Introduction

- Traumatic brain injury (TBI) contributes to morbidity in children and boys are disproportionately represented. Hypotension is common and worsens outcome after TBI.
- Although effects of TBI have been well described for adult animal models, few have investigated effects in a pediatric model. Piglets with gyrencephalic brains containing substantial white matter that is selectively vulnerable to injury share advantages over rodent TBI models, which are less similar to humans.
- In the context of the neurovascilar unit, CBF is thought to contribute to cellular outcome and therefore offers an important therapeutic target. Systemic pressor support is often used to optimize cerebral perfusion pressure (CPP).
- Mitogen activated protein kinases (MAPK), a family of at least 3 kinases, ERK, JNK, and p38, is upregulated after TBI. MAPK contributes to impaired cerebral hemodynamics after fluid percussion injury (FPI) in the piglet.
- Membrane potential is an important contributor to vascular tone and K channels are important regulators of membrane potential. Activation of ATP and Ca (Kap and Kca) channels produce cerebrovasodilation and contribute to autoregulation, both impaired after FPI. Adrenomedullin (ADM) is an endogenous neuroprotective Kapt agonist that is upregulated after FPI in female but not male piglets.
- The spasmogen endothelin-1 (ET-1) contributes to impaired autoregulation through blunted K channel function via release of O2.
- Elevation of CPP with phenylephrine sex dependently prevents impairment of cerebral autoregulation during hypotension after FPI through modulation of ET-1 release and subsequent sequential O2 and ERK MAPK upregulation mediated impairment of Kapt and Kca induced cerebrovasodilation.

Purpose

This study hypothesized that pressor choice to elevate CPP is important in improving cerebral hemodynamics after TBI and that dopamine (DA) will prevent impairment of autoregulation in both male and female pigs because it will equally protect K channel mediated cerebrovasodilation in both sexes.

Methods

- Male and female newborn pig, 1-3 days old
- Closed Cranial Window
- Lateral FPI
- Microspheres for CBF determination
- Hypotension, moderate and severe
- 25 and 45% reduction in MAP
- papaverine
- Dopamine, 15µg/kg/min iv
- Cromakalim, Kap agonist
- NS 1619, Kca agonist

Results

Figure 1. CBF (ml/min .100g) in the parietal cortex during normotension and severe hypotension (hypotension) in sham, FPI, and FPI + DA (15 µg/kg/min iv) pre and post-treated newborn male and female pigs, n=5. CBF compared with corresponding sham value: *p<0.05 compared with corresponding normotension value; #p<0.05 compared with corresponding FPI pretreated value.

Figure 2. Influence of moderate and severe hypotension on pial artery diameter in newborn male (A) and female (B) pigs before injury (control), 1 h after FPI, 1 h after FPI treated 30 min prior to injury with DA (15 µg/kg/min iv) and 1 h after FPI treated with DA 30 min after injury, n=5. *p<0.05 compared with corresponding sham value; #p<0.05 compared with corresponding FPI pretreated value.

Figure 3. Influence of papaverine (10-8, 10-6 M) on pial artery diameter in newborn male and female pigs before injury (sham control), before injury treated with DA (15 µg/kg/min iv), 1 h after FPI treated 30 min prior to injury with DA, and 1 h after FPI treated with DA 30 min after injury, n=5. #p<0.05 compared with corresponding control value; *p<0.05 compared with corresponding FPI pretreated value.

Figure 4. Phosphorylation of ERK MAPK in CSF prior to FPI (sham), as a function of time after FPI (in pigs treated with vehicle (FPI), DA (15 µg/kg/min iv) pre- or post- treatment (30 min) + FPI, or in pigs treated with vehicle + U0126 (1 µg/kg) iv + FPI, n=5. Data expressed as percent of control. #p<0.05 compared with vehicle + U0126 treated value; *p<0.05 compared with corresponding vehicle treated value; #p<0.05 compared with corresponding female value.

Figure 5. Influence of cromakalim (10-8, 10-6 M) on pial artery diameter in newborn male (A) and female (B) pigs before injury (control), 1 h after FPI, 1 h after FPI treated 30 min prior to FPI with DA (15 µg/kg/min iv), and after FPI treated with DA 30 min after FPI, n=5. *p<0.05 compared with control; #p<0.05 compared with corresponding FPI pretreated value.

Figure 6. Influence of NS 1619 (10-8, 10-6 M) on pial artery diameter in newborn male (A) and female (B) pigs before injury (control), 1 h after FPI, 1 h after FPI treated 30 min prior to FPI with DA (15 µg/kg/min iv), and after FPI treated with DA 30 min after FPI, n=5. *p<0.05 compared with control; #p<0.05 compared with corresponding FPI pretreated value.

Figure 7. Comparison of proposed mechanisms for Phe (a) and DA (b) in control of cerebral hemodynamics after FPI. Arrow thickness in proportion to probability of action.

Conclusions

These data indicate that DA protects K channel mediated cerebrovasodilation equally in male and female piglets because of equivalent blockade of ERK MAPK upregulation in both sexes after FPI. Identification of a therapeutic which protects K channel function equally in males and females is an approach to limit sex dependent differences in outcome when systemic pressors are used to normalize CPP after TBI.