Preterm transient hypoxia-ischemia: effects on behavior and brain morphology

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AIMS
Characterize the effects of premature birth caused by neonatal hypoxia-ischemia on neonatal developmental milestones and on anxiety and cognition in adulthood. Examine if these possible alterations are accompanied by changes in neurogenesis and in the expression of cholinergic markers and neuropeptide Y (NPY).

INTRODUCTION
It is estimated that annually preterm birth affects about 1 out of 10 infants, making a total of 15 million premature births worldwide. From these, approximately 1 million die due to complications related to prematurity. In Portugal, 7.7% of all births in 2014 were premature, making it one of the European countries with higher prematurity rates. Preterm birth has a complex syndromic nature, therefore demanding laborious continuous work in an effort to understand, and hypothetically prevent, its repercussions.

MATERIALS AND METHODS

Control
Pregnant Wistar Rat
Laparotomy and no treatment
Rat pups delivered n=6

TSHI
Pregnant Wistar Rat
Laparotomy ED18 and occlusion of UA 60 min
Rat pups delivered n=6

• Neonatal development milestones
• After weaning: Morris water maze, elevated plus-maze and open-field
• One month after Weaning: deeply anesthetized, perfused and processed for immunohistochemistry for doublecortin (DCX), Vesicular acetylcholine transporter (VAChT) and NPY

NEONATAL DEVELOPMENT MILESTONES

CONCLUSION
Transient hypoxia-ischemia induced several significant changes in neonatal developmental milestones and in cognitive behaviors. These behavioral alterations were associated with changes in the cholinergic system, NPY expression and neurogenesis in the adulthood. The present TSHI model was able to recapitulate many features characteristic of preterm birth.

SPATIAL LEARNING AND MEMORY
(A) TSHI animals display spatial learning impairment. They also showed significant differences in long-term (B) and short-term memory (C). Dots and columns represent means and vertical bars represent 1.S.E.M.

ANXIETY
Open-field (A), and elevates plus-maze test (B,C). Columns represent means and vertical bars correspond to 1.S.E.M. * P<0.05. There was no significant differences.

MORPHOLOGY AND NEUROGENESIS
NPY-immunoreactive cells

VAChT-IR varicosities

DCX-IR cells

Dendritic Arborization of DCX-IR cells

Density of DCX-immunoreactive (IR) cells in the hilus of the stratum lacunosum moleculare (A), Density of aberrantly located DCX-IR cells, Granular layer and dentate hilus (B). Columns represent means and vertical bars correspond to 1.S.E.M. * P<0.05.

Conclusions
The TSHI model recapitulated key features characteristic of preterm birth and is a promising tool to further investigate the effects of TSHI on neurodevelopment. These findings highlight the importance of understanding the underlying mechanisms and could potentially inform strategies for prevention and intervention.