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Short communication

Impact of maternal separation on neural cell adhesion molecules expression in dopaminergic brain regions of juvenile, adolescent and adult rats

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Abstract:
Stressful experiences in the early stages of life can influence brain development and maturation, and they can also increase the risk for some psychiatric disorders; however, the specific mechanisms of this effect are still poorly understood. Neural cell adhesion molecules (NCAM 120, 140, 180 kDa) are known to play an important role in normal brain development and synaptic plasticity. Therefore, we decided to investigate whether maternal separation (MS) in rats, a paradigm which models an early life stress, has any impact on the expression of NCAM proteins in the juvenile, adolescent and adult brains of both male and female rats. Specifically, we focused our efforts on the brain regions associated with dopaminergic neurotransmission. In juvenile rats, MS decreased the levels of NCAM-140 in the substantia nigra (SN) of females and NCAM-180 in the ventral tegmental area of males. During adolescence, a reduction in NCAM-180 levels in the SN and medial prefrontal cortex (mPFC) of MS females was revealed. Finally, in adulthood, a decrease in NCAM-180 expression was observed in the mPFC of MS males. The results that we obtained indicate that early life stress can affect maturation and NCAM-driven plasticity in dopaminergic brain areas at different stages of ontogenesis and with a sex-specific manner.

Key words:
maternal separation, NCAM, substantia nigra, ventral tegmental area, medial prefrontal cortex, nucleus accumbens, striatum, Western blot

Introduction

There is a growing body of evidence that stressful experiences in the early stages of life can influence brain development and, consequently, increase the risk for some psychiatric disorders, such as depression, anxiety, personality disorders, drug abuse and schizophrenia [20]. However, knowledge is still limited about the exact mechanisms by which early life stress exerts its detrimental impact on the development and maturation of the central nervous system.

Recently, much attention has been focused on the important role of neural cell adhesion molecules (NCAM) in the proper functioning of the brain during all stages of development and throughout adulthood (for review see [8] and the papers quoted therein). NCAM proteins belong to the immunoglobulin superfamily of cell adhesion molecules, and they are expressed in the vertebrate nervous system as three main isoforms of different molecular weights (i.e., NCAM-120, NCAM-140 and NCAM-180). All of these isoforms are the products of alternative splicing of a sin-

gle *NCAM* transcript, and they usually undergo further posttranslational modification; for example, the isoforms can be modified by polysialylation (PSA-NCAM) [8, 15].

NCAM are involved in many important processes, including neurite outgrowth, axon fasciculation and guidance, synaptic stabilization and plasticity [8], as well as learning and memory [11]. Most of the above functions result from the activation of specific intracellular signaling pathways following cell – cell and cell – extracellular matrix adhesion processes mediated by NCAM. Recently, however, accumulating data point towards other functions of NCAM that are not associated with adhesion. It has been found, for example, that NCAM regulates the process of dopamine D2 receptors internalization as well as dopamine-related signaling and locomotor activity in mice [22]. Moreover, it has been revealed that NCAM mediates the effects of glial cell line-derived neurotrophic factor ((GDNF), a specific neurotrophin for midbrain dopamine neurons) on dopamine neurons survival during development and dopamine turnover in adulthood [5, 6].

There are many reports that state that an alteration in NCAM expression can underlie the pathomechanisms of some mental disorders. In clinical studies, it has been shown that patients with bipolar mood disorders and schizophrenia have increased levels of NCAM in the cerebrospinal fluid (soluble NCAM fragments) and in the hippocampus and cortex (transmembrane NCAM) (for review see [16]). Additionally, in animal studies it has been revealed that NCAM knockout mice display increased lateral ventricle size (morphological hallmark of schizophrenia) [21] and several behavioral abnormalities, like increased aggression and anxiety [18]. Moreover, transgenic mice with an overexpression of a soluble form of NCAM also exhibit several functional and anatomical dysfunctions that resemble those typical for schizophrenia, such as deficits in prepulse inhibition (PPI); they also exhibit enhanced responsiveness to dopaminergic agonists and anatomical deficits in GABAergic cartridges in the medial prefrontal cortex (mPFC) [14].

It has also been well documented that chronic corticosterone treatment [17], and the application of various types of chronic stress in adult animals, causes a decrease in NCAM expression in the hippocampus and the mPFC (for review see [16]); this decrease is dependent on the severity of the stress applied. The aforementioned brain regions are representative for NCAM-based neuronal plasticity, the malfunction of which has been implicated in the pathogenesis of depression [16] and memory/learning deficits [1]. In contrast, the amount of data showing the impact of stress, especially early life stress, on NCAM expression in other brain structures and at different stages of ontogenesis is limited [1, 7, 10, 19].

The above findings, together with data demonstrating that the quality of maternal care also regulates NCAM expression [10], prompted us to investigate the immediate and long-term effects of early life stress on NCAM expression, specifically in brain structures that are strongly related to dopaminergic neurotransmission and implicated in the pathogenesis of bipolar disorder and schizophrenia (that is the substantia nigra, ventral tegmental area, nucleus accumbens, striatum and the mPFC). As a model of early life stress, we applied the procedure of prolonged maternal separation (MS) in rats. The consequences of MS were examined in juvenile, adolescent and adult male and female rats.

Materials and Methods

Animals

All of the experimental procedures were approved by the Committee for Laboratory Animal Welfare and the Ethics Committee of Institute of Pharmacology, PAS in Kraków, and they met the requirements of the European Council Guide for Care and Use of Laboratory Animals (86/609/EEC).

The animals used in the present study were the offspring of primiparous Wistar dams (Charles River, Germany), mated in the animal facility at the Institute of Pharmacology, PAS, Kraków. The dams were housed individually under standard conditions on an artificial 12-h light/dark cycle (lights on from 07:00 to 19:00) with food and tap water freely available. The day of birth was designated as postnatal day (PND) 0. On PND 1, the litter size was standardized to eight pups per litter (four males and four females), and the litters were assigned to one of the following rearing conditions until PND 14: maternal separation (MS) or animal facility reared- (AFR) control animals.

Maternal separation (MS)

On each of PNDs 1–14, the dams and the pups were removed from the maternity cages for 3 h (09:00 to 12:00). The mothers were placed individually in holding cages, while each litter was placed in a plastic container lined with fresh bedding material, moved to an adjacent room and located in an incubator with a constant temperature of 34°C. After the 3-h separation, the pups and the dams were returned to the maternity cages. Once a week, the maternity cages were cleaned during one of the separation procedures. Control (AFR) animals were left undisturbed with their mothers, except during the cage cleaning that was performed once a week. The animals, excluding those examined on PND 15, were weaned at PND 22 and housed in standard conditions (as above) in groups of 4–5 animals of the same sex and the same treatment protocol until adolescence (PND 35) and adulthood (PND 75). The final experimental groups consisted of subjects that originated from different litters. For each developmental time point (i.e., PND 15, PND 35, PND 75), and for each sex, five MS and five AFR animals were sacrificed.

Western blot

The animals were sacrificed by decapitation, and the brains were rapidly removed from the skulls. Afterwards, the samples of the substantia nigra (SN), ventral tegmental area (VTA), striatum (STR), nucleus accumbens (NAc) and the mPFC were dissected from 1 mm-thick coronal slices using rodent brain matrix (Ted Pella), and the samples were quickly frozen in liquid nitrogen and stored at –80°C until they needed to be used. Then, the tissue was homogenized (TissueLyser, Retsch) in ice-cold 50 mM TBS containing 0.5% Triton X-100, 0.5% SDS, 1 mM EDTA, 1 mM EGTA, 50 mM NaF, 1 mM PMSF and a protease inhibitor cocktail (1:200, Sigma). The homogenates were centrifuged for 15 min at 15,000 × g at 4°C. Supernatants were assayed for the total protein concentration by the BCA method (Sigma). Equal amounts of protein (7–10 μg, depending on the developmental time point and structure) were loaded in each lane and run on 7.5% SDS-polyacrylamide gels with the Laemmli buffer system, and then they were transferred to a nitrocellulose membrane (BioRad). The blots were probed with mouse anti-NCAM (1:1000, Sigma) and with mouse anti-β-actin (1:10,000, Sigma) antibodies. Afterwards, the blots were visualized by ECL (Lumi-Light^{Plus} Western Blotting Kit, Roche) and evaluated with a luminescent image analyzer (Fujifilm LAS-4000). The relative levels of immunoreactivity were quantified using Image Gauge software (Fujifilm). To normalize for small variations in loading and transfer, the NCAM level/actin level ratio was calculated for each sample. The final data were presented as the percent change of protein expression in relation to the values obtained from the control animal samples (% of AFR). Protocols and the experimental procedure have been previously described by Maćkowiak et al. [11, 12].

Statistical analysis

The data are presented as the means ± SEM. The statistical evaluation was performed for each NCAM isoform using a one-way analysis of variance ANOVA (Statistica 8, StatSoft Inc.), where rearing conditions (MS *vs*. AFR) were regarded as the independent variable. A p value of < 0.05 was considered to be statistically significant.

Results

In the present study, the applied antibody recognized two major immunoreactive bands with molecular weights of 140 kDa and 180 kDa (Fig. 1, 2, right panels), corresponding to NCAM-140 and NCAM-180, respectively, the two main isoforms of the NCAM protein. The third isoform of NCAM, NCAM-120, was barely detected (which is in line with our previous data [11]); thus, it was excluded from the analysis.

In juvenile animals (PND 15), a statistically significant impact of MS on NCAM expression was revealed in the SN of females (Fig. 1A) and in the VTA of males (Fig. 2A). Specifically, a decrease in NCAM-140 expression (35%) in the SN of MS females ($F(1,8) = 11.10$, $p < 0.01$; Fig. 1A) and a reduction in NCAM-180 expression (24%) in the VTA of MS males ($F(1,8) = 6.96$, $p < 0.03$; Fig. 2A) were observed. In the remaining structures studied (in the STR, NAc and mPFC), MS did not affect the levels of NCAM-140 or NCAM-180 proteins (for data summary, see Tab. 1).

On PND 35, NCAM expression was influenced by MS only in female rats (Fig. 1B, C). It was observed

Tab. 1. Schematic view of the overall impact of maternal separation on NCAM proteins levels in all studied structures, sexes and developmental time points

	PND 15		PND 35		PND 75	
	Females	Males	Females	Males	Females	Males
SN	35%↓ NCAM-140	–	30%↓ NCAM-180	–	–	–
VTA	–	24%↓ NCAM-180	–	–	–	–
STR	–	–	–	–	–	–
NAc	–	–	–	–	–	–
mPFC	–	–	37%↓ NCAM-180	–	–	22%↓ NCAM-180

The values express the percentage of change in NCAM expression in relation to control (AFR rats), if it is statistically significant. Abbreviations: ↓ significant decrease; – no change; mPFC – medial prefrontal cortex; NAc – nucleus accumbens; PND – postnatal day; SN – substantia nigra; STR – striatum; VTA – ventral tegmental area

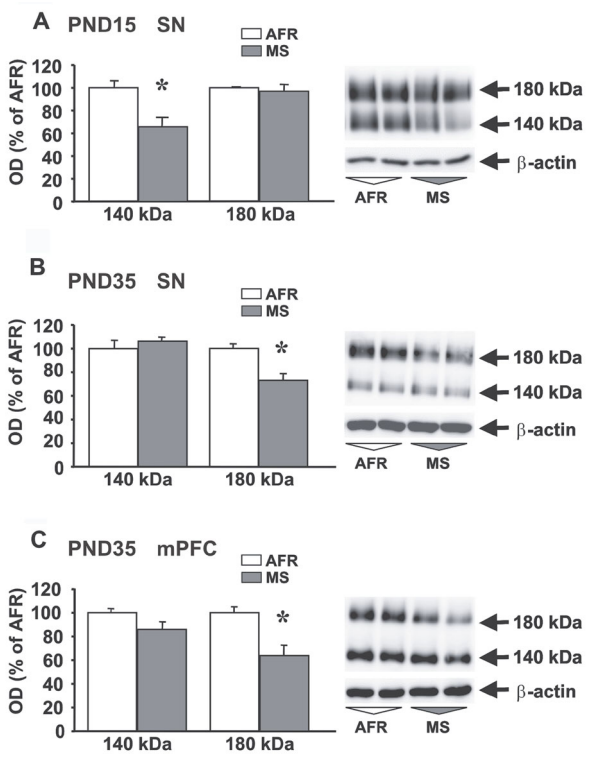

Fig. 1. The effects of maternal separation on NCAM proteins expression in female rats: (**A**) in the SN of juveniles – PND 15; (**B**) in the SN of adolescents – PND 35; and (**C**) in the mPFC of adolescents – PND 35. Data are presented as the group means ± SEM, and they are expressed as a percentage of control (AFR rats) values; n = 5 per group, * $p < 0.05$ *vs.* AFR rats (ANOVA). Right panels: representative immunoblots showing the expression of NCAM-140 and NCAM-180 in studied brain regions and developmental time points. Abbreviations: AFR – animal facility reared; MS – maternally separated; mPFC – medial prefrontal cortex; OD – optical density; PND – postnatal day; SN – substantia nigra

that adolescent MS females displayed a decrease in NCAM-180 expression in the SN (30%; $F(1,8) = 12.85$, $p < 0.007$; Fig. 1B) and mPFC (37%; $F(1,8) = 12.68$, $p < 0.007$; Fig. 1C). There was no change in NCAM protein levels in the other brain regions of MS females that were studied, including the VTA, STR, and NAc. Additionally, there was no change in any of the brain structures of adolescent MS males that were studied (for data summary, see Tab. 1).

In adult animals (PND 75), MS exclusively affected the NCAM expression in the mPFC of the male rats (Fig. 2B). In particular, a reduction in NCAM-180 expression (22%) was detected in the mPFC of MS adult males ($F(1,8) = 12.82$, $p < 0.007$). No other brain areas of interest were affected in adult MS males; additionally, none of the brain regions in adult MS females that were studied were affected (for data summary, see Tab. 1).

Discussion

The present study was focused on the effects of early life stress, in the form of prolonged MS, on NCAM expression in brain structures strongly associated with dopaminergic neurotransmission. The key finding of our examination was that MS decreased NCAM expression in a structure-, age-, sex- and isoform-specific manner. Our data are generally in agreement with the few existing studies that show that naturally occurring or experimentally evoked disturbances in early life cause decreases in NCAM expression in different brain regions [1, 7, 10, 19]. It has been demonstrated that juvenile (PND 17) and adult male offspring of mothers that show low levels of pup licking and grooming during the first week of nursing exhibited a reduction in levels of NCAM-140 and NCAM-180 in the hippocampus [10]. Similarly, males that experienced prolonged (from PND 2 until PND 21) MS displayed a decrease in NCAM-140 levels in the hippocampus in adulthood [1]. Moreover, male rats reared in artificial conditions (artificially fed without any maternal contact) showed a reduction in NCAM-

180 in the mPFC, amygdala, NAc and hypothalamus, but not in the STR, in adolescence and adulthood [7]. Changes in NCAM expression in these animals were reversed by daily 'licking-like' stimulation throughout early development. It has also been demonstrated that animals exposed to stressors from PND 27 until PND 29 exhibited a reduction in total NCAM levels in the hippocampus, amygdala and entorhinal cortex; this reduction did not occur immediately after stress, but later in adulthood [19].

To our knowledge, this study is the first that shows that early life stress affects NCAM levels in midbrain dopaminergic structures, that is in the SN of females (on PND 15 and 35) and in the VTA of males (on PND 15). Our results indicate that MS, *via* NCAM proteins, may have a substantial impact on dopaminergic neurons and their function. Although the mechanism of interaction may be a matter of speculation, now it is worth stressing the role of GDNF, which is considered a specific neurotrophic factor for midbrain dopaminergic neurons [5, 6]. It has recently been discovered that NCAM is a signaling receptor for GDNF [5, 6]. Using function-blocking anti-NCAM antibodies, it has been demonstrated that NCAM mediates the effects of GDNF on dopaminergic neuron survival, outgrowth, dopamine turnover, and locomotor activity in rats [6]. On the other hand, it has been established that subchronic GDNF administration to the pars compacta of SN increases NCAM expression [6]. Other studies revealed that NCAM-deficient mice exhibited a reduction in the number of tyrosine hydroxylase-positive dopaminergic neurons in the SN and showed enhanced locomotion [22]. Therefore, our findings (which show that MS decreased NCAM expression in the SN, VTA and mPFC in juvenile and adolescent animals, as well as in the mPFC of adults) strongly implicate that early life stress can interfere with dopaminergic system maturation, and consequently leads to abnormalities in its function throughout ontogenesis. Thus, the present results can further support the hypothesis of stress-sensitive periods during development and their role in the pathogenesis of some mental disorders, in accordance with clinical studies showing that stressful experiences in early life can increase the risk for depression, anxiety, drug abuse and schizophrenia and accelerate the manifestations of the aforementioned diseases [3, 20]. Additionally, our data provides evidence that apparent susceptibility to psychiatric disorders may be associated with age, brain structure and gender.

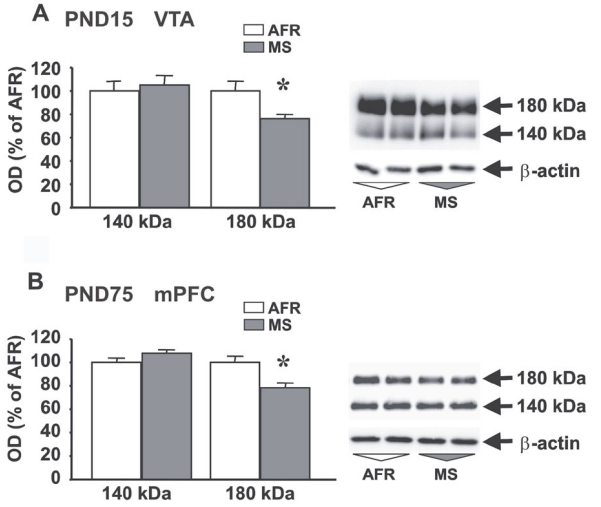

Fig. 2. The effects of maternal separation on NCAM proteins expression in male rats: (**A**) in the VTA of juveniles – PND 15; and (**B**) in the mPFC of adults – PND 75. Data are presented as the group means ± SEM, and they are expressed as a percentage of control (AFR rats) values; n = 5 per group, * $p < 0.05$ *vs.* AFR rats (ANOVA). Right panels: representative immunoblots showing the expression of NCAM-140 and NCAM-180 in studied brain regions and developmental time points. Abbreviations: AFR – animal facility reared; MS – maternally separated; mPFC – medial prefrontal cortex; OD – optical density; PND – postnatal day; VTA – ventral tegmental area

In the future, it will be of great interest to study the relationship between MS-induced alterations in NCAM expression in the mesocortical dopaminergic system and the efficacy of cognitive functions regulated by dopaminergic neurotransmission in the mPFC (such as working memory and executive functions) [9], which are often impaired in bipolar disorder and schizophrenia (for review see [13]). This kind of association, between MS-induced decreases in markers of synaptic plasticity (NCAM-140, BDNF and synaptophysin) in the hippocampus and impairments of cognitive functions regulated by this brain structure (e.g., spatial memory), has recently been demonstrated in adult MS animals [1, 2].

In the present study, we revealed that the isoform NCAM-180 was particularly vulnerable to MS. It is well documented that NCAM-180 is preferentially expressed in neurons, and it mainly localizes postsynaptically [8]; this pattern of expression indicates that consequences of MS, as they relate to NCAM levels, should have an impact on neuronal plasticity and possibly on the efficacy of neurotransmission (in the context of the present study, a dopaminergic one). For example, the latest data show that NCAM-180, but not NCAM-140, interacts with dopamine D2 re-

ceptors, and that it is involved in agonist-induced internalization of those receptors [22]. There is also evidence that NCAM-180 knockout mice exhibit increased lateral ventricle size and reduced PPI, which are typical features that accompany schizophrenia [21].

Finally, it should be recognized that not only the expression of NCAM proteins but also the post-translational modification of NCAM, specifically the addition of α-2,8-linked polysialic acid (PSA), is required for synaptic plasticity, learning and memory (for review see [16]). Polysialylation of NCAM (PSA-NCAM) is known to regulate the NCAM-mediated adhesion processes. PSA-NCAM is highly expressed during brain development and persists until adulthood, but only in restricted brain areas known for ongoing neuronal and synaptic plasticity (for example, in the dentate gyrus, hypothalamus, olfactory bulb and mPFC) [16]. It has been established that chronic stress in adult animals (for review see [16] and papers quoted therein), as well as exposure to stressors during juvenility [19] and chronic antidepressant treatments (for review see [16]) cause an increase in PSA-NCAM levels in hippocampal formation and in the mPFC. Conversely, in the postmortem hippocampus of schizophrenics, decreases in PSA-NCAM expression have been observed [4]. Thus, in the future it will be worthwhile to extend our study to search for the impact of early life stress (MS) specifically on PSA-NCAM levels in selected dopaminergic brain areas, such as in the mPFC.

In conclusion, we demonstrated that early life stress in the form of MS decreased NCAM expression in midbrain dopaminergic structures and in the mPFC in a sex- and age-specific manner. These data indicate that early life stress, resulting from interference with mother-pup interactions, can affect the maturation and plasticity of the brain, particularly in dopaminergic systems. Consequently, this can change the ability of dopaminergic neurons for plastic adjustments to the stage of ontogeny or environmental demands. These malfunctions can possibly underlie the pathomechanisms of some mental disorders, like depression (which has an age- and gender-dependent appearance) or schizophrenia (which exhibits an age-dependent manifestation).

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