New molecular insights into the mechanism of lithium action at the dopaminergic D2 receptor

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Introduction

Despite the therapeutic relevance of lithium in the treatment of psychiatric disorders, its mechanism of action remains unknown. Several of the proposed mechanisms of action of lithium are related to the downstream signaling of G protein-coupled receptors (GPCRs) (e.g. inositol depletion, interference with cAMP mediated processes or disruption of the Akt/βArr-2/PP2A complex) [1]. The pharmacological response of GPCRs is typically triggered by ligand binding to the orthosteric site, but can be fine-tuned by allosteric modulation (monovalent cations are an example of the agents that can exert such allosteric modulation) [2]. The dopamine D2 receptor (D2R) is a GPCR, and our group previously simulated a cation-binding site for this receptor. There a Na+ ion is trapped in a hydrogen-bonding network (HBN), stabilizing the receptor in a distinct conformation [3]. The ability of other monovalent cations that may interact with the D2R cation-binding site has not been explored yet.

Aim of the study

The similarity of Na+ with the Li+ ion suggests that the mechanism of Li+ pharmacological activity could involve competing for binding with Na+ deep inside receptor the D2R and, by doing so, destabilizing the sodium-induced GPCR conformation.

Methods

A realistic three-dimensional structure of the D2R was modelled using a previously reported modeling protocol [3]. Three all-atom models were generated using the AMBER99SB force-field and simulated using ACEMD software. The three simulated all-atom systems consisted of the dopaminergic D2 receptor embedded in a hydrated membrane bilayer environment ionized up to a physiological ionic strength of 150 mM K+, Na+ or Li+ ions.

Results

All three ions are able to spontaneously penetrate the D2R. The propensity of ions to enter the D2 receptor is higher for larger-sized Na+ and K+ ions. In addition, there is a preference of smaller Li+ and Na+ ions to bind at the allosteric site over the orthosteric site (Figure 1). The most interesting observation of our simulation is an ion size dependent binding pattern at the extracellular loop (ECL) region that produces changes on the conformation of the receptor entrance. The binding of lithium at ECL produces a structural rearrangement of the ECL region. Interestingly, this closed loop conformation seems to be specific for the small Li+ ion (Figure 2).

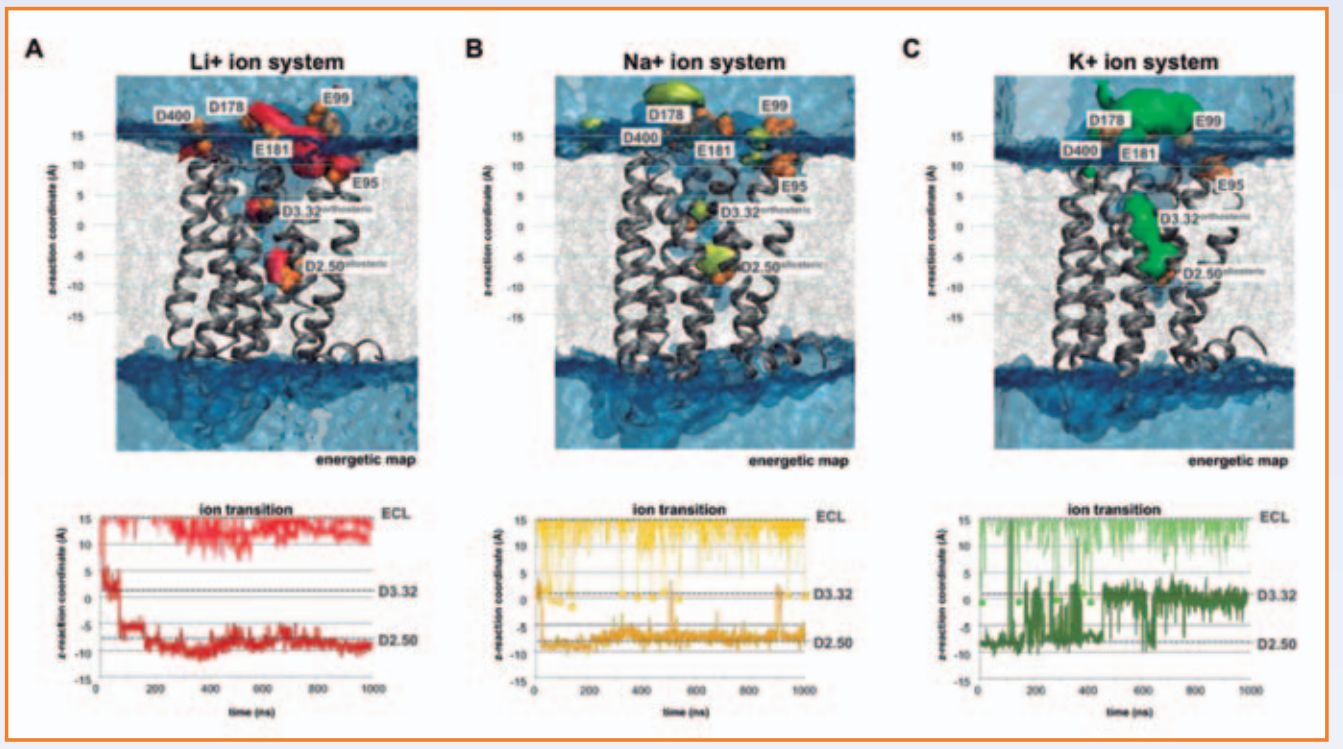

Figure 1. Cation binding sites and transition into the dopaminergic D2 receptor. Ion transition (bottom panel) into the receptor are shown for (A) Li+, (B) Na+ and (C) K+ ions. Thicker lines represent the transition of the first ion towards the orthosteric and allosteric site. Thinner lines reflect additional cation binding in the ECL region at the receptor entrance.

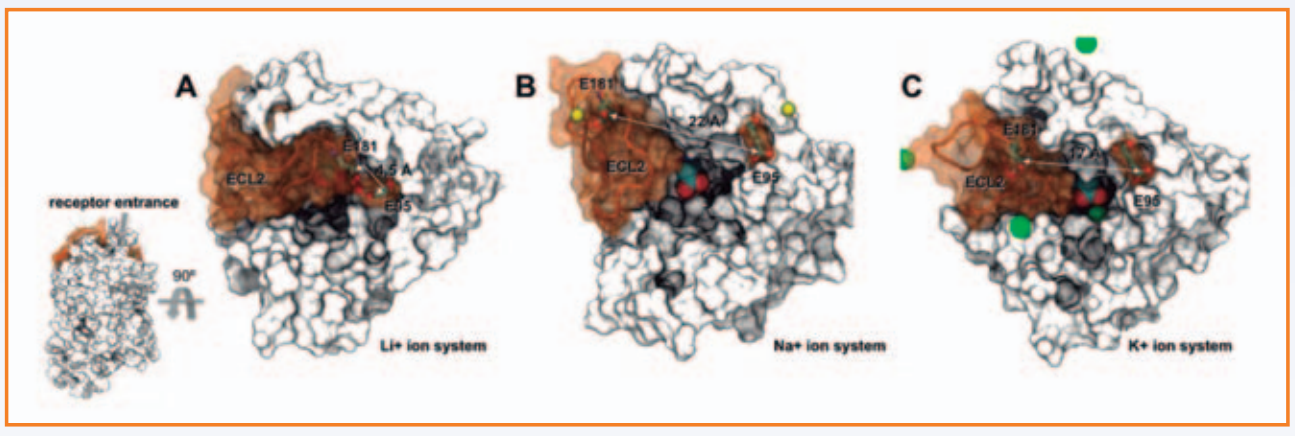

Figure 2. Conformation of the ECL 2 (orange trasnparent) shapes the receptor entrance. (A) Li+ obstructive entrance. (B) Na+ open entrance. (C) K+ open entrance. Snapshots are taken at 970ns of the production run.

Conclusions

The most important finding is the formation of an unprecedented ionic salt bridge at the extracellular receptor region (at the ECL region) induced by lithium that can have major implications for D2R functionality. This results in an obstruction of the receptor entrance. Since the ECL is known to serve as a "lid" of the receptor entrance, the observed Li+-induced partial receptor closure will most likely affect the entrance/exit of small molecules into/out of the binding pocket. The tendency of Li+ ions to partially close the D2 receptor entrance suggests an ion-induced impact on the kinetics of ligand binding. There are several cases reported of severe neurological toxicity in patients treated in combination with lithium and haloperidol [4], and our study could partially explain the molecular mechanisms underlying this effect.

References

[1] Beaulieu, J.M., Caron, M.G., 2008. Looking at lithium: molecular moods and complex behaviour. Mol Interv 8(5), 230-41.
[2] Schetz, J.A., 2005. Allosteric modulation of dopamine receptors. Mini Rev Med Chem 5(6), 555-61.
[3] Selent, J., Sanz, F., Pastor, M., De Fabritiis, G., 2010. Induced effects of sodium ions on dopaminergic G-protein coupled receptors. PLoS Comput Biol 6(8), pii: e1000884.
[4] Spring, G., Frankel, M., 1981. New data on lithium and haloperidol incompatibility. Am J Psychiatry 138(6), 818-21.

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