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Connecting the Dots between G Proteins, G Protein Coupled Receptors and Neuronal Nicotinic Acetylcholine Receptors

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Kabbani et al. [1] in their article in the Hypothesis section of the present volume, present a strong case for functionally important interactions between heterotrimeric G proteins (guanosine nucleotide-binding proteins), G protein coupled receptors (GPCRs), and neuronal nicotinic acetylcholine receptors. They compile information from an impressive array of relevant findings in the literature and couple this with a new analysis of receptor structure to generate a testable hypothesis that certain amino acids in the major intracellular loop of neuronal nicotinic acetylcholine receptors form the binding site for G proteins. Why is this of interest? For one, the GPCRs provide important targets for a large number of drugs and have been implicated in numerous physiological functions. Similarly, nicotinic acetylcholine receptors (nAChRs) have been widely studied as representative of the family of neurotransmitter receptors that produce their major effects through their intrinsic ligand-gated ion channels. Could some members of these disparate receptor families be linked through a network of protein interactions involving G proteins as intracellular messengers?

Some of the strongest evidence for an interaction between nicotinic acetylcholine receptors and G proteins comes from a limited number of functional and proteomic studies of the neuronal nicotinic acetylcholine receptor made up of the alpha7 subunit. The alpha7 nAChR is considered to be ancestral in many respects as its presence extends to a wide number of invertebrate species. Phylogenetic analysis supports this view as well as the fact that the alpha7 nAChR nicotinic acetylcholine receptor is a pentamer consisting of only one type of subunit, i.e., alpha7, unlike all other nAChRs, which have apparently evolved through gene duplication and selection as a heterogenous array of heteromeric pentamers formed from about a dozen different subunits in mammals including humans. Notably, the alpha7 subunit has also drawn attention in recent years for its expression in a variety of non-neuronal tissues and cell types including murine macrophages where the alpha7 subunit nAChR has been implicated in the regulation of inflammation through stimulation of the vagus nerve [2]. In many cases, it is unclear whether the alpha7 subunit containing nAChRs located in non-neuronal tissue function as ligand-gated ion channels, as it can be very technically challenging to demonstrate alpha7-mediated ion flux even in neurons.

A potentially exciting extension of the hypothesis proposed in the report by Kabbani et al. [1], and consistent with previous proteomic studies of mouse brain nAChRs and their interacting proteomes, would be that intracellular protein-protein interactions, perhaps

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involving G proteins, may play a major role in mediating the alpha7-mediated actions of nicotinic agonists such as acetylcholine and nicotine in non-neuronal cell types.

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