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Highly conserved tyrosine 37 stabilizes desensitized states and restricts calcium permeability of ATP-gated P2X3 receptor

Jindrichova M., Khafizov K., Skorinkin A., Fayuk D., Bart G., Zemkova H., Giniatullin R.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

Tyrosine 37 in the first transmembrane (TM1) domain is highly conserved in ATP-gated P2X receptors suggesting its fundamental role. We tested whether Y37 contributes to the desensitization of P2X3 receptors, which is currently not well understood. By combining electrophysiological, imaging and modeling approaches, we studied desensitization of various Y37 P2X3 mutants and potential partners of Y37. Unlike the membrane current of the WT receptor, which desensitized in seconds, Y37A mutant current did not fully desensitize even after minutes-long applications of β,γ-meATP, α,β-meATP, ATP or 2MeS-ATP. The fractional calcium current was enhanced in the Y37A mutant. Y37F did not rescue the native P2X3 phenotype indicating a role for the hydroxyl group of Y37 for the WT receptor. Homology modeling indicated I318 or I319 in TM2 as potential partners for Y37 in the receptor closed state. We tested this hypothesis by creating a permanent interaction between the two residues via disulfide bond. Whereas single Y37C, I318C and I319C mutants were functional, the double mutants Y37C-I318C and Y37C-I319C were non-functional. Using a cyclic model of receptor operation, we suggest that the conserved tyrosine 37 links TM1 to TM2 of adjacent subunit to stabilize desensitized states and restricts calcium permeability through the ion channel. © 2011 International Society for Neurochemistry.

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Keywords

ATP receptor, calcium imaging, desensitization, patch clamp, receptor-operated channels