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Review

The ubiquitous neural cell adhesion molecule (N-CAM)

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ABSTRACT

Adhesive interactions are important for cell trafficking, differentiation, function and tissue differentiation. Neural cell adhesion molecule (NCAM) is involved in a diverse range of contact-mediated interactions among neurons, astrocytes, oligodendrocytes, and myotubes. It is widely but transiently expressed in many tissues early in embryogenesis. Four main isoforms exist but there are many other variants resulting from alternative splicing and post-translational modifications. This review discusses the actions and association of N-CAM and variants, PSA CAM. L1CAM and receptor tyrosine kinase. Their interactions with the interstitial cells of Cajal – the pacemaker cells of the gut in the manifestation of gut motility disorders, expression in carcinomas and mesenchymal tumours are discussed.

1. Introduction

Cellular recognition phenomena are both diverse and fundamental in living systems. They include the development of specialized and stereotyped contact relationship in embryogenesis particularly those involving the nervous system, the interaction of cells with neurotransmitter and hormonal signals and most formidably, the integrative functioning of the brain. The neural cell adhesion molecule (NCAM) is an immunoglobulin-like neuronal surface glycoprotein which binds to a variety of other cell adhesion proteins to mediate adhesion, guidance, and differentiation during neuronal growth. At least 27 alternatively spliced NCAM mRNAs are produced, giving a wide diversity of NCAM isoforms [1–3]. NCAM mediates cell adhesion through homophilic as well as through heterophilic interactions. The extracellular domain of NCAM consists of five immunoglobulin-like (Ig) domains followed by two fibronectin type III (FNIII) domains. The different domains of NCAM have been shown to have different roles, with the Ig domains being involved in homophilic binding to NCAM, and the FNIII domains being involved in signalling leading to neurite outgrowth [4]. NCAM promotes neurite outgrowth via homophilic (NCAM–NCAM) as well as heterophilic (NCAM-fibroblast growth factor receptor) interactions which activate a number of intracellular signalling cascades [5,6]. NCAM-induced intracellular signalling has been dependent on the cytoplasmic calcium concentration but the molecular basis remains unclear [7]. By mediating cell adhesion to other cells and to the extracellular matrix, NCAM influences cell migration, neurite extension, fasciculation and formation of synapses in the brain [2,3]. Thus the implications of neuronal plasticity in learning and nerve regeneration (Fig. 1).

NCAM-induced intracellular signalling has been shown to be mediated by the ubiquitous FGFR, a member of the receptor tyrosine kinase (RTK) family. Inhibitors of both RTKs and the Src (protein tyrosine kinases) family e.g. Lavandustin A affects NCAM-induced signalling and thus neurite outgrowth [4,5].

In Alzheimer's disease, where plaque deposits affect the neurofibrillar protein network, a replay of N-CAM neurodevelopmental events in memory formation may be inhibited, and in ageing, the loss of neurons may limit the synaptic connectivity changes associated with memory acquisition and consolidation [8]. The 'neuronal plasticity' theory of depression indicates the potential roles of NCAM/PSA-NCAM proteins in depression [9].

L1CAM was first described as a neural cell adhesion molecule and has been shown to play key roles in the development of the nervous system, including cell adhesion, neurite outgrowth, axon guidance, neural cell migration, and myelination [10,11]. L1CAM promotes cellular activities through L1 homophilic interaction, as well as heterophilic interaction with other neuronal members of the Ig superfamily, integrins, extracellular matrix proteins and cell surface receptors [12]. It is re-expressed in tumorogenesis [13].

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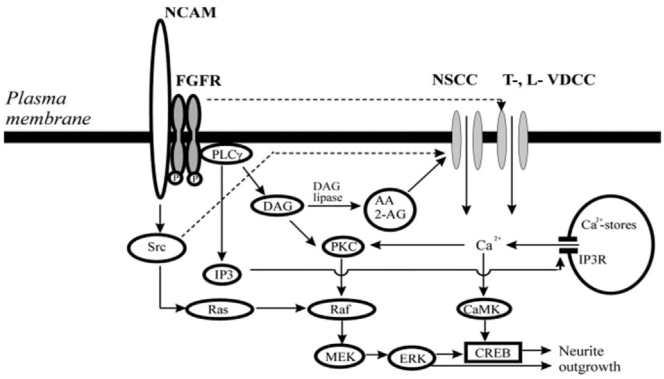

Fig. 1. Molecular mechanism of NCAM action [7].

2. Plasticity of synaptic connections

Plasticity is defined as any persistent change in the functional properties of single neurons or neuronal aggregates. It may manifest as plasticity of synaptic transmission by the phenomenon of potentiation, or as axonal sprouting and formation of new synapses. Although this phenomenon was first demonstrated in the peripheral nervous system in the 1950s, sprouting of central axonal connections in the CNS has been unequivocally demonstrated with greater understanding of the nature of these plastic changes since 1968. It is the plasticity of neuronal networks that form the basis of short-term memory and learning. The NCAM glycoforms can be post-translationally modified by the addition of polysialic acid (PSA). This decrease its homophilic binding properties that would lead to reduced cell adhesion and thus facilitate cell migration and invasion. It also renders some functional recovery following CNS injury e.g. head injury especially in the young with still greater plasticity of synaptic connections. The CNS glial cells (e.g. oligodendrocytes) inhibit regeneration of CNS axons following injury unlike the facilitating Schwann cells of peripheral nerves [14]

2.1. Developmental replay

More specifically, the neuroconnectivity changes have been proposed to be a localized replay of the developmental acquisition of synaptic connectivity, where there is an initial local over-innervation of neurons, most of which are subsequently retracted, giving rise to stabilization of new specific connections. An analogy may be drawn in lesion-induced synaptogenesis in the CNS where there is re-expression of molecular cues normally seen in development, for the guidance of collateral sprouts to the vacated synaptic sites, according to a hierarchy of specificities, but with functional recovery being more favourable in the younger animal [14]. Experimental modulation of synapse turnover in later life could be an extension of the developmental process.

3. Memory formation

3.1. Learning and memory

If learning and memory formation in the adult are indeed an extension of the developmental process, then functional developmental processes may also play a critical role in information storage in the adult mammalian nervous system. Learning refers to the processes whereby new knowledge about events in the surroundings are acquired and memory refers to the processes through which knowledge is retained [14]. Short-term memory (STM) develops immediately during memory formation and lasts from seconds to minutes and occurs as a result of changes in neuronal activity brought about by an increased potassium ion conductance across neuronal membranes. Intermediate-term memory (ITM) develops at 10–15 min after learning and lasts for up to 60 min which serves as a preliminary store of information until long-term memory formation has been completed. This period involves changes in synaptic structures such as dendritic swelling and irreversible conformational changes in macromolecular structure. Long-term memory (LTM) develops after several hours and requires regulation of gene expression and/or post-translational regulation, and it is this that determines the duration and reversibility of a memory trace [15,16].The effects of protein synthesis inhibitors suggest that protein synthesis is not necessary for the initial stages of memory formation but is required for the later events leading to memory consolidation (>4 h after training) [17].

3.2. Neural cell adhesion molecule (N-CAM) replay

The memory trace involves an initial proliferation of synapses, and stabilization of some of these new synapses in association with a replay of N-CAM neurodevelopmental events. N-CAM being a specific neural cell surface glycoprotein that mediates neural cell adhesion consists of (1) an extracellular N-terminal binding domain, (2) an extracellular sialic acid binding domain and (3) a membrane associated domain. Each molecule is heavily glycosylated by units of 10–12 sialic residues in alpha 2–8 linkages. The strength of the interaction between two molecules of N-CAM would be dependent on the amount of negatively-charged sialic acid present. The more extracellular sialic acid binding domain present, the greater the repulsion, and thus less adhesion. The embryonic form of N-CAM is highly glycosylated. This would be expected since there would be more repulsion than adhesion concurrent with the idea that not many neuronal pathways would have been made permanent. The sialic acid content, which is controlled by a sialytransferase enzyme, has been found to decrease during development from 30% (w/w) to 10% in the adult, thereby leading to an increase in adhesion and stabilization of the synaptic network [18,19]. In memory formation, there is an increased resialylation of N-CAM molecules leading to new neuronal collections [20]. Thus, the manifestation of a neurodevelopmental replay. The negative charge of the sialic acid components repels each other, giving rise to less adhesion and stability until the memory trace is consolidated. In about the first hour post-passive avoidance training, there is an over-production of synapses, N-CAM becomes heavily sialylated at 12 h and remain so until 24 h during which time synapse selection is believed to occur, thereafter, N-CAM sialylation is gradually lost (desialylation) [21]. Removal of polysialic acid (PSA) from NCAM by the enzyme endoneuraminidase (EndoN) has been shown to abolish long-term potentiation (LTP) and long-term depression (LTD) [2,3].

3.3. Practical implications of adhesion molecules – lectins

Studies of mammalian CNS morphogenesis have begun to focus on the molecular basis underlying specific pattern formation events which lead to functional circuitry arrangements. The rodent somatosensory cortex had been exploited in pattern formation studies because of its distinct vibrissae-related “barrel field” by using lectin cytochemistry on the glycoconjugate expression by certain glial cells and glial fibrillary acidic protein immunocytochemistry during a limited period in early post natal development [22]. Because memory has been associated with localized restructuring in the adult brain it was considered worthwhile to determine if lectin-binding to the glycosylated molecules would