only increased HIF-1α/VEGF and vessel density but also improved neurobehavioral functions.

Oxidative stress (peroxynitrite) causes a sustained activation of AMPK in the acute phase leading to BBB disruption and edema. On the other hand, pharmacological inhibition of AMPK activity in the chronic phase hampers functional recovery. These observations provided us rationale for the use of GSNO which protected BBB integrity by reducing peroxynitrite in the acute phase. In the chronic phase, GSNO aids in functional recovery by up regulating the neurorepair-associated HIF-1α/VEGF pathway and angiogenesis. GSNO is a natural molecule and its exogenous administration has not shown toxicity or side effects in humans.

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Key words
AMPK, functional recovery, GSNO, HIF-1 alpha, neurorepair, vessel density

C2-27

KNOCKOUT OF CYCLOPHILIN D PREVENTS INCREASED INTRINSIC AND SYNAPTIC NEURONAL EXCITABILITY AFTER MILD TRAUMATIC BRAIN INJURY (MTBI)

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Mitochondria are central to Ca^{2+} homeostasis. Dysfunction resulting in mitochondrial permeability transition pore (MTP) opening has been reported after mTBI. Cyclophilin D is an integral part of the MTP. Recently our group has found that the extent of axonal injury was diminished in neocortex after mTBI in cyclophilin D knockout (KO) mice. Here we tested whether this KO could also provide protection from the increased intrinsic and synaptic neuronal excitability previously described. In these experiments a central fluid percussion injury was given to 6–8 week old YFP-h mice. Whole cell patch clamp recordings from axotomized (AX) and intact (IT) YFP + layerV pyramidal neurons were made after 1–2 day survival. Action potentials (AP) were recorded in current-clamp mode while neurons were maintained at − 60 mV. Excitatory post synaptic currents (EPSCs) were recorded in voltage-clamp mode with neurons held at − 70 mV. While AP are increased in amplitude in AX at 1–2 days and in IT at 1 day after injury, in KO mice this increase was prevented. After mTBI in KO mice, the amplitude of AP in IT and AX neurons was not different (1–2 day survival) from that in naïve KO mice (ANOVA, $p > 0.05$, $n \geq 9$ cells). There was however a trend towards an increased AP amplitude for IT neurons at 1day ($p < 0.5$ with t-test). Thus, there may be additional factors that contribute to the alteration of this intrinsic property. This KO also prevented the changes in EPSCs previously observed after mTBI. The frequency and amplitude of spontaneous and miniature (1 mM TTX in bath) EPSCs were not different between naïve and mTBI at 1–2 day survival times for AX and IT neurons from KO mice (ANOVA, $p > 0.05$, $n \geq 8$ cells). Thus, the CypD-mediated mitochondrial permeability transition pore is linked to the cellular and synaptic perturbations observed in the pathogenesis of mTBI. These data support the idea that therapies aimed at mitochondrial protection should prove clinically useful. Supported by NIH grant NS077675. Mouse strain supplied by Michael Forte, Vollum Institute, OHSU.

Key words
action potential, cyclophilin D, excitatory synaptic transmission, mitochondria

C2-28

THE NRF2-ARE PATHWAY AS A THERAPEUTIC TARGET IN TRAUMATIC BRAIN INJURY: GENETIC AND PHARMACOLOGICAL APPROACHES FOR NEUROPROTECTION

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The pathophysiological importance of oxidative damage after traumatic brain injury (TBI) has been extensively demonstrated in experimental models. The transcription factor Nrf2 mediates antioxidant genes by binding to antioxidant response elements (ARE) within DNA and upregulating these genes creating a pleiotropic cytoprotective-defense pathway. Previously, we determined the post-TBI time-course of Nrf2-ARE mediated gene expression in cortex and hippocampus utilizing the unilateral controlled cortical impact (CCI) model. Increased Nrf2-ARE mediated expression closely followed that of post-TBI oxidative damage markers 4-HNE and 3-NT (Miller et al., J. Neurotrauma, March 2014, in press). Moreover, pre-treatment 48 hours prior with Nrf2-ARE activating drug carnosic acid (CA) (single 1.0 mg/kg i.p. administration) provides protection to cortical mitochondria bioenergetics after exposure to the toxic aldehyde 4-HNE *ex vivo* that was accompanied by decreased 4-HNE bound to mitochondrial proteins (Miller et al., Free Rad. Biol. Med. 57:1-9, 2013). In addition, we conducted a post-TBI dose response of CA and found that a single 1.0 mg/kg i.p. administration 15 minutes post-TBI reduced levels of oxidative damage markers in cortex and hippocampus. In the current study, we demonstrate for the first time that CA can significantly improve ($p < 0.05$) cortical mitochondrial respiratory function at 24 hours post-TBI as compared to vehicle animals which is accompanied by a concomitant reduction in oxidative damage to mitochondrial proteins. Additionally, we have found that oxidative damage is increased in Nrf2-knockout mice but attenuated in mice overexpressing Nrf2. Current studies are determining if genetic manipulation attenuates behavioral deficits and neurodegeneration. Pharmacological studies are also assessing the therapeutic window of CA wherein initial administration is delayed to 1, 4, or 8 hours post-TBI. Furthermore, an evaluation of CA's capability to attenuate behavioral deficits and neurodegeneration post-TBI is also underway. These studies will determine if targeting the Nrf2-ARE pathway post-TBI has clinical relevance.

Key words
gene expression, neuroprotection, oxidative stress, TBI, transcription factor

C2-29

EFFECTS OF ETHYL PYRUVATE ON MARKERS OF OXIDATIVE STRESS AND GLYCOLYTIC FUNCTION AFTER TRAUMATIC BRAIN INJURY

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The current study examined potential mechanisms by which ethyl pyruvate (EP) improves cerebral glucose metabolism and reduces neuronal injury after experimental traumatic brain injury (TBI). Adult male Sprague-Dawley rats received sham injury or TBI (contusion) to the left parietal cortex followed by injections of EP (40 mg/kg, IP) or no treatments at 0, 1, 3 and 6 h. At 7 h post-injury left cortical tissue was harvested and processed for Western blots, levels of nicotinamide adenine dinucleotide (NAD^+) and GAPDH enzyme activity. Protein