Proc. Natl. Acad. Sci. U. S. A.*, **2005**, *102*, 1911.
[186] Chuang, D.M. *Crit. Rev. Neurobiol.*, **2004**, *16*, 83.
[187] Tsai, G.; Coyle, J.T. *Prog. Neurobiol.*, **1995**, *46*, 531.
[188] Gross, C.G. *Nature Rev. Neurosci.*, **2000**, *1*, 67.
[189] Chuang, D.M.; Chen, R.W.; Chalecka-Franaszek, E.; Ren, M.; Hashimoto, R.; Senatorov, V.; Kanai, H.; Hough, C.; Hiroi, T.; Leeds, P. *Bipolar Disord.*, **2002**, *4*, 129.
[190] Cui, H.; Meng, Y.; Bulleit, R.F. *Brain Res. Dev. Brain Res.*, **1998**, *111*, 177.
[191] Williams, R.S.; Cheng, L.; Mudge, A.W.; Harwood, A.J. *Nature*, **2002**, *417*, 292.

[192] Menager, C.; Arimura, N.; Fukata, Y.; Kaibuchi, K. *J. Neurochem.*, **2004**, *89*, 109.
[193] Cremona, O.; Di Paolo, G.; Wenk, M.R.; Luthi, A.; Kim, W.T.; Takei, K.; Daniell, L.; Nemoto, Y.; Shears, S.B.; Flavell, R.A.; McCormick, D.A.; De Camilli, P. *Cell*, **1999**, *99*, 179.
[194] LaFerla, F.M. *Nature Rev. Neurosci.*, **2002**, *3*, 862.
[195] Khachaturian, Z.S. *Ann. N. Y. Acad. Sci.*, **1989**, *568*, 1.
[196] Khachaturian, Z.S. *Ann. N. Y. Acad. Sci.*, **1994**, *747*, 1.
[197] Verkhratsky, A.; Toescu, E.C. *Trends Neurosci.*, **1998**, *21*, 2.
[198] Ripova, D.; Platilova, V.; Strunecka, A.; Jirak, R.; Hoschl, C. *Physiol. Res.*, **2004**, *53*, 449.
[199] Ripova, D.; Platilova, V.; Strunecka, A.; Jirak, R.; Hoschl, C. *Neurobiol. Aging*, **2000**, *21*, 729.
[200] Strunecka, A.; Ibrahim, N.; Palecek, J.; Kmonickova, E.; Krpejsova, L.; Potter, B.V. *Receptor - Humana Press*, **1991**, *1*, 141.
[201] Fergusson, M.A. *Parasitology Today*, **1994**, *10*, 48.
[202] Chesebro, B.; Trifilo, M.; Race, R.; Meade-White, K.; Teng, C.; LaCasse, R.; Raymond, L.; Favara, C.; Baron, G.; Priola, S.; Caughey, B.; Masliah, E.; Oldstone, M. *Science*, **2005**, *308*, 1435.
[203] McLaurin, J.; Golomb, R.; Jurewicz, A.; Antel, J.P.; Fraser, P.E. *J. Biol. Chem.*, **2000**, *275*, 18495.
[204] Pei, J.J.; Tanaka, T.; Tung, Y.C.; Braak, E.; Kabal, K.; Grundke-Iqbal, I. *J. Neuropathol. Exp. Neurol.*, **1997**, *56*, 70.
[205] Leroy, K.; Boutajangout, A.; Authelet, M.; Woodgett, J.R.; Anderton, B.H.; Brion, J.P. *Acta Neuropathol.*, **2002**, *103*, 91.

Received: ?????????????? Revised: ?????????????????? Accepted: ??????????????