Lipid Profile and Functional Characterization of the Human α4 β2 Nicotinic Acetylcholine Receptor Detergent Complexes.

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Nicotinic acetylcholine receptors (nAChR) are widely known for their role in fast cellular responses. The human $\alpha4\beta2$ nAChR is the most abundant nAChR in the human brain, and has been directly linked to nicotine addiction and other common neurodegenerative conditions.[1] Recently, two 3-dimensional structures of the $\alpha4\beta2$ nAChR were reported using X-ray crystallography[2] and cryo-electron microscopy (cryo-EM).[3] The expressed receptors were characterized for function using the whole-cell patch clamp method. However, protein preparations in these studies include the detergent solubilization of cell membranes containing the expressed receptor, which has been known to hamper protein function. Two-electrode voltage clamp (TEVC) studies on reconstituted muscle-type nAChR-Detergent complexes (nAChR-DCs) in *Xenopus* oocytes,[4,5] showed that the detergent used in the latter studies damages receptor function, and due to the similarity of neuronal and muscle-type receptors, similar results may be observed in $\alpha4\beta2$ nAChR-DCs. The reason behind this loss of function has been reported to be mainly related to detergent delipidation, causing unfavorable changes in the lipid composition of nAChR-DCs leading to denaturation.[6] We aim to express, solubilize and purify the $\alpha4\beta2$ nAChR-DCs to measure their function and stability using detergents that have been reported to stabilize muscle-type nAChR-DCs.[7] Moreover, the lipidic composition of the same $\alpha4\beta2$ nAChR-DCs will be quantified to verify if a correlation exists between detergent-delipidation and receptor function. This work will directly advance the knowledge in membrane protein preparation for structural studies, which can eventually lead to high resolution structures. Subsequently, future high resolution structures will be paramount for the development of specific drugs that can target existing neurodegenerative diseases, and nicotine addiction.

References:

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