Decoding the P2X1 Receptor Structural Insights and Drug Development

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Despite the alarming rate of over 300,000 unintended pregnancies occurring daily, there are still only two available options for male contraceptives. The P2X1 receptor has garnered attention as a genetically validated target for male contraception, offering a promising avenue for research and development.[1] However, existing P2X1 receptor antagonists, discovered through high-throughput screening or structure-activity relationship studies, require improvements in both potency and selectivity. My research aims to accelerate drug discovery efforts at the P2X1 receptor by determining the P2X1 receptor structure using cryogenic electron microscopy (cryo-EM) and to use the structure to develop potent P2X1 receptor antagonists. Overcoming the severe preferred orientation of the P2X1 receptor in vitreous ice by using a secondary detergent enabled the determination of the receptor's structure at 1.96 Å in an ATP-bound active state and at 2.61 Å in a NF449-bound closed state. Molecular binding characteristics of ligands and metal ion binding were studied using mutagenesis revealing important residues for receptor ligand mediated activation and inactivation. The availability of high-resolution P2X1 receptor structures and purified protein facilitated a virtual ligand screen and a DNA-encoded chemical library screen to identify novel P2X1 receptor binders. These newly identified P2X1 receptor modulators demonstrated low micromolar activity, paving the way for further drug development.

1. White CW, Choong Y-T, Short JL, et al (2013) Male contraception via simultaneous knockout of α1A-adrenoceptors and P2X1-purinoceptors in mice. Proceedings of the National Academy of Sciences of the United States of America 110:20825–20830. https://doi.org/10.1073/pnas.1318624110