available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

SNP improves cerebral hemodynamics during normotension but fails to prevent sex dependent impaired cerebral autoregulation during hypotension after brain injury

William M. Armstead[a,b,*], J. Willis Kiessling[a], W. Andrew Kofke[a], Monica S. Vavilala[c]

[a]Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, PA 19104, USA
[b]Department of Pharmacology, University of Pennsylvania, Philadelphia, PA 19104, USA
[c]Department of Anesthesiology, Pediatrics, and Neurological Surgery, University of Washington, Seattle, WA, USA

ARTICLE INFO

Article history:
Accepted 6 March 2010
Available online 16 March 2010

Keywords:
Brain injury
Cerebral circulation
Newborn
Autoregulation
Signal transduction

ABSTRACT

Traumatic brain injury (TBI) is a leading cause of morbidity in children and boys are disproportionately represented. Hypotension is common and worsens outcome after TBI. Previous studies show that adrenomedullin, a cerebrovasodilator, prevented sex dependent impairment of autoregulation during hypotension after piglet fluid percussion brain injury (FPI). We hypothesized that this concept was generalizable and that administration of another vasodilator, sodium nitroprusside (SNP), may equally improve CBF and cerebral autoregulation in a sex dependent manner after FPI. SNP produced equivalent percent cerebrovasodilation in male and female piglets. Reductions in pial artery diameter, cortical CBF, and cerebral perfusion pressure (CPP) concomitant with elevated intracranial pressure (ICP) after FPI were greater in male compared to female piglets during normotension which was blunted by SNP. During hypotension, pial artery dilation (PAD) was impaired more in the male than the female after FPI. However, SNP did not improve hypotensive PAD after FPI in females and paradoxically caused vasoconstriction in males. SNP did not prevent reductions in CBF, CPP or autoregulatory index during combined hypotension and FPI in either sex. SNP aggravated ERK MAPK upregulation after FPI. These data indicate that despite prevention of reductions in CBF after FPI, SNP does not prevent impairment of autoregulation during hypotension after FPI. These data suggest that therapies directed at a purely hemodynamic increase in CPP will fail to improve outcome during combined TBI and hypotension.

1. Introduction

Pediatric traumatic brain injury (pTBI) is a global public health concern (Langlois et al., 2005; Newacheck et al., 2004). Boys are disproportionately represented and young children have devastating outcomes (Langlois et al., 2005). Hypotension is common and worsens outcome after TBI (Coates et al., 2005). By definition, cerebral autoregulation denotes constant cerebral blood flow (CBF) during changes in mean arterial blood pressure. Hypotension can lead to cerebral ischemia when cerebral autoregulation is impaired. Since impaired autoregulation renders CBF dependent on cerebral perfusion pressure

* *Corresponding author*. Department of Anesthesiology and Critical Care, 3620 Hamilton Walk, JM3, University of Pennsylvania, Philadelphia, PA 19104, USA. Fax: +1 215 349 5078.
E-mail address: armsteaw@uphs.upenn.edu (W.M. Armstead).

0006-8993/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2010.03.024

(CPP) and CBF may contribute to neuronal cell integrity, optimal management of CPP to limit tissue hypoxia with low CPP is critical. Administration of a cerebrovasodilator such as sodium nitroprusside (SNP) can improve cerebral hemodynamics after TBI by reducing intracranial pressure (ICP) and increasing CPP. However, CBF can increase in response to cerebrovasodilator administration in the absence of impaired cerebral autoregulation in the setting of TBI. Since ethical constraints preclude mechanistic studies of cerebral autoregulation in children, we have used an established porcine model of fluid percussion injury (FPI) that mimics many of the pathophysiological features of pTBI to corroborate clinical observations after pTBI (Armstead et al., 2009, 2010; Armstead and Vavilala, 2007). Piglets offer the unique advantage of a gyrencephalic brain containing substantial white matter, which is more sensitive to ischemic/TBI damage, similar to humans.

It is unclear whether beneficial outcome depends on increases in CPP or on signaling pathways which link improved cerebral autoregulation to limited tissue injury after pTBI. Mitogen activated protein kinase (MAPK), a family of at least 3 kinases, extracellular signal-related kinase (ERK), p38, and c-Jun N-terminal kinase (JNK) is upregulated and may contribute to injury after TBI (Alessandrini et al., 1999; Armstead et al., 2009, 2010; Laher and Zhang, 2001). For example, activation of ERK MAPK contributes to hypoperfusion after FPI to greater extent in male compared to female pigs (Armstead et al., 2010). Our recent studies show that adrenomedullin, a cerebrovasodilator, prevented sex dependent impairment of autoregulation during hypotension after piglet FPI through inhibition of ERK MAPK upregulation (Armstead et al., 2010; Armstead and Vavilala, 2007). Inhibition of ERK MAPK upregulation also prevents reductions of CBF after FPI (Armstead et al., 2009). However, it is unknown whether SNP modulates ERK MAPK upregulation. We hypothesized that the concept that administration of a cerebrovasodilator improves cerebroautoregulation in the setting of TBI was generalizable and that administration of another cerebrovasodilator, such as SNP, may equally improve CBF and cerebral autoregulation in a sex dependent manner after piglet FPI. If this is found to be the case, then the ability of SNP to modulate ERK MAPK upregulation will also be explored.

2. Results

2.1. SNP prevents sex dependent reductions in pial artery diameter and CBF after FPI

SNP (0.1 mg/kg iv) in the absence of FPI produced equivalent decreases in mean arterial blood pressure (37±4 and 35±2% respectively) and increases in pial artery diameter (12±2 and 17±4% respectively) in male and female pigs. Changes in pial artery diameter and mean arterial blood pressure were short (1–3 min) after acute bolus administration of SNP. FPI produced greater pial small artery vasoconstriction and reduction in CBF in male compared with female newborn pigs (Fig. 1). SNP treatment 30 min prior to FPI (pre-treatment) or 30 min post-injury (post-treatment) blunted pial artery vasoconstriction and reductions in CBF at 1 and 4 h post insult (Figs. 1 and 2). On a percentage basis, the protection afforded by SNP on reductions in pial diameter and CBF were greater in the male compared with the female.

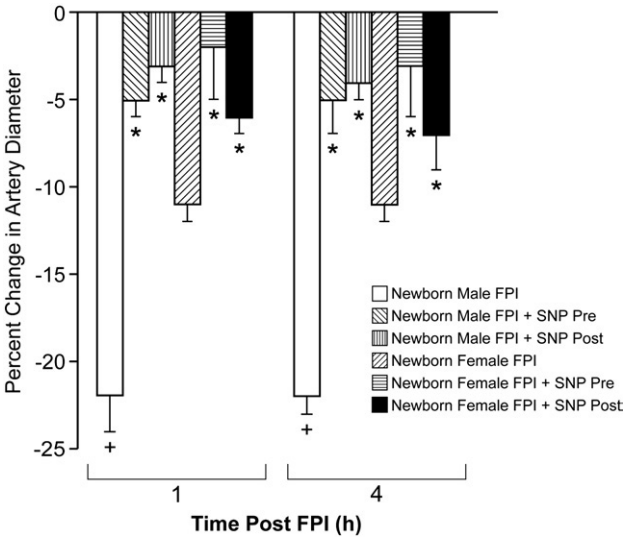

Fig. 1 – Influence of FPI (1, 4 h) on pial artery diameter in vehicle (FPI) and SNP (0.1 mg/kg iv) pre-treated newborn male and female pigs, $n=6$. $^{*}p<0.05$ compared with corresponding FPI vehicle value $^{+}p<0.05$ compared with corresponding female value.

2.2. SNP aggravates sex dependent loss of pial artery dilation during hypotension after FPI

Moderate and severe hemorrhagic hypotension and papaverine (10^{-8}, 10^{-6} M) elicited reproducible dilation of pial small arteries and arterioles. Prior to FPI, hemorrhagic hypotensive pial artery dilation was significantly less in male than female pigs (Fig. 3), similar to that recently published (Armstead et al., 2010). Within 1 h of FPI, hypotensive pial artery dilation was impaired in both sexes, but the degree of impairment was greater in the male compared with the female (Fig. 3). However, SNP pre-treatment and post-treatment did not augment hypotensive pial artery dilation after FPI in the female and paradoxically caused vasoconstriction after FPI in the male (Fig. 3). The numeric values for mean arterial blood pressure during normotension, moderate and severe hypotension were no different between FPI vehicle and FPI SNP treated piglets (72±8, 55±6, and 41±4 versus 67±7, 52±5, and 38±4 mm Hg, respectively). Absolute values for pial artery diameter for normotension, moderate, and severe hypotension conditions before and after FPI in the male were: 137±7, 151±8, and 165±9 versus 134±9, 130±10, and 126±12 μm, respectively). In the female, these values were: 122±7, 141±8, and 157±10 versus 123±7, 132±8, and 143±9 μm, respectively. Autoregulatory pial artery dilation during hypotension was unchanged by SNP in the absence of FPI (Fig. 3). Papaverine induced pial artery vasodilation was unchanged by FPI and SNP (Fig. 4), indicating that impairment of cerebral autoregulatory pial artery dilation by SNP is not an epiphemonenon.