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Dysregulation of the neural cell adhesion molecule and neuropsychiatric disorders

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Abstract

Cell adhesion molecule proteins play a diverse role in neural development, signal transduction, structural linkages to extracellular and intracellular proteins, synaptic stabilization, neurogenesis, and learning. Three basic mRNA isoforms and potent posttranslational modifications differentially regulate these neurobiological properties of the neural cell adhesion molecule (N-CAM). Abnormal concentrations of N-CAM 105–115 kDa (cN-CAM), N-CAM variable alternative spliced exon (VASE), and N-CAM secreted exon (SEC) are related to schizophrenia and bipolar neuropsychiatric disorders. These N-CAM isoforms provide potential mechanisms for expression of multiple neurobiological alterations between controls and individuals with schizophrenia or bipolar illness. Multiple processes can trigger the dysregulation of N-CAM isoforms. Differences in neuropil volume, neuronal diameter, gray matter thickness, and ventricular size can be related to N-CAM neurobiological properties in neuropsychiatric disorders. Potential test of the N-CAM dysregulation hypothesis of neuropsychiatric disorder is whether ongoing dysregulation of N-CAM would cause cognitive impairments, increased lateral ventricle volume, and decreased hippocampal volume observed in schizophrenia and to a lesser extent in bipolar disorder. An indirect test of this theory conducted in animal experiments lend support to this N-CAM hypothesis. N-CAM dysregulation is consistent with a synaptic abnormality that could underlie the disconnection between brain regions consistent with neuroimaging reports. Synapse stability and plasticity may be part of the molecular neuropathology of these disorders.

Keywords: Schizophrenia; Bipolar disorder; Depression; Memory; Synaptic plasticity; Ventricle enlargement; Neurocognitive impairment

1. Neurobiological properties of neural cell adhesion molecule (N-CAM)

The N-CAM protein was discovered around 1978 by two different groups (Jorgensen and Mikoshiba, 1978; Rutishauser et al., 1978) and since that time there have been more than 2500 reports (National Library of Medicine, Bethesda, MD) about N-CAM. A selection of these papers is discussed in relation to the findings that N-CAM isoforms are dysregulated in neuropsychiatric disorders in brain and cerebrospinal fluid (CSF).

1.1. Biochemical

The genetic sequence of the three isoforms of human N-CAM (Hemperly et al., 1990) showed a total of 20 exons that theoretically could give rise to over 27 distinct mRNAs (Reyes et al., 1993). Three major N-CAM isoforms, N-CAM 180, N-CAM 140, and N-CAM 120 result from exon splicing in the transmembrane and cytoplasmic region of the C-terminus (Cunningham et al., 1987). A fourth putative isoform N-CAM 105–115 kDa was reported in human brain (Vawter et al., 1998a). Alternative splicing of the N-CAM mRNA produces isoforms that attach to the cell membrane by transmembrane insertion, by a glycosylphosphatidylinositol linkage, or are secreted. Members of the homeobox (Hox) and paired box (Pax) transcription factors regulate N-CAM transcription (Jones

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et al., 1993). However, the subsequent neurochemical events are largely unknown for regulation of factors that determine N-CAM 180-, 140-, and 120-kDa isoforms. Thus, N-CAM isoforms can be categorized by membrane insertion motif, alternative spliced exons, molecular weight, and posttranslational modifications. These variations lead to multiple morphoregulatory activities in the developing nervous system (Edelman and Cunningham, 1990). A combination of these biochemical properties give rise to neurobiological roles described below for N-CAM, which may account for some features of schizophrenia and bipolar disorder.

1.2. Polysialylated N-CAM

The addition of polysialic acid to N-CAM (Finne, 1989) can add 10–20% to the molecular weight of N-CAM 180. A prevalent posttranslation modification of N-CAM consists of alpha-2,8-linked polysialic acid residues (Cunningham et al., 1983). Polysialylated N-CAM expression is developmentally regulated (Boisseau et al., 1991), involved in learning (Doyle et al., 1992a; Fox et al., 1995; O'Connell et al., 1997a) and found in human hippocampus (Ni Dhuill et al., 1999). Enzymatic cleavage of the polysialic acid modification of N-CAM results in excessive collateral sprouting in the mossy fibers enervating CA3 pyramidal cell apical dendrites (Seki and Rutishauser, 1998), deficits in learning (Morris Water Maze) and synaptic plasticity (long-term potentiation) in the hippocampus (Becker et al., 1996a), altered cell adhesion (Rutishauser et al., 1985), and altered migration of neuronal progenitor cells from the subventricular zone (Doetsch et al., 1997). Thus, the alpha-2,8-polysialic acid modification of N-CAM has potent neurobiological consequences.

1.3. Alternative spliced exons — variable alternative spliced exon (VASE) and secreted exon (SEC)

N-CAM mRNA occurs with a 30 base pair VASE, which remains between exons 7 and 8 in N-CAM (Small and Akeson, 1990). Several lines of evidence suggest an association between VASE expression and decreased neural plasticity. VASE leads to downregulation of neurite outgrowth (Doherty et al., 1992a). VASE is undetectable in the olfactory neuroepithelium that continues to regenerate olfactory neurons in adults (Small and Akeson, 1990). VASE levels in rat brain are low in the embryonic and early postnatal period; however, as maturation proceeds, VASE increases and eventually is present in up to 50% of the total N-CAM (Small and Akeson, 1990). In the hippocampus, embryonic neurons respond to N-CAM by increased neurite outgrowth and express low levels of VASE, while postnatal neurons have a greater proportion of transcripts containing VASE (Walsh et al., 1992).

The secreted (SEC) N-CAM isoform (Gower et al., 1988) results from an alternative splicing event. SEC exon results in a premature interruption of translation and a protein lacking a cytoplasmic or transmembrane domain. The SEC isoform has not been characterized extensively.

1.4. Adhesion

The adhesion of brain cells to one another and cells to substrates coated with extracts that contained N-CAM protein (Rutishauser et al., 1976) led to the understanding that N-CAM proteins bind through homophilic binding (Hall et al., 1990) and heterophilic binding sites (Grumet et al., 1993; Storms et al., 1996). N-CAM is found on glial and neuronal cells and can bind these cells together because of homophilic binding of N-CAM.

1.5. Neurite outgrowth

Substrates coated with N-CAM are permissive for neurite extension (Rutishauser, 1985; Doherty et al., 1992b; Beggs et al., 1994; Doherty and Walsh, 1996) and VASE N-CAM protein reduces neurite outgrowth as mentioned above (Doherty et al., 1992a; Arce et al., 1996). Neurite outgrowth is dependent on calcium influx (Williams et al., 1995) and occurs through homophilic N-CAM binding and heterophilic binding of N-CAM to other CAMs, such as L1-adhesion molecules, or extracellular matrix molecules (Hall et al., 1996; Ronn et al., 1998). A peptide ligand of N-CAM can also specifically interfere with N-CAM mediated neurite outgrowth (Ronn et al., 1999).

1.6. Brain development

The expression of N-CAM mRNA transcripts of different sizes changes during brain development and correlates with the appearance of N-CAM protein isoforms (Gennarini et al., 1986). There is a regional and temporal expression of N-CAM isoforms during brain development. N-CAM 180 knockout mice have minor developmental anomalies (Tomasiewicz et al., 1993), such as a decrease in size of the olfactory bulb (Treloar et al., 1997) due to difficulties of cells migrating from the subependymal zone to final positions in the olfactory bulb. N-CAM 180 knockout mice also show learning deficits in Morris Water Maze, anterior ventricle enlargement, hippocampal dentate gyrus thinning, and deficits in prepulse inhibition of startle (Wood et al., 1998). Targeted gene conversion of all N-CAM isoforms to a soluble N-CAM isoform (lacking transmembrane or cytoplasmic domains) proved to be lethal to the embryo (Rabinowitz et al., 1996). The soluble N-CAM fragments indicates a major toxicity to an organism during development.

N-CAM is involved in axonal guidance and migration of neurons in the developing central nervous system (CNS) (Edelman and Jones, 1997). Antibodies specific to N-CAM extracellular epitopes disrupt neuronal migration and arrangement of layers (Buskirk et al., 1980; Rutishauser,

1985; Doherty and Walsh, 1991; Bronner-Fraser et al., 1992).

1.7. Signal transduction

Binding of the extracellular domains of N-CAM to the basic fibroblast growth-factor receptor is believed to induce signaling events in the neuron cytoplasm through arachidonic acid and activation of protein kinase C (Williams et al., 1994). A second signal pathway involves the N-CAM-Ras-mitogen-activated protein (MAP) kinase pathway (Krushel et al., 1998). A third N-CAM pathway depends on activation of p59 (Fyn), a nonreceptor protein tyrosine kinase, and p125 focal adhesion kinase (Beggs et al., 1994; 1997). A model of N-CAM signaling involving these pathways must be developed to integrate the diverse biological properties of N-CAM. Two pathways, the arachidonic acid and MAP kinase pathways, are linked by protein kinase C and could reinforce activity in either circuit leading to a longer-term neuronal activity (Kolkova et al., 2000).

The physical modulation of the internal neuronal environment is also accomplished by structural connection of N-CAM cytoplasmic domains on N-CAM 180 to intracellular structural molecules, such as fodrin (Woo and Murray, 1994), spectrin (Pollerberg et al., 1986), and linkage to actin. As a result of these connections of N-CAM 180, its lateral mobility in the cell membrane is reduced compared to N-CAM 140 (Pollerberg et al., 1987).

1.8. Synaptic plasticity

N-CAM levels are modulated by activity of the neuron and if an excess of N-CAM is present in the synapse, then new synapses are inhibited from formation (Martin and Kandel, 1996). There appears to be an optimal level of N-CAM that is permissive for activity-dependent synaptic sprouting (Bailey, 1999). N-CAM disappears from the membrane of neurons after neurotransmitter receptor stimulation (Mayford et al., 1992) by a putative membrane internalization pathway (Hu et al., 1993). N-CAM may be recycled to maintain the synapse at optimal N-CAM proportions for development, maintenance and retraction of synaptic contacts. Polysialylated N-CAM further appears to be a necessary component in long-term potentiation and long-term depression induction (Muller et al., 1996). Long-term potentiation deficits are noted when antibodies to N-CAM are applied to the hippocampus (Luthl et al., 1994; Ronn et al., 1995, 1998). During induction of long-term potentiation, it was shown that metalloproteinase inhibitors inhibit formation of CAM fragments, thereby inhibiting long-term potentiation (Hoffman et al., 1998a,b) and that N-CAM and AMPA receptors might be functionally linked during long-term potentiation (Hoffman et al., 1997). Glutamate receptor activation also appears to induce the N-CAM promoter (Holst et al., 1998). These observations suggest a role of N-CAM in maturation and plasticity of the synapse in the adult CNS (Ronn et al., 2000).

1.9. Neurogenesis

The ultimate remodeling capability of the brain may be derived from pluripotent stem cells born in diverse regions of the brain, such as the subependymal zone in the lateral ventricle and the dentate gyrus of the hippocampus (Alvarez-Buylla and Lois, 1995; Eriksson et al., 1998). These "new" cells are generally N-CAM polysialic acid-positive (Doetsch et al., 1997) and are capable of migrating and undergoing neurite outgrowth in the appropriate target. This supply of new neurons could affect subsequent synaptogenesis, synaptic stabilization, and learning that appear related to the neurobiological properties of N-CAM.

1.10. Learning

N-CAM antibodies disrupt learning during a vulnerable protein-dependent period when memory traces are being formed at about 5.5 h posttraining (Doyle et al., 1992b; Rose, 1995b; Alexinsky et al., 1997). Peptide ligands that bind to N-CAM can interfere with memory consolidation (Gallagher et al., 1999) and N-CAM fragments injected into the brain interferes with learning and inhibits consolidation of memory (Rose, 1995a). N-CAM antisense oligonucleotides can also attenuate passive avoidance memory retention (Mileusnic et al., 1999). Polysialylated N-CAM increases at 10–12 and 24 h time points following training (Doyle et al., 1992a; O'Connell et al., 1997b). Treatment of the hippocampus with endo-neuraminidase, which removes polysialic acid from N-CAM disrupts spatial learning tasks and long-term potentiation (Becker et al., 1996a).

2. Features of schizophrenia and bipolar disorder

2.1. Schizophrenia

One feature of schizophrenia is ventricular enlargement (Nelson et al., 1998; Wright et al., 2000), which may be progressive over the course of the disease (Garver et al., 1999) and results from gray matter thinning, reduction of subcortical brain structure size, neuronal loss, or a host of other potential causes. Temporal lobe volume is reduced in patients with schizophrenia (Becker et al., 1996b) and hippocampal and amygdala volume is reduced $\sim$5% in patients with schizophrenia (Nelson et al., 1998; Wright et al., 2000) with a smaller reduction in overall cerebral volume. Gliosis is not present in a majority of schizophrenia neuropathological examinations (Bachus and Kleinman, 1996). These neuroimaging studies reinforce the neurobiological roots of schizophrenia.

Cognitive impairment is another hallmark finding in schizophrenia. The performance on the neurocognitive do-

mains of verbal and nonverbal memory, bilateral and unilateral motor performance, visual and auditory attention, general intelligence, spatial ability, executive function, and language tests show at least moderate reductions compared to controls (Heinrichs and Zakzanis, 1998). Schizophrenia is characterized by a broadly based cognitive impairment in some patients. A remediation of these neurocognitive performance deficits has been demonstrated with atypical antipsychotic medications (Keefe et al., 1999). First-episode patients with schizophrenia also manifest similar neurocognitive deficits (Mohamed et al., 1999) as found in chronic patients. These cognitive findings are in addition to the clinical psychiatric ratings of positive, negative, and disorganized symptoms (Andreasen et al., 1982) listed in the Diagnostic and Statistical Manual of Mental Disorders criteria set for schizophrenia (APA, 1994). Thus, cognitive impairment, brain volume reductions, and ventricular enlargement appear to be biological features of schizophrenia.

2.2. Bipolar disorder

Specific differences in brain structure reported in bipolar disorder are increased frequency of subcortical signal hyperintensities on magnetic resonance images (McDonald et al., 1999), hippocampus volume decrease (Swayze et al., 1992), cerebellar vermal atrophy (DelBello et al., 1999), larger temporal horn volume (Roy et al., 1998), and amygdala enlargement in bipolar disorder (Strakowski et al., 1999). These findings are not consistent in bipolar patients (Pearlson, 1999). A notable concordance between neuroimaging and neuropathology was reported in the subgenual prefrontal cortex (Ongur et al., 1998; Drevets, 1999) with a reduction of glial density in bipolar disorder by neuropathological examination and reduced gray matter in the left subgenual prefrontal cortex (Drevets, 1999).

Cognitive performance is also decreased in bipolar disorder although not as severe as schizophrenia (Goldberg et al., 1993a). Bipolar patients score less than controls on executive function (Ferrier et al., 1999) and declarative memory (van Gorp et al., 1999). Poor neuropsychological functioning and correlation with right hippocampal volume (Ali et al., 2000) was found in bipolar patients. Although very few neuropathological reports from bipolar patients have been reported compared to schizophrenia, bipolar disorder is nevertheless seen as a neurobiological disorder.

3. Relationship of N-CAM with schizophrenia and bipolar disorders

3.1. Embryological hypothesis

A theoretical impetus to form a connection between schizophrenia and abnormal N-CAM concentrations in the brain occurred with the embryological hypothesis (Conrad and Scheibel, 1987). Briefly, disorientation of the hippocampal pyramidal cells in patients with schizophrenia might be related to an in utero exposure of the embryo to neuraminidase activity resulting from a maternal viral infection (Conrad and Scheibel, 1987). The neuraminidase enzyme carried by viruses could remove the polysialic acid from N-CAM and disrupt the migration of neurons into the developing hippocampus in utero (Conrad and Scheibel, 1987). Influenza virus infections in the second trimester account for a small amount of the subsequent risk for developing schizophrenia in epidemiological studies (Takei et al., 1996), while other studies do not find an association between influenza infection rates and schizophrenia risk (Torrey and Rawlings, 1996). However, influenza virus is only one way of disrupting embryonic N-CAM, as there are three neuraminidase genes (*NEU1*, *NEU2*, and *NEU3*) in humans capable of disrupting polysialic acid bonds (Bonten et al., 1996 ; Monti et al., 1999; Wada et al., 1999).

3.2. Initial clinical studies of N-CAM in neuropsychiatric disorders

The levels of a fragment of N-CAM in serum of patients with schizophrenia was increased (Lyons et al., 1988) while patients with autism had a decrease in N-CAM (Plioplys et al., 1990) compared to controls. These findings are based upon N-CAM 70 kDa, which is an isoform others have failed to locate the (Poltorak et al., 1995), although the fragment might be derived from N-CAM 140 found in natural killer cells (Lanier et al., 1991).

Depressed patient's CSF N-CAM increased after treatment and improvement (Jorgensen et al., 1977), while CSF N-CAM was significantly lower before treatment (Jorgensen, 1988). There were no differences reported before and after treatment for bipolar disorder in CSF N-CAM. CSF levels of N-CAM were decreased slightly before treatment in schizophrenia. Patients that were recovered from alcohol-induced delirium tremens increased CSF N-CAM by 200% upon recovery. CSF N-CAM was not related to amyotrophic-lateral sclerosis (Werdelin et al., 1989), anoxic-ischemic coma (Karkela et al., 1993). Nonacute-phase multiple-sclerosis patients showed a decrease in CSF N-CAM (Massaro et al., 1987). Thus, neurodegeneration or brain injury per se does not increase CSF N-CAM, although recovery from depression, alcohol-induced delirium tremens, and acute-phase multiple-sclerosis patients show increases in CSF N-CAM during clinical improvement.

Many initial studies measured CSF N-CAM by enzyme-linked immunoadsorbent assay or rocket immunoelectrophoresis that did not reliably discriminate N-CAM isoforms. Total immunoreactive N-CAM was analyzed; therefore, comparison of these clinical reports to reports that detected N-CAM isoforms by western immunoblotting is difficult.

3.3. Specific N-CAM isoforms in schizophrenia and bipolar disorders — CSF

CSF N-CAM 100–120 kDa was modestly increased in bipolar I and unipolar patients, while much larger increases in CSF N-CAM of up to 200% occurred in chronic patients with schizophrenia (Poltorak et al., 1995; Poltorak et al., 1996; van Kammen et al., 1998). The increase in CSF N-CAM did not appear in neuroleptically naive first-episode patients with schizophrenia (Vawter et al., 1998b). Neuroleptically treated first-episode patients with schizophrenia showed a decrease in CSF N-CAM compared to normal controls (Vawter et al., 1998b). Chronic patients with schizophrenia did not show any reduction in the elevated CSF N-CAM when withdrawn from neuroleptic treatment (Poltorak et al., 1995; van Kammen et al., 1998). Gender may play a modulating role in CSF studies of N-CAM as male patients show increased levels of CSF N-CAM compared to females with schizophrenia (Vawter, M., van Kammen, D., Sedvall, G., and Freed, W., unpublished results). Gender differences in disease severity and illness progression of male patients compared to female patients might be related to N-CAM differences.

In a study of discordant monozygotic twins, an elevation in CSF N-CAM was seen in chronic schizophrenia but not in their normal monozygotic twin (Poltorak et al., 1997). There is no linkage of the N-CAM gene region with schizophrenia (Eubanks et al., 1992; Wang et al., 1993; Vicente et al., 1997).

CSF VASE protein immunoreactivity is significantly increased in patients with schizophrenia, but not in patients with bipolar I, bipolar II, or unipolar affective disorders (Vawter et al., 2000). The increase in CSF VASE concentrations in chronic schizophrenia is consistent with prior findings of increased CSF N-CAM in chronic patients with schizophrenia (Poltorak et al., 1995). However, CSF N-CAM is elevated in the CSF of patients with bipolar type I and unipolar affective disorders (Poltorak et al., 1996), while CSF VASE is not changed in affective disorders.

3.4. Specific N-CAM isoforms in schizophrenia and bipolar disorders — brain

There is a downregulation of polysialylated N-CAM in the hippocampus of patients with schizophrenia (Barbeau et al., 1995), while levels of N-CAM were normal in the parahippocampal gyrus, hilar region, and frontal cortex (Barbeau et al., 1995), although the specific isoforms of N-CAM were not reported. This evidence is consistent with the embryological hypothesis of altered expression of embryonic N-CAM (Conrad and Scheibel, 1987; Conrad et al., 1991) as a possible cause of the disorientation of pyramidal cells in the hippocampus. Total N-CAM was also normal in the frontal cortex and hippocampus of patients with schizophrenia and alcoholics (Breese et al., 1995).

3.4.1. N-CAM 105–115 kDa (cN-CAM)

The cytosolic N-CAM isoform 105–115 kDa (cN-CAM) was elevated in patients with schizophrenia (+55%) compared to controls in the hippocampus (Vawter et al., 1998a). The hippocampal tissue concentrations of cN-CAM were significantly decreased in bipolar disorder (−140%) compared to schizophrenia. Further, cN-CAM was also elevated in prefrontal cortex of patients with schizophrenia as compared with controls. The N-CAM isoforms (180-, 140-, and 120-kDa) were normal in the cytosolic and membrane fractions of hippocampus and prefrontal cortex in schizophrenia and bipolar disorders (Vawter et al., 1998a). Since bipolar disorder patients, presumably exposed to neuroleptics, showed a dramatic reduction in cN-CAM compared to schizophrenia, alterations in brain N-CAM 105–115 kDa may not be explained solely by neuroleptic treatment. Alternatively, patients with bipolar disorder might respond differently to neuroleptic treatment compared to schizophrenia.

cN-CAM is a putative novel isoform and appears most prominently in CSF and cytosolic brain extracts (Vawter et al., 1998a,b). The source of cN-CAM in CSF from the brain has not been proven. However, indirect evidence indicates that cN-CAM in the CSF is likely to be derived from the CNS since the cN-CAM isoform does not appear in serum. The potential mechanisms of release of cN-CAM from brain tissue into the CSF may occur through shedding of membrane-associated isoforms, secretion of intact isoforms, or enzymatic cleavage of isoforms from the cell surface (Krog et al., 1992; Olsen et al., 1993; Hoffman et al., 1998a; Jie et al., 1999). Other possible mechanisms for the release of cN-CAM isoforms from the brain into the CSF include an active transport of N-CAM isoforms across the choroid plexus, or release of N-CAM within the spinal cord.

3.4.2. VASE of N-CAM

VASE N-CAM protein expression was examined in bipolar disorder and schizophrenia by quantitative Western immunoblot (Vawter et al., 1998c). Cytosolic VASE 140 kDa was increased in the hippocampus of patients with bipolar disorder as compared to controls, patients with schizophrenia, and suicide cases. In the prefrontal cortex, cytosolic VASE 140 kDa was also increased in bipolar patients. Membrane extracted VASE isoforms were not different between groups. VASE immunostaining colocalized with GFAP-positive astrocytes in the hippocampus and was also localized in the cytoplasm of CA4 pyramidal neurons (Vawter et al., 1998c). VASE-positive glial cells at the glia limitans with foot processes raises the possibility that CSF VASE N-CAM may be released from these cells.

N-CAM mRNA was significantly lower in the bipolar disorder group in hippocampal regions as compared to control, schizophrenia, and suicide groups (Vawter, 1997). No difference in VASE mRNA expression was found

between groups. However, the ratio of N-CAM/VASE mRNA in serial sections was decreased in bipolar disorder compared to the other groups, suggesting an increased splicing of VASE transcripts in N-CAM mRNA. The origin of the increases in VASE mRNA transcripts as a proportion of N-CAM, and increases in VASE N-CAM protein in bipolar disorder is not clear. VASE could originate from both glial and neuronal cells in line with immunohistochemistry and in situ hybridization (Vawter et al., 1998c). VASE colocalization with GFAP-positive astrocytes in the hippocampus is consistent with cell culture work showing an upregulation of VASE in astrocytes treated with dibutyryl cAMP (Gegelashvili et al., 1993). Interestingly, astrocyte proliferation is markedly decreased by N-CAM infusion (Krushel et al., 1995; Krushel et al., 1998). The reductions in glial numbers noted in the frontal cortex of patients with bipolar disorder (Ongur et al., 1998) might be related to the increases in proportion of VASE to N-CAM transcripts.

3.4.3. Secreted isoform of N-CAM (SEC N-CAM)

SEC N-CAM protein (108 and 115 kDa) was measured in the hippocampus of schizophrenia and bipolar disorder patients using a purified antibody to SEC N-CAM raised against the SEC sequence (Gower et al., 1988). Bipolar disorder patients have an increased SEC N-CAM 115 kDa/108 kDa ratio compared to controls. Thus, bipolar disorder patients show alterations in another splice variant of N-CAM in the hippocampus. Interestingly, SEC N-CAM does not appear in CSF; thus, alterations in cN-CAM and VASE N-CAM in CSF may be unrelated to the source of SEC N-CAM expression (Vawter et al., 1999).

3.4.4. Cell adhesion molecule / synaptic protein ratio

Alterations in the ratio of N-CAM/synaptic proteins has been suggested to be an indicator of synapse remodeling or neural plasticity, i.e. higher ratios are related to loss of mature synapses or an increase in immature synapses (Jorgensen, 1995). Elevated cN-CAM/synaptophysin (Vawter et al., 1999) in the hippocampus and "total" N-CAM/synaptophysin ratios in the cingulate cortex (Honer et al., 1997) indicates a high level of "immature" synapses in schizophrenia. The "immature" synapse index was not altered in bipolar patients or nonpsychotic suicide victims' hippocampus (Vawter et al., 1999). The total N-CAM/synaptosomal-associated protein 25 ratio was not changed in depressed patients in the hippocampus and frontal cortex (Jorgensen and Riederer, 1985).

4. Theoretical linkage of N-CAM neurobiological properties to deficits in schizophrenia and bipolar disorder

The neurobiological properties of N-CAM (Section 1), the schizophrenia and bipolar phenotype (Section 2), and association of N-CAM with each phenotype (Section 3) have been presented. The properties of N-CAM that could result in, or maintain, the pathophysiology of schizophrenia and bipolar disorders will be integrated in the following sections.

4.1. Memory and learning

N-CAM is involved in memory, learning, and neuronal plasticity. N-CAM appears to be linked to modulation of synaptic structures and AMPA signaling appears to induce N-CAM synthesis (Holst et al., 1998). Alterations in cN-CAM and VASE N-CAM disrupts long-term potentiation, learning, and memory since synapse stabilization is dependent upon N-CAM contacts. Synapse remodeling requires optimal N-CAM concentration and internalization of N-CAM in neurons appears to occur with receptor stimulation as a mechanism of adjusting N-CAM levels on the neuron membrane.

Memory and learning are impaired in schizophrenia patients compared to their unaffected monozygotic twin (Goldberg et al., 1993b). In this same monozygotic twin cohort, the CSF N-CAM levels were elevated in only the affected twin, and not the unaffected twin (Poltorak et al., 1997). Elevated CSF N-CAM and decreased neurocognitive ability in monozygotic twins strengthens an association between behavioral effects and elevated N-CAM. The genetics, family of origin, and early environment would be somewhat equivalent in these monozygotic twins. The cognitive impairment that is often found in schizophrenia, and to a lesser extent, bipolar disorder, might result from the molecular machinery of the synapse where memory and learning are believed to occur. Functional neuroimaging data suggest that schizophrenia reflects abnormal activity in, and integration of, the circuits involving the prefrontal cortex, hippocampus and subcortical structures and this could be either a synaptic deficit or neuronal plasticity. The dysregulation of N-CAM hypothesis of neuropsychiatric disorders is consistent with involvement of N-CAM in mediating disconnection between regions of the brain via either local synaptic inputs or by interconnections between regions. (Friston, 1998).

4.2. Psychiatric symptoms

Elevations in CSF VASE and N-CAM are correlated with illness severity and duration in schizophrenia. Illness severity, as defined by the total subscale score of positive behavior symptoms was correlated with CSF VASE concentrations (Vawter et al., 2000). There was no correlation observed between VASE concentrations in affective disorder and Hamilton Depression Scale Scores. Premorbid maladjustment, which is thought to be an indicator of a neurodevelopmental subtype of schizophrenia, was correlated with CSF N-CAM (Vawter et al., 1998b). Further,

illness duration appears significantly related to CSF N-CAM independent of age (Vawter et al., 1998b). Total CSF N-CAM and negative symptoms were not correlated in schizophrenia (van Kammen et al., 1998).

4.3. Brain morphology

Soluble N-CAM fragments appear to be toxic and could disrupt cell migration during development and neurogenesis. N-CAM infusion can inhibit astrocyte proliferation that would alter neuronal density and size through decreased contact between neuron and glial cell membranes. Thus, N-CAM could lead to an absence of gliosis, which would have long-term effects upon production and release of cN-CAM and VASE N-CAM in the adult CNS. Since bipolar disorder hippocampus tissue shows increased VASE expression and schizophrenia patients show an increase in CSF VASE, modulation of neurite outgrowth is predicted as part of the N-CAM dysregulation hypothesis.

Morphological changes in brains of patients with schizophrenia could be induced by N-CAM isoforms as shown in transgenic mice lacking N-CAM 180 (Tomasiewicz et al., 1993; Treloar et al., 1997; Wood et al., 1998). In these mice, the weight and size of brain are decreased by 10%, the volume of the lateral ventricle is increased along with decreases in prepulse inhibition (Wood et al., 1998), analogous to increases of the lateral ventricle and decreases in prepulse inhibition in schizophrenia. The CSF space in the brain might be altered due to changes in cell–cell adhesion, and lateral mobility of N-CAM occurring through alterations in homophilic and heterophilic binding that alter neuron and glial adhesion. It is tempting to speculate that alterations in N-CAM isoforms mimic some of the biological markers in schizophrenia.

Hippocampal disarray in schizophrenia has not been replicated (Harrison, 1999). There are hippocampal abnormalities in N-CAM 180 transgenic mice. Neurogenesis in the adult hippocampus (Eriksson et al., 1998) is thought to utilize embryonic polysialylated N-CAM. Alterations in N-CAM could lead to hippocampal neuron dysgenesis in adults, or earlier in development, and might underlie some of the subtle neuroanatomical pathology, such as reductions in synaptic proteins in the hippocampus (Harrison, 1999). Since these newly born neurons in the dentate gyrus extend axons into CA3 (Hastings and Gould, 1999), a reduction in these neurons would lead to reduced synaptic inputs in CA3. Hippocampal nonpyramidal cells are thought to be reduced in size (Benes et al., 1991; Arnold et al., 1995) and this might be either cause or effect of a synaptic denervation brought on by dysregulated N-CAM. N-CAM and synaptic protein has been found altered in the hippocampus of patients with schizophrenia (Vawter et al., 1999). Hippocampal disarray might be pronounced at the molecular synapse level compared to traditional neuropathological abnormalities.

4.4. Testing the dysregulation of N-CAM hypothesis of neuropsychiatric disorders

The biological markers of schizophrenia involving ventricular and cognitive changes could be tested by infusions of various N-CAM peptides into brain regions. An animal model that uses a controllable N-CAM promoter, or with gene knock-down strategies, could elucidate whether there are changes resulting from over- and under-expression of N-CAM. cN-CAM infusion might perpetuate some of the cardinal features, such as ventricular enlargement, working memory deficits, hippocampal tissue volume decrease, decreased synaptic protein concentrations, prepulse inhibition change, and long-term potentiation disruption. The subjective psychiatric symptoms of patients with schizophrenia or bipolar disorder cannot be tested in animal models.

5. Summary

The recent human studies reveal strong associations of schizophrenia with cN-CAM and VASE N-CAM found in CSF, but not with the parent molecule N-CAM. Further, VASE N-CAM and SEC N-CAM, but not the parent molecule N-CAM, are associated with bipolar disorder. The synaptic maturity marker is altered in schizophrenia but not affective disorders. The neurobiological properties of N-CAM have been linked to phenotypic characteristics found in schizophrenia and bipolar disorder. It is postulated that dysregulated N-CAM can lead to alterations in synaptic activity and remodeling. Network interconnectivity in various brain regions could be affected by N-CAM dysregulation by neurite outgrowth and synaptic input defects. The findings of differences in N-CAM isoforms and synaptic proteins in bipolar disorder and schizophrenia implicates neural plasticity and synaptic remodeling in the pathophysiology of these disorders. The N-CAM dysregulation hypothesis would be linked to synaptic abnormalities since one major isoform N-CAM 180 is localized at the synapse (Persohn et al., 1989) and participates in synapse plasticity. Cognitive components of memory and learning are believed to be modulated by synaptic activity and these impairments would seem logically to reside in some aspect of the synaptic function.

In vivo testing of the hypothesis in animal models could answer fundamental questions. Does N-CAM dysregulation induce alterations in synaptic proteins, modulate neuronal size, induce morphological variations in developing brain, and restrict neurogenesis and subsequent axonal projections from the hippocampus dentate gyrus into CA3?

Transcription factors that regulate N-CAM, such as Pax and Hox, may have associations to schizophrenia subtypes, such as an atrophic subtype (progressive ventricular enlargement) compared to a neurodevelopmental subtype (static ventricle) (Garver et al., 1999). It is not surprising

that genetic linkage to schizophrenia was not reported for N-CAM since a single point mutation in the L1 cell adhesion molecule gene causes tremendous brain and mental abnormality (Yamasaki et al., 1997). Since alteration in N-CAM produced a lethal mutation, the evidence suggests that alterations in N-CAM expression will be environmentally induced, perhaps with a genetic predisposition.

The dysregulation of N-CAM isoforms would influence cognitive function through learning, synaptic plasticity, and long-term potentiation effects. Dysregulation of N-CAM isoforms also convey morphological and navigational information, fundamental for wiring the CNS. Thus, neuropsychiatric disorders affect a wide variety of experiences some that are influenced by N-CAM. The evidence shows that N-CAM isoforms influences behavior in a manner perhaps conceptually similar to those proposed by Dr. David de Wied in his thinking on vasopressin and memory (De Wied et al., 1974). Dr. David de Wied's seminal neuropeptide work continues in the hands of other researchers and serves to enlighten researchers in the study of proteomics and neuropsychiatric disorders.

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