The loss of Aristaless related homeobox (ARX) transcriptional repression activity on cation channel TRPV2 gene causes aberrant neuronal activity: implication for epilepsies

1)Iannotti Fabio Arturo 2) Marina Damiano 3)Poeta Loredana 4)Valentino MariaElena 6) Vincenzo Di Marzo 5)Miano MariaPia

Istituto di Chimica Biomolecolare ICB - CNR

TRP channels encompass a large subfamily of ion channels characterized by weak voltage sensitivity and a non-selective permeability to monovalent and divalent cations including Mg2+, Ca2+ and Na+. TRP channels are expressed throughout the body and their activation in neurons serves to transduce chemical or physical stimuli into nerve impulses to transmit to the brain [1]. Recent study demonstrated that an increased TRPV1 channels expression and/or activity is importantly associated with the development of electrical and PTZ-induced kindling [2]. On the other hand, PTZ-induced clonic seizures were reported to be reduced in TRPV1 knockout mice [3]. By contrast, to the best of our knowledge, there has been no previous report of TRPV2, or other TRPV channels, being directly associated with models of epileptiform activity and acute seizure. Moreover, the regular brain development and functioning electrical activity is driven by the activity of the transcription factor named Aristaless-Related homeobox gene (ARX). Mutations in ARX gene cause a spectrum of neurodevelopmental disorders pattern [4] including a severe X-linked lissencephaly with abnormal genitalia (XLAG) and West syndrome characterised by clusters of axial spasms, psychomotor retardation and an hypsarrhythmic interictal EEG pattern [5]. Arx-Knock out (KO) and polyalanine Knock in (KI) mice closely reproduce the morphological anomalies observed in XLAG and West syndrome patients [4,6].

In this study, we aim at investigating the potential involvement of TRPV1 and TRPV2 channels in dysregulated ARX signaling condition. To this purpose, we have analyzed the expression profile of TRPV1 and TRPV2 channels in the brain of Arx-KO and Arx-polyalanine KI mice. We found that, in both the animal models, the altered functionality of ARX was associated to significant changes in the expression levels of TRPV2, and to a lesser extent of TRPV1, in both the hippocampus and cortex region. In human embryonic kidney 293 (HEK293)-ARX transfected cells, we observed a significant down-regulation of TRPV2 expression. Opposite results were instead observed in silenced ARX cells.

Interestingly, by the use of bio-informatic analysis, we show for the first time that the upstream and downstream region of TRPV2 gene contains potential consensus binding sites for ARX. By chromatin immunoprecipitation (ChiP) and luciferase assay, we are verifying that ARX binds and functionally acts to suppress the transcriptional activity of TRPV2.

In conclusion, the findings summarized here suggest a novel role for TRPV2 as disease marker of neurodevelopmemtal disorders. Indeed, our study uncovers a ARX-TRPV2 interaction potentially exacerbating neuronal over-activity in ARX-related diseases. and points to pharmacological antagonism of TRPV2 receptors as a promising novel therapy for epilepsies, including those not responding to commonly used anti-epileptic drugs.

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