The Effects of Neuroactive Progesterone Metabolites in the Fetal CNS

Allopregnanolone may interact with type A γ-aminobutyric acid receptors (GABA A-γ) to inhibit fetal CNS activity from mid-gestation. Some data indicates that this inhibition may contribute to maintaining the sleep-like behavior and low incidence of arousal-type activity typical of fetal life (Crossley et al. 2003). Previous research (Mellor et al. 2005) also suggest the uterus key role in providing chemical and physical factors in keeping the fetus continuously asleep. The mechanism providing the permanent sleep status in the fetus combines neuroinhibition of a powerful EEG suppressor with a sleep inducing agent (adenosine), two GABAergic steroid anesthetics (allopregnanolone, pregnanolone) and a potent sleep-inducing hormone (prostaglandin D2), acting together with a putative peptide inhibitor and other placental factors (Mellor et al. 2005). To assess the impact of the steroid's anesthetics on the permanent sleeping status of the fetus, we have quantified the levels of progesterone, 20α-dihydroprogesterone, 5α- and 5β-dihydroprogesterone, 4 pregnanolone isomers and their polar conjugates, 5α,20α- and 5β,20α-tetrahydroprogesterone and their polar conjugates, 4 pregnanediols and their polar conjugates in the blood umbilical vein, umbilical artery and in the maternal venous blood. The differences among individual steroids, steroid ratios, and their time profiles in the third trimester were evaluated in 50 subjects both at premature labor and labor at term (28th – 41st week of gestation) using repeated measure ANOVA model consisting of subject factor, within-subject factor body fluid, between-subject factor gestational age, and interaction body fluid × gestational age.

Concerning the role of GABAergic steroids in suppressing the nociceptive pathways in the fetus, our data shows 2-3 times lower levels of most abundant GABAergic steroid allopregnanolone in the fetal circulation compared to maternal, while the levels of the second most abundant GABAergic steroid pregnanolone in umbilical venous blood exceed those in MV 1–2.5 times. The total amount of GABAergic progesterone metabolites is only slightly higher in the fetal compartment, predominantly due to the contribution of unconjugated pregnanolone. Therefore peripheral GABAergic steroids exert a comparable effect on the maternal and fetal CNS. Even when considering the 1.5–3 fold excess of progesterone in the fetal circulation (when compared to maternal blood), progesterone transport into the brain and its subsequent conversion to the GABAergic steroids, the Resulting contribution of GABAergic steroids originating from peripheral sources do not pronouncedly differ between mother and fetus. Therefore the importance of GABAergic steroids for maintenance of permanent fetal sleeping is still open to discussion.