Ability to Prevent K Channel Mediated Impairment As A Determinant in Sex Dependent Pressor Choice To Protect Cerebral Autoregulation After Pediatric TBI

William M. Armstead[1], John Riley[1] , and Monica S. Vavilala[2]

University of Pennsylvania, Philadelphia, PA[1] and University of Washington, Seattle, WA[2]

Introduction

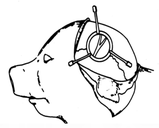
- Traumatic brain injury (TBI) contributes to morbidity in children and boys are disproportionately represented. Hypotension is common and worsens outcome after TBI.
- Although effects of TBI hav e been well described for adult animal models , few have investigated effects in a pediatric model. Piglets with gyrencephalic brains containing substantial white matter that is selectively vu lnerable to injury offer advantages over rodent TBI models, which are less similar to humans.
- In the context of the neurovas cular unit, CBF is t hought to c ontribute to cellular outcome and therefore often i s an important therapeutic target. Systemic pressor support is often used to optimize cerebral perfusion pressure (CPP).
- Mitogen activated protein kinas e (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 (Katp and Kca) channels produce cerebrovasodilation and contribute to autoregulation, both impaired after FPI. Adrenomedullin (ADM) is an endogenous neuroprotectant Katp 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 O_2^-.
- 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 O_2^- and ERK MAPK upregulation mediated impairment of Katp and Kca induced cerebrovasodilation.

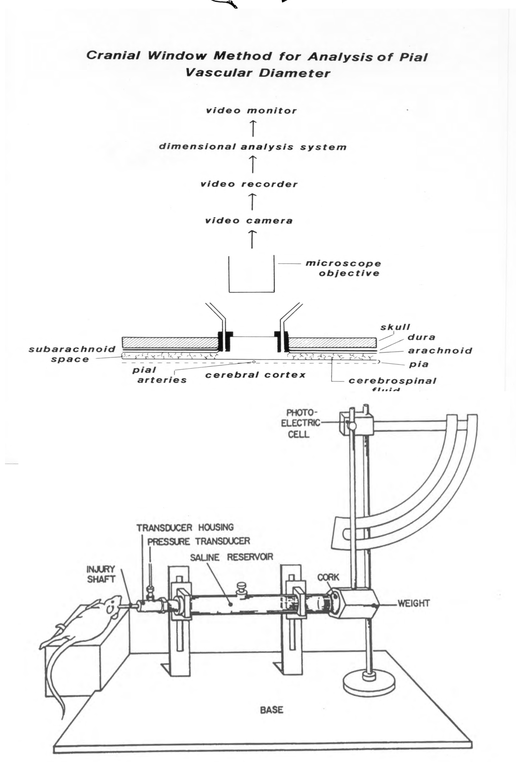
Purpose

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 mediation dilation in both sexes.

Methods

- Male and female newborn pig, 1-3 days old ≈ 1-2yr old human
- 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
- ELISA
- Cromakalim, Katp agonist
- NS 1619, Kca agonist





Results

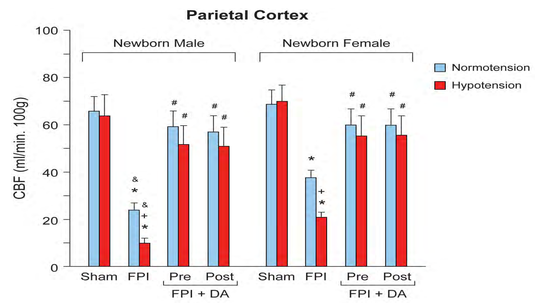


Figure 1. CBF (ml/min .100g) in the parietal cortex during normotension and severe hypotension (hypotension) in sham, FPI, and FPI + DA (15 μg/Kg/min iv) pre and post-treated newborn male and female pigs, n=3-5. *p<0.05 compared with corresponding sham value +p<0.05 compared with corresponding normotension value #p<0.05 compared with corresponding FPI non-treated value &p<0.05 compared with corresponding female value.

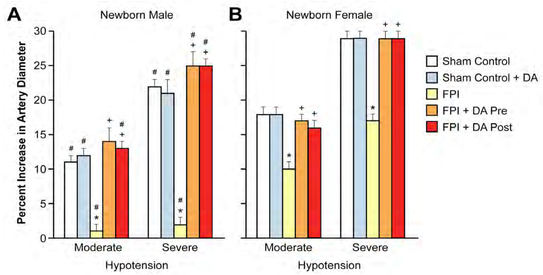


Figure 2. Influence of moderate and severe hypotension on pial artery diameter in newborn male (A) and female (B) pigs before injury (sham control), before injury treated with DA (15 μg/Kg/min iv), 1 h after FPI, 1h after FPI treated 30 min prior to injury with DA, and 1h after FPI treated with DA 30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

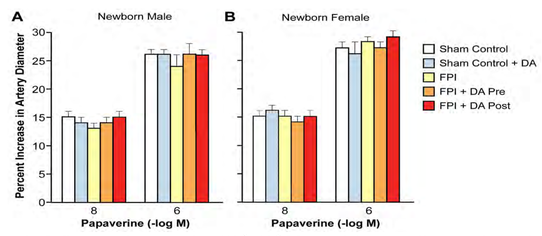


Figure 3. Influence of papaverine (10^{-8}, 10^{-6} M) on pial artery diameter in newborn male and female pigs before injury (sham control), before injury treated with DA (15 μg/Kg/min iv), 1 h after FPI, 1h after FPI treated 30 min prior to injury with DA, and 1h after FPI treated with DA 30 min after injury, n=5.

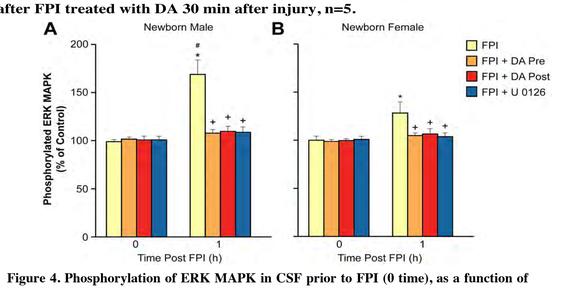


Figure 4. Phosphorylation of ERK MAPK in CSF prior to FPI (0 time), as a function of time after FPI (h) in pigs treated with vehicle (FPI), DA (15 μg/Kg/min iv) pre- or post-treatment (30 min) + FPI, or U0126 (1 mg/kg iv) + FPI, n=5. Data expressed as percent of control by ELISA determination of phospho ERK MAPK and total ERK MAPK isoforms and subsequent normalization to total form. A: newborn male, B: newborn female. *p<0.05 compared with corresponding 0 time value + p<0.05 compared with corresponding vehicle treated value #p<0.05 compared with corresponding female value

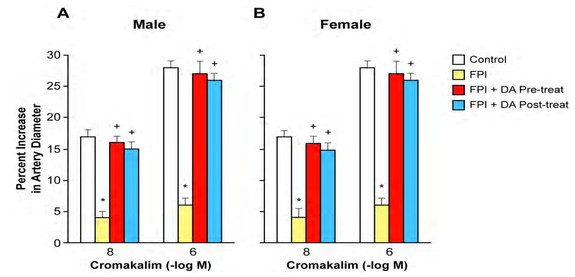


Figure 5. Influence of cromakalim (10^{-8},10^{-6} M) on pial artery diameter in newborn male (A) and female (B) pigs before injury (control), 1 h after FPI, 1h after FPI treated 30 min prior to FPI with DA (15 μg/kg/min iv), and 1h after FPI treated with DA 30 min after FPI, n=5. *p<0.05 compared with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

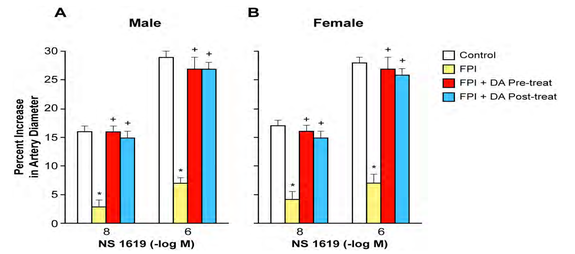


Figure 6. Influence of NS 1619 (10^{-8},10^{-6} M) on pial artery diameter in newborn male (A) and female (B) pigs before injury (control), 1 h after FPI, after FPI treated 30 min prior to FPI with DA (15 μg/kg/min iv), and after FPI treated with DA 30 min after FPI, n=5. *p<0.05 compared with control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

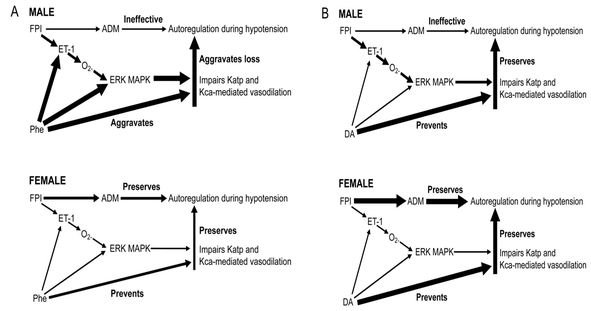


Figure 7. Comparison of proposed mechanisms for Phe (a) and DA (b) in control of cerebral hemodynamics after FPI. Arrow thickness in proportion to probability of action.

Conclusions

These data indicate that DA protects K channel mediated cerebrovasodilation equally in male and female piglets because of equivalent blockade of ERK MAP 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.