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From Bacteria to Brain: Structure and Pharmacology of Neurotransmitter Receptor Channels

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Abstract

Orthologs of the pentameric receptor channels that mediate fast synaptic transmission in the central and peripheral nervous systems have been discovered in several bacterial species and in a single archaea genus. Recent X-ray structures of bacterial and invertebrate pentameric receptors point to a striking conservation of the structural features within the whole family, even between distant prokaryotic and eukaryotic members. These structural data reveal general principles of molecular organization that allow allosteric membrane proteins to mediate chemoelectric transduction. Notably, several conformations have been solved, including open and closed channels with distinct global tertiary and quaternary structure. The data reveal features of the ion channel architecture and of diverse categories of binding sites, in particular those that bind allosteric modulators, such as general anesthetics, ivermectin, or lipids, opening new avenues for drug design. Recently, several groups have discovered that gut flora could affect the functional development of the mammalian brain and modify gene expression and behavior. A possible contribution of bacterial receptors to the microbiome–gut–brain axis is discussed.

Biography

As a PhD student in Jacques Monod laboratory, Jean-Pierre Changeux work on the bacterial regulatory enzyme, l-threonine deaminase, lead to the general discovery that chemical signals that regulate the biological activity of proteins act at « allosteric » sites distinct from the biologically active sites (1961) and involve a cooperative conformational transition (Monod-Wyman-Changeux 1965) viewed as a general molecular mechanism of signal transduction. His subsequent career lead to the chemical identification of eukaryotic acetylcholine nicotinic receptor - the first identified neurotransmitter/drug membrane receptor and ion channel – together with the demonstration of its allosteric properties and of its structural homology with prokaryotic receptors. In addition to the novel concept of allosteric modulators that creates a revolution in the field of drug design, JPC has brought new perspectives on nicotine addiction, the higher function of the brain and their pathologies.