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.
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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–N-CAM) 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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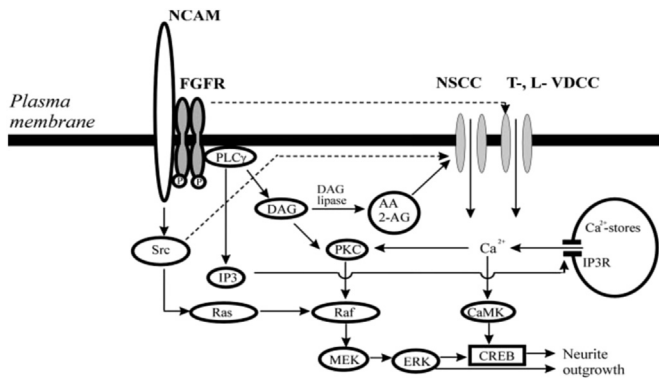E-mail address: elroypat@yahoo.co.uk (E.P. Weledji).

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

similarly identify the discrete areas associated with memory formation. Concanavalin A was selected as it is a plant lectin that binds specifically to the sugar mannose which forms the carbohydrate core of glycoproteins in nerve cell membranes. The Concanavalin A is labelled with fluorescein to facilitate its localization by fluorescence microscopy [23]. As N-CAM is present in all neurons and Man NAc incorporated into all glycoproteins, direct immunofluorescence studies using anti-NCAM, or autoradiographic studies using ^{3}H-N-acetyl-ᴅ-mannosamine (Man NAc), a sialic acid precursor, may not have sufficient resolution to demonstrate local change. However, the use of an antibody specific for the alpha-2,8 sialic acid linkages of resialylated N-CAM may prove useful. The expression of the polysialylated PSA-NCAM which contributes more specifically and dynamically to the structural plasticity in the brain would be better tested. This is especially so as the anti-PSA-NCAM antibody works well in the staining of rat brains [24].

4. Chronic intestinal pseudo-obstruction (CIPO)

Congenital pseudo-obstruction is a broad clinical spectrum of motility disorders of closely similar aetiology that extends from the chronic intestinal obstruction of the newborn (CIPO) to Hirschsprung's disease. It is commonly neuropathic than myopathic in origin and, may be primary (familial) or secondary to in utero-insults e.g. foetal-alcohol syndrome or post-natal injuries such as ischaemic events or viral infections. Recently, abnormalities of the gastrointestinal pacemaker cells (the interstitial cells of Cajal) have been described in patients with motility disorders [25–27]. Alterations of the neural cell adhesion molecule L1 (L1CAM) glycoprotein may cause a qualitative defect in the differentiated Cajal's cells in the anterior part of the gut [28]. L1CAM mutations cause a variable clinical spectrum. This gene is located at Xq28 and encodes a transmembrane glycoprotein involved in neurite outgrowth and neuronal migration [29]. Hirschsprung's disease has been reported to involve an L1CAM mutation that manifests as a quantitative defect in the migration of neural crest cells in distal segments of the gut. The presentation of chronic intestinal pseudo-obstruction (CIPO) in the newborn period is no longer a rare event and the prognosis appears worse than that presenting in childhood or adulthood [25–30]. Many are born prematurely and the symptoms resolve with time as the interstitial cells of Cajal fully develop [31]. It may be self-limiting in some neonates [25,30]. Many others have associated abnormalities such as urological disorders, dysautonomia, and structural gastrointestinal abnormalities such as malrotation and gastroschisis [25,32]. Chronic constipation with secondary spurious diarrhoea later in childhood is the uncommon presentation in most Western hospitals today. Treatment for CIPO remains variable. Prokinetic therapy with rectal cisapride may be helpful and colonic decompression is indicated if pain from the distension is severe or there is imminent caecal perforation (caecum > 10 cm) [25,32]. Most affected segments are identified by radiological contrast studies, manometry or by finding localized massive dilatation at laparotomy. Hirschsprung's disease is due to the absence of intramural ganglia in the distal bowel with the commonest site in the recto-sigmoid (95%) and rarely in small bowel. Meconium is not passed by 24 h after birth. Plain abdominal X-ray shows no gas in rectum and a contrast enema X-ray shows a collapsed rectum (aganglionic segment in spasm) with a tapering transition zone to grossly dilated and hypertrophied bowel (megacolon) above. However, 10% of neonates may not have developed the proximal distention and so the transition zone cannot be reliably determined by contrast enema [33]. Most (with access to this modality) would proceed to rectal biopsy (with or without preceding enema contrast study) to exclude low segment Hirschsprung's disease.

4.1. Obstructive hydrocephalus

The association of a congenital idiopathic intestinal pseudo-obstruction and hydrocephalus from stenosis of the aqueduct of Sylvius suggest that L1CAM has a role in the developmental regulation of multiple systems. Further clinical descriptions of gastroenterological and neuropathological data are required to extend our understanding of the mechanisms underlying L1CAM function [29].

5. Neural cell adhesion molecule, tumorogenesis and molecular therapy

Recent reports have shown that L1CAM is aberrantly expressed in several different types of cancers, including colon carcinoma, ovarian and uterine carcinomas, malignant gliomas, recurrent neuroblastoma, cutaneous malignant melanoma, renal cell carcinoma, extrahepatic cholangiocarcinoma (ECC) and gallbladder carcinoma, and that its expression correlates with more advanced stages of tumour progression [34–36]. In addition, ectopic L1CAM expression in carcinoma cells enhances their migration, invasion, and tumorigenesis [37–40]. In addition to functioning as a cell surface adhesion molecule, the extracellular domain of L1CAM can be shed from the cell surface via proteolytic cleavage and can stimulate the migration and survival of tumour cells through autocrine/paracrine binding to integrins [41]. A monoclonal antibody (mAb) against L1CAM reportedly inhibits the growth and dissemination of ovarian carcinomas in nude mice [42].

A functional study of L1CAM suppression or over expression in intrahepatic chalangiocarcinoma (ICC) tumour cells indicated that L1CAM plays an important role in tumour progression of ICC by promoting cell proliferation, migration, and survival [40]. These results suggested that L1CAM may serve as a therapeutic target in ICC and that anti-L1CAM mAb may have potential as diagnostic and therapeutic agents for the treatment of ICC. As prognosis of ICC is very poor, new effective therapeutic strategies are urgently needed [43,44]. Thus molecular therapy may be useful especially as ICC is refractory to conventional chemotherapy and radiation treatment [45]. Complete surgical resection is currently the only treatment and cure. However, because of a lack of early diagnosis, most patients have occult metastasis or advanced local disease on clinical presentation [43,44].

5.1. NCAM and tumour angiogenesis

There have been reported expression of neural cell adhesion molecule (NCAM) in the immature and tumour endothelial cells of human carcinomas [46]. Molecular imaging in the detection of neoangiogenesis in tumours using highly efficient MRI contrast agents combined with the use of specific vectors targeting NCAM expression would guide anti-angiogenic therapy of Kaposi sarcoma [47]. NCAM has been used as a target molecule for experimental antibody-based immunotherapy. Successful radio-immunolocalisation of metastases was demonstrated after giving injections of NCAM-binding 123J-UJ13a or 131J-UJ13a radio-immunoconjugates to children with neuroblastoma. Patients with small cell lung cancer were treated with the anti-NCAM immuno-toxin huN901-DM1 in two different clinical studies, revealing acceptable toxicity and signs of clinical response [48,49].

6. Gastrointestinal stromal tumours (GISTS)

GISTS are tumours of mesenchymal origin that arise in the GI tract. Although rare (0.1–3%) they are the most common mesenchymal malignancies of the GI tract [50]. The discovery of CD34 expression in many GISTs suggested that they were a specific entity, distinct from smooth muscle tumours [51]. Electron microscopy and

Summary table. Neural cell adhesion molecules.

NCAM/PSA-NCAM	L1CAM	KIT receptor tyrosine kinase
Plasticity of synaptic connection I. Memory formation II. Learning III. CNS injury repair	Gut motility: gastrointestinal pacemaker cells (Interstitial cells of Cajal)	Gut smooth muscle function and fibroblast growth factor
Disorders: e.g. Alzheimer's depression Tumour angiogenesis	L1CAM mutation: CIPO, Hirschsprung's, obstructive hydrocephalus expression in carcinomas	c-KIT gene mutation: Gastrointestinal stromal tumours (GISTS) Gastrointestinal autonomic nerve tumour (GANT)

immunohistochemical studies indicated that only a minority of stromal tumours had the typical features of smooth muscle, with some having a more neural appearance and others appearing undifferentiated. Gastrointestinal autonomic nerve tumour (GANT) now recognized as a variant of GIST was also introduced to describe sarcomas with ultrastructural evidence of autonomic system differentiation [52,53]. It was observed that GISTS and the interstitial cells of Cajal, the pacemaker cells of the gut, expressed the receptor tyrosine kinase KIT (CD117) and, more recently, DOG1 [54,55]. The immunophenotype (CD117 positive) and ultrastructural features of GISTS suggest that they arise from a precursor of interstitial cells of Cajal. This hypothesis is supported by a report that an embryonic form of smooth myosin in GISTS is similar to that found in interstitial cells of Cajal [56]. The principal function of the interstitial cells of Cajal is to serve as pacemaker cells controlling gut motility, coordinating waves of peristalsis. KIT, the product of the KIT proto-oncogene is a member of the receptor tyrosine kinase family, closely related to the receptors for platelet-derived growth factor (PDGF), macrophage colony-stimulating factor (MCSF), and FMS-like receptor tyrosine kinase (FLT3) ligand [7]. Expression of the KIT proto-oncogene is considered essential for the development of the interstitial cells of Cajal and also for its slow wave activity. In addition KIT is functionally important and is widely expressed for example in germ cells, mast cells, some epithelial cells and in haemopoietic stem cells. KIT is a transmembrane receptor for a growth factor (stem cell factor) or mast cell growth factor. Extracellular binding of SCF to the receptor results in dimerization of adjacent KIT molecules with concomitant activation of the intracellular KIT kinase domain, leading to activation of intracellular signalling cascades controlling cell proliferation, adhesion, and differentiation. Thus activation of the KIT receptor tyrosine kinase involving a mutation within the c-kit gene is integral to the development of many GISTS [57]. The tyrosine kinase inhibitor *imatinib* (Gilvec) thus, represents a major breakthrough in the treatment of GISTS [58].

7. Conclusions

The ubiquitous feature of the neural cell adhesion molecule (NCAM) and its variants highlights the importance of biological communication and recognition. Cellular recognition via the surface membrane holds the key not only to understanding the complexities of biological communication and development, but also of cancer and other major human diseases. Diseases often are experiments of nature and the solution of such problems followed by manipulation of a previously obscure process to prevent disease or restore health is the quest of medical science.

Conflict of interest

None.

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