ASIC2a overexpression increases Lithium-induced inhibition of GSK3ß

M. Costa[1], N. Faucon Biguet[2], J. Roussel[2], P. Ravassard[2], M. Sestu[1], D. Congiu[1], A. Squassina[1], M. Del Zompo[1], R. Meloni[2]

[1] Dept. of Biomedical Sciences, Section of Neurosciences and Clinical Pharmacology, University of Cagliari, Italy
[2] Dept. of Biotechnology and Biotherapy, UPMC Paris 6, CNRS CRICM UMR 7225, Paris, France

Lithium (Li) is to date the first line treatment for acute episodes and maintenance of bipolar disorder (BD). Albeit 30% of patients show a high rate of Li response, a significant proportion of patients present patterns of partial or non-response (Garnham et al., 2007). Although the mechanisms responsible for the clinical response remain unclear, it has been shown that the variability in Li response is strongly influenced by genetic determinants (Grof et al., 2002).
In this perspective, a recent genome wide association study analyzing BD responders versus BD non responders to Li treatment found a suggestive evidence of association between Li response and a SNP (rs11869731) located in the first intron of the *ACCN1* gene (Squassina et al., 2011). This gene encodes for the amiloride-sensitive ion channel 2 (ASIC2), which has two spliced variants named ASIC2a and ASIC2b.
Together with ASIC1a, ASIC2a constitute the major functional subunit in neurons. While ASIC1a has been shown to be involved in synaptic plasticity, learning/memory and depression, less is known about ASIC2a function (Li et al., 2010).
In this study we explored the hypothesis that ASIC2a could modulate lithium influx in the cells thus potentially affecting lithium efficacy in pathological conditions. Using human neuroblastoma-derived SH-SY5Y cell lines, we evaluated the combined effect of Li treatment and lentiviral-mediated overexpression of the ASIC2a on GSK3ß, which is known to be inhibited by Li through Ser-9 phosphorylation. ASIC2a overexpression was confirmed by RT-PCR, western blot (WB) and immunocytochemistry. Thereafter, we evaluated in transduced and non-transduced SH-SY5Y cell lines the effect of LiCl treatment on GSK-3ß.
We established by WB analysis that the overexpression of ASIC2a increases in basal conditions GSK3ß Ser-9 phosphorylation without affecting the total level of GSK3ß and that this effect is further augmented by LiCl (10 mM) treatment. These preliminary results suggest that the ASIC2a subunit may intervene in the mechanisms of action of Li and further studies are warranted in order to establish the relevance of ASIC2 channel as a novel target for therapeutic interventions.

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