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Review

Potential roles of NCAM/PSA-NCAM proteins in depression and the mechanism of action of antidepressant drugs

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Abstract:
Recently, it has been proposed that abnormalities in neuronal structural plasticity may underlie the pathogenesis of major depression, resulting in changes in the volume of specific brain regions, including the hippocampus (HIP), the prefrontal cortex (PC), and the amygdala (AMY), as well as the morphology of individual neurons in these brain regions. In the present survey, we compile the data regarding the involvement of the neural cell adhesion molecule (NCAM) protein and its polysialylated form (PSA-NCAM) in the pathogenesis of depression and the mechanism of action of antidepressant drugs (ADDs). Elevated expression of PSA-NCAM may reflect neuroplastic changes, whereas decreased expression implies a rigidification of neuronal morphology and an impedance of dynamic changes in synaptic structure. Special emphasis is placed on the clinical data, genetic models, and the effects of ADDs on NCAM/PSA-NCAM expression in the brain regions in which these proteins are constitutively expressed and neurogenesis is not a major factor; this emphasis is necessary to prevent cell proliferation and neurogenesis from obscuring the issue of brain plasticity.

Key words:
antidepressant drugs, depression, NCAM, PSA-NCAM

Abbreviations: ADD – antidepressant drug, ADDs – antidepressants, antidepressant drugs, AMY – amygdala, FGFR – fibroblast growth factor receptor, FLU – fluoxetine, HIP – hippocampus, NCAM – neural cell adhesion molecule, PC – prefrontal cortex, PSA – 2,8-polysialic acid, PSA-NCAM – polysialylated form of neural cell adhesion molecule, SPT sucrose preference test, TST – tail suspension test

Introduction

The monoaminergic hypothesis that antidepressants (ADDs) act *via* inhibition of monoamine uptake has been called into question [30]. First, the pharmacological effect of these drugs, i.e., the blockade of serotonin and noradrenaline uptake, is not clearly associated with their clinical efficacy [30]. Moreover, the novel antidepressant (ADD) tianeptine is actually a serotonin reuptake enhancer [32]. In addition, the direct, rapid effect of ADDs on monoamines contrasts with the delayed onset of effectiveness of ADDs in the clinic [30]. Recent theories on the pathogenesis of major depression suggest that changes in neuronal plasticity may be responsible for the appearance of depressive symptoms and that ADDs alleviate symptoms by interfering with the mechanism responsible for plasticity of neuronal morphology [36]. These changes may reflect alterations in neuronal structure,

leading to disturbances in the balance of excitatory and inhibitory neurotransmission [15]. It has been demonstrated in animal models that chronic stress [35, 36] induces dendritic atrophy and reductions in spine density in principal neurons of the hippocampus (HIP) [31] and the medial prefrontal cortex (PC) [40]. Although it is not known whether prolonged stress is sufficient to evoke depression, it is often considered as a precipitating factor for depression in humans. Nevertheless, when chronic stress models are used with an understanding of the limitations, they can provide powerful information about the underlying molecular and cellular determinants of anatomical alterations in neuronal circuitry, which controls complex stress-related behaviors [36]. Certain types of prolonged stress, such as learned helplessness and chronic mild unpredicted stress, are accepted as realistic depression models [36]. These models indicate that it is not the stress *per se* but rather an inability to cope with stress that leads to depression [11]. Thus far, there are limited studies with data indicating that there is a reduction in neuronal size, spine density, or synapse density in realistic models of depression (chronic mild stress, learned helplessness) [2, 33].

In the last decade, an impressive body of clinical data has been collected using imaging techniques to examine the morphological and metabolic brain changes that are characteristic of depression [3, 10, 24]. Meta analyses (essential for reviewing findings from different studies and comparing results in a standardized fashion) investigating the changes in voxel-based morphometry have lead to the conclusion that, in the course of depression, there are significant decreases in morphological volume within the cortico-limbic circuit, including the amygdala (AMY), the fronto-medial cortex, the paracingulate cortex, and, depending on the analysis, the HIP [3, 10, 24]. Although it is not clear whether the observed changes in human brain volume are causative to depression, they raise an interesting question regarding the cause and effect between plasticity and depression. Shrinkage of the brain structure, as well as the size of individual neurons, is also observed in chronically stressed animals [31, 40]. In the present article, we focus our attention on the superfamily of adhesion molecules, which are proteins located on the cell surface that are involved in binding with other cells or with the extracellular matrix in a process called cell adhesion. Specifically, we consider the neural cell adhesion molecule (NCAM) and its polysialylated form (PSA-NCAM) as a cause of depression and potential target for ADDs.

Essentially, cell adhesion molecules help cells stick to each other and their surroundings. NCAM is a member of the immunoglobulin (Ig) superfamily of adhesion molecules, which are encoded by a single gene. The process of alternative splicing can yield two transmembrane NCAM isoforms – one 180- or 140-kDa isoform – or one 120-kD glucophosphatidyl inositol-linked isoform. The extracellular domain of NCAM is composed of five Ig-like domains followed by two fibronectin type III (FN3) domains. NCAM exhibits two modes of binding: homophilic and heterophilic. Homophilic binding consists of linkages to a series of counter-receptors, including tyrosine kinase receptors, such as the fibroblast growth factor receptor (FGFR), the brain-derived neurotrophic factor receptor, and the tropomyosin kinase receptor B. Heterophilic binding, i.e., linkages to other adhesion molecules and various extracellular NCAMs, is also critical for maintenance of proper neuronal connections. To bind 2,8-polysialic acid (PSA), NCAM attaches to the negatively charged long chains of PSA, conferring anti-adhesive properties on the molecule. A high degree of NCAM polysialylation on neuronal processes promotes a variety of developmental events, such as axonal growth and fasciculation, cell migration, initiation of synaptic reorganization, and synaptogenesis. The expression of PSA-NCAM is particularly high in the developing brain, as well as in adults in the brain regions that undergo persistent and sustained synaptic plasticity, such as the hypothalamo-neurohypophysial system, the olfactory bulb, the medial prefrontal, piriform and entorhinal cortices, the AMY, and the HIP. Thus, alterations in the expression of PSA-NCAM may signify that changes in plasticity are occurring in the adult brain (for examples from our laboratory, see [5, 25–27]). Elevated expression of PSA-NCAM may reflect changes in plasticity, whereas decreased expression implies a rigidification of neuronal morphology and an impedance of dynamic changes in synaptic structure (for a extensive review on NCAM/PSA-NCAM, see [12, 14]).

Clinical data

Clinical evidence regarding the involvement of NCAM proteins in depression and bipolar disorders is

sparse thus far. The soluble form of NCAM proteins was detected in cerebrospinal fluid for the first time in 1988 by Jorgensen [21] and further replicated by Poltorak et al. in 1996 [38]. Both reports indicated an increased concentration of the soluble form of NCAM in psychiatric patients suffering from bipolar mood disorder and major depression. Importantly, Poltorak found no effect of medication on NCAM concentration (primarily the 120-kDa isoform) [38]. This apparent effect raises the question of disease specificity. Unfortunately, a similar effect has been observed in patients suffering from schizophrenia [45], suggesting a common effect of schizophrenia and depression on brain plasticity, rather than a disease-specific pathology marked by apparently abnormal NCAM turnover in the CNS of patients with mood disorders. However, depressed patients exhibited decreased PSA-NCAM expression in the basolateral and basomedial AMY [44], while bipolar patients showed the opposite effect [44], as measured by stereological procedures. These effects have now been reproduced by western blot [28]. Interestingly, studies performed on brains donated by the Stanley Neuropathology Consortium, which includes controls, schizophrenia, bipolar and major depression patients, no changes in PSA-NCAM expression were observed in PC tissue of bipolar and depressed patients [15].

NCAM gene knockout as a model of depression

The transgenic animal model knocking out the gene encoding the NCAM proteins is a useful tool to verify its role as a potential cause of depression. Mice lacking all three major isoforms of NCAM (NCAM–/–) exhibit citalopram- and amitriptyline-sensitive anhedonia measured by the sucrose preference test (SPT) [1]. In the tail suspension test (TST), an assessment designed test invented to screen for the ADDs activity, NCAM–/– animals exhibit an increased time of immobility in comparison to their respective controls. The above effect has been blocked/attenuated by the classic ADDs amitriptyline and citalopram [22]. These findings indicate that a lack of NCAM proteins is sufficient to evoke "depressive-like" behavior, but is not sufficient to influence the therapeutic effect of ADDs [22]. The effect of NCAM knockout in the TST and SPT has also been reversed by a 15-amino acid-long peptide, called FGL. The FGL peptide mimics the interaction of NCAM with fibroblast growth factor receptors (FGFR), suggesting a novel therapeutic target for drugs aimed at treatment of depression [22]. Although the cognitive impairments observed in the NCAM–/– model may be regarded as models of indecisiveness which accomplishes depression, on one hand, on the other hand, they could interfere with animals' performance on test assessments evaluating their depressive state. This confound has been resolved using NCAM +/– heterozygous mice [23]. Again, such NCAM +/– animals display depressive-like symptoms in the TST, the SPT, and the novelty-suppressed feeding test; however, NCAM +/– mice are devoid of cognitive impairments [23]. It is worth noting here that NCAM–/– animals has exhibit an increased level of fear and anxiety [22], which is observed in the course of depression, and their reduced ability to cope with stress what may result again in their depressive vulnerability [1].

Impact of ADDs on expression of NCAM/PSA-NCAM protein

Thus far, we have found five separate articles demonstrating the impact of ADDs on expression of NCAM/PSA-NCAM protein (see Tab. 1 and its references). These studies are based on chronic ADDs administration [fluoxetine (FLU) (four reports) and imipramine (one study) – see Tab. 1 and references there)]. In all the studies mentioned, elevated expression has been noted in both young-adult and adult animals. Such consistent effects have been observed in the PC or its subregions, while decreased expression has been noted in the AMY in adult but not adolescent rats (see Tab. 1 and its references). Animal age is important because constitutive expression of NCAM/PSA-NCAM is decreased during the life span [12, 14]. An additional 3 separate experiments utilized a stress model, and both the ADD FLU and the novel ADD, agomelatine, were found to influence stress-induced elevation of NCAM/PSA-NCAM. Two studies indicated that stress elevates the expression of NCAM protein in the PC and the HIP, which is blocked by chronic administration of FLU [8, 9]. Agomelatine [39] normalized the stress- and learning-induced de-

Tab. 1. Impact of various antidepressant drugs on expression of NCAM or PSA-NCAM proteins in the rat brain

Antidepressant drug (dosage and treatment)	Species	Method of analysis	Paradigm	Brain region	Effect	Ref.
Fluoxetine, 21 days, 5 mg/kg *ip*	Young-adult male Wistar rats	Western blot, NCAM	Chronic social isolation	PC	Reduction of the PSA-NCAM level elevated by stress. In naive, no effect	[8]
Fluoxetine, 14 days, 10 mg/kg *ip*	Young-adult male Wistar rats	Immuno-cytochemistry, PSA-NCAM	Naive	PC, AMY, HIP	Increase in all analysed regions	[17]
Fluoxetine, 21 days, 5 mg/kg ip	Young-adult male Wistar rats	Western blot	Chronic social isolation	HIP	Reduction of the PSA-NCAM level elevated by stress. Alone, inactive	[9]
Fluoxetine, 21 days, 12 mg/kg *po*	Young and old male Wistar rats	Immuno-cytochemistry, NCAM/PSA-NCAM	Naive	AMY, DR, PC	AMY-increased in adolescent but decreased in adult. No effects in the other brain regions	[19]
Agomelatine, 22 days, 10 mg/kg *ip*	Adult male Sprague-Dawley rats	Immuno-cytochemistry	Spatial memory training with or without predator stress	vHIP	Treatment blocked the water maze-induced decrease in PSA-NCAM in both stressed and non-stressed animals	[7]
Fluoxetine, 14 days, 10 mg/kg, *ip*	Adult male Sprague-Dawley rats	Immuno-cytochemistry	Naive	PC, AMY	Increased PSA-NCAM expression in PC and decreased in AMY	[44]
Imipramine, acute 30 mg/kg *ip* and chronic, 21 days, 15 mg/kg *ip*	Adult male Wistar rats	Immuno-cytochemistry, PSA-NCAM	Naive	PEC, PIC, HIP	Increase only after chronic treatment	[41]
Fluoxetine, 14 days, 10 mg/kg *ip*	Young-adult male Wistar rats	Immuno-cytochemistry, PSA-NCAM	Naive	INC, PRC, CC	Increase	[43]

The table was developed using data compiled from a Medline search based on the following key words: antidepressant drugs and PSA-NCAM and antidepressant drugs and NCAM. Two articles were omitted because they address the question of proliferation but not neuroplastic changes. Abbreviations: AMY – amygdala, CC – cingulate cortex, DR – dorsal raphe nucleus, HIP – hippocampus, INC – infralimbic cortex PC – prefrontal cortex, PEC – perilimbic cortex, PIC – piriform cortex, PRC – prelimbic cortex, vHIP – ventral hippocampus, *ip* – intraperitoneal route of drug administration *po* – oral administration (per os)

creases in expression of PSA- NCAM observed in the ventral HIP.

Apart from the phenomenological observation that ADDs (predominately FLU) alters the expression of PSA-NCAM proteins, relatively little is known about the mechanism of above effects. Is not clear whether ADDs, or FLU specifically, directly influences PSA-NCAM or NCAM expression or leads to changes in expression *via* alterations in neurotransmission – for example, serotonergic transmission. To our knowledge, only one study addresses this issue. It has been found that acute administration of ondansetron, a specific antagonist of 5-HT_3 receptors, in an acute dose alleviated the increase in PSA-NCAM induced by chronic FLU administration [43]. This result appears to suggest that FLU alters PSA-NCAM *via* changes in serotonergic transmission and in a manner that involved 5-HT_3 receptors [43].

Finally, it bears mentioning two published articles that utilized the ability of ADDs to induce neuroplastic changes in a manner that is clearly distinct from their ADDs properties [13, 20]. The first study analyzed the impact of on alteration of NCAM expression in the HIP after kainic acid-induced seizure [20], and the second study analyzed the effect of prolonged administration of venlafaxine on alteration of NCAM expression in ischemic stroke [13]. Administration of kainic acid induces seizures and neuronal death largely in CA3 region, followed by a cascade of neuroplastic changes throughout the HIP, including temporary activation of neurogenesis, dispersion of granule cells, and reorganization of mossy fibres [20]. All of the above changes have been restored to control levels after administration of citalopram seven days before and 21 days after administration of kainic acid. It is also not clear whether citalopram directly influences neuroplastic changes or neuroplastic changes are attenuated by a decrease in seizure severity. The mechanism through which ADDs could alter seizure-evoked neuroplasticity is largely unknown. It has been speculated that the effectiveness of ADDs administered in a course typical for treatment of depression (i.e., chronic administration) is not only due to changes in neurotransmitter concentrations and/or receptor sensitivity but is also due to an improvement in brain plasticity and tissue remodelling [20]. There is one study analyzing the impact of chronic venlafaxine on expression of NCAM proteins in the mouse HIP after cerebral ischemia [13]. The rationale of these experiments is based on the assumption that ischemic brain injury often results in severe neurological damage, which may be the basis for the accompanying cognitive impairment and depressive states [13]. It has been observed that venlafaxine in a dose-dependent manner abrogates the ischemia-induced elevation of NCAM proteins in the HIP [13]. It will be of interest to further analyze the above pathway to investigate first, whether ischemic insults in mice lead to depressive symptoms and, secondly, whether acute or prolonged administration of venlafaxine after ischemic insults is also effective against the ischemia-induced elevation of PSA-NCAM. The results of both studies may indicate that ADDs may be used effectively in brain disorders caused by abnormalities in neuroplasticity [13, 20].

In summary, the data indicating a role of NCAM or PSA-NCAM proteins in realistic models of depression are yet to be discovered. The first step in that direction was a study by Bessa at al. [2] demonstrating that chronic mild stress leading to anhedonia (decreased sucrose preference) provoked an increase in the expression of NCAM mRNA in the rat nucleus accumbens. This effect was reversed by chronic administration of FLU and imipramine [2].

NCAM as potential target for new antidepressants

It is difficult to imagine that molecules of extracellular matrix could be targets for novel ADDs. However, drugs that may alter brain structure are of potential interest not only in the case of depression but also in several other disorders associated with either cognition or learning and memory. In the case of NCAM proteins, it may be proposed that inhibitors or activators of the polysialyltransferases ST8SiaII (STX) and ST8SiaIV (PST), selectively involved in polysialylation of the NCAM protein may constitute a potential drug target. As mentioned above, long negatively charged chains of PSA attached to NCAM confer anti-adhesive properties to the molecule and promote reorganization of the mature brain [12, 14]. STX regulates NCAM polysialylation during embryonic, perinatal, and early postnatal development, whereas PST is predominantly active in the postnatal brain [4, 29]. The data indicating that depression results from developmental origin, or traumatic life events STX and PST are the targets of choice. It is not known whether animals with the gene encoding STX or PST knocked out are "depressive" [4, 29]. Thus far, it has been observed that they display specific impairments in spatial memory but not conditioned fear memory in PST knockouts [29]. It has also been found that both STX and PST knockouts exhibit impaired sociability, while only STX exhibits an increased level of aggression and enhanced stress reactivity, as measured by corticosterone levels in response to stress [4]. Alternatively, alteration in the level of the circulating soluble form of NCAM may be another target. Soluble NCAM is an antagonist of membrane-bound NCAM. This antagonism can be achieved by either a specific antibody or a compound that influences or detaches the constitutive membrane-bound NCAM. The family of ADAM (a disintegrin and metalloproteinase) proteins is required for NCAM shedding and may consti-

tute a potential target for novel drugs [18]. Finally, linkage of NCAM to FGFRs is of potential interest. The ability of the FGL peptide to penetrate the CNS after peripheral administration supports further research of NCAM proteins as targets of novel ADDs [1, 42].

Conclusion

Although the concept that depression and the mechanism of action of ADDs are associated with remodelling of neuronal circuits that are essential for mood and cognition is interesting, it should, however, be suggested cautiously [36]. First, only a limited number of clinically effective ADDs have been tested (Tab. 1). Secondly, limited, if any, studies analyzed the time course of changes in expression of PSA-NCAM/NCAM after ADD treatment, and therefore, it is not clear whether the described effects are transient or persistent. In the absence of clear clinical data regarding the involvement of NCAMs in the etiology of depression, it is conceivable that these proteins may be involved in the mechanism of action of ADDs but not in the origination of depression. Thus far, the most probable explanation for the effect of ADDs is that they alter serotonergic transmission, precipitating brain remodelling [43]. Subsequently, it will be necessary to investigate symptoms of depression in animal models overexpressing the soluble form of NCAM. Such animals are available and display a schizophrenic-like phenotype [37]. However, the common feature of schizophrenia and depression on the level of mood does not rule out depressive symptoms. Finally, it will be important to confirm the effects of both chronic and acute administration of ADDs. The latter suggestion is important in the context of experiments performed on C6 glioma cells that indicated that even short exposure of these cells to FLU, such as 6 hours, increased expression of the NCAM protein [6]. NCAM/PSA-NCAM positive cells are present predominately, if not exclusively, in the population of inhibitory interneurons located in the PC, AMY, and HIP. PSA-NCAM-expressing cells constitute around 10% of the GAD67-expressing interneurons, i.e., GABAergic inhibitory interneurons [16, 34]. Many of the PSA-NCAM-expressing somata are positive for calbindin and somatostatin, and a very small population of these cells express parvalbumin, calretinin, and neuropeptide Y or vasointestinal peptide [16, 34]. Additionally, PSA-NCAM-positive cells in the neurophil co-expressed markers of GABAergic terminals and neurotransmission, such as the vesicular GABA transporter (VGAT) or GAD67, but virtually none of them expressed the vesicular glutamate transporter 1 (VGLUT1), a marker of glutamatergic neurons [16, 34]. The above characteristics are given here because they provide important information regarding the potential mechanism of action of ADDs. It is conceivable that *via* alteration in structural plasticity governed by PSA-NCAM, ADDs may shift the balance between inhibitory input and excitatory output in neuronal circuits associated with depression.

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