17th World Congress in Fetal Medicine

Survival and neurodevelopmental effects of Docosahexaenoic acid and Lactoferrin in an IUGR animal model

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Objective

To investigate the impact of maternal docosahexaenoic acid (DHA) or lactoferrin administration in survival and in the long-term offspring's neurodevelopment using an IUGR rabbit model.

Methods

IUGR was induced by ligating 40-50% of the uteroplacental vessels of each gestational sac from one horn at 25 days of gestation, whereas non-ligated vessels from the contralateral horn produced the controls. At the time of the IUGR induction, a subgroup of pregnant rabbits was randomly assigned to receive DHA or lactoferrin during the prenatal period until 30 days postpartum. Control and non-treated IUGR animals came from non-treated pregnant rabbits. In all the groups, at 30 gestational days, a cesarean section was performed obtaining: controls, non-treated IUGR animals, IUGR animals treated with DHA or IUGR animals treated with lactoferrin. At birth, biometric data and survival rates were recorded. Surviving animals were followed up until 70 days postpartum when the neurodevelopmental effects of both therapies were assessed. Functional evaluation was performed by means of specific neurobehavioral tests, whereas structural brain changes were assessed by the analysis of the brain networks obtained from diffusion resonance imaging and by neuronal connectivity markers, including dendritic spine density and perineuronal nets evaluation.

Results

Non-treated IUGR animals presented worse perinatal outcomes in comparison to control animals (mortality rate: 58% vs. 29%, p<0. 01; birth weight: 38g±8. 9 vs. 46g±7. 6, p<0. 01) and poorer functional performance at the long-term period, displaying higher levels of anxiety (seconds in the center area: IUGR 3±6 vs. controls 31±26, p<0. 01) and memory impairment (discriminatory index: IUGR -0. 08±0. 26 vs. controls 0. 28±0. 25, p<0. 01). Regarding the structural correspondence, an altered brain network infrastructure (average strength: IUGR 3. 98±0. 36 vs. controls 4. 46±0. 17, p<0. 01) and an abnormal neuronal connectivity were also detected in non-treated IUGR animals (dendritic spine density: IUGR 1. 45±0. 33 vs. controls 1. 8±0. 42, p<0. 01; perineuronal nets: IUGR 0. 15±0. 03 vs. controls 0. 29±0. 05, p<0. 01). On the contrary, perinatal administration of DHA or lactoferrin was associated with an increase in the survival rate in comparison to non-treated IUGR animals (mortality rate: DHA-IUGR 38%, p<0. 01; Lacto-IUGR 38%, p<0. 01). In the same line, both therapies were related with functional improvements at the long-term period (seconds in the center area: IUGR-DHA 28±18, p<0. 01; IUGR-lacto 27±33, p<0. 01; discriminatory index: IUGR-DHA 0. 5±0. 5, p <0. 01; IUGR-lacto 0. 3±0. 5, p<0. 01) along with a restoration of the structural brain abnormalities (average strength: IUGR-DHA 4. 85±0. 18, p<0. 01; IUGR-lacto 4. 97±0. 28, p<0. 01; dendritic spine density: IUGR-DHA 1. 49±0. 41, p=0. 31; IUGR-lacto 1. 52±0. 29, p=0. 03; perineuronal nets: IUGR-DHA 0. 21±0. 05, p=0. 03; IUGR-lacto 0. 24±0. 02, p<0. 01).

Conclusion

Maternal administration of DHA or lactoferrin improved perinatal and long-term neurodevelopmental outcomes in IUGR offspring. These results open opportunities for the application of perinatal therapies to reduce the deleterious effects of IUGR on survival, growth and long-term neurodevelopment.