Lithium acts as a potentiator of AMPAR currents in hippocampal CA1 cells by selectively increasing channel open probability

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Recent evidence suggests that lithium, which is used in the treatment of bipolar disorders, may act by influencing AMPAR properties at central glutamatergic synapses. While it is clear that lithium potentiates recombinant AMPAR responses in a subunit specific way, the origin of this potentiation is not known. We examined the effects of lithium on native AMPAR channels in CA1 pyramidal cells in hippocampal slices where AMPARs are expected to be associated with auxiliary subunits. We found that lithium produced a selective increase in single-channel open probability (P_{open}), with little effect on single-channel conductance or burst length. From the present and previous finding it is likely that lithium causes a reduction in the time to recovery from desensitization, resulting in the observed increase in P_{open}. This would be consistent with the view that lithium acts like certain other allosteric AMPAR modulators to reduce the time spent in the desensitized state, but differs from those that act by slowing dissociation of glutamate.

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Introduction

Lithium has long been used in the treatment of manic depressive disorders (bipolar disorders). Although the mechanism of the therapeutic action of this simple monovalent cation has been widely studied (reviewed by Zarate *et al.* 2003), little is know about its effects on AMPAR channels. These are possible targets for a number of centrally acting molecules (Rogawski, 2006) as they underlie the majority of fast excitatory transmissions at central synapses. Furthermore, there is increasing evidence that glutamate and its receptors play a role in depression (Paul & Skolnick, 2003; Du *et al.* 2004*a*; Alt *et al.* 2006), although the underlying mechanism is unclear. In CA1 cells, the EPSP field potentials and intracellular EPSCs are enhanced by exposure to Li^+ (3–30 mM) (Rinaldi *et al.* 1986; Keinanen *et al.* 1990; Valentin *et al.* 1997; Colino *et al.* 1998), without obvious change in the EPSC kinetics. It has been suggested that this enhancement may reflect increased transmitter release, related to a broadening of the presynaptic action potential (Colino *et al.* 1998). Furthermore, it has been reported that Li^+ produces an increase in the current mediated by recombinant AMPARs expressed in frog oocytes (Karkanias & Papke, 1999*a*). This effect is AMPAR subunit specific, with GluA3 and GluA2/3 receptors exhibiting the greatest enhancement (Karkanias & Papke, 1999*b*).

In principle, the increase in the AMPAR current could reflect an increased channel conductance, a higher channel open probability and/or a reduced desensitization of AMPARs giving rise to prolonged bursts of channel openings. However, the origin of the potentiation remains unknown.

Here we have examined the effects of Li^+ on single AMPAR channels in excised patches from CA1 pyramidal cells in hippocampal slices. At this age the AMPAR channels expressed in these cells are thought to be predominantly GluA2/GluA3 and GluA1/GluA2 assemblies (Keinanen *et al.* 1990; Wenthold *et al.* 1996). Our experiments indicate that lithium selectively increases the channel open probability with little effect on single-channel conductance or burst length of openings. In this respect, Li^+ appears to differ from other well studied AMPAR potentiators, which are suggested to act primarily by slowing down dissociation of the transmitter from the receptor (deactivation), or by altering receptor desensitization (O'Neill *et al.* 2004; Alt *et al.* 2006).

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Methods

Solutions, drugs and chemicals

Hippocampal slices were prepared in ice-cold external solution of the following composition (mM): 125 NaCl, 2.5 KCl, 1 $CaCl_2$ 2 $MgCl_2$, 25 $NaHCO_3$, 1.25 NaH_2PO_4, 25 glucose, 1 kynurenic acid; pH 7.4. The external solution contained (mM) 125 NaCl, 3 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 25 $NaHCO_3$, glucose, 1 μM tetrodotoxin (TTX; Sigma), 10 μM SR95531 (Tocris Cookson, Bristol), 2 μM strychnine (Sigma), 2 CsCl; pH 7.4. The external solution also contained the NMDA receptor blocker AP5 (50 μM) and 7-chlorokynurenic acid (20 μM). The non-competitive AMPAR antagonist SYM 2206 (20 μM) (Tocris Cookson, Bristol) was added to the external solution in some experiments. Patch pipettes contained an 'intracellular' solution of (mM): 125 CsCl, 10 Hepes, 10 BAPTA, 10 TEA-Cl, 1 *N*-(2,6-dimethylphenylcarbamoylmethyl) triethyl ammonium bromide (QX314), 2 Na_2ATP, 2 MgATP, 0.3 Na_3GTP, and 0.5 $CaCl_2$, adjusted to pH 7.25 with CsOH. Lithium chloride was added to the external solution to give a final concentration of 10 mM. We did not compensate for changes in osmolarity or ion concentration.

Preparation of hippocampal slices, and single-channel recording methods

Hippocampal slices were prepared in accordance with the UK Animals (Scientific Procedures) Act 1986. In brief, following decapitation of 12-day-old rats (P12) the brain was rapidly removed as previously described (Gebhardt & Cull-Candy, 2006). Slices were maintained in a chamber containing slicing solution saturated with 95% O_2–5% CO_2, pH 7.4 and kept at room temperature for at least 1 h. For electrophysiological examination, slices were viewed with an Axioskop-FS microscope (Zeiss, Welwyn Garden City, UK).

Glutamate at 20 mM was used for most of the single-channel recordings reported here, as this concentration gave the best resolved single-channel openings (see Gebhardt & Cull-Candy 2006). We obtained qualitatively similar results with 10 and 20 μM glutamate or 1 μM AMPA, where the change in osmolarity was considerably less. Single-channel currents measured between −100 and +60 mV gave an interpolated reversal potential close to 0 mV suggesting that this parameter was not detectably modified by the change in osmolarity.

Patch-pipettes were fabricated from thick-walled borosilicate glass capillaries (GC-150F; Harvard Apparatus Ltd, Edenbridge, UK), coated with Sylgard resin (Dow Corning, USA) and fire polished to a resistance of 10–12 MΩ. Outside-out patches were excised from visually identified pyramidal neurones in the CA1 layer. A root mean square noise level of <0.300 pA (bandwidth 5 kHz) was considered acceptable for recordings. Steady-state single-channel activity was recorded at room temperature with an Axopatch 200A clamp amplifier (Molecular Devices, Sunnyvale, CA, USA) and stored on digital audio tape (DC – 20 kHz; DTR-1204; BioLogic, Claix, France). Patches were examined over a range of potentials, but most of the single-channel data included here were obtained in outside-out patches held at −100 mV, to optimize resolution of single-channel events.

Data acquisition and analysis

Except for Fig. 1, where all point amplitudes were derived using Origin (OriginLab Corp., Northampton, MA, USA), all digitized records were analysed using SCAN (http://www.ucl.ac.uk/Pharmacology/dc.html; Colquhoun & Sigworth, 1995), as previously described (see Gebhardt & Cull-Candy, 2006 for further details). Distributions of amplitudes and open and shut times were formed from the time course fitted data. Data given are ± S.E.M.

Results

Experiments on recombinant AMPARs have demonstrated that the effects of lithium are subunit specific (Karkanias & Papke, 1999*a*,*b*). Li^+ has a marked potentiating effect on AMPARs, particularly GluA3-containing assemblies. We have attempted to determine the change in single-channel properties responsible for this potentiation in hippocampal CA1 cells.

Figure 1 shows the effect of lithium on single AMPAR-channels activated by 20 mM glutamate applied to an outside-out patch from a CA1 cell visually identified in an acutely isolated hippocampal slice. In these cells, glutamate application onto isolated membrane patches activates predominantly AMPARs (Spruston *et al.* 1995; Gebhardt & Cull-Candy, 2006). As is apparent from the figure, in patches where discrete single-channel openings could be readily distinguished under control conditions, the application of lithium greatly enhanced channel activity. While some individual openings could still be identified, many were superimposed and could no longer be individually resolved.

To quantify this potentiation, we constructed all point amplitude histograms for patches examined before and during lithium application. Figure 1*B* shows a typical example; each histogram was fitted with multiple Gaussian components. The area of the component that represented the time during which all channels were closed (0 pA; grey component) was significantly decreased in the presence of lithium (Student's *t* test <0.05). Its mean area decreased

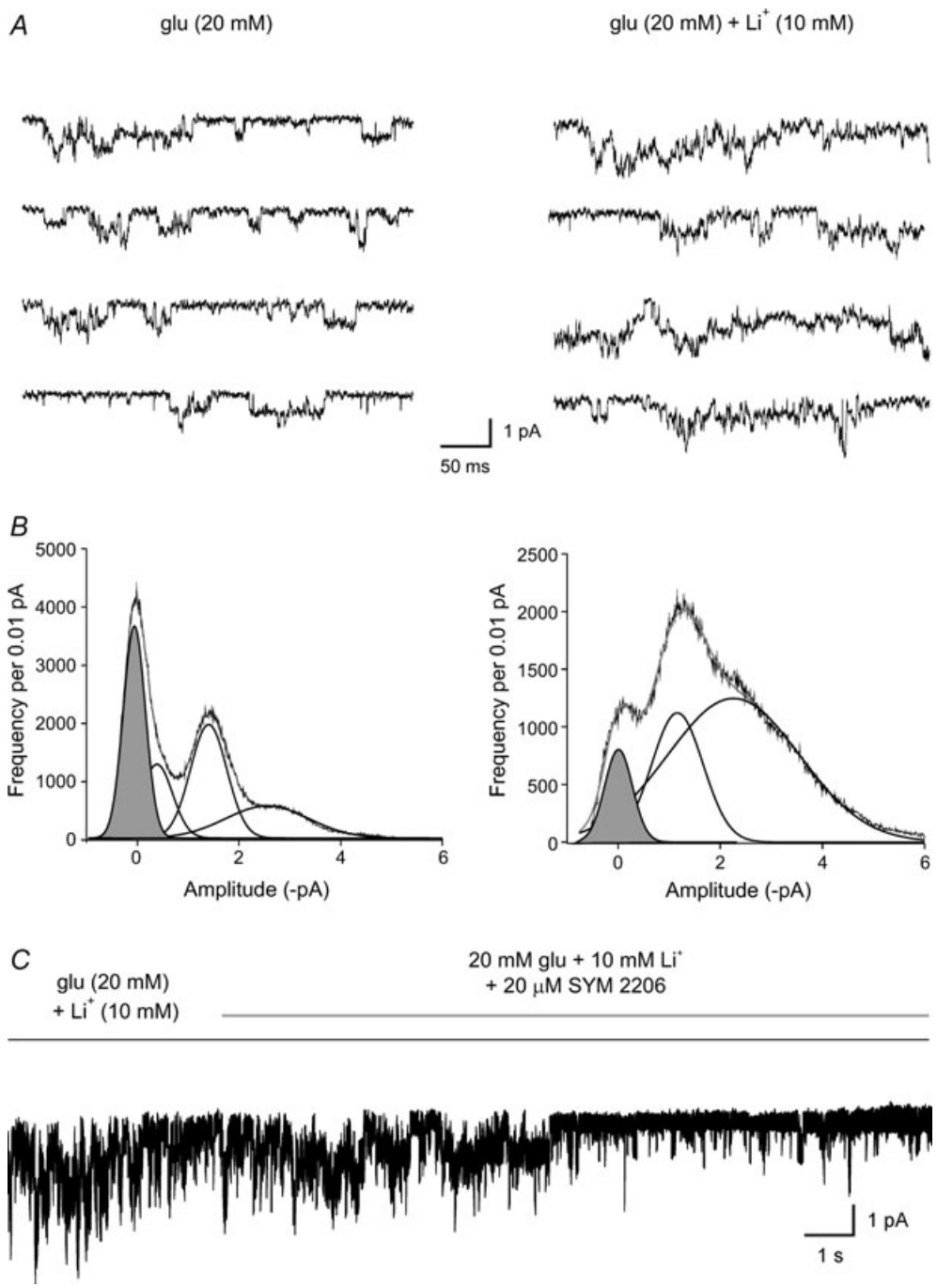

Figure 1. Effect of 10 mM lithium on single AMPA channel currents in CA1 cells
A, single-channel currents activated by 20 mM glutamate applied to an outside-out patch from a CA1 cell in control conditions (left-hand panel) and during exposure to 10 mM Li^+ (right-hand panel). Note the marked potentiation in channel activity in the presence of Li^+. *B*, all point amplitude histograms of the single-channel currents depicted in *A*, to illustrate the effect of Li^+ on charge transfer. The total time was the same for each data set. Histograms were fitted with multiple Gaussian components. The area under the Gaussian that represents the time during which all channels were in the closed state (0 pA; grey component) was decreased from 35% in the absence of Li^+, to 10% in the presence of Li^+; this change was statistically significant (see text). *C*, block of potentiated channel activity following bath application of the AMPA receptor antagonist SYM 2206 (20 μM). $V_m = -100$ mV; data were low-pass filtered at 1 kHz and digitized at 20 kHz.

from 35% of total (in control) to 9.6% in the presence of lithium (35 ± 9.0% in control *vs.* 9.6 ± 1.7%; $n = 5$ in Li^+, data from different animals). We found that this action of lithium was readily reversible. Furthermore, as shown in Fig. 1*C*, the potentiated current in the presence of Li^+ was rapidly blocked by bath application of the AMPAR antagonist SYM 2206.

To determine whether Li^+ was acting to modify the single-channel conductance or the kinetic properties of the channels, we used time-course fitting to analyse those openings that could be directly resolved (see Methods). This approach inevitably resulted in the exclusion of many events activated in the presence of Li^+. Furthermore, we restricted this analysis to three patches that showed a sufficiently large number of discrete events. Figure 2*A* illustrates an example of the single-channel current amplitude distributions, before and during application of Li^+. Only those transitions, from the closed to open state, with duration >1 ms were included in the amplitude histograms; furthermore, openings <0.2 pA could not be resolved from background noise and were therefore not included. In the example shown, the mean single-channel conductance was decreased slightly, from 13 pS in control to 10 pS in the presence of Li^+. The mean amplitude in 20 mM glutamate was 11.2 ± 0.2 pS ($n = 6$) in normal external solution and 10.7 ± 0.4 pS ($n = 3$) in the presence of 10 mM Li^+; this difference was not significant ($P > 0.05$, Student's t test). The open period distributions (Fig. 2*B*) were fitted with three exponential components. The time constants (and their relative areas) were estimated to be $\tau_1 = 0.3 \pm 0.1$ ms (35 ± 6%), $\tau_2 = 2.9 \pm 0.1$ ms (41 ± 6%) and $\tau_3 = 4.7 \pm 0.9$ ms (24 ± 4%). We found no significant change in the time constants of any of these components (see Table 1).

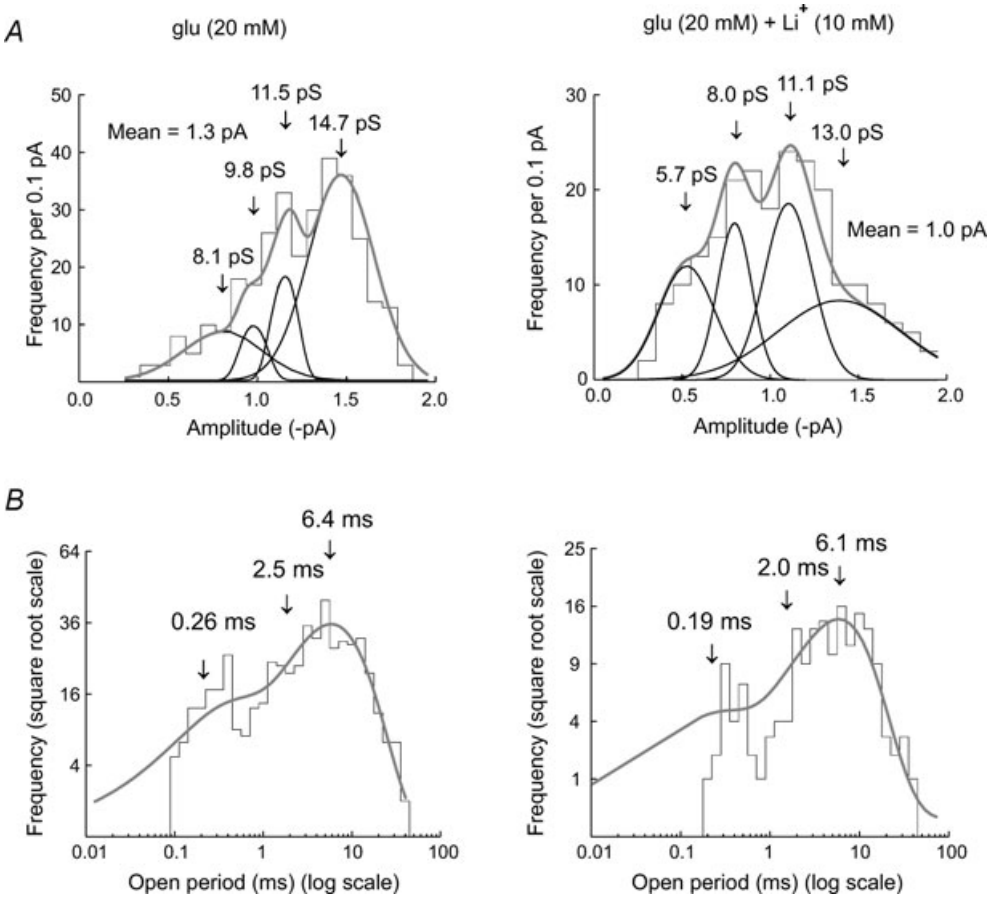

Figure 2. Lithium caused a small decrease in single-channel conductance, with no change in open period
A, amplitude distributions of single-channel currents activated by 20 mM glutamate. Histograms were fitted with multiple Gaussians in the absence (left) or presence (right) of Li^+ . The mean conductance value estimated for each Guassian is indicated by arrow. In this patch, the mean single-channel current amplitude decreased from 1.3 pA in control conditions to 1.0 pA in Li^+. Only transitions from the closed state with openings >1 ms, were included in distributions. *B*, open-period histograms in the absence and presence of Li^+, fitted with three exponential components; arrows indicate estimated time constants. There was no statistically significant change in open periods measured in the presence of Li^+ (see text). All distributions (in this and subsequent figures) were obtained from the time-course fitting method for analysis of events (see Methods); $V_m = -100$ mV.

Table 1. Distribution of open periods and burst lengths

Open periods	τ_1 (ms)	τ_2 (ms)	τ_3 (ms)	n
20 mM glutamate	0.15 ± 0.01 (37 ± 2)*	2.1 ± 0.2 (35 ± 4)	5.8 ± 0.7 (28 ± 5)	9
20 mM glutamate + 10 mM lithium	0.3 ± 0.1 (35 ± 6)	2.9 ± 0.1 (41 ± 6)	4.7 ± 0.9 (24 ± 4)	3
20 mM glutamate + 20 μM Sym 2206	0.21 ± 0.06 (34 ± 7)	2.9 ± 0.1 (48 ± 7)	4.7 ± 0.9 (18 ± 6)	5
20 mM glutamate + 20 μM Sym 2206 + 10 mM lithium	0.19 ± 0.08 (35 ± 12)	2.23 ± 0.3 (46 ± 11)	5.2 ± 0.5 (21 ± 3)	3

Burst length	τ_1 (ms)	τ_2 (ms)	τ_3 (ms)	Mean number of openings per burst
20 mM glutamate	0.24 ± 0.04 (40 ± 2)	2.9 ± 0.4 (31 ± 3)	9.1 ± 0.6 (29 ± 4)	1.61 ± 0.01
20 mM glutamate + 10 mM lithium	0.28 ± 0.07 (37 ± 5)	2.2 ± 0.7 (42 ± 4)	9.8 ± 0.8 (21 ± 6)	1.45 ± 0.08
20 mM glutamate + 20 μM Sym 2206	0.21 ± 0.08 (35 ± 6)	2.4 ± 0.5 (40 ± 5)	10.4 ± 0.9 (25 ± 5)	1.41 ± 0.05
20 mM glutamate + 20 μM Sym 2206 + 10 mM lithium	0.25 ± 0.1 (24 ± 6)	1.7 ± 0.3 (50 ± 5)	10 ± 0.6 (26 ± 6)	1.48 ± 0.07

*Numbers in parenthesis are relative areas (%).

These observations would be consistent with a view that the enhanced activity in the presence of Li^+ cannot be accounted for by an increase in single-channel conductance, or a change in open period. This therefore suggests that potentiation by Li^+ arises from an increase in channel open probability. However, as analysis of these data involved selectively examining only those events that remained well resolved, it could be argued that such openings arose predominantly from AMPAR channels that were unaffected by Li^+.

To overcome this problem it was necessary to reduce channel activity, and hence allow the resolution of all events. To accomplish this, while retaining well resolved single-channel openings, we combined a high concentration of glutamate (20 mM) with the AMPAR blocker SYM 2206. In these conditions the level of receptor occupation is expected to be high. We first examined the effect of this compound on AMPAR channels, to determine whether it altered their single-channel conductance or kinetic properties. As expected, the application of 20 μM SYM 2206 greatly reduced the glutamate evoked channel activity (Fig. 3*A*). In these conditions mean single-channel conductance was slightly reduced by SYM 2206, from 12.9 pS in control conditions to 10 pS in the presence of the antagonist (Fig. 3*B*). Similar results were obtained in four patches. The mean conductance in the presence of SYM 2206 was estimated to be 10 ± 1 pS ($n = 5$, $P \geq 0.05$, Student's t test). Furthermore, from the distributions shown in Fig. 3*C*, the open periods were unaffected by the presence of SYM 2206. The time constants were estimated to be $\tau_1 = 0.21 \pm 0.06$ ms (34 ± 7%), $\tau_2 = 2.9 \pm 0.1$ ms (48 ± 8%) and $\tau_3 = 4.7 \pm 0.9$ ms (18 ± 6%) ($n = 5$) (see Table 1).

As SYM 2206, by itself, did not significantly alter the kinetic properties of the channels and caused only a slight change in channel conductance, it was possible to use this compound to reduce channel activity. Figure 4*A* depicts a patch with a high level of glutamate activated channel activity in the presence Li^+ (left). Following application of 20 μM SYM 2206 (right), the number of superimposed openings was markedly reduced, facilitating analysis of virtually all events activated in the patch. Open period histograms could be adequately fitted with the sum of three exponential components (Fig. 4*B*). Our analysis of the open periods, under these conditions, demonstrated no significant change in any of the components. Furthermore, analysis of burst length indicated that none of the exponential components were significantly changed in the presence of Li^+. The time constants (and their relative areas) were: $\tau_1 = 0.25 \pm 0.1$ ms (24 ± 6%), $\tau_2 = 1.7 \pm 0.3$ ms (50 ± 5%) and $\tau_3 = 10.0 \pm 0.6$ ms (26 ± 6%) ($n = 3$ patches). The slowest component of the channel burst length distribution corresponds well to the decay time of EPSCs previously described in these cells (Hestrin *et al.* 1990; Spruston *et al.* 1995; Jonas 2000). The fact that the slowest component observed in the presence of Li^+

remains unchanged is consistent with the view that the kinetic properties of the AMPAR channels were unaffected by Li^+, underlining our conclusion that Li^+ acts as an AMPAR potentiator by increasing the open probability of the channels.

Discussion

Our main findings are as follows. Li^+ produced a marked increase in AMPAR open probability, without an accompanying change in single-channel conductance, open period or burst length. The absence of a change

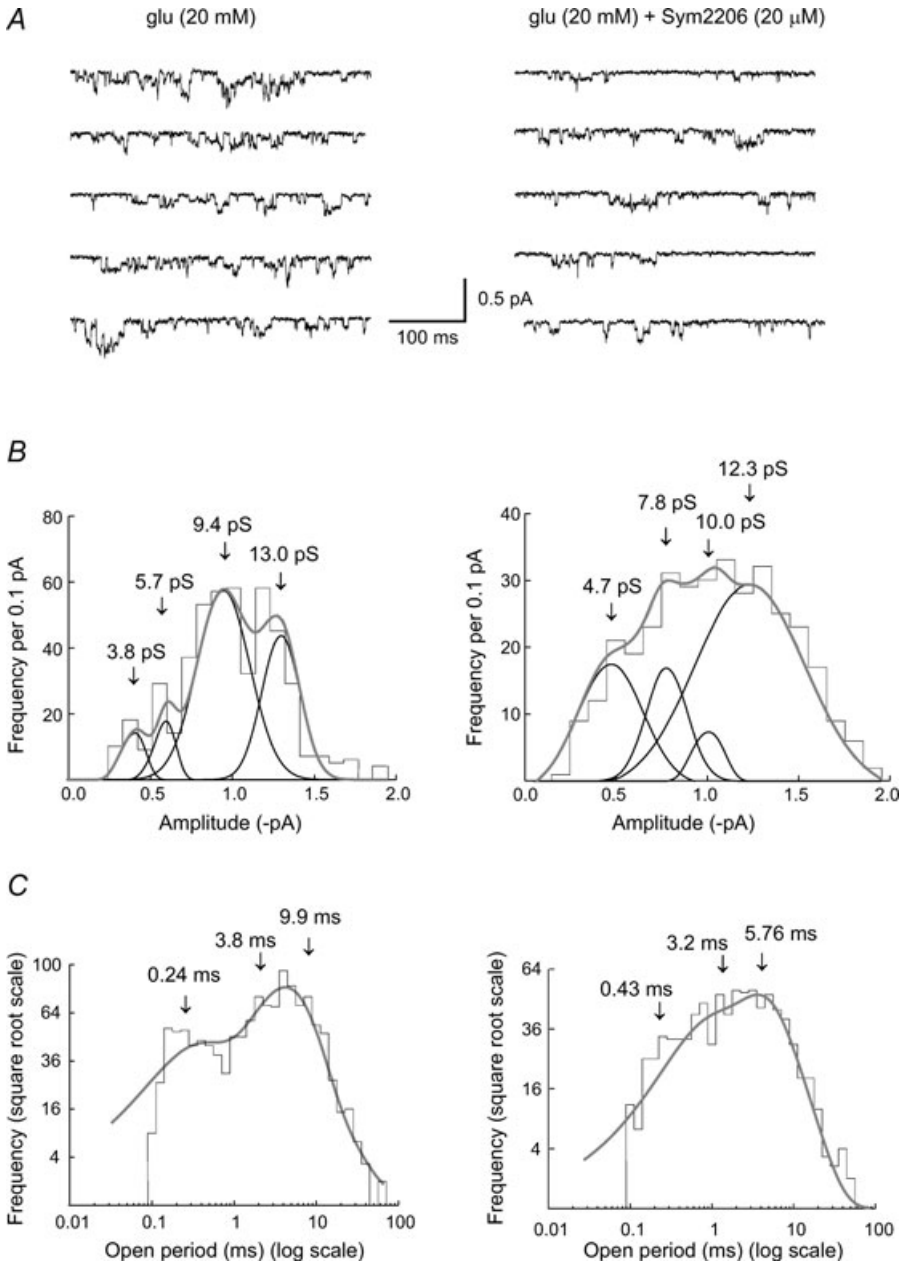

Figure 3. Use of a low concentration of the AMPAR antagonist, SYM 2206A, did not alter channel open period

A, single-channel currents in an outside-out patch exposed to 20 mM glutamate in control conditions (left) and in the presence of 20 μM SYM 2206 (right). *B*, corresponding amplitude distributions fitted with multiple Gaussians in the absence and presence of SYM 2206. The mean current amplitude decreased from 1.29 pA in control conditions to 1.0 pA in the presence of SYM 2206; the decrease was statistically significant (see text). *C*, open period distributions in the absence and presence of SYM 2206. Distributions were fitted with three exponential components; arrows indicate estimated time constants. Open periods were not significantly altered in the presence of SYM 2206. $V_m = -100$ mV; data were low-pass filtered at 1 kHz and digitized at 20 kHz.

in burst length is consistent with previous experiments in which extracellular Na^+ was completely replaced by Li^+ to inhibit glutamate uptake (Tong & Jahr, 1994). This also produced no apparent change in the decay time of spontaneous mEPSCs (Diamond & Jahr, 1997). Furthermore, the increased open probability that we have identified can fully account for the increase in AMPAR-mediated currents previously described for recombinant AMPARs in oocytes (Karkanias & Papke, 1999*a*). The therapeutic concentration of lithium is between 0.6 and 1.2 mM (see Cordeiro *et al.* 2003; Du *et al.* 2004*b*), and hence roughly 10 times less than that used in our experiments. By showing that single-channel conductance and kinetics were unaltered, we can therefore be reasonably confident these parameters are unaffected in the therapeutic range. We think our data make it likely

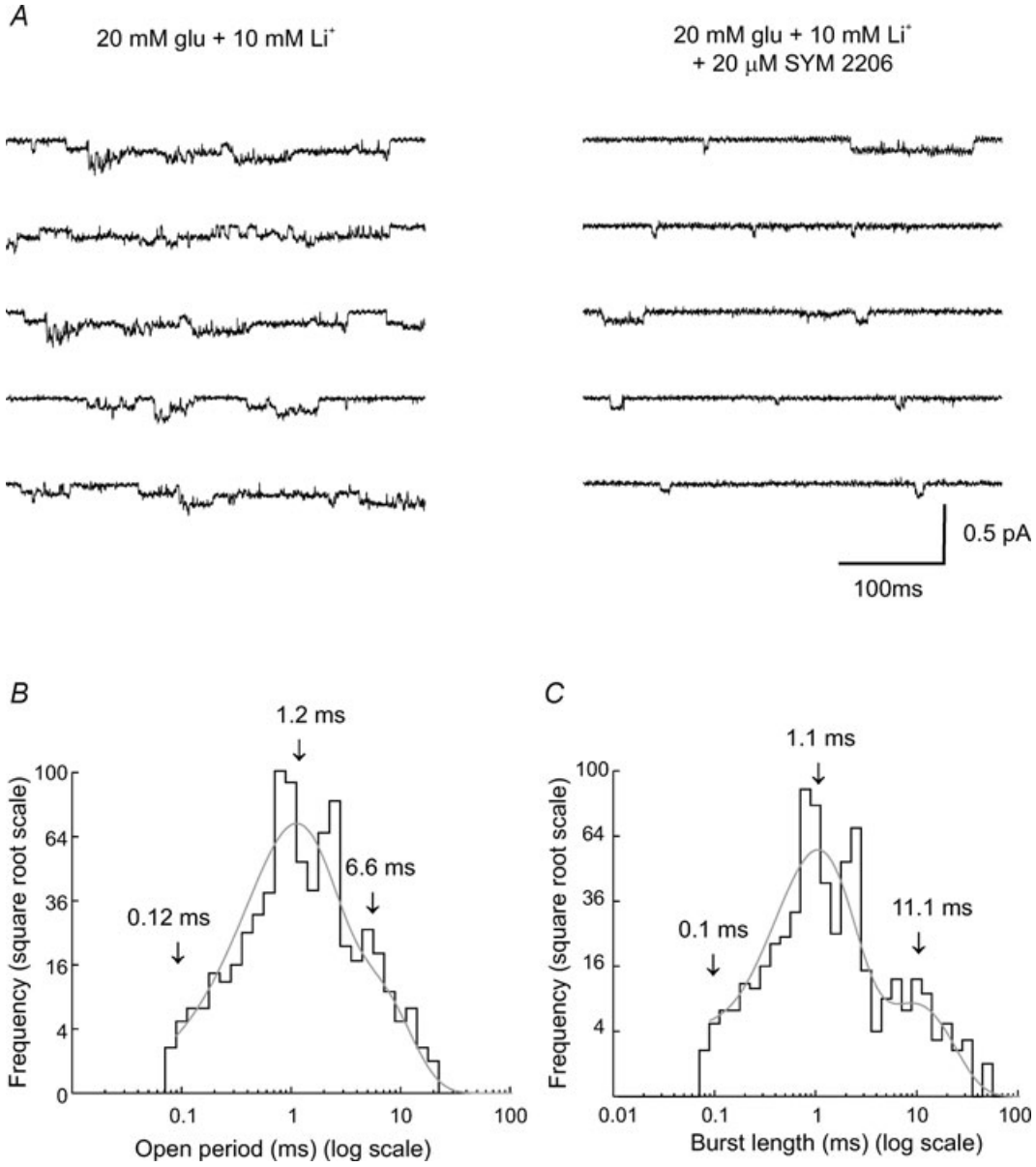

Figure 4. Application of SYM 2206 facilitated analysis of AMPAR channel kinetics in the presence of Li^+
A, single-channel currents in an outside-out patch exposed to 20 mM glutamate and 10 mM Li^+ in the absence (left), and presence (right) of 20 μM SYM 2206. Note that in the presence of SYM 2206, single-channel activity is reduced and hence discrete events are still readily identified. *B*, open period distribution of AMPAR channels in the presence of 10 mM Li^+ and 20 μM SYM 2206. The distributions were fitted with three exponential components; arrows indicate estimated time constants. *C*, burst length distributions were also fitted with three exponentials, and arrows indicate estimated time constants. These data confirm that open periods and burst lengths were not significantly altered in the presence of Li^+ (compare Fig. 3*C* right hand histogram with Fig. 4*B*). $V_m = -100$ mV.

that channel open probability is increased, to some extent, by the lower concentration of lithium used therapeutically. We will now consider the implications of these changes.

Banke *et al.* (2000) showed that phosphorylation of Ser 845 on the GluA1 AMPAR subunit gave rise to an increase in open probability, without any change in single-channel conductance, mean channel open period or burst length – resembling the situation observed with lithium. In contrast, it is reported that chronic Li^+ treatment *in vivo* causes a decrease in basal PKA activity, leading to a decreased phosphorylation at this same amino acid residue (Du *et al.* 2004*b*). Such an effect would be expected to result in a reduced P_{open} of the AMPAR channels. However, the possibility that acute exposure to Li^+ causes transient elevation in AMPAR phosphorylation was not excluded from the experiments of Du *et al.* (2004*b*), and could therefore underlie the increased P_{open} that we observe.

Other AMPARs potentiators are thought to stabilize the active conformation of the dimer assembly by a process that is modulated by the presence of transmembrane AMPAR regulatory proteins (TARPs) (Tomita *et al.* 2005; Priel *et al.* 2005; Tomita *et al.* 2006). Two possible mechanisms appear to be involved, which reduce AMPAR desensitization or slow deactivation. Cyclothiazide, is thought to exert its main action by binding at a specific site within the dimer interface of the non-desensitized receptor, stabilizing the interface and thereby reducing the time spent in the desensitized state (see Jin *et al.* 2003). Allosteric modulators such as aniracetam bind in the dimer interface near the hinge region of the ligand binding core to stabilize the 'clamshell' in its glutamate-bound active conformation and slow AMPAR deactivation (Laurence *et al.* 2003; Jin *et al.* 2003; Mayer, 2006; Mitchell & Fleck 2007). While the binding of two molecules of the potentiator cyclothiazide is required to block AMPAR entry into the desensitized state, only a single molecule of the potentiator aniracetam is involved.

Can lithium potentiation of GluA3 AMPARs be accounted for by a similar type of allosteric mechanism? Karkanias & Papke (1999*a*) have previously shown that lithium fails to potentiate responses from homomeric GluA3 AMPARs rendered non-desensitizing by the presence of a L507Y point mutation in the S1 region of the ligand binding domain (Stern-Bach *et al.* 1998). Rather, lithium ions slightly inhibit kainate responses from these AMPARs. This would be consistent with the view that Li^+ acts, at least in part, by selectively modulating desensitization of GluA3 AMPARs (Karkanias & Papke, 1999*a*). These observations, combined with our finding that enhanced activity in the presence of Li^+ cannot be explained by an simple increase in single-channel conductance or open period, would be consistent with the view that Li^+ also acts to stabilizes the interface and reduce the time spent in the desensitized state.

The effects of modulators that stabilize the 'clamshell' in its glutamate-bound active conformation (such as aniracetam) clearly differ from those we observe with Li^+, since we find no evidence for a change in channel properties (open period or burst length) that might be expected if lithium slowed deactivation. Interestingly, Karkanias & Papke (1999*a*) found that aniracetam, which potentiates wild-type AMPA receptors but is ineffective on the non-desensitizing GluA3, *potentiates* the effects of lithium on wild-type GluA3 AMPARs. This would suggest that lithium's action does not interfere with allosteric modulators that act near the hinge region of the ligand binding core. One possible explanation for the present, and previous, observations may be that there is a reduction in the time to recovery from desensitization, resulting in the observed increase in P_{open}.

As regards mechanism, two further points are worth mentioning. First, the precise origin of the subunit selectivity of Li^+ remains unclear, but would obviously deserve further investigation. Second, most native AMPARs are associated with TARPs, which greatly modify many of their biophysical and pharmacological properties. Since previous studies on the influence of lithium on basic AMPAR behaviour were carried out on recombinant AMPARs lacking associated TARPs, it is of considerable interest that we find a qualitatively similar potentiation of native AMPARs in CA1 pyramidal cells where AMPARs are likely to be predominantly GluA2/3 AMPARs (Wenthold *et al.* 1996; Keinanen *et al.* 1990), associated with the TARP γ8 (Tomita *et al.* 2003).

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Author contributions

Experiments and analysis were carried out both at UCL and at Charité-Universitätsmedizin Berlin. Both authors approved the final version of publication.

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