RIC-3's effect on nicotinic acetylcholine receptors (nAChRs) and the implications in health and disease

Signal transmission – cells sending and receiving signals from other cells – is the basis of physiology. Everything our body does essentially, is a result of this cell-to-cell communication and innumerable diseases are the results of this communication system failing.

In this study we focused on one specific player in signal transmission: receptors. Certain proteins in the central nervous system, called receptors, sit on the outer membranes of cells and are responsible for receiving signals from neighboring cells. One family of such receptors, called nicotinic acetylcholine receptors (nAChRs), are made up of five subunits which need to be combined into a single functioning unit. This functional unit, the nAChR, mediates signaling between neurons and muscle, between neurons and other neurons, and is also involved many types of signaling outside the nervous system including controlling inflammatory processes. The process of synthesizing subunits, organizing them into functioning receptors, and placing them on the outer membrane of the cell where they can receive external signals is a complicated and inefficient process. Therefore, various proteins facilitate the process, including RIC-3.

There are multiple versions (isoforms) of the RIC-3 protein in nature and in this study we analyzed the different ways various RIC-3 isoforms affect different receptors, in order to better understand the mechanism of RIC-3's affect on nAChRs. The particular receptors we looked at in this study are primary players in the major functions of nAChRs, signaling between neurons in the central and peripheral nervous system and controlling inflammation. We found that indeed the amount and isoform of RIC-3 present affected different receptors differently. Some receptors were far more active and some far less, depending on which RIC-3 isoform was present, which receptor was present, and the ratio between them.

Different combinations and amounts of different nAChRs and RIC-3 isoforms are found in different areas of the body; if we can understand the implications of those various arrangements, we may be able to manipulate those arrangements in diseases involving nAChRs to help the body use its own tools to reach better outcomes.

Furthermore, we found that in immune cells, how much and which RIC-3 isoform expressed depended on the level of inflammation. From this we could infer that when the body is inflamed, this causes certain amounts and types of RIC-3 to be expressed, which in turn causes different receptors to increase or decrease signal transmission, leading to different outcomes or responses to inflammation by the body.

Understanding exactly how these different factors work could help us better understand the many diseases involving nAChR including the body's reaction to inflammation and in turn help us better address neuroinflammatory diseases such as Multiple Sclerosis.

Yael Ben-David
Department of Medical Neurobiology, Faculty of Medicine,
The Hebrew University, Ein Kerem, Jerusalem, Israel

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