NPAS3, A Key Gene In Neurogenesis. A Possible Explanation For Schizophrenia?

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1. INTRODUCTION

The transcription factor NPAS3 is a member of the basic helix-loop-helix family of proteins. It is expressed by GABAergic interneurons, in particular, NPAS3 co-localizes with calretinin-expressing and reelin-producing interneuron subtypes.

It has a 90% of evolutionary conservation among mammals, which suggests a crucial role in neurodevelopment, neoplasia and neurobehaviour; and it contains the **largest cluster of noncoding-accelerated** regions in the human genome, suggesting a contribution in human brain evolution.

AIM: This review will try to characterize this gene and its functional role, as well as analyze different regulating factors and the pathologies derived from its altered function.

2. MATERIALS AND METHODS

Scientific literature search on PubMed database: Selection of recent papers and reviews on this database according to their quality and data of publication.

Papers used were related to neurogenesis in different stages of life and relevant data of NPAS3:

- Structure
- Function
- Correlation with psychiatric illness

3. NPAS3 EXPRESSION

DURING DEVELOPMENT

Late first trimester: from 10 to 14 weeks of gestational age

-Strong expression of NPAS3 is detected in the developing central nervous system→ nucleus of cells of the ventricular zone.

-Weaker level of expression in other zones, such as the lung, viscera and heart.

Early second trimester: 14 weeks of gestational age

-Ventricular and periventricular zone.

- Increasing expression in the cerebellum, which develops between the third and fourth month of fetal life.

From second trimester (23 WGA) to late-third trimester

-Cortical expression of NPAS3 increases as the cortical layers develop.

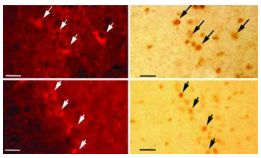
-Strongly expressed in the nucleus of cells of the hippocampal dentate gyrus (DG) during the third trimester and in the stratum radiatum of CA1 area of the hippocampus.

IN THE ADULT

INTERNEURONS: These neurons are linked to adult neurogenesis through neurotransmitters like GABA, and through different signaling molecules: NPAS3, reelin, apoE, and SDF-1 and its receptor CXCR4.

4. ASSOCIATION WITH SCHIZOPHRENIA

- Photomicrographs of a section through the CA1 area of the hippocampus double-labeled for NPAS3 (*Right*) and reelin (*Left*). Arrows indicate double-labeled cells that show that **reelin colocalizes with NPAS3 expressing neurons.**

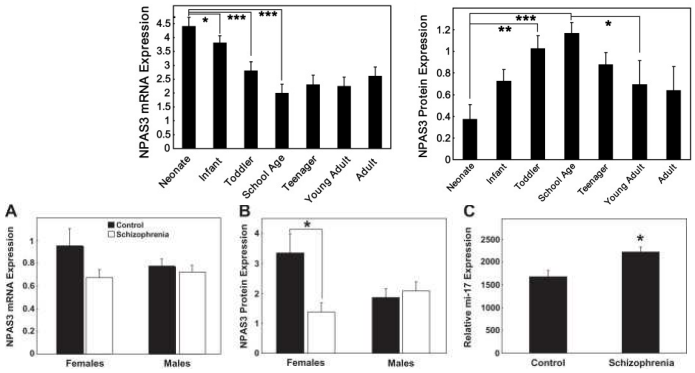


(Adapted from Erbel-Sieler et al, 2004)

- Family in which disruption of NPAS3 on chromosome 14q13 segregates with disease.
- **NPAS3 knockout mice display several schizophrenia-like behavioral abnormalities** such as, impaired social recognition, deficits in learning tests, stereotypic behavior at weaning, and increased locomotor activity in the Open Field paradigm.
- Reduction of hippocampal reelin and the FGF-2 receptor expression in NPAS3 knockout mice.
- These mice feature a marked reduction (85%) in hippocampal adult neurogenesis correlating with the thickness of the granule cell layer.

POST-TRANSLATIONAL REGULATION:

Indicated by lack of correlation between the levels of NPAS3 mRNA and NPAS3 protein expression.



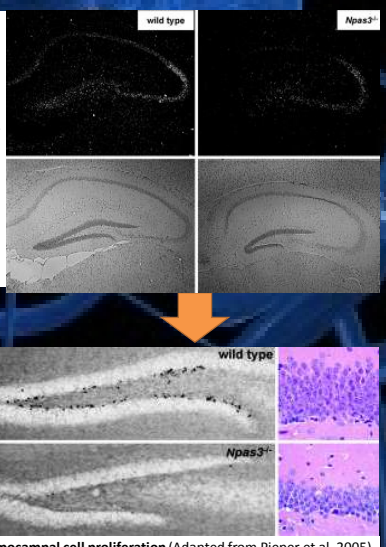
(Adapted from Wong et al, 2013)

A) No significant differences were detected in the levels of NPAS3 mRNA between healthy brains and brains of people suffering schizophrenia.

B) A difference in NPAS3 protein expression was detected among healthy females and females with schizophrenia.

C) miR-17 levels were increased in the prefrontal cortex of people with schizophrenia.

- Mice that lacked NPAS3 were deficient in **FGF-1 receptor mRNA** and had 85% less adult **hippocampal cell proliferation** than wild type mice.
- Central infusion of FGF-2 was unable to elevate hippocampal cell proliferation in NPAS3 knockout mice.



Decreased adult hippocampal cell proliferation (Adapted from Pieper et al, 2005)

5. CONCLUSIONS

- Co-localization with DCX, a marker of neuron-restricted progenitors, indicates a participation of NPAS3 in a later, post-proliferative, stage of neuronal differentiation **→NPAS3 mediates production of new neurons critical to growth or maintenance of the hippocampus throughout development and adulthood.**

- NPAS3 has post-translational regulation and it targets other genes with important roles in neurogenesis to regulate their expression.

- It is one of the many putative **risk factors for schizophrenia**. This gene shows an important field of study for the cure of schizophrenia and probably other related psychiatric illnesses such as bipolar disorder and depression.
  - Treatments: - NPAS3 is a SNP associated with **iloperidone** efficacy for schizophrenia
    - Administration of **P7C3** corrected hippocampal neurogenesis deficits in *Npas3*-NULL mice.

6. RELEVANT REFERENCES

Erbel-Sieler, C., Dudley, C., Zhou, Y., Wu, X., Estill, S.J., Han, T., Diaz-Arrastia, R., Brunskill, E.W., Potter, S.S. & McKnight, S.L. 2004, "Behavioral and regulatory abnormalities in mice deficient in the NPAS1 and NPAS3 transcription factors", Proceedings of the National Academy of Sciences of the United States of America, vol. 101, no. 37, pp. 13648-13653.

Pieper, A.A.(.1.)., Wu, X.(.1.)., Han, T.W.(.1.)., Estill, S.J.(.1.)., Dang, Q.(.1.)., Wu, L.C.(.1.)., Reece-Fincanon, S., Dudley, C.A.(.1.)., McKnight, S.L.(.1.)., Richardson, J.A. (2,3) & Brat, D.J.(.4.). 2005, "The neuronal PAS domain protein 3 transcription factor controls FGF-mediated adult hippocampal neurogenesis in mice", Proceedings of the National Academy of Sciences of the United States of America, vol. 102, no. 39, pp. 14052-14057.

Wong, J. (1,2,3), Duncan, C.E. (1,2), Beveridge, N.J. (1,4), Cairns, M.J. (1,4), Shannon Weickert, C. (1,2,6) & Webster, M.J.(.5.). 2013, "Expression of NPAS3 in the human cortex and evidence of its posttranscriptional regulation by miR-17 during development, with implications for schizophrenia", Schizophrenia bulletin, vol. 39, no. 2, pp. 396-406.