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BRAIN RESEARCH REVIEWS

Review

Receptor mosaics of neural and immune communication: Possible implications for basal ganglia functions

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ABSTRACT

Receptor assemblies seem to play a key role in the integration and modulation of molecular signals of cell–cell communications. This may be confirmed by recent discoveries of the immunological synapse and cytokine networks which can be also treated within a sort of meta-system—neuroimmune molecular network. On the examples of receptor superfamilies expressed both in the neural and immune cells, our review paper aims to show some implications of receptor–receptor interactions for basal ganglia functions in health and disease.

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Abbreviations: Ab, amyloid-beta protein; ABGA, antibasal ganglia antibody; AD, Alzheimer's disease; AGE, advanced glycation endproducts; AIDS, acquired immunodeficiency syndrome; ALS, amyotrophic lateral sclerosis; CA, cornu ammonis; CB, cannabinoid; CD, cluster designation antigen; CINC, cytokine-induced neutrophil chemoattractant; CNS, central nervous system; CR3, complement receptor; DA, dopaminergic; DC, dendritic cell; EGF, epidermal growth factor; EPO, erythropoietin; EPOR, erythropoietin receptor; GBR, Gist-Brocades receptor; GM-CSF, granulocyte macrophage colony stimulating factor; HAD, HIV-associated dementia; HIV, human immunodeficiency virus; HLA-DR, cell surface receptor encoded by the human leukocyte antigen class II; IFN, interferon; Ig, immunoglobuline; IRAK1, IL-1 receptor associated kinase; G-protein, guanine nucleotide-binding protein; GABA, gamma-aminobutric acid; GPCR, G-protein coupled receptor; HLA, human leukocyte antigen; JAK, janus kinase; LPS, lipopolysaccharide; LRR, leucine-rich repeat; Mac1, macrophage antigen complex; MACP, methyl-accepting chemotaxis protein; MCP, monocyte chemoattractant protein; MPTP, 1-methyl 4-phenil 1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NF, nuclear factor; NKCC, Na–K–2Cl cotransporter; NT, neurotensin; NTR, NT-receptor; OPR, opioid peptide receptor; PAMP, pathogen-associated molecular patterns; PBMC, peripheral blood mononuclear cell; PD, Parkinson's disease; PDGF, platelet-derived growth factor; PRR, pattern recognition receptor; RAGE, receptor for AGE; RM, receptor mosaic; ROS, reactive oxygen species; SDF, stromal cell-derived factor; SN, substantia nigra; SNc, substantia nigra pars compacta; SR-A1, scavenger receptor class A1; SRBC, sheep red blood cells; SST, somatostatin; STAT, signal transducer and activator of transcription; TAK1, TGF-beta activated kinase; TCR, T-cell receptor; TIR, toll/IL-1 receptor; TLR, toll-like receptor; TNF, tumor necrosis factor; TGF, tumor growth factor; TH-IR, tyrosine hydroxylase immunoreactive nerve fibers; TRAF6, TNF receptor-associated factor

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Contents

1. Introduction

The concept of the synapse as a nexus of communication between neurons is now well over 100 years old. It is only recently, however, that the immunological counterpart has been identified (Dustin and Colman, 2002). A critical difference in the functional context of the neural and immune synapses is in the basic "wiring" of the systems. The central nervous system (CNS) is to a great extent hardwired and retains precise connectivity patterns throughout adult life, with neurons projecting long axonal processes that form synapses on complex dendritic trees of other neurons that may be quite distant from the cell nucleus. Whereas CNS synapses may be formed and pruned back in the adult, the long dendritic and axonal processes anchor the cell bodies and prevent cell migration. Thus, the CNS synapse is an "action at a distance" junction (Dustin and Colman, 2002), in relation to the nucleus where transcription takes place. In contrast, the immune system operates through rapidly migrating T-cells and their partners, the dendritic cells (DCs), that congregate in tissues like lymph nodes. This is essential to the operation of the immune system, because each T-cell expresses a different antigen specificity and the point at which an antigen will enter the body to become associated with a DC is not predictable. So it is essential that T-cells and DCs congregate and make many random contacts to possibly find a match and form a synapse. Migrating T-cells assume morphologies similar to the growth cones of neurons but move at least 50 times faster. Thus, the T-cell and DC cover greater distances than neurons in search of foreign antigens, but when the synapse is formed, it is immediately proximal to the transcriptional machinery in the nucleus.

In spite of this difference in operation of the CNS and the immune system, multiprotein signaling complexes constitute the principle signaling units of both neuronal and immunological synapses. Unfortunately, little is known about the structures of these assemblies, where they are localized within the cells, and how their localization influences signaling. Understanding these issues, however, could lead to new strategies to precisely control receptor function and therefore cellular responses. Although there remains a need to explore the role of receptor localization and assembly, the data acquired to date suggest some general basic principles for communication between the receptors.

2. Main players

The formation of signaling complexes in neural and immune synapses is not restricted to any particular receptor class. Data from microscopy, covalent cross-linking, and X-ray crystallography experiments have revealed that cell-surface receptors from many structural classes assemble into multireceptor complexes. The size of these ensembles varies: some complexes are composed of two receptors while others contain thousands. Some receptors are so highly concentrated that they dominate certain cellular regions. Receptors can exchange information through direct protein–protein contacts or through intermediary proteins where the features of the immune synapse illustrate some of the issues relevant for elucidating the function of signaling complexes (Kiessling et al., 2006). For example, agrin – a glycoprotein known to be important in the formation of neural synapse, particularly for the clustering of receptors at the neuromuscular junction – now has been found on the surface of T-cells and may also be important in immune synapse formation (Trautmann and Vivier, 2001; Shaw and Allen, 2001; Dustin, 2002; Zhang et al., 2006a). Experimental data suggest that some members of G-protein coupled receptor (GPCR) superfamily and immunoglobuline (Ig) superfamily are expressed both in the neural and immune synapses.

GPCRs are found on the surface of all cells of multicellular organisms. They are major mediators of intercellular communication and act as cell surface receptors responsible for the transduction of endogenous signals (hormones, neurotransmitters, chemokines, odorants, tastants) into a cellular response (Zhang et al., 2006b). GPCRs form one of the largest superfamilies of cell surface receptors (Uings and Farrow, 2000) and the largest class of cell surface receptors in mammalian genomes. In human, the estimated number of GPCRs is approximately 948 (Takeda et al., 2002), where about 300 to 400 mediate the effects of endogenous ligands, with the remainder being sensory receptors (Prinster et al., 2005). This corresponds to about 5% of the total number of human genes (Collins, 2004). However, GPCRs represent the most widely targeted pharmacological protein class (Premont and Gainetdinov, 2007). More than 45% of all modern drugs target GPCRs; these represent around 25% of the 100 top-selling drugs worldwide (Flower, 1999; Drews, 1996, 2000).

GPCRs share a consistent general topology (Sakmar, 2002), with an N-terminal extracellular domain, seven transmembrane hydrophobic helices separated by loop regions of varying sizes, and an intracellular C-terminal domain (Fig. 1). The interaction of an agonist with a GPCR binding pocket elicits or stabilizes a conformational change in the receptor's transmembrane domains. This conformational change allows the receptor to associate with heterotrimeric G-proteins and initiate a signaling cascade inside the cell leading to a physiological response (Lefkowitz et al., 1993). Although the