Arachidonic Acid Interactions with Human Acid-Sensing Ion Channel 3

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Acid-sensing ion channels (ASICs) are trimeric, proton-gated cation channels and are important to pain sensation in relation to tissue acidification [1]. Although known to be proton-gated, recent evidence suggests that the inflammatory membrane lipids, arachidonic acid (AA) (Smith et al. *J Neurosci* 2007) and lysophosphatidylcholine (LPC) (Marra et al. *EMBO J* 2016), activate the ASIC3 subtype through a direct effect without a change in pH. However, this mechanism of activation and possible binding sites are unknown. Using computational homology modelling and molecular dynamics (MD) simulations, we have simulated models of human ASIC1 and ASIC3 channels in a membrane environment containing AA, LPC and POPC. Exploiting the MARTINI coarse grained model and force field (Marrink et al., *J. Phys. Chem. B* 2007), we have compared lipid interactions with the two subtypes of ASICs. We have identified putative binding sites for AA through analysing lipid residence times and binding poses. Our data propose that specific residues, which differ between ASIC1 and ASIC3, are crucial for the AA interaction patterns observed in hASIC3. The identified binding sites are further explored through atomistic resolution MD simulations for more mechanistic insight.

[1] Wemmie, J. A., Taugher, R. J., & Kreple, C. J., Acid-sensing ion channels in pain and disease. *Nature Reviews Neuroscience*, 14(7), 461-471, (2013).