P064

PRENATAL PHARMACOTHERAPY WITH A BDNF MIMETIC RESTORES NEUROGENESIS IN THE Ts65Dn MOUSE MODEL

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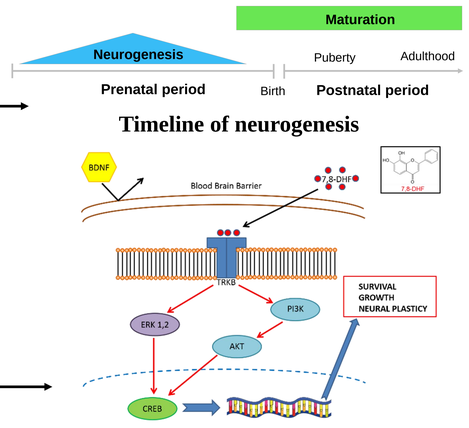
BACKGROUND

No therapies currently exist for intellectual disability in DS. The **prenatal period** represents a crucial time **window of opportunity** that may be exploited in order to restore neurogenesis and, thus, overall brain development in DS.

The brain-derived neurotrophic factor (**BDNF**) plays a crucial role in neurogenesis through its specific binding to the TrkB receptor. Evidence for reduced BDNF levels in the DS brain (1-3) suggests that this defect may play a role in neurogenesis disruption and that BDNF may be used to restore neurogenesis. Unfortunately, BDNF is characterized by a poor blood-brain barrier penetration.

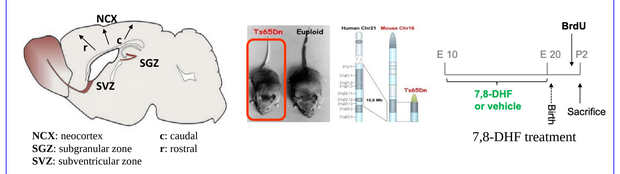
It has been shown that a flavonoid, the 7,8-Dihydroxyflavone (**7,8-DHF**), that crosses the blood brain barrier, is able to bind with high affinity and specificity to the TrkB receptor, activating its down stream signaling cascade (4).



GOAL

The goal of our study was to **establish whether it is possible to restore neurogenesis impairment** in the Ts65Dn model of DS with **prenatal therapy** with **7,8-DHF**.

MATERIALS AND METHODS



NCX: neocortex **c**: caudal
SGZ: subgranular zone **r**: rostral
SVZ: subventricular zone

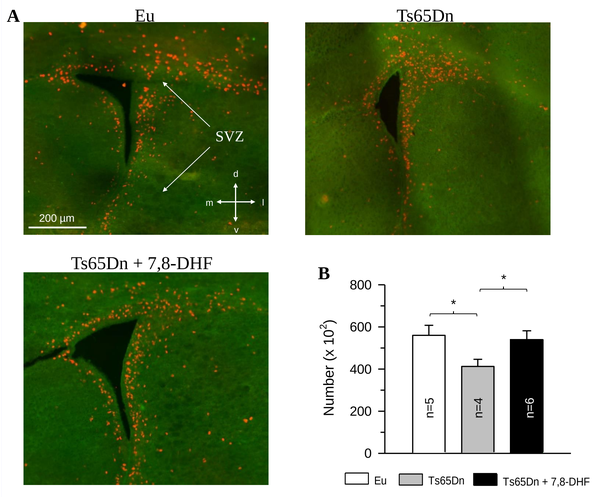
Experimental protocol: Pregnant Ts65Dn females received a daily subcutaneous injection of 7,8-DHF (5 mg/Kg) or saline from embryonic day 10 until delivery. On postnatal day 2 (P2), the pups received an injection (150 µg/g) of BrdU in order to label neural progenitor cells (NPCs) and were killed after 2 h.

Histological procedures: The brains of euploid (Eu) and Ts65Dn pups were cut in 8 µm-thick coronal sections. Proliferating cells were detected with immunohistochemistry for BrdU and evaluated in various forebrain regions.

Statistical analysis: two-way ANOVA with genotype and treatment as factors followed by post hoc Fisher LSD test *(* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).*

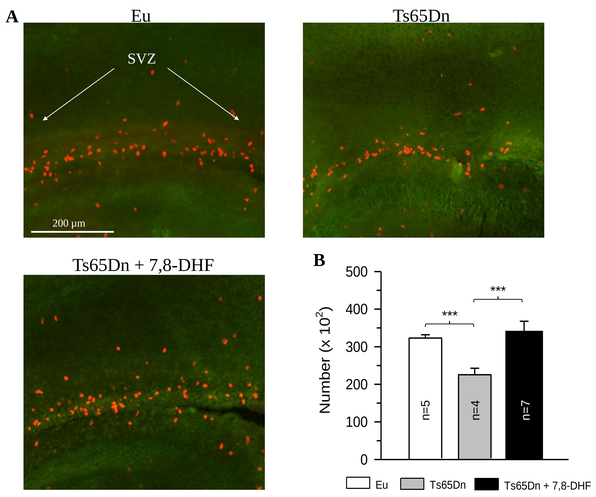
RESULTS

Prenatal treatment with 7,8-DHF restores neurogenesis in the rostral SVZ



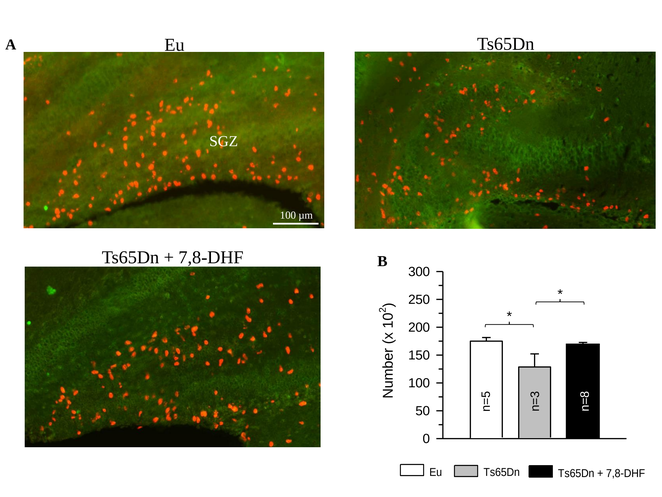
A. Examples of sections immunostained for BrdU from the rostral part of the SVZ. Calibration bar=200 µm. B. Total number of BrdU-positive cells in the rostral SVZ.

Prenatal treatment with 7,8-DHF restores neurogenesis in the caudal SVZ



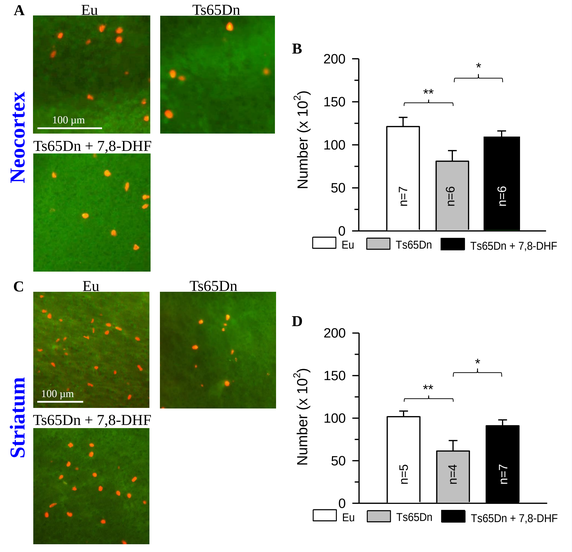
A. Examples of sections immunostained for BrdU from the caudal part of the SVZ. Calibration bar=200 µm. B. Total number of BrdU-positive cells in the caudal SVZ.

Prenatal treatment with 7,8-DHF restores neurogenesis in the hippocampal dentate gyrus



A. Examples of sections immunostained for BrdU from the hippocampal DG. Calibration bar=100 µm. B. Total number of BrdU-positive cells in the hippocampal dentate gyrus.

Prenatal treatment with 7,8-DHF restores neurogenesis in the neocortex and striatum



A,C. Examples of sections immunostained for BrdU from the neocortex (A) and striatum (C). Calibration bar=100 µm. B,D. Total number of BrdU-positive cells in the neocortex (B) and striatum (D).

CONCLUSIONS

This study provides evidence that **prenatal treatment with the BDNF mimetic 7,8-DHF** is able to **fully restore** neural progenitor cell proliferation in the forebrain of newborn Ts65Dn mice.

FUTURE DIRECTIONS

To establish whether restoration of neurogenesis translates into behavioral improvement.

BIBLIOGRAPHY

1.Bianchi P, Ciani E, Guidi S, Trazzi S, Felice D, Grossi G, Fernandez M, Giuliani A, Calza L, Bartesaghi R (2010) Early pharmacotherapy restores neurogenesis and cognitive performance in the Ts65Dn mouse model for Down syndrome. J Neurosci.30(26):8769-79.
2.Bimonte-Nelson HA, Hunter CL, Nelson ME, Granholm AC (2003) Frontal cortex BDNF levels correlate with working memory in an animal model of Down syndrome. Behav Brain Res.139(1-2):47-57.
3.Guedj F, Sebrie C, Rivals I, Ledru A, Paly E, Bizot JC, Smith D, Rubin E, Gillet B, Arbones M, Delabar JM (2009) Green tea polyphenols rescue of brain defects induced by overexpression of DYRK1A. PLoS One.4(2):e4606.
4.Liu X, Chan C-B, Jang S-W, Pradoldej S, Huang J, He K, Phun LH, France S, Xiao G, Jia Y, Luo HR, Ye K (2010) A synthetic 7,8-dihydroxyflavon

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