Characterization of a Novel TRPC1/4/5 Channel Blocker (Pico145)

Hussein N Rubaiy¹, Mathias Christmann², Katsuhiko Muraki³, David J Beech⁴

¹*Centre for Atherothrombosis and Metabolic Disease, University of Hull, UK,* ²*Institute of Chemistry and Biochemistry, Freie Universitat Berlin, Germany,* ³*Faculty of Life Sciences, Kyoto Sangyo University, Japan,* ⁴*Schools of Medicine, University of Leeds, UK*

Functional Transient Receptor Potential Canonical 4 and 5 proteins (TRPC4 and TRPC5) assemble as homomers or heteromerize with TRPC1 to form non-selective cationic Ca²⁺ permeable channels. They are ubiquitously expressed in vertebrate cells and involved in many important diseases and disorders such as epilepsy, pain, and cardiac remodelling. However, the boundaries to modulate these channels have been the lack of potent and selective blocker. Therefore, this study aimed to characterize the C31 blocker reported from a patent by utilizing chemical synthesis approach, electrophysiological patch-clamp, and Ca²⁺ measurement in native and over-expressed channels (1, 2).

The C31 blocked the englerin A-evoked (10 nM, potent activator of TRPC1/4/5) Ca²⁺ entry with less potency (IC₅₀=1300 pM) against homomeric channel TRPC5 and most potency (IC₅₀=33 pM) against concatemer heteromeric TRPC4-TRPC1 channel in overexpressed HEK-293 cells. The whole cell patch-clamp data confirmed the potency of C31 (IC₅₀=42 pM). Since the C31 blocked the TRPC1/4/5 channels in picomolar range we named the C31, Pico145. Also, the results showed Pico145 had no effect on other channels, including TRPC3, TRPC6, TRPV1, TRPV4, TRPA1, TRPM2, TRPM8 and store-operated Ca²⁺ entry mediated by Orai1 suggesting Pico145 has specificity for TRPC1/4/5 channels.

Taken together, this study for the first time reports that Pico145 is a selective, potent, and subtype-specific antagonist of TRPC1/4/5 proteins channels. Perhaps this unique pharmacological tool, Pico145, will be useful to investigate the critical role of TRPC1/4/5 channels in different human diseases and disorders.

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