

Effect of Fetal Cardiopulmonary Bypass on Myocardial and Placental cAMP and PKA

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Background

Certain congenital heart defects may benefit from fetal intracardiac surgery; however, placental and myocardial dysfunction typically follows fetal cardiac bypass. Fetal bypass profoundly elevates vasopressin, but the downstream effects on cAMP and PKA are unknown. We examined selective vasopressin receptor antagonism and cAMP stimulation with fetal cardiac bypass.

Methods

We studied 17 pregnant sheep (110-120 days gestation) undergoing 30 minute fetal bypass and 120 minute post-bypass follow-up. Fetal venous infusions of forskolin (2.5mcg/kg/min, n=5) to stimulate cAMP production or vasopressin V1a antagonist (100ng/kg/min, n=9) to allow unopposed V2 receptor-mediated vasodilatation began at hysterotomy and ended at termination of bypass. Treatment groups were compared to conscious fetal baseline values and bypass-control animals (n=3, saline infusion). Serial fetal plasma samples were collected throughout the protocol. Fetal myocardium, including right and left ventricle, and placental cotyledon were collected from 3 animals in each bypass group. PKA activity and cAMP levels were measured in plasma and tissue lysates using commercially available assays. Statistical comparisons were by one-way ANOVA and Student's T-test, with $p < 0.05$ considered significant.

Results

Fetal plasma levels of cAMP and PKA activity were very low and did not change with treatment. Forskolin and V1a antagonism increased placental cAMP following bypass when compared to bypass controls (3.8 ± 1.1 and 6.0 ± 2.1 vs. 1.5 ± 0.1 pmol/mg, respectively), while V1a antagonism decreased placental PKA activity when compared to un-instrumented controls. Bypass decreased cAMP in the left ventricle vs. un-instrumented controls (29.7 ± 8.2 vs. 60.2 ± 12.0 pmol/mg), but forskolin increased cAMP in the left (53.7 ± 7.8 vs. 29.7 ± 8.2 pmol/mg) and right (59.1 ± 9.6 vs. 28.4 ± 11.5 pmol/mg) ventricles when compared to bypass controls. Bypass did not change myocardial PKA activity from un-instrumented controls, but V1a antagonist treatment increased PKA activity in the left and right ventricles compared to both controls, while forskolin only increased right ventricular PKA activity. PKA activities were much higher in the right ventricle than left ventricle with forskolin (2.8-fold) and V1a antagonism (1.4-fold).

Conclusion

Fetal plasma cAMP and PKA did not change. Forskolin and V1a antagonism increase placental cAMP, but not PKA. Bypass decreases ventricular cAMP, but forskolin and V1a antagonism elevate cAMP and PKA. There is more elevation of cAMP and PKA following treatment in the right ventricle, the main pump in fetal life.