# ALTERATIONS IN BDNF-MEDIATED SIGNALING AND SEROTONERGIC NEUROTRANSMISSION IN NCAM-DEFICIENT MICE

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## Introduction

For several years the main hypotheses of the development of depression were the monoaminergic and brain derived neurotrophic factor (BDNF) theories, and recently it was suggested that mood disorders are also induced by reduced brain plasticity and not only due to the alterations in monoaminergic and neurotrophic factors.

The main promoter of brain plasticity in the central nervous system is neural cell adhesion molecule which belongs to the immunoglobulin superfamily of adhesion molecules. In the organism NCAM is present in two forms, in the adulthood NCAM itself and during the brain development the polysialylated form of NCAM (PSA-NCAM). In adulthood the PSA-NCAM is present in the restricted brain areas where the adult neurogenesis occurs. NCAM is able to regulate brain plasticity via interaction with several interaction partners including fibroblast growth factor receptor (FGFR), Fyn kinase and also in vitro studies demonstrated that PSA-NCAM modulates BDNF-mediated signaling via promoting BDNF presentation to the neurotrophin receptor TrkB. All these signaling cascades activate 3 main intracellular paths which all lead to the common endpoint, activation of transcription factor CREB.

In our previous studies we found that in mice constitutionally deficient in all isoforms of NCAM exhibit depressive-like phenotype which was accompanied by reduced activation of FGFR and calcium/calmodulin dependent kinases II and IV (CaMKII and IV) and also CREB.

## Aims of the study

Given the proposed roles of the serotonergic and neurotrophic signaling systems in the mechanisms of depression and the observed depressive-like phenotype in NCAM-deficient mice, the aims of the present study were:

- To determine whether deficiency of NCAM affect serotonin transporters.
- To determine whether deficiency of NCAM affect BDNF signaling in NCAM-deficient mice.

## Materials and methods

NCAM-knockout mice and their wild-type littermates at the age of 3-5 months and with an average weight of 26.0 g were used. Immunohistochemical and western blotting techniques were used to determine the density of serotonergic fibres and TrkB levels. For determination of BDNF content, commercial kit was used (ChemiKine Brain Derived Neurotrophic factor (BDNF) Sandwich ELISA Kit (Chemicon International Inc., USA).

## Results

### Reduced levels of pTrkB in NCAM-deficient mice

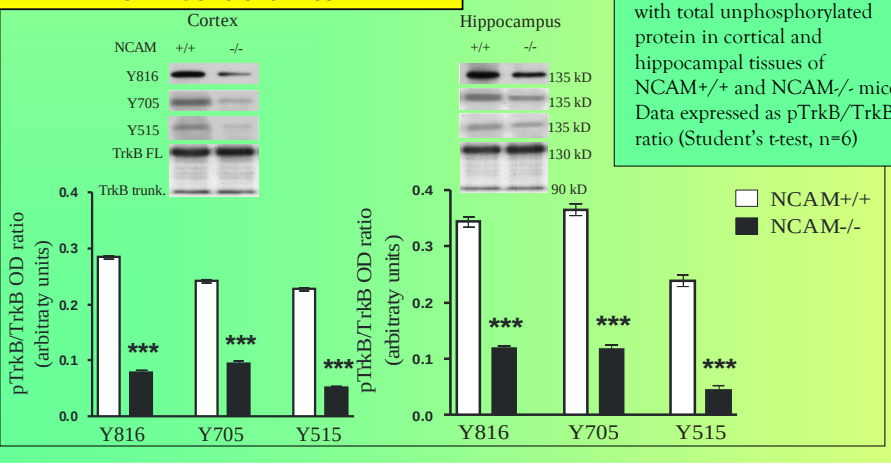


Fig.1. Western blotting image highlighting the phosphorylation chages of TrkB with total unphosphorylated protein in cortical and hippocampal tissues of NCAM+/+ and NCAM-/- mice. Data expressed as pTrkB/TrkB ratio (Student's t-test, n=6)

### Unchanged number of serotonergic neurons in Raphe nuclei but reduced serotonergic nerve fibre density in NCAM-deficient mice

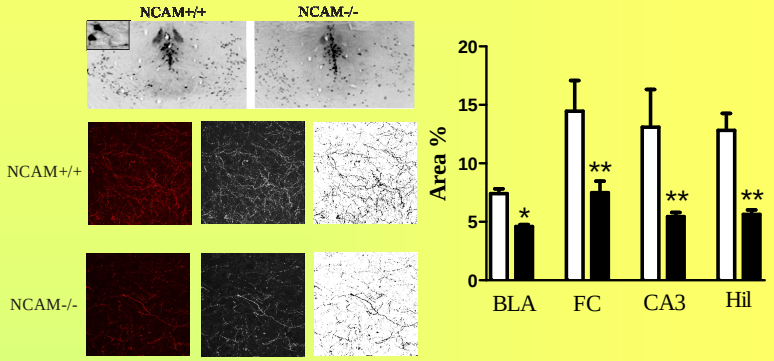


Fig. 2. The number of serotonergic neurons in raphe nucleus (upper panel). The density of serotonergic fibers in the basolateral nucleus of amygdala (BLA), frontal/prefrontal cortex (FC), and CA3 and Hilus (Hil) regions of hippocampus of NCAM+/+ and NCAM-/- mice.
The data are given as mean±SEM of percentage of area covered by the serotonergic fibers (lower panel). *p<0.05; **p<0.01 as compared with NCAM+/+ mice (Student's t-test, n=6)

### Reduced levels of BDNF in cortical and Hippocampal tissues in NCAM+/+ and NCAM-/- mice

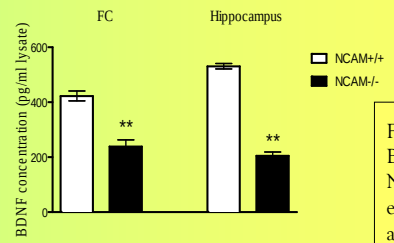


Fig. 3. Reduced levels of BDNF in NCAM+/+ and NCAM-/- mice. Data expressed as mean protein amount pg/ml lysate. (Student's t-test, n=6)

## Conclusions

Our data demonstrate an importance of the NCAM molecule for the development and functional activity of the BDNF signaling and serotonergic neurotransmission. Since both serotonergic system and BDNF signaling have important roles in the regulation of neural plasticity, their reduction in NCAM-deficient mice might have an impact on the behavioural phenotype and in particular on the depression-like behaviours.

### References

Vutskits et al., Eur J Neurosci 2001
Walmod et al., Neurochem Res 2004
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### Conflict of interest

The authors do not have a commercial or other association that might pose a conflict of interest.

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