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REVIEW

Lithium: a potential estrogen signaling modulator

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Summary
Estrogen replacement therapy (ERT) engenders much debate since several studies contradict its efficacy as a palliative therapy for cognitive decline and neurodegenerative diseases. Signaling transduction pathways alter brain cell activity, survival, and morphology by facilitating transcription factor activation and protein production. The steroidal hormone estrogen and the anti-depressant drug lithium can interact also through these signaling transduction pathways resulting in transcription factor activation. The transcription factor cAMP response element binding protein (CREB) is affected by both estrogen and lithium, and CREB regulates genes involved in learning, memory and neuronal survival. CREB is activated upon phosphorylation at serine 133 by protein kinases and, estrogen and its receptors (ER) facilitate this phosphorylation. Glycogen synthase kinase-3beta (GSK-3β) attenuates CREB's transcriptional properties via subsequent phosphorylation of its serine 129, and lithium is known as a negative regulator of GSK-3β, thus facilitating CREB response element binding. Interestingly, ERα function and DNA-binding properties are facilitated by GSK-3β. In this review we include protein modeling depicting the interaction of CREB/GSK-3β and ERα/GSK-3β using I-TASSER and PatchDock web servers. Understanding the molecular pathways of estrogen will assist in identifying a palliative therapy for menopause-related dementia, and lithium may serve this purpose by acting as a selective estrogen-mediated signaling modulator.

Key words: estrogen; lithium; hormone therapy; brain

Abbreviations used:

AD, Alzheimer's disease; APP, amyloid precursor protein; bcl-2, B-cell lymphoma/leukemia-2; BDNF, brain derived neurotrophic factor; CREB, cAMP response element binding protein; ER, Estrogen receptors (α, alpha; β, beta); ERK, extracellular signal-regulated kinases; ERT, Estrogen replacement therapy; GPCR, G-protein coupled receptors; GSK-3β, glycogen synthase kinase-3beta; PI3-K, phosphatidylinositol-3-kinase; PELP1, proline-, glutamic acid-, and leucine-rich protein-1; PDB, Protein data bank; PKA, cAMP dependent protein kinase; Akt/PKB, protein kinase B; PKC, protein kinase C; SERMs, selective estrogen receptor modulators; StAR, steroidogenic acute regulatory protein; STRAP, structure based sequences alignment program; I-TASSER, Threading/ASSEmbly/ Refinement; τ, tau protein; TMHMM, TransMembrane prediction using Hidden Markov Models.

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INTRODUCTION

Estrogen and lithium exert neuroprotective properties and may act as palliative treatments for neurodegeneration and cognitive decline (Manji et al. 1999, Goodenough et al. 2003). Alzheimer's disease (AD) in post-menopausal women is related to estrogen deficiency, and estrogen replacement therapy (ERT) may benefit post-menopausal women in reducing the risk of developing AD (Garcia-Segura et al. 2001). Other studies, however, contradict these findings and suggest that hormone therapy does not improve cognitive decline during menopause, specifically episodic memory (Henderson 2009). There is a high risk of developing breast cancer, marked by increased incidences of lobular carcinoma, in post-menopausal women undergoing ERT (Newcomer et al. 2003). Furthermore, women suffering from depression during peri- and post-menopause are often prescribed lithium (Kukopulos et al. 1985, Burt and Rasgon 2004). Few studies focus on how estrogen and lithium may augment or counteract neuroprotective qualities these two agents possess, and studies demonstrating estrogen and lithium's affect on learning and memory are conflicting. Many underlying mechanisms still remain to be studied and ever increasing proteonomic- and genomic-generated data suggest these as complex mechanisms.

Using I-TASSER (Threading/ASSEmbly/ Refinement) web server (Wu et al. 2007, Zhang 2007, 2008) we fabricated 3-D protein models represented in Figs 1–6. Due to limited parent structures in the protein data bank (PDB), some models presented in this review display low complexity regions (e.g. indicated primarily by the lighter colored region in the background of Fig. 1; subsequent figures are not highlighted as such, though). To choose the best model for this review, predicted models by I-TASSER were compared to superimposed crystallography structures from the PDB, aided by the structure based sequences alignment program (STRAP) and Pymol for visualizing the superimposition (see table 1 for accession number used to compare each predicted models). We used TransMembrane prediction using Hidden Markov Models (TMHMM) web server to locate and specify transmembrane domains by representing a predicted hydrophobicity chart. Literature mining and using the BLAST conserved domain web server (NCBI) assisted in locating specific amino acids specifying binding residues to produce the hypothetical protein-protein interactions in this review. Figures depicting these protein-protein interactions were provided by the PatchDock web server (Duhovny et al. 2002, Schneidman-Duhovny et al. 2005).

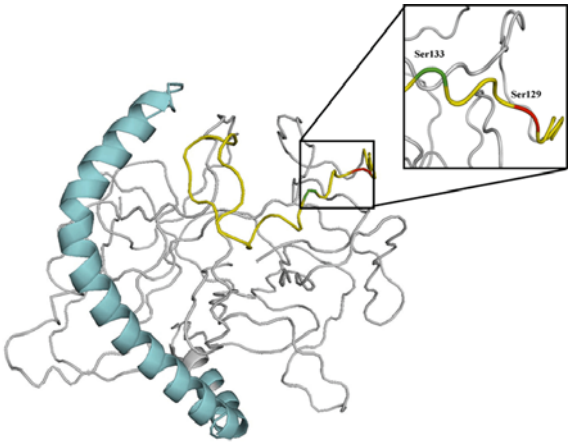

Fig. 1. **CREB.** Phosphorylating CREB at its serine 133 (green) causes a conformational change in its leucine zipper region (cyan) causing CREB to dimerize with CREB binding protein. This dimerization facilitates CREB response element binding. The conformational change that occurs, however, exposes CREB's serine 129 region (red) allowing a subsequent phosphorylation attenuating CREB's response element binding. (The yellow depicts the kinase inducible domain of CREB. The light colored region indicates the low complexity region).

NEUROSTEROIDS AND ESTROGEN REPLACEMENT THERAPY

Menopause is marked by a massive drop in circulating estrogen. The growing concern with estrogen deficiency is the increase incidence of neurodegenerative diseases and cognitive decline. Circulating estrogen permeates the blood-brain barrier (Lee and McEwen 2001), and some speculate α-fetoprotein, a fetal plasma protein with a high affinity for estrogen, facilitates estrogen neuromechanisms (McEwen et al. 1975 , Bakker and Baum 2008). Estrogen is primarily produced by the gonads and the adrenal gland, but hormones, known as neurosteroids, are also produced in the brain (Sierra 2004). Production of steroids by the gonads requires steroidogenic acute regulatory protein (StAR) to facilitate intermembrane passage of cholesterol, and StAR is ubiquitously expressed in the brain, but at low levels (Sierra 2004). Women with a mutation in the StAR gene suffer from hormone deficiency leading to spontaneous puberty and an early onset of menopause (Bhangoo et al. 2007). Cholesterol is transported by StAR to the inner

Table 1. **Specific amino acid sequences used to fabricate 3-D protein models.** These predicted models were superimposed with crystallography structures from PDB to justify predicted structures.

Predicted Protein	NCBI Accession #	Comparison Protein	PDB Accession #
CREB	NP_604391.1	CREB Leucine Zipper	1dh3
GSK-3β	NP_002084.2	GSK-3β	1q4l
ERα	NP_000116.2	ERα	1l2i
GPR30	NP_001091671.1	Rhodopsin	2J4Y

mitochondrial membrane where cytochrome P450 converts cholesterol into pregnenolone, the steroidal precursor (Sierra 2004). Astrocytes are a source for steroidogenesis and glia-mediated steroidal production is linked to neuronal synaptic formation and to facilitating synaptic transmission (Hu et al. 2007). Interestingly, StAR is expressed in glia and this co-localization is linked to glia-mediated steroidogenesis (Sierra 2004). Little is known about how ERT affects StAR or how ERT affects the production of neurosteroids. Should research be directed towards replacing estrogen in post-menopausal women, or geared towards enhancing neurosteroidogenesis and estrogen-mediated brain cell signaling pathways?

The benefits of ERT are a controversial topic. As mentioned, women undergoing ERT increase their risk of breast cancer (Newcomer et al. 2003), but there also lies a dichotomy with ERT in relation to enhancing cognitive function and reducing neurodegenerative diseases. For instance, in 1994 Henderson (Henderson et al. 1994) concluded that ERT may reduce the risk of AD and cognitive decline during post-menopause, but in 2009 Henderson is skeptical of ERT neuroprotective and neuroenhancing properties. There is also a debate about a *critical window hypothesis*. The hypothesis states that if ERT is initiated at a younger age, prior to menopause, it will reduce the risk of AD (Sherwin 2003); but Henderson considers these studies systematically bias (Henderson 2009). Selective estrogen receptor modulators (SERMs) do provide an alternative to ERT, and studies show a decrease in breast cancer incidence and a slowing in the progression of osteoporosis (Jordan et al. 2001). But SERMS use does not seem to improve cognitive functioning (Natale et al. 2004, Palmer et al. 2008). If SERMs do not influence cognitive functioning, an alternative treatment should be investigated since estrogen does affect several brain cell signaling pathways involved in learning, memory and neuroprotection.

LEARNING, MEMORY AND NEUROPROTECTION VIA ESTROGEN/ESTROGEN RECEPTOR-MEDIATED PATHWAYS

Estrogen facilitates brain cell signaling pathways that enhance synaptic plasticity (Leranth et al. 2002), reduce glutamate excitotoxicity (Honda et al. 2001), increase neuroprotection of adult hippocampal cells (Liu et al. 2001), regulate neurotrophic factors (Solum and Handa 2002), and facilitate transcription factor activation (McEwen 2001). Learning and memory are products of gene regulation, and transcription factors. For example, cAMP response element binding protein (CREB) regulates genes responsible for critical brain functions, including synaptic plasticity, learning, memory and neuroprotection (Pugazhenthi et al. 2000, Walton and Dragunow 2000, Honda et al. 2001, Kandel 2001). CREB activation is facilitated by estrogen (McEwen 2001) leading to the transcription of immediate early genes (e.g. *c-fos* and *c-jun*), which in turn promotes phenotypical changes – e.g. synaptic plasticity (Sanyal et al. 2002). In fear conditioning experiments mice exhibit an upregulation of immediate early genes in the hippocampus and this upregulation is mediated by the amygdala (Huff et al. 2006). Mice with targeted mutations of CREB exhibit deficiencies in long-term memory storage, but not short-term memory storage (Bourtchuladze et al. 1994). Activation of CREB's signaling pathway is initiated by adenylyl cyclase which catalyzes ATP into cAMP that then activates cAMP dependent protein kinase (PKA). PKA then phosphorylates CREB at its serine133 site (Fig. 1) (Bullock and Habener 1998). Estrogen and its receptors (ER) facilitate non-genomic molecular pathways by increasing CREB activity (McEwen 2001) and estrogen is known to increase cAMP levels by binding to G-protein coupled receptors (GPCR) that stimulate adenylyl cyclase activity (Filardo et al. 2002).

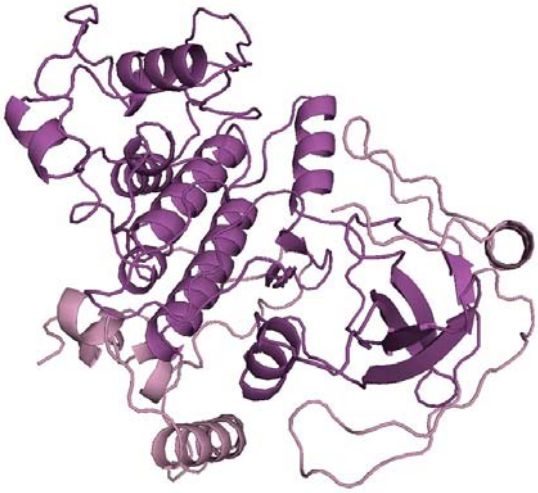

Fig. 2. **GSK-3β.** The darker magenta areas depict the protein kinase domains of GSK-3β. These regions possess ATP binding, catalytic, activation and substrate binding domains.

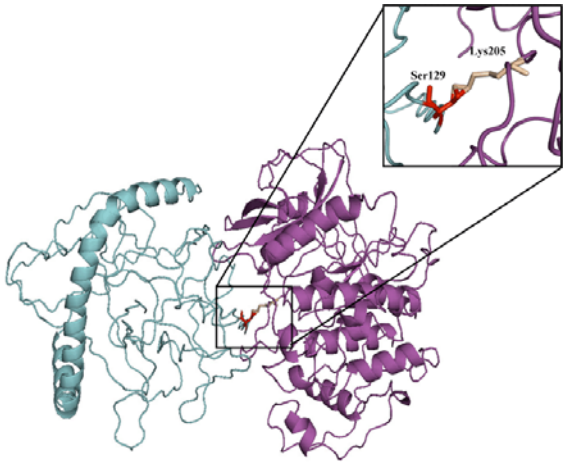

Fig. 3. **Protein-protein interaction of CREB and GSK-3β.** Subsequent phosphorylation of CREB (cyan) at serine 129 (red) attenuates response element binding, thereby reducing cAMP-dependent transcription. Subsequent phosphorylation is mediated by GSK-3β (magenta) and interaction is noted at lysine 205 (wheat) of GSK-3β.

Glycogen synthase kinase-3beta (GSK-3β; Fig. 2) is a negative regulator of CREB via subsequent phosphorylation of CREB at serine 129 (Fig. 3) and this subsequent phosphorylation can only occur after the initial phosphorylation of serine 133 (Bullock and Habener 1998, Grimes and Jope 2001a). The serine 129 phosphorylation attenuates CREB transcriptional properties thus inhibiting CREB's neuroprotective mechanisms (Bullock and Habener 1998, Grimes and Jope 2001a). Classically, GSK-3β is well known for its inhibition of the transcription factor β-catenin in the *Wnt* signaling pathway (Grimes and Jope 2001b). β-catenin is necessary for activating genes responsible in general for embryonic development and more specifically, for central nervous system development (Grimes and Jope 2001b). When bound by its ligand estrogen, ERα causes an ephemeral inhibition of GSK-3β via phosphorylation of its serine residues (Cardona-Gomez et al. 2004). ERs also act as ligand-activated transcription factors for the promoter region estrogen response element (ERE) (Macgregor and Jordan 1998, Garcia-Segura et al. 2001).

To date, there are two known ERs: ERα and ERβ (Shughrue et al. 1997). In the nervous system, ERs are mainly located in the hypothalamus and amygdala (two areas responsible for the gonadal distribution of hormones), but they are also located in regions of the cerebral cortex (Merchenthaler et al. 2004) and hippocampus (Shughrue et al. 1997, Garcia-Segura et al. 2001). ERs are expressed in pyramidal cells of the hippocampus and Solum and Handa (2002) measured brain derived neurotrophic factor (BDNF) mRNA expression in gonadectomized rats and found that BDNF mRNA decreased in the hippocampus of these gonadectomized rats, but was reversed with a single injection of estrogen. This group also found that ERα is co-localized with BDNF in pyramidal cells of the hippocampus (Solum and Handa 2002), suggesting that ERs may play a role in memory and cognition (Shughrue et al. 1997, Fugger et al. 2000, McEwen 2001). By increasing the activation of second messenger signaling, such as calcium and cAMP that activate protein kinases (Gu et al. 1996), which in turn activate CREB, estrogen indirectly increases CREB activation (McEwen 2001). Wu et al. (2005) proposed that estrogen/ER complex leads to neuroprotection by recruiting phosphatidylinositol-3 kinase (PI3K). The recruitment of PI3K by ERs increases intracellular calcium; calcium acts as a second messenger involved in several cell signaling pathways. One specific downstream target of calcium is protein kinase C (PKC) which activates Src protein (Wu et al. 2005). Src, a tyrosine kinase then activates extracellular signal-regulated kinase (ERK) signaling leading to the transcription of B-cell lymphoma/leukeimia-2 (Bcl-2), via phosphorylated CREB (Wu et al. 2005). PI3K also facilitates Bcl-2 anti-apoptotic activity by activating Akt (also known as protein kinase B) which inhibits attenuating factors of Bcl-2 (Wu et al. 2005). Promotion of intracellular calcium levels via ER-mediated signaling is debatable since evidence shows a rapid increase in intracellular calcium is mediated by estrogen binding to GPR30, a serpentine

transmembrane GPCR (Belcher 2008, Prossnitz and Maggiolini 2009). Human keratinocytes treated with estrogen increase phosphorylated CREB levels and GPR30 anti-sense oligonucleotides attenuate this increase (Kanda and Watanabe 2004). The difference in calcium influx mediated by ERs or GPR30 may be that ERα has a binding affinity for a Src recruiter known as proline-, glutamic acid-, and leucine-rich protein-1 (PELP1) (Brann et al. 2008). The recruitment of PELP1 binds Src and may lead to the PI3K/ERK/CREB pathway proposed by Wu et al. (2005).

The dominant form of estrogen, 17β-estradiol (E2), has an affinity for ERα (Fig. 4) leading to transcription factor activation, but E2 can mediate protein signaling pathways through ERs and non-ERs. As mentioned, PELP1 is a co-regulator of ERα and this interaction leads to Akt/PI3K signaling pathways (Brann et al. 2008) – a pathway facilitated by lithium involving GSK-3β inhibition (De Sarno et al. 2002). But E2 also binds to the G-protein coupled receptor (GPCR), GPR30 – a serpentine receptor. GPR30 expression takes place in the plasma membrane but it is also expressed in the endoplasmic reticulum (Raz et al. 2008). GPCRs are members of the rhodopsin family and they possess seven transmembrane α-helices; GPR30 shares these conserved domains (Fig. 5A). Ligand binding by E2 activates GPR30 (Fig. 5B) and this binding facilitates cAMP production (Raz et al. 2008). Fig. 5B depicts ligand binding by E2 at the outer and inner membrane – these are hypothetical binding sites using PatchDock web server.

Response element binding of ERα relies on GSK-3β phosphorylation and this phosphorylation is inhibited in the presence of lithium. Medunjanin et al. (2005) suggested that when GSK-3β is phosphorylated at serine 9 it disassociates itself from ERα, allowing ERα to migrate to the nucleus for a subsequent phosphorylation by GSK-β – consequently activating ERα transcriptional properties (Fig. 6). Palindromic DNA sequences are recognized by ERα, and expressed in promoter regions for NMDA receptor subunits (Watanabe et al. 1999); thus, estrogen has a direct genomic role in NMDA receptor subunit expression.

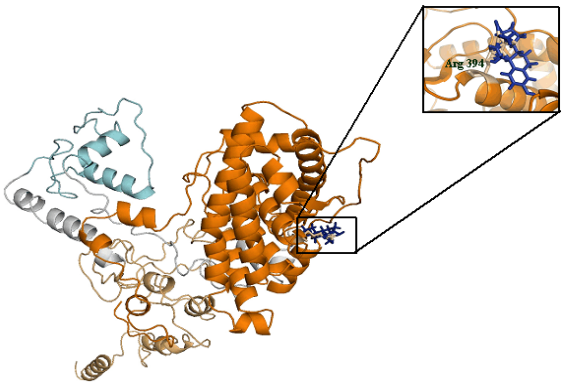

Fig. 4. **ERα.** This figure depicts ERα bound by E2 (blue) at arginine 394 within the ligand binding domain (foreground; orange). The ligand binding domain also contains the co-activator recognition site and dimer interface. Domains are conserved in ERα classifying it as part of the ER family (background; light orange) and as a transcription factor due to its zinc finger domain (cyan).

LITHIUM

To elucidate lithium's prophylactic properties for bipolar disorder, investigators postulated mechanisms involving inositol depletion (Harwood 2004) and GSK-3β inhibition (Gould and Manji 2002). *Inositol depletion hypothesis* states that lithium inhibits inositol monophosphatase thus depleting the amount of free inositol (Harwood 2004). Inositol signaling ultimately releases calcium stored in the endoplasmic reticulum affecting several signaling pathways. Inositol signaling via glutamate receptor increases protein kinase activity, transcription factor activation (O'Riordan et al. 2006) and is highly involved in synaptic plasticity (Fernandez de Sevilla et al. 2008). Using *Dictyostelium* and human neutrophil cell line (HL60), King et al. (2009) systematically investigated the hypothesis that lithium suppresses inositol-mediated signaling. This group showed that lithium reduces phosphoinositide and this reduction is reversed by over expressing inositol monophosphatase (King et al. 2009). Two inositol monophosphatases have been identified (IMPA1 and IMPA2) and IMPA2 is highly associated not only with bipolar disorder, but schizophrenia as well (Yoshikawa et al. 2001). A high concentration of magnesium and a high pH are required for IMPA2 compared with IMPA1 (Ohnishi et al. 2007). Ohnishi et al. (2007) showed that lithium also inhibits IMPA2 and this inhibition hinders magnesium concentrations. Bipolar patients treated with lithium show a decrease in inositol monophosphatase activity in red blood cells compared with non-treated bipolar patients (Kofman and Belmaker 1993), but cerebrospinal fluid from lithium-treated patients suffering from bipolar illness or schizophrenia show an increase in inositol monophosphatase activity (Atack et al. 1998).

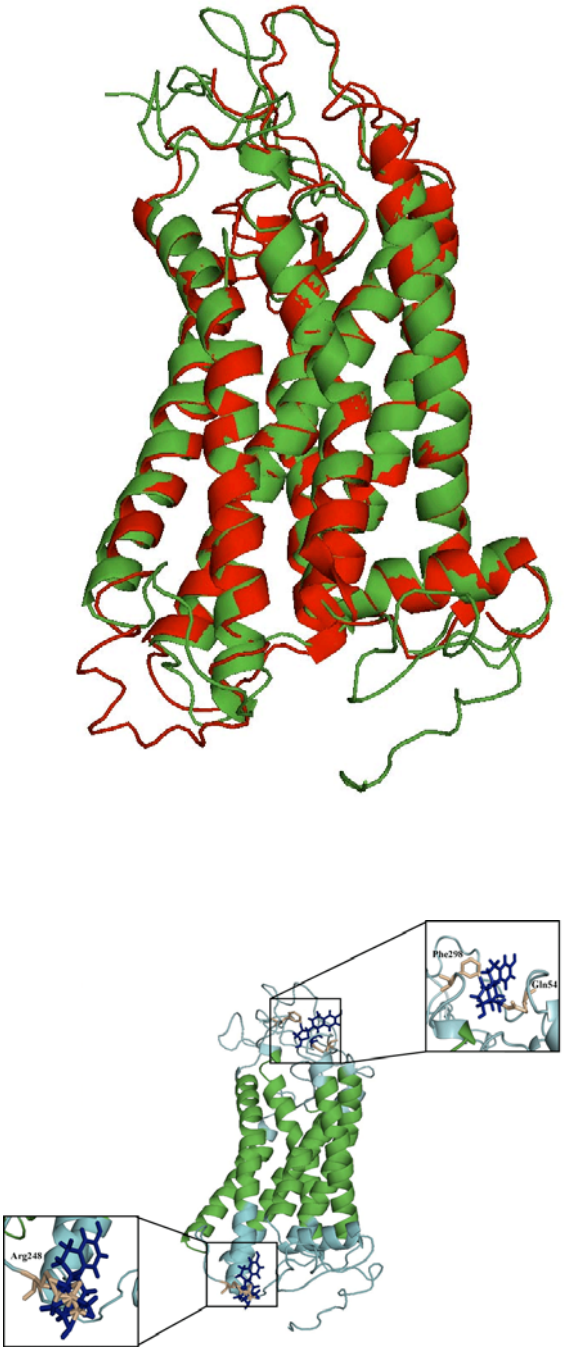

Fig. 5A–5B. **GPR30.** This superimposition depicts GPR30 (green) sharing similar structure to rhodopsin (red) (A). GPR30 express seven α-helices transmembrane domains (green) and putative binding of E2 (blue) is shown on the outer membrane (cyan) at phenylalanine 298 and glutamine 54, and inner membrane (cyan) at arginine 248 (B).

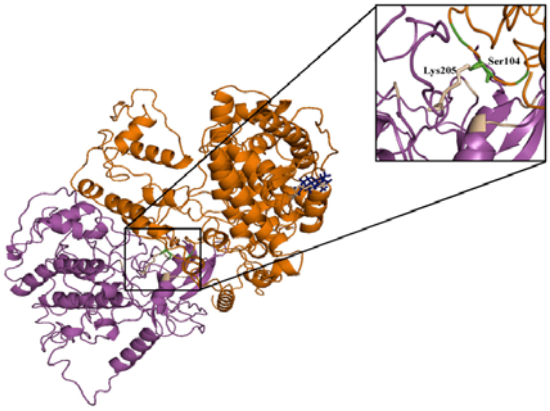

Fig. 6. **Protein-protein interaction of ER- and GSK-3β**. Once bound by estrogen (blue), ERα (orange) mediates cell signaling pathways or acts as a transcription factor. Response element binding of ERα is facilitated by GSK-3β (magenta) phosphorylation. This figure depicts binding of ERα at serine 104 (green) by lysine 205 (wheat) of GSK-3β. The non-bound residues in green (ERα) and wheat (GSK-3β) are the binding sites described by Medunjanin et al. (2005) and Ilouz et al. (2006), respectively. The GSK-3β amino acid residue responsible for phosphorylating ERα depicted in this figure is the same residue that phosphorylates CREB at serine 129 (Fig. 3).

For over a decade, and within the last year, studies have shown that lithium specifically inhibits GSK-3β (Klein and Melton 1996, Engel et al. 2008) and this inhibition is associated with reducing apoptotic activity (Hongisto et al. 2003), enhancing neurotrophic factors (Angelucci et al. 2003), and facilitating CREB DNA binding (Ozaki and Chuang 1997, Grimes and Jope 2001a). Interestingly, learning and memory centers of the brain are influenced by lithium, since lithium increases performance in hippocampal-dependent spatial memory tasks (Sharifzadeh et al. 2007). An extensive study using GSK-3β heterozygous knockout mice analyzed behavioral parameters ranging from apomorphine-induced stereotypic behavior to startle response and found no distinct differences in behavior (Bersudsky et al. 2008). This may lead one to postulate that lithium may affect learning and memory through GSK-3β independent pathways.

Though the mechanism remains elusive, GSK-3β inhibition by lithium is described as acting through both direct and indirect mechanisms. Indirectly, lithium inhibits GSK-3β by activating protein kinases that phosphorylate GSK-3β at its inhibitory serine 9 residue or by inactivating phosphatases that remove the serine 9 phosphate group (Jope 2003). Enzymatic activity is highly dependent on magnesium and lithium directly inhibits GSK-3β by acting as a

competitive inhibitor of magnesium; magnesium being a cofactor for ATP in GSK-3β activation (Fig. 4) (Ryves and Harwood 2001). Thus, GSK-3β inhibition by lithium protects/rescues the brain from apoptotic cell death; and neural dysfunction results from the failure to completely inhibit GSK-3β (Grimes and Jope 2001a). In addition, lithium-treated rats show an upregulation of Bcl-2 in layers II and III of the frontal cortex, dentate gyrus and striatum (Manji et al. 1999). Therefore, long-term administration of lithium could provide neuroprotection by increasing neuronal survival. Neuroprotective qualities of lithium are also associated with increasing BDNF expression and facilitating BDNF signaling via tyrosine kinase receptor. Rat cortical neurons treated with lithium or BDNF had similar neuroprotective qualities; however, lithium required a chronic treatment (6 days) as opposed to an acute action by BDNF (1 day) (Hashimoto et al. 2002). These neuroprotective qualities are attenuated by BDNF neutralizing antibodies and specific inhibitors for tyrosine kinase (Hashimoto et al. 2002). The BDNF/tyrosine kinase receptor signaling also activates PI3K/Akt signaling pathways, ultimately leading to neuronal survival and increasing Bcl-2 expression (Patapoutian and Reichardt 2001). Neuroprotection of cerebellar granule neurons by lithium via tyrosine kinase activity is also documented, since this neuroprotection is abolished with tyrosine kinase inhibitors (Grignon et al. 1996).

Phencyclidine (PCP), also known as angel dust, is an NMDA receptor antagonist and its actions result in schizophrenic-like behavior (Choi et al. 2009); clinically, lithium is also prescribed for schizophrenia (Citrome 2009). PCP inhibits PI3K/Akt and ERK signaling pathways, and PCP activates GSK-3β by facilitating the dephosphorylation of its serine 9 residue, however, lithium reverses PI3K/Akt and ERK inhibition and GSK-3β activation (Xia et al. 2008). Lithium indirectly affects NMDA receptor signaling pathway by reducing phosphorylation and activation of Src-tyrosine kinase activity. Furthermore, phosphorylation of NR2 subunits of NMDA receptor by Src tyrosine kinases is essential for the receptor's signal transduction activity and Hashimoto et al. (2003) demonstrate that phosphorylated levels of Src tyrosine kinase decrease in a time-dependent fashion when treated with lithium. Although NMDA receptor is highly involved in learning and memory it also mediates glutamate excitotoxicity, and this mediation reduces phosphorylated CREB levels (Kopnisky et al. 2003). Diminished phosphorylated CREB is regulated by protein phosphatase 1 (Kopnisky et al. 2003), a factor involved in GSK-3β activation (Zhang et al. 2003). When Kopnisky et al. (2003) chronically treated neuronal cultures with lithium, protein phosphatase 1 activity decreased, and phosphorylated CREB levels increased; lithium also increased ERK signaling pathway. Post-synaptic glutamate receptors, like NMDA receptors, facilitate synaptic connectivity and conductivity, and lithium enhances this facilitation. Interestingly, enhanced synaptic plasticity is correlated with phosphoinositide depletion and not GSK-3β inhibition (Kim and Thayer 2009). Lithium is double-edged in interacting with glutamate receptors, but only to balance the properties of glutamate receptor signaling pathways. This suggests that lithium attenuates glutamate receptor-mediated excitoxicity (Hashimoto et al. 2002), but also facilitates, maintains and strengthens glutamate receptor-mediated synaptic connectivity and communication (Kim and Thayer 2009). If lithium is a competitive inhibitor of magnesium (Ryves and Harwood 2001) and glutamate receptor channels bind magnesium (Clarke and Johnson 2008), could lithium then directly affect glutamate receptor? Would lithium's direct interaction lead to glutamate receptor inhibition or facilitate its activity, or both?

ESTROGEN AND LITHIUM; OR, LITHIUM AS A SELECTIVE ESTROGEN-MEDIATED SIGNALING MODULATOR

To date, few studies focus on the neurobiological affects of combined estrogen and lithium. Several studies employ lithium in taste aversion tasks and in inducing seizures. Seizures are induced by injecting lithium in specific stereotactic brain regions to induce status epilepticus (e.g. seizures). Estrogen protects rat hippocampus from these induced seizures; however, this protection is gender specific (Galanopoulou et al. 2003). Lithium permeates cells through sodium-potassium ATPase pumps and this permeation is dependent on sodium-lithium counterflow and exchange (Pandey et al. 1978), which increases cytoplasmic pH levels thus altering cell activity (Kobayashi et al. 2000). Sodium-lithium counterflow is increased by long-term use of oral contraceptives (Adebayo et al. 1998); interestingly, lithium does not alter ERα expression in murine uterine tissue, but ovariectomized mice treated with combined estrogen and lithium show reduced uterine ERα expression (Gunin et al. 2004).

Taste aversion tasks use lithium to cause an adverse reaction to a rewarding stimulus (e.g. sucrose

water) and studies show that estrogen hinders ovariectomized rats ability to detect dilute sucrose solutions (Curtis et al. 2005). Estrogen accelerates extinction of conditioned taste aversion behavior, but this is dependent on when estrogen is administered (e.g. before or during extinction) (Yuan and Chambers 1999). Combined lithium and estrogen decrease inflammation of stomach lining, but individual treatment does not affect gastric erosions (Abouzeit-Har et al. 1982). Both estrogen and lithium affect enkephalins, a regulator of nociceptic responses (e.g. noxious stimuli). In analyzing rat anterior pituitary, Yoshikawa and Hong (1983), found that enkephalin expression is sex dependent – males express higher levels than females. Administering estrogen to male rats decreases enkephalins, but testosterone increases enkephalins in female rat anterior pituitary (Yoshikawa and Hong 1983). Rats were also administered lithium and Yoshikawa and Hong (1983) noted a decrease in enkephalins of the anterior pituitary for both male and female rats. This led them to conclude that the enkephalin system is mediated by the dopamine pathway (Yoshikawa and Hong 1983). Parkinson disease and clinical disorders, such as bipolar disorder, are highly associated with the dopamine pathway, a pathway affected by estrogen and lithium combined (Silverstone 1985, Morissette et al. 2008).

An increase in intracellular sodium concentration mediated by dopaminergic pathways is a characteristic of bipolar disorder and lithium normalizes this increase (Roberts et al. 2009). Studies show that combined estrogen and lithium alter serotonin and dopamine metabolites. Estrogen does not change serotonin levels, dopamine or dopamine metabolites in the frontal cortex of ovariectomized rats, but when estrogen is combined with lithium, dopamine drastically decreases (Morissette and Di Paolo 1996). This decrease is associated with higher serotonin levels and dopamine metabolites (Morissette and Di Paolo 1996). Apomorphine is a dopaminergic agonist that increases stereotyped-behavior (e.g. Parkinsonian symptoms) as noted in ovariectomized rats after discontinuing chronic treatment of estrogen; but this increase in stereotyped-behavior is diminished with lithium (Dorce and Palermo-Neto 1992).

Lithium does not affect basal levels of cAMP, but when stimulated by dopamine, lithium inhibits adenylyl cyclase activity and this effect has been observed *in vitro* and *in vivo* (Montezinho et al. 2007). Lithium's inhibition of dopamine-stimulated adenylyl cyclase is not through GPCR signaling pathway, as indicated using the dopamine receptor agonist, quinpirole (Montezinho et al. 2007); interestingly, GTP hydrolysis is decreased by lithium, but not when stimulated by catecholamines (i.e. dopamine and epinephrine) (Odagaki et al. 1997). There instead seems to be a direct inhibition of adenylyl cyclase by lithium but only when adenylyl cyclase is activated (Mann et al. 2008). Studies show that lithium hinders hormone and dopamine-stimulated adenylyl cyclase activity in rat cerebral cortex, with the conclusion that lithium is causing this hindrance via competitive inhibition (e.g. magnesium) (Newman and Belmaker 1987). Will lithium inhibit GPR30-stimulated adenylyl cyclase activity?

There is a correlation between adenylyl cyclase activity and progression of AD. Post-mortem hippocampi of AD patients showed a decrease in adenylyl cyclase activity due to a hindrance in the catalytic domain (Ohm et al. 1991). Progression of AD is associated with producing excessive amounts of the insoluble form of amyloid beta protein – a proteolytic product of amyloid precursor protein (APP) cleaved by β-secretase (Glenner 1982). Cleavage of APP by alpha secretase can produce a soluble product rendering it benign. Estrogen does increase alpha secretase cleavage and lithium mimics this increase – potentially through GSK-3β inhibition (Goodenough et al. 2003). Post-mortem AD brains also show a decrease in NMDA receptor subunit mRNA for NR1 and NR2B in the hippocampal formation with advancement of the disease (Mishizen-Eberz et al. 2004). Our laboratory has shown that a 48 h treatment of combined estrogen and lithium reduces gene expression of NR1, a critical subunit of NMDA receptors and increases glutamate excitotoxicity in primary cultures of mouse hippocampal and cortical cells predominated by glia (Valdés and Weeks 2009).

Estrogen facilitates calcium influx and promotes factors involved in neuronal survival and synaptic plasticity (Sarkar et al. 2008). Neurodegenerative diseases, like AD, are marked by increased excitotoxicity, due to high intracellular calcium levels in brain cells (Dong et al. 2009), and postmenopausal women suffer from AD (Henderson 2009). Should women with a higher likelihood of progressive neurodegenerative functions be prescribed ERT? Or should postmenopausal therapy be directed towards modulating estrogen brain cell signaling pathways? Lithium is extremely toxic if serum levels exceed the therapeutic range (0.6–1.4 mM) as shown by treating rats for up to 28 days and this study also showed that lithium increases estrogen levels via antagonizing ERs (Allagui et al. 2006). Recent studies, however, indicate that lithium facilitates proliferation of epithelial cells and these cells show increased ER expression (Polotsky et al. 2009); lithium also

facilitates increases in estrogen production (Choe et al. 2003). Although lithium is classically used to treat bipolar syndrome it has an incredible propensity for stabilizing molecular mechanisms. Jope (1999) proposed a bimodal model for lithium, since lithium regulates positive and negative cell signaling mechanisms resulting in raising basal activities and reducing maximal activities or by increasing basal levels and reducing maximal levels of cell signaling mechanisms (Jope 1999). Lithium's bimodal mechanism may facilitate ER-mediated brain cell signaling during post-menopause by increasing the activity level in a system deprived of its basal level of estrogen.

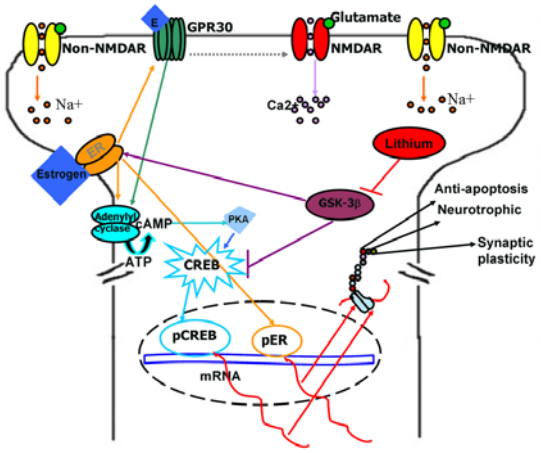

Fig. 7. **A post-synaptic cell signaling schematic of the mechanism described in this review.** ATP, adenosine triphosphate; CREB, cyclic adenosine monophosphate (cAMP) response element binding protein; ER, estrogen receptor; GPR30, G-protein coupled receptor 30; GSK-3β, glycogen synthase-3beta; NMDAR, *N*-methyl-D-aspartate; PKA, cAMP dependent protein kinase
(⇢ putative interaction, → activating/interacting, ⊣ inhibitory).

CLOSING REMARKS

Previous literature stress the risk of ERT due to incidences of endometrial and lobular carcinoma and that patients under ERT should be monitored for these adverse effects (Weiss 1975, Newcomer et al. 2003). Gambrell (1982) acknowledges the benefits of ERT that include reducing vasomotor symptoms, urogenital atrophy, psychosomatic complaints, osteoporosis, cardiovascular disease, lipid metabolism, and that these benefits can be maximized if risks of ERT are closely monitored (i.e. endometrial cancer, endometrial hyperplasia, breast cancer, coagulation factors, and gallbladder disease). Ten years later, Gambrell (1992) stresses the point that adequate dosage and inclusion of progestogen (progestin) will increase ERT benefits than with estrogen alone. However, as aforementioned, Henderson (2009) debates ERT benefits.

The benefits mentioned by Gambrell contribute to the reasons why ERT is so widely used to treat post-menopausal women, as opposed to other forms of treatment. Lithium treatment also warrants caution since lithium toxicity result in adverse symptoms if dosage and treatment length are not closely monitored. Detailed accounts of lithium's adverse effects are described by Grandjean and Aubry (2009). As this clinical update mentions, the common complaints of long-term lithium usage are gastrointestinal pain, diarrhea, tremor, polyuria, nocturnal urination, weight gain, edema, and exacerbation of psoriasis (Grandjean and Aubry 2009). This clinical update extensively describes less common adverse affects such as hypothyroidism, thyrotoxicosis, hyperparathyroidism, hypercalcaemia, and hypermagnesaemia. Lithium may also contribute to adverse neurological effects such as postural tremors and extrapyramidal symptoms, and cognitive impairments in memory, vigilance, reaction time and tracking (Grandjean and Aubry 2009). Lithium may affect fetal development via the GSK-3β catenin pathway (Kao and Elinson 1998) and lithium treatment should not be used during the first trimester of pregnancy (Grandjean and Aubry 2009). The most common adverse effect of lithium is nephrogenic diabetes insipidus, characterized by excess thirst and overly diluted urine (Grünfeld and Rossier 2009). Recent studies infer that the root cause of diabetes insipidus is lithium targeting principal cells of the collecting duct resulting in downregulation of aquaporin 2, a cell membrane protein that regulates renal water flow (Grünfeld and Rossier 2009).

Although there are adverse effects for both estrogen and lithium usage, post-menopausal therapy should be directed towards enhancing estrogen-mediated neuromechanisms instead of supplementing the system with estrogen (or hormones in general). SERMs do provide an alternative to ERT, and, although advancement of neurodegenerative diseases are attenuated (Dhandapani and Brann 2002), SERMs do not improve cognitive functioning (Natale et al. 2004, Palmer et al. 2008). Over 60 years ago John Frederick Joseph Cade, an Australian psychiatrist, first recognized the calming effects of lithium on small animals and on himself (Cade 1949).

Since then lithium has been used to treat bipolar disorder and over a decade has passed since molecular mechanisms for lithium began to be recognized (Klein and Melton 1996). These molecular implications have expanded lithium's profile as a cognitive enhancer and an anti-neurodegenerative agent (Manji et al. 1999). As discussed in this review, both estrogen and lithium facilitate a plethora of signaling transduction pathways resulting in anti-apoptosis, protein expression, learning and memory. Fig. 7 depicts pathways discussed in this review, shows the multitude of pathways affected by estrogen and suggests ways in which lithium interacts with these signaling transduction pathways. We believe to further study the involvement of antidepressants and hormones will provide a better treatment regime for post-menopausal women. Perhaps a palliative therapy could consist of a combination of estrogens and lithium, maximizing the benefits of both agents – but clearly further investigations are needed to procure a proper treatment regime.

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