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Treatment with kaempferol: a possible tool to restore neurogenesis in Down syndrome

F. Stagni[1], M.E. Salvalai[2], S. Guidi[1], A. Giacomini[1], M. Emili[1], B. Uguagliati[1], M. Grilli[2], R. Bartesaghi[1]

1) Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
2) Department of Pharmaceutical Sciences, University of Piemonte Orientale, Novara, Italy

INTRODUCTION AND BACKGROUND

In Down syndrome (DS) triplication of chromosome 21 causes various medical problems but the most invalidating feature of this genetic condition is **intellectual disability** (ID).
No therapies are currently available for ID, and individuals with DS live a non-autonomous life.
The ID in DS is mainly attributable to a reduced number of neurons forming the brain (1). This defect is due to a reduction in the size of the pool of actively dividing neural progenitor cells (NPCs) (Fig. 1) starting from the critical time window of brain development. The reduction in proliferation potency is worsened by the fact that NPCs exhibit reduced acquisition of a neuronal phenotype and an increase in the acquisition of an astrocytic phenotype (Fig. 1).

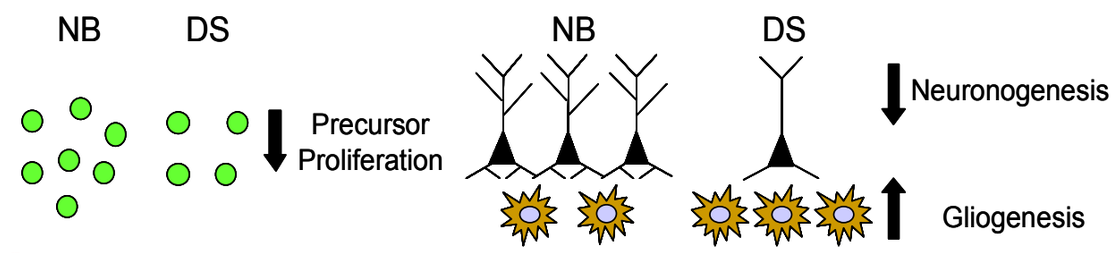


Fig.1

No study has explored so far the possibility to pharmacologically correct the trisomy-linked defects in the acquisition of a neuronal phenotype.

In the framework of an in vitro screening campaign of FDA-approved drugs we found that the flavonoid **kaempferol had the unique capability to promote neuronal differentiation** of NPCs from a mouse model of DS (Fig. 2A), **at the expense of astrogliogenesis** (Fig. 2B). It is important to observe that kaempferol has been shown to inhibit the activity of the kinase DYRK1A (2). Since DYRK1A is overexpressed in the DS brain and plays an important role in the DS-associated brain phenotype (3), the positive effects of kaempferol observed *in vitro* may be linked to the inhibition of DYRK1A.

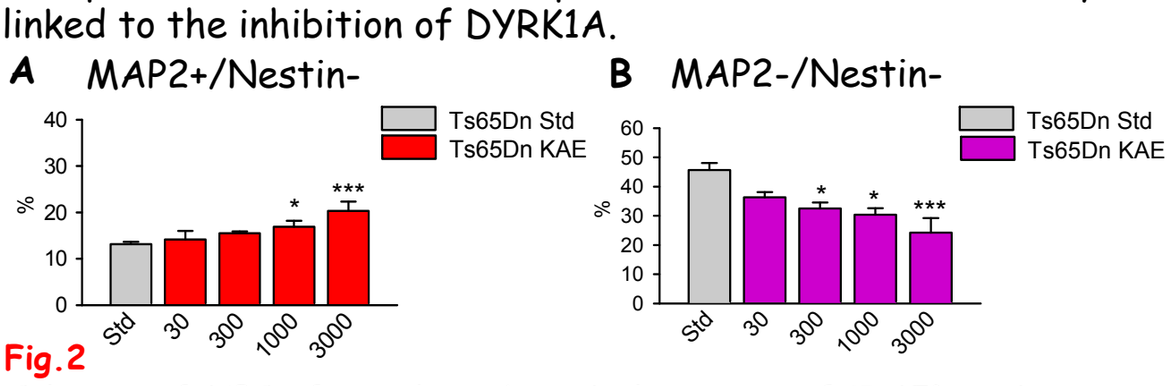


Fig.2

*Cultures of NPCs from the subvetricular zone of Ts65Dn mice grown under differentiating conditions and exposed to vehicle (DMSO 0.05%) or different concentrations of kaempferol for 96 h. The asterisks indicate a difference in comparison with untreated cultures exposed to vehicle alone: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ (Fisher's LSD test after ANOVA).*

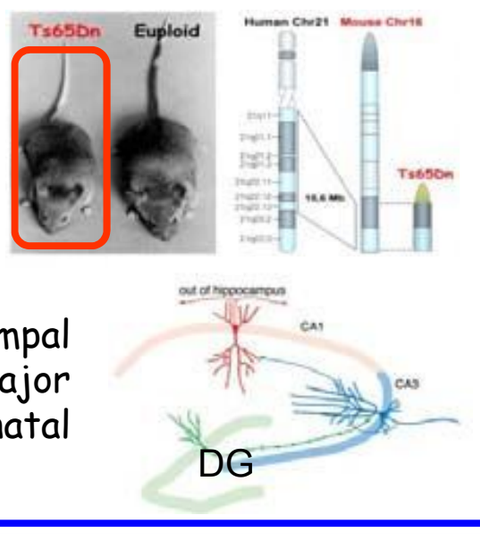
GOAL OF THE STUDY

Based on the *in vitro* findings, **the goal of the current study was to establish whether treatment with kaempferol can restore trisomy-linked neurogenesis defects** *in vivo* in the Ts65Dn mouse model of DS. We focused on the hippocampal formation, a region that plays a fundamental role in long-term declarative memory and mainly develops in the early postnatal period in rodents.

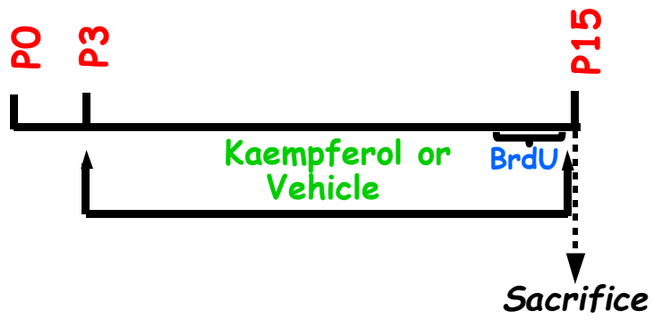
METHODS

Mouse model: The Ts65Dn mouse exhibits triplication of numerous genes that are orthologous to those of HChr21 and exhibits numerous features of DS.

Analysed region: Hippocampal dentate gyrus (DG), a major neurogenic niche of the postnatal brain.



Treatment: In the postnatal period P3-P15 mice received a daily subcutaneous injection of kaempferol (10.0 mg/kg) or vehicle. On P15, mice received an injection (150 µg/g) of BrdU (5-bromo-2-de-oxyuridine), a marker of proliferating cells and were killed after 2h.

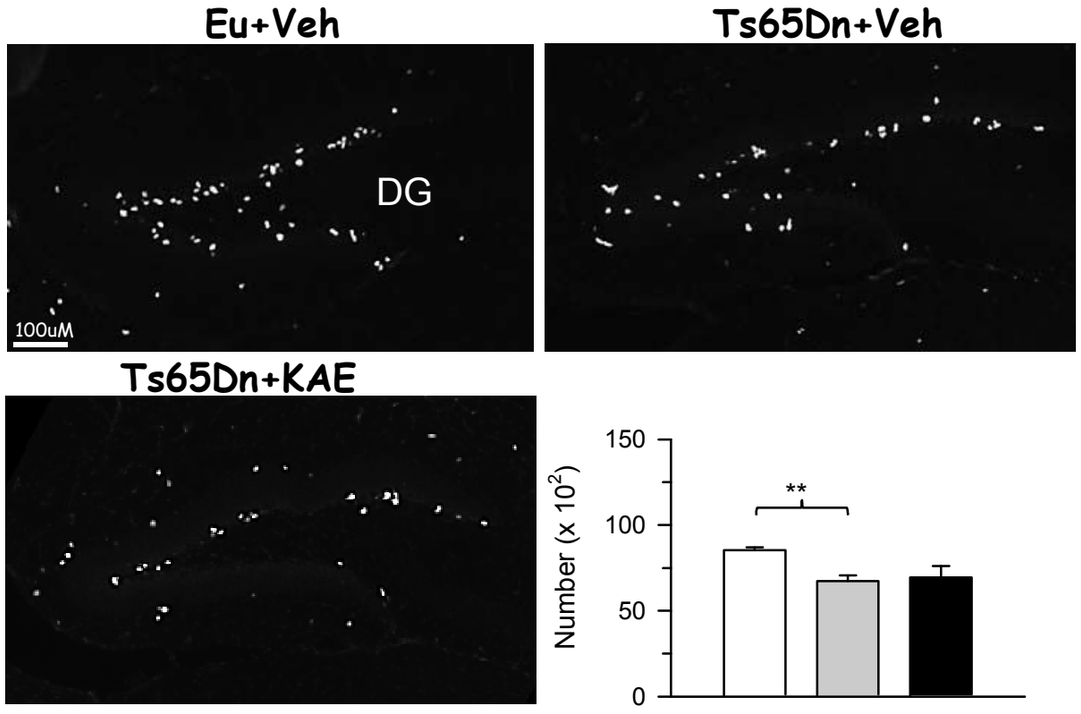


Brain processing: i) Immunohistochemistry for BrdU; ii) Hoechst staining.
Statistical analysis: two-way ANOVA followed by *post hoc* Fisher LSD test.

RESULTS

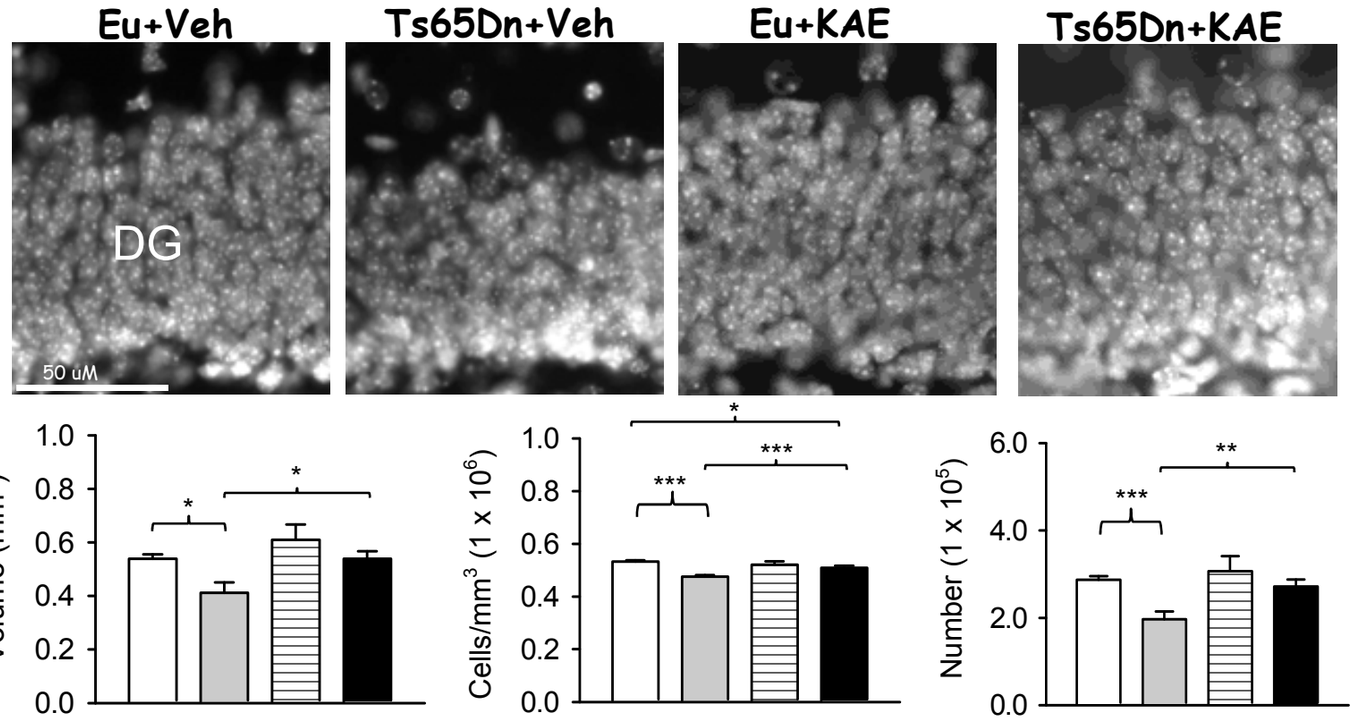
Kaempferol does not increase the proliferation rate of NPCs of the DG

BrdU-positive cells



Kaempferol, however. restores the number of granule neurons of the DG, confirming that it fosters the acquisition of a neuronal phenotype

Granule neurons



Values represent mean ± SE. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Fisher LSD test after ANOVA).

CONCLUSIONS

This study provides novel evidence that **early treatment with kaempferol restores hippocampal neurogenesis** in a mouse model of DS. In view of its safe nature, treatment with kaempferol may be regarded as a therapy with a good translational impact for the improvement of brain development in Down syndrome.

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The authors have no conflict of interest to declare.