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Research Article

Regulation of Cortical 5-Hydroxytryptamine$_{2A}$-Receptor Mediated Electrophysiological Responses in the Rat Following Daily Oral Lithium Administration

Marek GJ*
CNS & Pain, Astellas Pharma Global Development, USA

***Corresponding author:** Marek GJ, CNS & Pain, Astellas Pharma Global Development, 1 Astellas Way, Northbrook, IL 60062, USA

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Abstract

Down-regulation of 5-Hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors has been a consistent effect induced by most antidepressant drugs. Lithium is the antimanic drug with the most comprehensive clinical literature in both unipolar depression and manic-depressive illness. With respect to unipolar depression, lithium is best established as an augmenting agent, but lithium also possesses modest antidepressant properties when used as monotherapy. The question of 5-HT$_{2A}$ receptor sensitivity during chronic antidepressant administration is important since activation of 5-HT$_{2A}$ receptors is associated with impulsivity and since down-regulation of 5-HT$_{2A}$ receptor binding/function has been associated with most antidepressant treatments. Therefore, the effects of subchronic oral lithium administration (one or two weeks) on pharmacologically characterized electrophysiological response mediated by 5-HT$_{2A}$ receptor activation in the Prefrontal Cortex (PFC) and the piriform cortex were examined. The concentration-response curve for 5-HT-induced EPSCs and 5-HT-induced firing of GABAergic interneurons recorded from the PFC and piriform cortical slices, respectively, was unchanged following subchronic lithium treatment. The efficacy of AMPA receptor activation was attenuated in the piriform cortex. While not having an effect on the concentration-response of 5-HT-induced EPSCs in the medial PFC, lithium did enhance both the onset and magnitude of desensitization for 5-HT-induced EPSCs in the PFC. Interestingly, lithium did not appear to attenuate the resensitization of 5-HT-induced EPCS. This asymmetric effect of lithium on 5-HT$_{2A}$ desensitization vs. resensitization in the PFC may be relevant for understanding the regulation of 5-HT$_{2A}$ receptor trafficking by lithium.

Keywords: Antidepressant drugs; 5-HT$_{2A}$ Receptors; Prefrontal cortex; Pyramidal cells; Interneurons; Mood stabilizers

Abbreviations

5-HT$_{2A}$: 5-hydroxytryptamine$_{2A}$; ACSF: Artificial Cerebrospinal Fluid; AMPA: α-Amino-3-hydroxy-5-Methyl-4-isoxazolepropionate; Cg1: anterior cingulate cortex; Cg3: prelimbic cortex; DOI: 1(2,5-Dimethoxy-4-iodophenyl-2-aminopropane); EPSCs: Excitatory Postsynaptic Currents; GABA: γ–hydroxybutyric acid; mPFC: medial Prefrontal Cortex; PFC: Prefrontal Cortex; SSRIs: Selective Serotonin Reuptake Inhibitors

Introduction

Lithium was the first medication established as a mood stabilizer for the treatment of manic-depressive illness [1]. Lithium also has a well-documented track record demonstrating efficacy in augmenting the antidepressant effect for a number of different antidepressant drug classes including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and atypical antidepressants such as mianserin [2-4]. Lithium also possesses modest, though frank antidepressant properties when used in monotherapy [1]. Furthermore, lithium also appears to reduce suicide risk [5], though this effect may be most robust when used in combination with antidepressant and/or antipsychotic medications [6-8]. A number of suggestions have been raised over the last 30 years to account for these robust clinical effects ranging from the phosphoinositide depletion hypothesis to alterations in neurotrophic signaling cascades [9-12].

One strategy emphasized by Manji and colleagues over the last decade has been to compare the effects of lithium with valproate and carbamazepine to triangulate upon downstream intracellular processes that all three agents share in common and that may account for the mood-stabilizing properties of these drugs in patients with bipolar disorder. However, lithium also possesses other actions described above for which valproate and carbamazepine have not been demonstrated to be active (e.g., augmentation of antidepressants in unipolar depression, frank antidepressant action in unipolar depression, and antisuicide effects).

The 5-HT$_{2A}$ receptor coupled to G_q/G_{11} and phospholipase C may be a link between therapeutically relevant pharmacological actions lithium and other known antidepressants. Involvement of lithium in the phosphatidyl inositol pathway, more specifically the "inositol sink" hypothesis was one of the earlier widely accepted proposals

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to explain at least some of the therapeutic effects of lithium [9,10]. Interaction of lithium with 5-HT_{2A} receptors is of interest since most antidepressant drugs, outside the possible exception of fluoxetine and SSRIs, tend to decrease 5-HT_{2A} receptor density and sensitivity in the PFC [13,14]. Furthermore, the post-mortem findings in suicidal depressed patients suggest that an up-regulation of 5-HT_{2A} receptors may occur in certain regions such as Brodmann area 9 [15-17]. Conversely, clozapine, which potently blocks 5-HT_{2A} receptors in addition to other pharmacological effects, is known to decrease suicidality in schizophrenic patients [18]. Some authors have suggested that other atypical antipsychotics possessing potent 5-HT_{2A} receptor blockade (e.g., olanzapine) may also have some degree of similar action [19,20].

Evidence for lithium-induced changes in 5-HT_{2A} receptor binding and function in forebrain regions is mixed. For example two studies suggest that subchronic lithium treatment decreases 5-HT_{2A} receptor binding in the rat PFC [21,22] while several other studies suggest that there is no change in the rat or mouse [23,24]. With regard to transduction pathways downstream from the receptor, lithium also failed to alter the 5-$HT_{2A/2C}$ receptor-mediated arachidonate response in most cortical regions outside of several sensory areas [25]. The 1-(2,5-Dimethoxy-4-iodophenyl-2-aminopropane (DOI)-induced c-fos induction in the cortex is increased by both acute and subchronic lithium administration, despite lack of evidence in this report for changes in 5-HT_{2A} receptor binding with subchronic lithium treatment [24]. The most widely used behavioral model for 5-HT_{2A} receptor function, DOI-induced head shakes, is not altered by subchronic lithium administration except for an interaction with TCAs in ACTH-treated rats [26]. Given these conflicting findings, it is important to understand whether subchronic lithium treatment modulates the electrophysiological effects of 5-HT_{2A} receptor activation that by definition are generally measured in more homogeneous and discrete cellular compartments in different cortical regions such as the medial PFC and the piriform cortex.

Materials and Methods

Animals

Male Sprague-Dawley rats (n=51; Camm, Wayne, NJ) were 120-200 g at the beginning of subchronic lithium treatment (approximately 5-7 weeks in age). All rats were provided a 7 day adaptation period following arrival from the supplier. They were housed in suspended stainless steel wireless cages (18 x 36 x 20 cm) with two rats occupying each cage. The colony room was maintained at 20°C and relative humidity (60%). The room was illuminated 12 h/day (0700-1900 hr). All rats had free access to laboratory chow (Teklad 4% Rat Diet) and regular drinking water in addition to hypertonic saline during the treatment phase. The principles of laboratory animal care (NIH publication No. 80-23, revised 1996) were followed. All procedures were approved by the Yale University Animal Care and Use Committee.

Lithium treatment

All subjects were treated with either normal drinking water and hypertonic saline during the treatment phase to prevent dehydration. All rats either continued on Teklad 4% Rat Diet (sham treatment) or were fed pellets containing 0.24% (wt/wt) lithium carbonate for 7, 14 or 28 days (including availability of hypertonic saline to prevent dehydration). The only exception to the above conditions was a portion of subjects in the 5-HT_{2A} receptor desensitization experiment which were naïve to treatment (n=4), but were tested concurrently with the rats administered either the lithium-containing pellets or the sham diet treatment. An additional cohort of 13 rats were treated with lithium via the lithium-containing pellets or the sham treatment for 1 week prior to examining desensitization of 5-HT-induced EPSCs in the mPFC (n= 7, lithium; n=6, control). Overall, 29 rats were treated for 1, 2 or 4 weeks with lithium and compared with 35 control rats. Male Sprague-Dawley rats previously treated for 6 days to 4 weeks [27] have been found to have serum lithium levels within the target range for the acute treatment of bipolar patients (0.98 + 0.18 and 1.1 + 0.25 mM, respectively).

Brain slice preparation

Brain slices were prepared as described previously [14]. Briefly, rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and decapitated. Coronal slices (500 μM) were cut with an oscillating-blade tissue slicer at a level corresponding to approximately 2.5 mm anterior to bregma for recording from the medial Prefrontal Cortex (mPFC) or to approximately 2.2 mm anterior to bregma for recording from the anterior piriform cortex. A slice containing the mPFC or piriform cortex was then transferred to the stage of a fluid-gas interface chamber, which had a constant flow of humidified 95% O_2, 5% $C0_2$. The slices were perfused in a chamber heated to 34°C with normal ACSF, which consisted of 126 mMNaCl, 3 mMKCl, 2 mM $CaCl_2$, 2 mM $MgSO_4$, 26 mM $NaHC0_3$, 1.25 mM NaH_2P0_4, and 10 mM D-glucose.

Electrophysiological recording

Intracellular recording and single-electrode voltage clamping were conducted in prefrontal cortical layer V pyramidal cells by using an Axoclamp-2A (Axon Instruments, Inc., Foster City, CA) as previously described [14,28]. Stubby electrodes (~8 μm, shank to tip) with relatively low capacitance and resistance (30-60 MOhms) were filled with 1M potassium acetate. The cells were voltage clamped at -70 mV. Phase lag was used to prevent oscillations; false clamping was avoided by utilizing optimal capacitance neutralization and by allowing settling to a horizontal baseline, as verified by monitoring input voltage continuously. Layer V pyramidal cells were recorded in a zone one-half to two-thirds the distance between the pial surface and the white matter in the mPFC (anterior cingulate and prelimbic area; Cg1, Cg3). The Excitatory Postsynaptic Currents (EPSCs) recorded under these conditions do not appear to be contaminated by reversed inhibitory postsynaptic currents as previously discussed [28]. The voltage-clamp signals were low-pass filtered (1000 Hz) and data were acquired with a pCLAMP/Digidata 1200 system (Axon Instruments, Inc., Foster City, CA).

Extracellular recordings were conducted using an Axoclamp-2A (Axon Instruments, Burlingame, CA, USA) [29]. Placement of the recording electrodes was guided by visualizing the three layers of the piriform cortex at low magnification under reflected light. Extracellular recordings from interneurons located in layer III of the piriform cortex were made using glass microelectrodes filled with 2 M NaCl (5-10 MOhms) as described previously [29]. Cells were found by searching while the slice was perfused with 30 μM 5-HT in order to activate quiescent cells. 5-HT was applied for no longer than

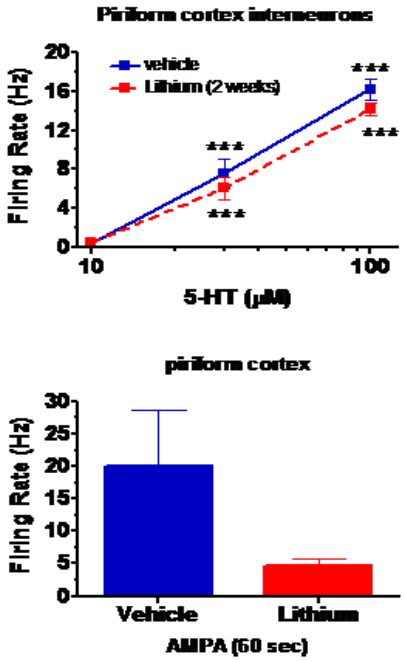

Figure 1: Repeated daily treatment with lithium fails to alter the activation of piriform cortical interneurons in the piriform cortex induced by 5-HT2A receptor activation but does alter the activation induced by AMPA. Top panel: Subchronic lithium administration (14 days; n=8) does not modulate the firing rate induced by 5-HT (10-100 μM) of piriform cortical interneurons compared to interneurons from sham-treated rats (n=10). Bottom panel: The firing rate of these same piriform cortical interneurons induced by AMPA (5 μMx60s) was significantly attenuated by lithium treatment compared interneurons from sham-treated rats.

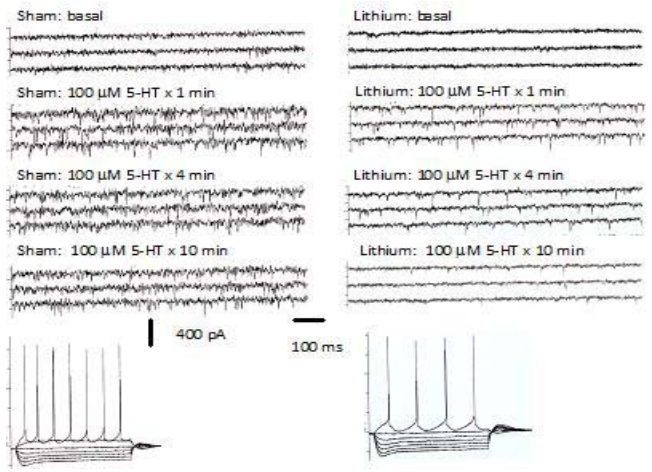

Figure 2: Repeated daily sham or lithium treatment enhances desensitization of 5-HT-induced synaptic currents from mPFC pyramidal neurons mediated by activation of 5-HT2A receptors. Left panel: Subchronic sham administration does result in desensitization of 5-HT-induced EPSCs at 4 or 10 min compared to the initial result following 1 min bath application of 5-HT. The inset at the bottom shows the voltage-current relationship for a layer V pyramidal cell with an initial 0.4 nA current followed by -0.2 nA current steps. Right panel: Subchronic lithium administration (p.o. for 14 days; n=4) does appear to enhance the desensitization of synaptic currents induced by 5-HT2A receptor activation (100 μM 5-HT) compared to neurons from sham-treated rats (n=9). The inset at the bottom of the right-hand panel shows the voltage-current relationship for a layer V pyramidal cell with an initial 0.2 nA current step followed by -0.2 nM current steps. This neuron from a lithium-treated rat was recorded the one day prior to the neuron from the sham-treated rat shown in the left panel.

15 min and was turned off for an equivalent period if necessary to search for an additional cell. Cells identified as interneurons had the ability to sustain rapid firing rates as previously characterized by both intracellular and extracellular recording [29,30]. Once an interneuron was located, the solution was switched from 30 μM 5-HT back to control ACSF and the 5-HT activated cells gradually slowed and, in almost all cases, ceased firing. Then the effects of 5-HT creatine sulfate (Sigma Chemical Co., St. Louis, MO, USA) and α amino-3-hydroxy-5-methyl-isoxazoleproprionate (AMPA; RBI, Natick, MA, USA) were tested. It should be noted that continuous 5-HT application has not been found to produce significant tachyphylaxis (>10-15%) of the 5-HT-induced firing rate in the piriform cortex either when measured during continuous application or when measuring the steady-state response to 30 μM 5-HT with 15 min durations between consecutive applications (not shown).

Data analysis

For the intracellular recordings, EPSC frequencies were obtained from 10 consecutive episodes (1 s duration) during the baseline and drug treatment periods. EPSC frequencies were determined with Axograph peak detect software; signals <10 pA were excluded from the measurements. The determination of EC_{50} values for the suppression of 5-HT-induced increases in EPSC frequency were calculated by nonlinear curve fitting (Graphpad Prism; www.Graphpad.com). For the extracellular recordings, the total number of spikes for each concentration of 5-HT (10, 30, 100 and 300 μM) was recorded. A two-factor (5-HT concentration and drug treatment) repeated measures ANOVA was performed. Post-hoc follow-up of significant results utilized the Newman-Keuls test. Comparisons for treatment effects on AMPA-mediated responses utilized a paired t-test. Significance levels was set at $p<0.05$.

Results

Subchronic lithium: Piriform cortical interneurons

A two-week exposure to lithium carbonate, in concentrations previously demonstrated to alter downsteam intracellular transduction pathways for surface G-protein coupled receptors, failed to result in a significant effect for the lithium exposure *vs.* sham treatment ($F(1,16)=1.81$, $p=0.197$; Figure 1) when examining 5-HT-induced activation of GABAergic interneurons of the piriform cortex (n=8 lithium treated rats; n=10 control rats). An expected highly significant effect of 5-HT concentration was found ($F(3,48)=175.57$, $p<0.001$). The interaction of these two factors was not significant ($F(3, 48)=0.933$, $p=0.43$). In a subset of these cells, subchronic lithium exposure did attenuate the response of piriform interneurons to bath application of AMPA (5 μM; $t(7)=2.82$, $p<0.05$; Figure 1; lithium n=6; control n=3). Extending the lithium exposure to a four week period did not appear to alter the 5-HT concentration-response curve in limited set of cells (n=4, lithium; n=3, sham treatment, not shown).

Subchronic lithium: PFC layer V pyramidal cells

All of the layer V pyramidal cells recorded from in the mPFC were regularly spiking pyramidal cells, similar to those previously described (Figure 2). In current clamp, 5-HT did not induce action potentials in any of these cells as expected when using slices from

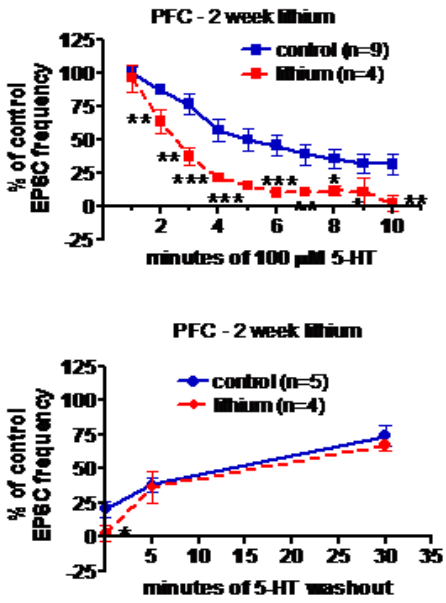

Figure 3: Repeated daily treatment with lithium enhances desensitization of 5-HT-induced synaptic currents from mPFC pyramidal neurons mediated by activation of 5-HT2A receptors. Top panel: Subchronic lithium administration (p.o. for 14 days; n=4) does enhance desensitization of excitatory synaptic currents induced by 5-HT2A receptor activation (100 µM 5-HT) compared to neurons from sham-treated rats (n=9). Bottom panel: The recovery of 5-HT-induced EPSCs following a 10 min exposure of rat PFC slices was similar for both lithium-treated (n=4) and sham-treated (n=5) rats.

rats 21 days of age and older [31]. 5-HT did induce spontaneous (not electrically-evoked) EPSCs when recording under voltage clamp (Figure 2). Consistent with previous work [28,32] in preliminary experiments the 5-HT-induced EPSCs increased in a concentration-dependent manner from 3 to 300 µM with a near maximal effect at 100 µM, independent of treatment condition (n=2, p.o. lithium treatment x 2 weeks, n=2, sham treatment). Previous studies with tricyclic antidepressant imipramine had revealed an obvious down-regulation of the 5-HT concentration response for imipramine *vs.* control treated rats after just the first two subjects in each condition [14]. Since this apparent lack of effect of lithium on the 5-HT concentration-response relationship in the PFC was highly similar to the lack of effect observed in the piriform cortex, additional experiments addressed the effect of lithium on the potential desensitization of the 5-HT-induced EPSCs.

5-HT (100 µM)-induced EPCs demonstrated a relatively rapid tachyphylaxis consistent with a previous report [33]. The frequency of 5-HT-induced EPSCs recorded from prefrontal cortical cells with a sham treatment decreased to 50% of control following 5 min of continuous 5-HT exposure to the slice (Figure 3). The 5-HT response was only ~32% of control values following 9-10 min of continuous 5-HT perfusion on the slice. Overall, a significant effect of time was seen with continuous 5-HT exposure to the slice ($F(10, 110)=72.7$, $p<0.001$). A significant effect of chronic oral lithium treatment (2 weeks; $F(1,11)=8.55$, $p<0.05$) was also observed. The frequency of 5-HT-induced EPSCs recorded from cells of lithium-treated rats were reduced to 22% of the original frequency after 4 min and continued to decline to 5% of the original frequency after 10 min (n=4). A significant interaction of lithium treatment x time was also found ($F(10, 110)=3.08$, $p<0.0017$). The pattern of 5-HT desensitization was similar for the rats have to treatment (n=4) and the rats administered the sham treatment (n=5), thus these two groups were combined for the control condition in this experiment.

In contrast to the acceleration and apparent increased maximal desensitization of 5-HT-induced EPSCs following two weeks of oral lithium treatment, the resensitization of 5-HT-induced EPSCs was similar for both the lithium and sham treatment groups at the 5 and 30 min time points. Five minutes after turning off the 5-HT bath application, the frequency of 5-HT-induced EPSCs was 38 and 37% for the lithium and sham treatment groups, respectively. Thirty minutes following the end of the 10 min exposure of the slice to continuous bath 5-HT application, the frequency of the 5-HT-induced EPSCs was 74 and 67 % of the lithum and sham treatment group's original 5-HT response (n=4, lithium treated rats; n=5, control rats).

Unlike the results following 2 weeks of lithium administration, a 1 week treatment with lithium did not significantly enhance the desensitization of 5-HT-induced EPSCs (not shown). The frequency of 5-HT-induced EPSCs recorded from prefrontal cortical cells with a sham treatment decreased to 60% of control following 5 min of continuous 5-HT exposure to the slice; and further decreased to only ~40% of control values following 9-10 min (n=6), of continuous 5-HT perfusion on the slice. Following a 1 week lithium treatment, the frequency of 5-HT-induced EPSCs decreased to ~45% after 5 min and ~ 27% following 10 min of continuous 5-HT exposure.

Discussion

The present results are the first intracellular recordings from prefrontal cortical pyramidal cells that measure a 5-HT_{2A} receptor-mediated response following daily treatment with lithium. The main finding from the present study is that lithium enhanced desensitization of 5-HT-induced EPSCs in the mPFC during extended bath application of 5-HT, despite a lack of effects ofsubchronic lithium treatment on the initial steady-state frequency of 5-HT-induced EPSCs in the mPFC/neocortex. Since the 5-HT-induced EPSCs are mediated indirectly through activation of AMPA receptors, by extrapolation the present results is consistent with the hypothesis that lithium does not alter these AMPA responses in the mPFC [28,34]. The failure of a two week period of lithium treatment to alter excitatory synaptic currents induced by 5-HT_{2A} receptors is consistent with the general lack of effect of lithium on 5-HT_{2A} receptor binding in the prefrontal cortex and neocortex [23,24], although exceptions have been noted [21,22]. Subchronic treatment with a tricyclic antidepressant drug which is well-known to down-regulate 5-HT_{2A} receptors, imipramine, did induce a marked down-regulation in 5-HT-induced EPSCs without a significant change on AMPA responses in the PFC [14]. In contrast, subchronic treatment with the SSRI fluoxetine, which has generally not resulted in a change in 5-HT_{2A} receptor density also did not alter the concentration-response relationship for the 5-HT-induced EPSC frequency [13]. While subchronic lithium treatment did accelerate desensitization of the 5-HT-induced EPSCs, lithium did not prevent resensitization of the 5-HT-induced EPSCs. One limitation in the interpretation of these preliminary findings is whether the desensitization of 5-HT-induced EPSCs was due to an effect on the 5-HT_{2A} receptor and its transduction pathway versus an effect on regulation of AMPA receptor-mediated responses. Nonetheless, these results are consistent with some previous findings

generally failing to observe an effect of lithium on 5-HT_{2A} receptor regulation in the PFC or other regions. These present results on the enhanced desensitization of 5-HT-induced EPSCs in the rat mPFC are also striking given the consistency of the time course of 5-HT-induced EPSC desensitization in the present experiments compared to a previous study [13].

In addition to recording a 5-HT_{2A} response involving modulation of excitatory synaptic currents in glutamatergic layer V pyramidal cells of the PFC, we also examined the excitatory response of a subpopulation of GABAergic interneurons in the piriform cortex in response to 5-HT (mediated by 5-HT_{2A} receptor activation) and AMPA, respectively. Like in the PFC, the 5-HT concentration-response relationship or the maximal 5-HT response of piriform interneurons was not altered by subchronic lithium treatment (2-4 weeks). Still unknown is whether subchronic lithium treatment might alter 5-HT_{2A} receptor trafficking for these piriform cortical interneurons, which show relatively little desensitization in response to prolonged exposure (10-15 min) to 5-HT. However, the AMPA response of these same interneurons was attenuated by subchronic lithium treatment. This finding is similar in valence to the effect of lithium on AMPA responses reported from the hippocampus where subchronic lithium decreased hippocampal synaptosomal GluR1 levels and also attenuated GluR1 phosphorylation at a specific PKA site (GluR1p845) thought to be important for AMPA receptor reinsertion into the membrane [35]. The attenuation of GluR1 expression in the hippocampus was related to potential antimanic effects as chronic imipramine exerted an effect on GluR1 expression in the opposite direction. Similarly, mood-stabilizing agents with predominantly clinical antidepressant profiles (e.g., lamotrigine and riluzole) also enhanced surface expression of AMPA receptor subunits unlike a mood stabilizer (valproate) with a predominantly antimanic action [36].

The physiological significance of the relatively slow developing desensitization of 5-HT-induced EPSCs in the mPFC is might be related to demonstrated augmentation by lithium of most antidepressant drugs in depressed patients. Furthermore, the observation that subchronic lithium treatment enhances desensitization of 5-HT_{2A} receptors in the mPFC is intriguing in light of the role that 5-HT_{2A} receptors play in certain forms of impulsivity that may be related to mood disorders and suicide. For example, activation or blockade of 5-HT_{2A} receptors enhance or attenuate, respectively, impulsivity as measured in the 5-Choice Serial Reaction Time Test (5-CSRTT) and Differential-Reinforcement-of Low rate (DRL) schedules of reinforcement [37-42]. A polymorphism of the non-protein coding region of the 5-HT_{2A} receptor gene was associated with lack of tolerability (including agitation and sleep disturbances) for high dose paroxetine in a group of elderly patients [43]. Two different polymorphisms of the 5-HT_{2A} receptor were also associated with impulsivity as assessed by a Go/No-go task and the continuous performance task [44,45]. An increase in the density of 5-HT_{2A} receptors in the PFC (especially Brodmann area 9) has been reported in some, though not all, studies of suicide victims with a diagnosis of either depression or schizophrenia or alcoholism [16,17, 46-48]. Conversely, most antidepressant drugs, with the general exception of Selective Serotonin Reuptake Inhibitors (SSRIs), down-regulate cortical 5-HT_{2A} receptors.

The potential interaction between tricyclic antidepressants and lithium at the level of regulating 5-HT_{2A} receptor trafficking is especially intriguing given the clinical data that lithium can augment the effects of tricyclic antidepressants with respect to antidepressant actions [4]. Additional preclinical experiments studying DOI-induced head twitches have found a pharmacodynamics interaction between these different therapeutic agents at least under some condition [26]. These relationships raise the question as to what are the effects of combined treatment with lithium and a tricyclic antidepressant on both serotonergic and glutamatergic signaling in the mPFC. This potential pharmacodynamic interaction between tricyclic antidepressants and lithium may be relevant in attempting to account for evidence that lithium decreases suicide risk when combined with other treatments (tricyclic antidepressants and antipsychotic drugs) that down-regulate PFC 5-HT_{2A} receptors [6-8]. These present results add to past results demonstrating that subchronic lithium treatment, when added to SSRIs, monoamine oxidase inhibitors and tricyclic antidepressants increase tonic activation of 5-HT_{1A} receptors in the hippocampus [49]. Further work will be of interest in understanding how downstream intracellular signaling pathways for antidepressant drugs and lithium interact to produce the myriad clinical effects of these drugs both alone and in combination with each other.

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