Lithium Pharmacology and a Potential Role of Lithium on Methamphetamine Abuse and Dependence

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Abstract: Background: The effectiveness of lithium salts in neuropsychiatric disorders such as bipolar disorder, Alzheimer’s disease, and treatment-resistant depression has been documented in an extensive scientific literature. Lithium inhibits inositol monophosphatase, inositol polyphosphate 1-phosphatase, and glycogen synthase kinase-3 and decreases expression level of tryptophan hydroxylase 2, conceivably underlying the mood stabilizing effects of lithium, as well as pro-cognitive and neuroprotective effects. However, the exact molecular mechanisms of action of lithium on mood stabilizing and pro-cognitive effects in humans are still largely unknown.

Objective: On the basis of the known aspects of lithium pharmacology, this review will discuss the possible mechanisms underlying the therapeutic effects of lithium on positive symptoms of methamphetamine abuse and dependence.

Conclusion: It is possible that lithium treatment reduces the amount of newly synthesized phosphatidylinositol, potentially preventing or reversing neuroadaptations contributing to behavioral sensitization induced by methamphetamine. In addition, it is suggested that exposure to repeated doses of methamphetamine induces hyperactivation of glycogen synthase kinase-3β in the nucleus accumbens and in dorsal hippocampus, resulting in a long-term alterations in synaptic plasticity underlying behavioral sensitization as well as other behavioral deficits in memory-related behavior. Therefore it is clear that glycogen synthase kinase-3β inhibitors can be considered as a potential candidate for the treatment of methamphetamine abuse and dependence.

Keywords: Lithium, methamphetamine abuse, phosphoinositide turnover, glycogen synthase kinase-3, nucleus accumbens, neuropsychiatric disorders.

1. INTRODUCTION

Lithium is an alkali metal, and the salt form of a cationic lithium ion in association with carbonate or citrate are one of the oldest known psychotropic medications [1]. Seventy years ago the Australian psychiatrist John Cade described that lithium ions have a sedative effect which might be effective for the treatment of mania (i.e. bipolar disorder) [2]. More recently, lithium has been investigated for the treatment of several other disorders, including not only bipolar disorder, a psychiatric illness characterized by alternating episodes of elevated mood and depression [3-5], but also Alzheimer’s disease [6-8] and treatment-resistant depression [9, 10]. Despite it being on the WHO Model List of Essential Medicines [11] as medicine for bipolar disorder, the exact molecular mechanism of lithium whereby it effectively improves symptoms of bipolar disorder has not been revealed. However, a number of mechanisms have been suggested, which are discussed in detail below. Since, the effects of lithium in these conditions include both normalization of mood dysfunction, as well as improvement of some cognitive impairments, it is perhaps not surprising that similar symptoms associated with drug abuse and withdrawal have also been investigated. Alleviation of abused drug (i.e. amphetamines and cocaine)-induced pathology by treatment with lithium has also been reported in preclinical [12-14] and clinical investigations [15-17], suggesting that lithium might be a candidate for the treatment of some consequences of drug abuse and dependence. The toxicity and adverse effects of lithium have been well-documented because lithium has a notoriously narrow therapeutic index [18-21].

Once incorporated into the body, lithium is rapidly absorbed from the gastrointestinal tract and distributed throughout the body because of its small molecular size [22, 23]. Thus, despite the apparent therapeutic advantages of lithium, it is difficult to assess the exact molecular targets
with which the lithium ion actually interacts to exert those effects. In line with the current literature available, the pharmacology of lithium action is first considered in this review, followed by a discussion of the potential role of lithium as a treatment for methamphetamine (METH) abuse and dependence. Successful treatments for METH addiction remain elusive [24, 25] despite worldwide METH abuse as an illicit drug [26] so that the utility of lithium in this regard would be an important advance in the treatment of this condition.

2. LITHIUM PHARMACOLOGY

In the literature, lithium is reported to possess inhibitory effects on some intracellular enzymes in mammals. The following discussion considers lithium mechanisms of action.

2.1. Lithium as an Inhibitor of Inositol Monophosphatase

Inositol monophosphatase (IMPase) (also known as inositol-1 (or 4)-monophosphate phosphatase, EC3.1.3.25) is a magnesium-dependent enzyme which hydrolyses myo-inositol-1 (or 4)-monophosphate to generate free myo-inositol and phosphate. IMPase functions as an important component of inositol phospholipid metabolism which is closely associated with heterotrimeric GTP-binding protein-coupled cell membrane receptor-mediated intracellular signaling pathways (i.e. phosphoinositide (PI) turnover) [27, 28]. IMPase activity consists predominantly of the activities of two isozymes, IMPase 1 and IMPase 2, in humans [29]. In a biochemical assay for their function, lithium ions have been conventionally used to inhibit PI turnover at the metabolic point of myo-inositol release from inositol monophosphatase in order to evaluate the activity of phospholipase C-coupled receptor signal transduction systems in terms of inositol monophosphate accumulation [30-32].

Repeated METH exposure results in a reduction of histamine-stimulated PI hydrolysis in the frontal cortex of mice, suggesting that this mechanism might be a critical regulator of neuroadaptations in the frontal cortex contributing to behavioral sensitization [33]. Lithium ceases to release free myo-inositol in the cytoplasm by inhibiting IMPase and IP-Pase activities, resulting in inhibition of synthesis of phosphatidylinositol [27, 28]. It is possible that lithium treatment reduces the amount of newly synthesized phosphatidylinositol, potentially preventing or reversing neuroadaptations contributing to behavioral sensitization.

In in vitro studies, lithium inhibits IMPase in a non-competitive manner with half-maximal activity of approximately 0.8 mM [34] (Fig. 1). The accumulation of inositol monophosphate by lithium is also reported in human brains in vivo [35]. Evidence from terbium-fluorescence quenching and the two metal kinetic titration curves suggests that lithium ion binds at the active site of IMPase, thereby inhibiting the enzyme [36, 37]. Both IMPase 1 and IMPase 2 activities are sensitive to lithium and considered to be implicated as its therapeutic targets for the treatment of bipolar disorder and schizophrenia [38].

In clinical investigations, it is likely that lithium reduces neuronal excitation by inhibiting inositol phospholipid metabolism as a consequence of inhibition of IMPase, and reduces PI turnover that is stimulated by numerous neurotransmitters and hormones. Attenuation of PI turnover has been proposed as the mechanism for the efficacy of lithium in the treatment of several disorders including bipolar disorder [39] and schizophrenia [40].

2.2. Lithium as an Inhibitor of Inositol Polyphosphate 1-phosphatase

In the PI metabolic pathway, inositol polyphosphate 1-phosphatase (IPPPase; EC3.1.3.57) hydrolyzes the 1-position phosphate from inositol 1,3,4-trisphosphate and inositol 1,4-bisphosphate [27, 28]. Using purified recombinant bovine IPPase, lithium ions have been shown to non-competitively inhibit hydrolysis of both substrates, with apparent Ki values of 16.3 mM and 1.4 mM for inositol 1,4-bisphosphate and inositol 1,3,4-trisphosphate, respectively [41]. The consequence of inhibition of IPPase by lithium is attenuation of PI turnover.

There are only a few studies of the effects of lithium on IPPase in humans. Studies of polymorphisms in the human gene for IPPase indicate that there are four common polymorphisms in the coding region of the gene. These polymorphisms were all reported to be single base substitutions, of which one (A682G) predicted an amino acid change (Thr228Ala), whereas the remaining three (G153T, G348A and C973A) were silent. The frequencies of the four single base substitutions were not significantly different between lithium-treated bipolar patients and healthy control individuals, although one allele (C973A) may be associated with a favorable lithium response in bipolar patients among specific populations, suggesting that further studies are needed to focus on the effect of lithium on the IPPase as a candidate to explain the mood-stabilizing action of lithium in bipolar disorder [42].

One report mentioned the possible association of genetic variation in the IPPase and serotonin transporter genes [43]. The serotonin transporter gene is one of the most widely studied candidate genes in psychiatric genetics [44-46], and polymorphisms in this gene have been associated with affective disorders. In particular, a case-control study revealed an association between bipolar disorder and the insertion-deletion polymorphism of the 5’ regulatory region of the serotonin transporter (5-HTTLPR) [47]. However, an association study conducted to examine genetic variation in the IPPase and serotonin transporter genes did not support the hypothesis of an association between either polymorphism (the 5-HTTLPR and C973A polymorphism of IPPase gene) and bipolar disorder [43].

2.3. Lithium as an Inhibitor of Glycogen Synthase Kinase-3

Glycogen synthase kinase-3 (GSK-3; EC2.7.11.26) is a proline-directed serine/threonine kinase that was first identified as a regulator of glycogen synthase [48, 49]. GSK-3 is widely distributed throughout the body and lies downstream of multiple intracellular signaling pathways [50], suggesting a fundamental role in physiological functions [51, 52], beyond its initially identified role in insulin signaling [53, 54]. In humans, two highly conserved isoforms of GSK-3 are encoded by two distinct genes, namely GSK-3α and GSK-3β which map to 19q13.2 and 3q13.3, respectively [55]. There are
two splice variants of GSK-3β (i.e. GSK-3β and GSK-3β2) [56]. The two isozymes of GSK-3 are both constitutively active and are primarily regulated by inhibition [57-59]. Therefore, inhibitors of GSK-3 have been suggested to be candidates for the treatment of illnesses that may be related to dysfunction of GSK-3 or cellular signaling associated with GSK-3 [60]. GSK-3β is expressed abundantly in the brain [61] so that it is speculated that inhibitors of GSK-3β might be particularly effective for some brain diseases such as Parkinson’s disease [62, 63], schizophrenia and bipolar disorder [64].

Lithium is one of the well-known inhibitors for GSK-3 with Ki values of 3.5 mM and 2 mM for GSK-3β and GSK-3β2, respectively, as assayed in vitro [65, 66]. The direct inhibition of GSK-3 by lithium may be due to the displacement of magnesium binding at a specific site(s) in GSK-3 by lithium in a non-competitive manner [67, 68]. In addition to the direct inhibition of GSK-3 isozymes by lithium, it can inhibit GSK-3 indirectly by affecting the Akt (or protein kinase B) pathway [69, 70]. Activated Akt can phosphorylate the N-terminus of the GSK-3 protein (Ser9 and Ser21 for GSK-3α and GSK-3β, respectively), resulting in the inhibition of GSK-3 activity [71]. Lithium potently activates Akt, causing an indirect inhibition of GSK-3 [72]. Whether or not the actions of lithium on GSK-3 are direct or indirect, the effectiveness of lithium to bipolar disorder has been well-documented in terms of GSK-3 inhibition [73, 74].

3. POTENTIAL ROLE OF LITHIUM ON METHAMPHETAMINE ABUSE AND DEPENDENCE

Although the exact molecular mechanisms of lithium action underlying its therapeutic effects in humans are not understood [66], it is clear that multiple molecular targets of lithium have been identified and may be involved. Drug dependence shares many features of affective disorders. Affective symptoms are observed during drug withdrawal, and pre-existing affective disorders may be a driving force in many addictions ([75]; see also discussion of this issue in [76]). Consequently, the potential of lithium for the treatment of drug dependence and addiction has been investigated in animal models. Indeed, as early as the 1970s, it was reported that lithium inhibits METH-induced hyperlocomotion in mice [77] and amphetamine-induced reinforcement in rats as evaluated by intracranial self-stimulation [78]. Flemenbaum and colleagues reported that lithium also effectively blocks cocaine-induced hyperlocomotion and stereotypy in rats [79]. Its clinical effects are less well-studied, but it has been reported to block some cocaine-induced effects in humans [80].

Of possible molecular targets of lithium that might explain its therapeutic effects in drug dependence, the GSK-3β intracellular signaling pathway has been investigated in animal models of drug abuse utilizing behavioral sensitization. Repeated administration of METH induces a progressive augmentation of locomotor activity in response to the same drug in rodents [81-83]. This phenomenon is called behavioral sensitization, which is accompanied by lasting neurobiological adaptations induced by repeated administration of abused drugs occurring in the mesolimbic dopaminergic pathway [84, 85] in parallel with synaptic plasticity in the ventral striatum, and in particular the Nucleus Accumbens (NAc) [86-88]. Lu and colleagues reported that repeated administration of rats with METH initiates and induces behavioral sensitization in rats and pretreatment with lithium chloride effectively blocks the initiation and expression of METH-induced behavioral sensitization [13]. As described above, lithium inhibits GSK-3β and GSK-3β2. To determine the involvement of GSK-3 in this process, Lu and colleagues applied SB216763, another potent inhibitor of GSK-3 isozymes, directly into the NAc core of rats. In the animals administered SB216763, METH-induced behavioral...
sensitization was suppressed. GSK-3 activity depends on site-specific phosphorylation of Tyr216 on GSK-3β that activates GSK-3β, while phosphorylation of Ser9 on GSK-3β inhibits activity [89, 90]. Repeated administration with METH decreases phosphorylation of Ser9 of GSK-3β in NAc, suggesting that accumbal GSK-3β is activated after repeated METH exposure [13]. These observations suggest that repeated METH-induced behavioral sensitization might be mediated by stimulation of synaptic plasticity in the NAc through the hyperactivation of GSK-3β, and therefore inhibition of GSK-3β expressed in the NAc might suppress METH-induced behavioral sensitization. Cocaine-induced hyperlocomotion in rats is also inhibited by pretreatment with lithium or SB216763 [91], suggesting a role of GSK-3 in behavioral responses to other abused drugs in addition to METH.

More recently, Yan et al. [92] focused on possible involvement of GSK-3β in repeated METH-induced alterations of memory-related behaviors in mice. Repeated administration of adolescent mice with METH significantly decreased time spent in the novel arm of a novel spatial exploration test, as well as the social recognition score in the social interaction test after a 38 day period of drug abstinence. They also investigated phosphorylation of GSK-3β and synaptic ultrastructure in the dorsal hippocampus of mice after a battery of behavioral tests, finding that (1) repeated METH exposure decreased phosphorylation of Ser9 of GSK-3β expressed in the dorsal hippocampus, the number of Gray’s type-1 asymmetric synapses (i.e. excitatory synapses [93]), and the thickness of the postsynaptic densities at the thickest part of the synapses located in the CA1 region of the dorsal hippocampus, and that (2) pretreatment with lithium chloride reversed the behavioral and ultrastructural alterations produced by METH [92]. These observations [13, 92] strongly suggest that exposure to repeated doses of METH induces hyperactivation of GSK-3β in the NAc and in the dorsal hippocampus, resulting in long-term alterations in synaptic plasticity underlying behavioral sensitization as well as other behavioral deficits in memory-related behaviors. Dysphoric state of chronic METH administration during the period of drug abstinence has been recognized as depressive syndromes, such as anhedonia, depression, anxiety, and social inhibition which are opposite states compared with positive symptoms appeared after acute METH administration [94]. In METH withdrawal GSK-3 activities are likely to be reduced. This hypothesis has been confirmed by Cuesta et al. [95], suggesting that GSK-3 proteins might be relevant to treat METH symptoms.

As described above, GSK-3β is constitutively active and is primarily regulated by inhibition [57-59]. Repeated METH exposure-induced alterations of synaptic plasticity appear to be a result of a long-term hyperactivation of GSK-3β located in target brain regions. How might GSK-3β be hyperactivated continuously after repeated METH exposure, even after a period of drug abstinence? These effects might be due to alterations in the activity of kinases or phosphatases that regulate GSK-3 activity. This might include inhibition of kinases such as Akt that phosphorylate Ser9 of GSK-3β, and/or increased activity of phosphatases that dephosphorylate Ser9 of phosphorylated GSK-3β. To our knowledge, there is no evidence that repeated METH exposure inhibits or downregulates Akt activity in the long-term. However, in support of this hypothesis, it has been reported that phentermine, a chemical with a structure similar to METH, activates Akt in the NAc, which is associated with increased reinforcing effects of phentermine [96]. Therefore, it might be supposed that repeated METH exposure might produce similar effects, or perhaps activate phosphatases which dephosphorylate Ser9 of phosphorylated GSK-3β. This hypothesis needs to be examined in further investigations of the mechanisms underlying behavioral responses to METH.

CONCLUSION

As shown in Fig. (1), it is clear that GSK-3β inhibitors can be considered as a potential candidate for the treatment of METH abuse and dependence, as well as potential treatments for other related CNS diseases [97-99]. Alternatively, regulators of GSK-3β activity (especially phosphatases) might be targets for the treatment of METH abuse and dependence. An association between METH exposure and alteration of PI turnover has not been established, but lithium effectively inhibits IMPase and IPPase activities, and may consequently alter signaling pathways mediating METH-induced neuroplasticity [33]. Regulation of PI hydrolysis might be an effective strategy for treating METH abuse. Overall, understanding of lithium pharmacology, and the roles of GSK-3, IMPase and IPPase, will help in the development of novel therapeutic approaches for the treatment of METH abuse and dependence.

LIST OF ABBREVIATIONS

Akt = Protein Kinase B

DhIPP = Dorsal Hippocampus

FCx = Frontal Cortex

GSK-3 = Glycogen Synthase Kinase-3

5-HT = 5-Hydroxytryptamine (Serotonin)

IMPase = Inositol Monophosphatase

IPPase = Inositol Polysphosphate 1-Phosphatase

METH = Methamphetamine

NAc = Nucleus accumbens

pGSK-3 = Phosphorylated Glycogen Synthase Kinase-3

PI = Phosphoinositide.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.
Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3. [PMID: 7482796]


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