Antenatal corticosteroids and brain development : the use of S100B as an early predictor of brain impairment

Summary

Infant respiratory distress syndrome (RDS) is a life-threatening disorder caused by developmental insufficiency of surfactant production and structural immaturity in the lungs of preterm infants. The use of antenatal betamethasone (AB) has resulted in a significant decrease in neonatal mortality and morbidity. However, this treatment strategy may also cause a wide range of side effects in humans, like impairments in somatic growth, brain development and hypothalamic-pituitary-adrenal function. In the present work, the short- and long-term consequences of AB on offspring development were analyzed in human infants and in the rat. Within the rat model, a lower dose regimen of AB was used in order to assess whether lowering the dose might induce milder side effects. The main findings of this thesis are:

In the clinic, AB induced a reduction of neurotrophic S100B protein in the urine of the human newborns *(Chapter 2)*. Of note, in this clinical study, only the standard dose regimen (12 mg twice 24 hours apart) was used.

In the rat, AB resulted in a significant dose-dependent growth restriction in both genders. Moreover, AB reduced hippocampal S100B concentrations and cell proliferation within the brain of neonatal male offspring *(Chapters 3 and 4)*. S100B levels were also reduced in the male blood by the the lower dose (6 mg) of AB.

In adult offspring AB did not affect cognition- and anxiety-related behavior and synaptophysin immunoreactivity (IR) within the hippocampus. However, MAP2-IR was reduced in male adult rats treated with AB *(Chapter 5)*.

Overall, males were more affected as compared to females, the latter of which showed no impairment in neonatal hippocampal S100B levels, brain cell proliferation and MAP2-IR within the adult hippocampus.

Halving the dose of AB resulted in less growth restriction. Further, no impairment of neonatal hippocampal S100B concentration and cell proliferation within the brain was observed by using the lower dose.

In conclusion, the present work confirms that a single course of AB might induce permanent consequences on offspring development. A lower dose of AB (equivalent to 6 mg twice 24 hours apart) induced milder effects, supporting the idea that reducing the dose might be less harmful. First however, clinical trials need to show whether different dose regimens could promote proper lung maturation without impairing brain development.