

Introduction

For many years the main hypothesis of the development of depression has been the monoaminergic theory. Numerous reports link the mechanisms of mood disorders in particular with dysfunction of the serotonergic system. Recently it has also been suggested that mood disorders are induced by reduced brain plasticity. The main promoter of brain plasticity in the CNS is the neural cell adhesion molecule (NCAM) which belongs to the immunoglobulin superfamily of adhesion molecules and can regulate brain plasticity by its interaction with the fibroblast growth factor (FGF) receptor. It has been suggested that dysregulated NCAM-mediated signaling is implicated in the pathogenesis of mood disorders.

A 15 amino acid long peptide, named FGL, has been developed, and it has been shown to bind and activate the FGF receptor. In vivo, after systemic administration, the FGL peptide was found to enhance cognitive behavior, and to ameliorate the signs of depression in NCAM-deficient mice.

Aims of the study

The aim of the present study was to explore whether NCAM knockout mice have a dysfunction of the serotonergic system, and whether the FGL peptide can ameliorate alterations observed in these animals.

Results

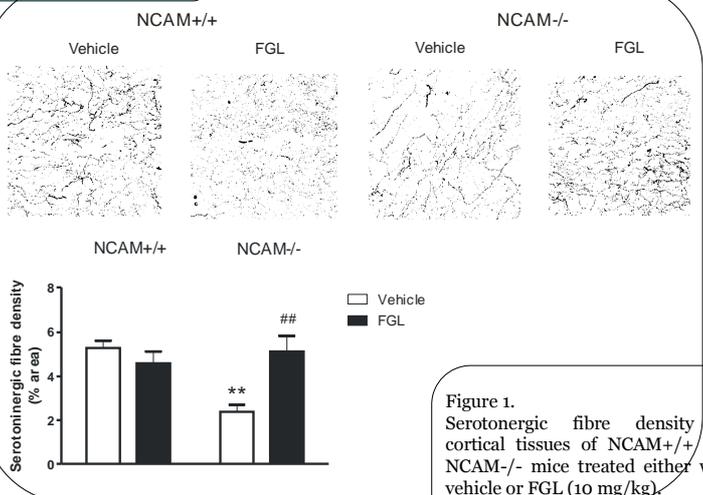


Figure 1. Serotonergic fibre density in cortical tissues of NCAM+/+ and NCAM-/- mice treated either with vehicle or FGL (10 mg/kg). ** p < 0.01 as compared to wild-type littermates; ## p < 0.01 as compared to corresponding vehicle control.

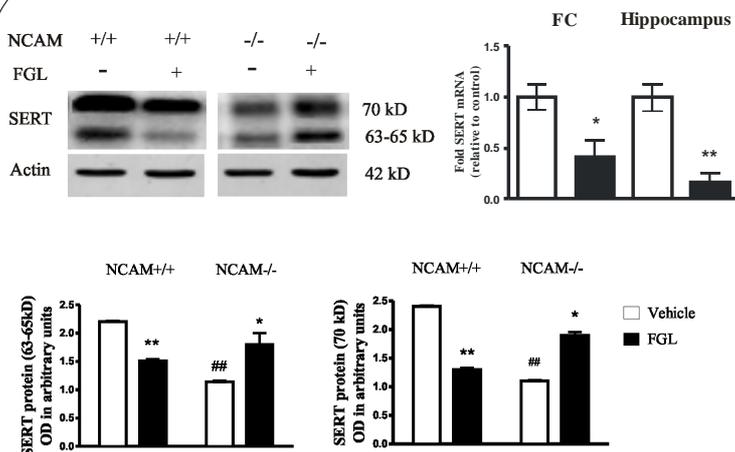


Figure 2. Representative western blotting image and SERT protein levels in cortical tissues of NCAM+/+ and NCAM-/- mice treated either with vehicle of FGL (upper left and bottom panel). Fold SERT mRNA in cortical and hippocampal tissues of NCAM+/+ and NCAM-/- mice. * p < 0.05 as compared to wild-type littermates.

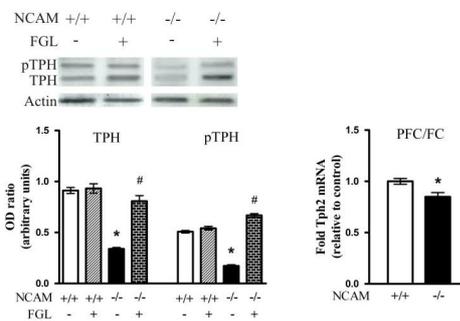


Figure 3.

Representative western blotting image of phosphorylated and total tryptophane hydroxylase (TPH) and mRNA of TPH in cortical tissues of NCAM+/+ and NCAM-/- mice. * p < 0.05 as compared to wild-type littermates; # p < 0.05 as compared to corresponding vehicle control.

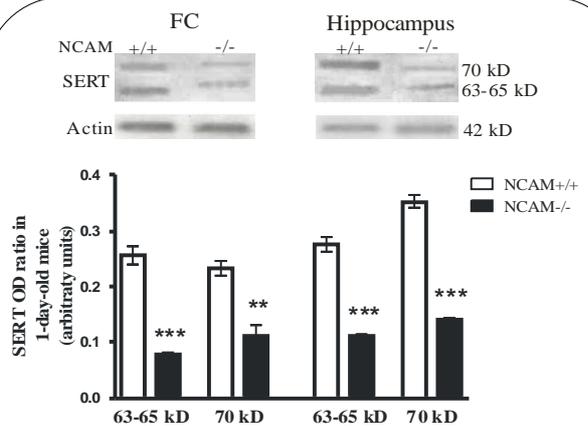


Figure 4.

Representative western blotting image of SERT protein in newborn NCAM+/+ and NCAM-/- mice. ** p < 0.01 as compared to wild-type littermates.

Conclusions

We propose that the observed changes in the serotonergic system in NCAM knockout mice are related to the depression-like phenotype described in these animals and the ability of FGL peptide to restore activity of serotonergic system explains the antidepressant-like activity of this molecule. These data open new avenue for the search of new peptide molecules which mimic the actions of NCAM for the treatment of depression.

Grant support and conflict of interest

This study was supported by EU FP6 grant LSHM-CT-2005-512012 (Promemoria) and Estonian Science Foundation Grant 6504, the European Regional Development Fund and the Archimedes Foundation. The authors do not have commercial or other association that might pose a conflict of interest.