21st Annual SAFAR SYMPOSIUM

Continuum of Care in the Treatment of Hypoxic Ischemic Insults 2024 Update

ABSTRACTS

Multi-Departmental Trainees' Research Day

Thursday April 25th, 2024 | 2:00 pm to 5:30 pm | University Club

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DEPARTMENT OF ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE

Oral Abstract O1

OXYTOCIN RECEPTOR IN THE SPINAL NEURAXIAL MODULATION OF VENTRICULAR EXCITABILITY

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Introduction: Cardiac sympathoexcitation is a major contributor to the pathogenesis of ventricular tachyarrhythmias (VTs) during ischemia reperfusion (I/R) and chronic myocardial infarction (MI). Afferent network connections in the intermediolateral cell column (IML) and dorsal horn (DH) control sympathetic output to the heart. Our team reported spinal cord stimulation (SCS), decreased cardiac sympathoexcitation and reduced VTs during ischemia. Oxytocin (OXT) is a known neuromodulator; however, whether OXT signaling can modulate the cardiospinal neural network is unknown.

Hypothesis: SCS neuromodulation is reducing sympathoexcitation and VTs through OXT signaling pathways.

Methods: Two models of cardiac ischemia were used in Yorkshire domestic swine. In acute I/R, a suture was placed around the left anterior descending (LAD) coronary artery, after sternotomy. Chronic infarction (MI) was created by accessing the femoral with fluoroscopy guidance. Polystyrene microspheres (1ml) were injected via a 3mm angioplasty balloon catheter to the LAD. Animals then recovered post-MI for 6-8wk. SCS treatment was delivered through a four-pole lead which was inserted in the epidural space (T1-T4)(50Hz, 0.4ms pulse duration). T2-T4 spinal cord was collected postmortem for molecular analysis. Fluorescence *in situ* hybridization (FISH) protocol for RNAscope Fluorescent v2 Assay (ACD) was followed. Cell counts represented as 3 puncta or more centered around DAPI.

Results: We report that OXT receptor positive cells significantly decreased as a result of I/R and MI ($p<0.001$, two-way ANOVA n=4-5 animals, average of 2-3 slices per animal). Within the DH the majority of OXT positive cells were inhibitory GABAergic neurons. Within the IML, a majority of the cells regulated by I/R and MI were microglia, and both an inhibitory and excitatory population contributed to the onset of ischemia. SCS treatment after I/R and MI resulted in the recovery of this OXT receptor cell population.

Conclusions: By evaluating the role of OXT in reducing cardiac sympathoexcitation at the level of the spinal cord, we provide new insights into optimizing current neuromodulation approaches and developing new pharmacologic therapies.

Significance: With an increasing number of patients at risk for SCD due to ischemic heart disease, it is imperative to develop alternative effective therapies. Evaluating the role of OXT in reducing cardiac sympathoexcitation at the level of the spinal cord will provide new insights into optimizing current neuromodulation approaches and developing new pharmacologic therapies.

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Abstract 1

MAST CELLS AND VEGFR2 DRIVE CHRONIC PELVIC PAIN IN A MOUSE MODEL OF ENDOMETRIOSIS

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Introduction: Endometriosis (EM) impacts approximately 10% of women globally (Zondervan et al., 2020), yet the underlying biological mechanisms that drive EM-associated chronic pelvic pain (EM-CPP) are poorly understood. Human EM lesions contain activated mast cells (MCs) (Matsuzaki et al., 1998) and elevated vascular endothelial growth factor (VEGF) (Rein et al., 2009). We will focus on MC-derived VEGF because 1) MCs derived from human visceral tissue (lungs) can express VEGF (Detoraki et al., 2010), and 2) VEGF (Tiago et al., 2023), and VEGF receptor 2 (VEGFR2) (Bourlev et al., 2006) concentrations are elevated in human endometrial lesions. EM-CPP presents not only as pain originating from the uterus but also as referred pain from the abdomino-pelvic muscles. A proxy for this referred pain is called pelvic tactile allodynia in rodent models of EM-CPP (Fattori et al., 2020). Here, we will use a non-invasive EM mouse model to demonstrate that MC-derived VEGF and VEGFR2 mediate pelvic tactile allodynia.

Hypothesis: MC stabilizers and VEGFR2 inhibition decrease pelvic tactile allodynia in EM mice.

Methods: C57BL/6J (B6) donor mice (6-8 weeks old) received a subcutaneous injection of estradiol benzoate (EB; 10µg) and 4 days later each uterine horn was excised, placed in Hank's Balanced Salt Solution (HBSS), and minced. Recipient mice received an intraperitoneal (i.p.) injection of either HBSS (500µl; "Shams") or HBSS+minced uterine horn (500µl; "EM mice") extracted from donors. To assess pelvic tactile allodynia in EM mice, von Frey (vF) was conducted before (baseline) and 7, 14, 21, and 28 days after tissue injection. We then i.p. administered the MC stabilizer β-nicotinamide mononucleotide (NMN; 150mg/kg, n=4) on day 28 and vF thresholds were assessed at 3, 9, 18, and 36 hrs. Next, we i.p. delivered the VEGFR2 blocker SKLB1002 (SB; 100mg/kg, n=7) on day 28, and vF thresholds were assessed at 15, 30, 60, 90, and 180 mins. In a separate dose-response study of VEGF, we infused either intrauterine (i.u.) saline (10µl) or VEGF (0.001pg (n=6), 0.01pg (n=6), 0.1pg (n=7), and 1pg (n=7)) on days 1, 4, and 7 after baseline and vF tested from day 7 to 56.

Results: We evaluated the effect of NMN, SB, and saline on mechanical hypersensitivity in Sham control or EM mice. In Shams, neither saline, NMN, nor SB changed mechanical thresholds. In EM mice, NMN and SB but not saline reversed hypersensitivity ($p<0.05$). Next, in mice without EM, we demonstrated that i.u. saline or 0.001-0.01pg VEGF does not induce mechanical hypersensitivity. VEGF at 0.1pg revealed mechanical hypersensitivity for 14 days ($p<0.05$). VEGF at 1pg induced mechanical hypersensitivity for up to 56 days ($p<0.05$). Next, we investigated the effect of NMN (50mg/kg) on VEGF-induced pelvic tactile allodynia. Mechanical thresholds remain unchanged in controls (0.9% saline) that received i.u. saline or NMN. However, i.u. NMN but not saline reversed VEGF-induced hypersensitivity ($p<0.05$).

Conclusions: 1) MC activity contributes to pelvic tactile allodynia in EM mice, 2) stabilizing MCs or blocking VEGFR2 alleviates pelvic tactile allodynia, and 3) intrauterine VEGF elicits pelvic tactile allodynia that is reversible with blunting of MC activity.

Significance: Mast cell stabilizers and VEGFR2 blockers may serve as effective therapeutics to treat EM-CPP. VEGF infused i.u. may serve as a new model to study the development of pelvic tactile allodynia in mice.

Research Support: University of Pittsburgh Start-Up funds (PI: Kenny Roman, PhD and Co-PI: Bradley K. Taylor, PhD)

Abstract 2

DECIPHERING THE MECHANISM OF SEX DIFFERENCES IN PROTEIN KINASE A SIGNALING OF CHRONIC POSTSURGICAL PAIN

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Introduction: Pain is reported more frequently in women than men, and the past decade has witnessed an explosion of research on the relationship between sex and pain, particularly with respect to estrogens and estrogen receptors. By contrast, only a few studies have studied the contribution of testosterone and its cognate androgen receptor (AR) to pain. In a mouse model of chronic postsurgical pain (CPSP), we reported that intrathecal administration of the protein kinase A (PKA) inhibitor H89 prevented kappa opioid receptor (KOR) antagonist-induced reinstatement of mechanical hypersensitivity in male but not female mice. These data indicate that the intracellular signaling of latent postsurgical pain sensitization (LS) is driven by PKA signaling in the dorsal horn of male but not female mice.

Hypothesis: A major gap is the underlying mechanism of this sex difference. To address this question, we tested the hypothesis that ARs activate PKA to drive CPSP.

Methods: In C57BL/6 mice (7-8 wk), we incised the skin and underlying plantaris muscle at the left hindpaw, and then waited 3 wk for hypersensitivity (von Frey filaments) to resolve. We then pharmacologically or surgically activated or inhibited ARs with 4 experiments: 1) in female mice, we administered testosterone enanthate (TE, 0.45 mg/kg, subcutaneous) or vehicle (sesame oil) for two weeks (n = 5-8); 2) in female mice, we spinally administered TE (10 µg, intrathecal) or vehicle (cremophore: ethanol: saline – 1:1:8) (n = 6-8); 3) in male mice, we administered flutamide (50 mg/kg, subcutaneous) to block AR (n = 6-12); 4) male mice received orchiectomy (surgical removal of testes) or sham surgery (n = 6-8). After each of these interventions, we administered vehicle, PKA inhibitor H89 (10 nmol, i.t.), and/or KOR antagonist LY2456302 (10 µg, i.t.) in a 2x2 design in both male and female mice.

Results: Neither vehicle nor H89 alone changed mechanical threshold in any group. LY2456302 reinstated mechanical hypersensitivity in all 4 groups, consistent with previous studies indicating that incision causes concomitant latent postsurgical pain sensitization that is masked by endogenous KOR signaling. In female mice that received systemic or intrathecal TE, preadministration of H89 prevented LY2456302-induced reinstatement of mechanical hypersensitivity. On the other hand, in male mice that received subcutaneous AR blocker or orchiectomy, preadministration of H89 failed to prevent LY2456302-induced reinstatement of mechanical hypersensitivity.

Conclusions: These data show that endogenous testosterone facilitates the PKA signaling component of LS, and that this can be mimicked in females with exogenous testosterone. This could explain why H89 prevents KOR antagonist-induced reinstatement of hypersensitivity in male but not female mice.

Significance: These data promote ARs as a target for the development of novel analgesics for CPSP, particularly in men. Current studies are using the Cre-lox system, pharmacological, and surgical approaches to determine whether ARs located on sensory or spinal neurons are responsible for activating PKA in CPSP. Furthermore, we will evaluate the effects of estradiol in PKA-mediated CPSP since testosterone can be converted to estradiol by aromatase.

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Abstract 3

CHRONIC ALCOHOL EXPOSURE INDUCES A LONG-LASTING LATENT PAIN STATE THAT IS KEPT IN REMISSION BY OPIOID RECEPTORS

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Introduction: Alcohol Use Disorder (AUD) is a chronic medical condition known to be comorbid with acute pain. For example, we recently reported that 4 weeks of chronic intermittent ethanol vapor in male and female C57BL/6J (B6J) mice was associated with mechanical and heat hypersensitivity when tested up to 48 hours after its cessation. We coined the term “chronic alcohol withdrawal induced pain (CAWIP)” to describe this model.

Hypothesis: The current studies were designed to test the hypotheses that CAWIP transitions to states of: 1) extended withdrawal; and 2) chronic pain.

Methods: Sensitivity to mechanical (von Frey) and heat (hotplate) at the plantar skin was measured at 1, 2, 3, 7, 14, 21, 28, and 35 days after cessation of 4 weeks of chronic intermittent ethanol vapor (CIEV) to determine the duration of mechanical and heat hypersensitivity in CAWIP. Conditioned place preference (CPP) to three days of gabapentin (100 mg/kg i.p.) was completed 4 days after cessation of CIEV. Next, we determined whether chronic alcohol causes latent pain sensitization that can be unmasked with pharmacological administration of opioid receptor antagonist / inverse agonists, as we have observed in other models of chronic pain. To address the question, we waited for the resolution of CAWIP, administered naltrexone (NTX; 3 mg/kg s.c.), and then evaluated: 1) mechanical and heat sensitivity at 30, 60, 90, and 120 minute timepoints; and 2) conditional place aversion (CPA).

Results: Both male (n=8) and female (n=8) B6J mice demonstrated mechanical hypersensitivity that peaked at 24-48 hour after cessation of CIEV. 4 days after CIEV, CPP to the gabapentin-paired chamber was exhibited by female mice (n=4, P=0.004). Remarkably, mechanical hypersensitivity persisted for three additional weeks in a pain state that we term extended withdrawal. Heat hypersensitivity did not continue into extended withdrawal as it was never seen in males and persisted for only three days in females. After the resolution of extended withdrawal (4 weeks after cessation of CIEV), NTX caused a profound reinstatement of mechanical hypersensitivity in female (n=8, P=0.002), but not male mice (n=8). Lastly, female mice exhibited a trend towards CPA to the NTX paired chamber (n=4, P=1.175), however, small subject size precludes a definitive answer.

Conclusions: We found that mechanical hypersensitivity persisted in males and females for 3 weeks after cessation of alcohol; this extended withdrawal indicates that chronic alcohol produces a long-lasting dependence. Mechanical hypersensitivity could only be reinstated with naltrexone in females; these data suggest that latent sensitization is sex dependent. Gabapentin caused place preference in females but not males; these results demonstrate that chronic alcohol causes aversion upon its cessation and promotes gabapentin for the treatment of CAWIP. Future studies will determine the neurochemical signaling mechanisms of chronic alcohol-associated latent sensitization and its inhibition by G protein-coupled receptors.

Significance: Our work will help us understand how chronic pain manifests from alcohol withdrawal and will aid in the development of novel treatments for these comorbid disorders.

Support: We gratefully acknowledge the support NIH/NIAAA, NIH/NIDA, and NIH/NINDS grants AA024836 (SPF), AA020889 (SPF), AA030257 (SPF), DA037621 (BKT), NS045954 (BKT), NS112632 (BKT), NS073548 (AJB), and AA031431 (AJB), and pilot grant funding from Bridging Connections in Addiction Research and the Pittsburgh Foundation.

Abstract 4

LIDOCAINE-MEDIATED CHANGES IN FUNCTIONAL BRAIN CONNECTIVITY

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Introduction: Intravenous lidocaine is a commonly used adjunct medication for perioperative anesthesia, but the neural correlates of its effects during pain are not well understood.

Hypothesis: Intravenous lidocaine affects pain perception and changes brain functional connectivity.

Methods: Twenty-eight participants completed resting state functional MRI scans under saline and drug conditions. Functional connectivity analyses were performed using CONN 21.a and SPM 12. Preprocessing steps included Gaussian kernel smoothing (8 mm FWHM), motion correction and physiologic noise correction (5 CompCor noise components). ROI-to-ROI connectivity was calculated for 132 Harvard-Oxford Atlas regions in a general linear model characterizing the association between BOLD signals for each pair of ROIs. Connection-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual ROIs. ROI-level inferences were based on parametric multivariate statistics, combining the connection-level statistics across all connections from each individual ROI. Data-driven hierarchical clustering grouped correlated connections. Results were thresholded using a familywise corrected p-FDR < 0.05 ROI-level threshold.

Results: Lidocaine *decreases* functional connectivity in 16 clusters of ROI-to-ROI connections compared to saline, including regions of association cortex as well as the anterior cingulate, amygdala, insula, hippocampus, and basal ganglia. Lidocaine *increases* connectivity in one cluster comprising the right supramarginal gyrus and the right middle temporal gyrus $F(2,26) = 12.11$; p-FDR = 0.018709.

Conclusions: The results of the resting-state functional connectivity analyses demonstrate the neural underpinnings of intravenous lidocaine, including regions classically implicated in pain and fear circuitry, as well as association cortices and other regions whose role in limbic pathways is not yet clear.

Significance: Identifying regions implicated in these biologic processes can aid targeted pharmacologic research and clinical practice in the future. Individual variation in response to sedation contributes to sub-optimal pain control and memory ablation. Identifying more definitive measures of amnesia and analgesia have important implications for the management of pain and memory during surgery.

Research/Grant Support: NIH grant R35GM146822

Abstract 5

MULTIMODAL ANALGESIA VERSUS INTERSCALENE NERVE BLOCK FOR ARTHROSCOPIC SHOULDER SURGERY

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Introduction: Interscalene block has long been used as an effective means of controlling the pain of shoulder surgery. However, multi-modal analgesia (MMA), incorporating a variety of agents to address pain through different mechanisms, has become a prominent part of anesthesia care. General anesthesia with MMA has not been specifically compared to nerve block in this setting. This study aims to compare block plus sedation versus general anesthesia with MMA in terms of 1) PACU discharge time 2) Pain Scores 3) Opioid requirement during recovery.

Hypothesis: We hypothesized that PACU discharge time would be significantly lower for patients undergoing ISB with sedation as compared to general anesthesia with MMA, and that pain control would be superior, as reflected in pain scores and opioid requirements during recovery.

Methods: Through EMR review, we identified patients who had undergone outpatient, arthroscopic shoulder surgery utilizing interscalene nerve block, and compared them to those who underwent general anesthesia with MMA. The primary outcome measure was duration of PACU stay. Secondary outcomes included VRS pain score, opioid administration in PACU, and unexpected admission to the hospital. All outcomes were compared with a Paired Wilcoxon Signed-Rank test for statistical significance. A p-value of 0.05 or less was considered significant.

Results: A total of 64 charts were evaluated, 32 who received ISB with propofol sedation, and 32 who received general anesthesia with MMA. The duration of time spent in PACU was significantly lower in the ISB group. Pain scores were both clinically and statistically significantly lower in the ISB group, while opioid requirements were also significantly lower. No patients required admission to the hospital.

Conclusion: Peripheral nerve blockade still appears to be superior for minimizing recovery time, as well as for control of postoperative pain and minimization of opioids, at least in the early postoperative period.

Significance: This study provides further evidence that ISB should continue to be used over other anesthesia methods for arthroscopic shoulder surgery which can help direct clinical care in the future.

Research/Grant Support: Richard Chao was funded by the Center For Innovation In Pain Care, University of Pittsburgh Department of Anesthesiology and Perioperative Medicine.

Abstract 6

THERMAL GRADIENT TEST FOR *IN VIVO* ASSESSMENT OF PAIN IN RODENTS

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Introduction: Classical pain evaluation in rodents, such as the Hargreaves and Von Frey tests for thermal and mechanical hypersensitivity respectively, heavily rely on an animal's reflexive response to a noxious stimulus. These threshold tests require intrusive human interactions with the animals and the quality of the data varies dependent on researcher experience due to supraspinal reflexes being misinterpreted as pain.

Hypothesis: We hypothesize that from animals' spontaneous behavioral responses to a range of thermal stimuli generated by the TGT device, we are able to differentiate among multiple animal variables including sex, nociceptive pain state, and effects of analgesic treatment.

Methods: We have engineered a thermal gradient device using a ½ inch thick piece of aluminum with two Peltier heating and cooling units fixed at each end. Four plastic lanes 137-cm long and 10-cm wide are placed on top of the aluminum to give us a testing corridor for animals to freely roam. The Peltier units create a linear thermal gradient from ~4 °C to ~58 °C along the aluminum surface and as animals experience this variable thermal stimulus, we collect behavioral position data with the video recording and analysis software AnyMaze. Utilizing a 30 second sliding window analysis of distance traveled (activity level) it was determined that the most useful data was collected between 30 and 600 seconds without interference from initial exploratory behavior. Data analysis of thermal preference (TP), as indicated by mean location selection along the thermal gradient, and thermal sensitivity (TS), as indicated by standard deviation of location selection, are used to differentiate between groups. Student and paired t-test analysis of thermal preference and thermal sensitivity was used to differentiate between measures. Repeated measure mixed design two-way ANOVA analysis of position data allowed us to identify interactions between thermal preference and animal condition. After data collection, the arena was split into six, nine-degree Celsius temperature zones and comparisons were made between measures using a Bonferroni post-*hoc* analysis.

Results: Quantified thermal preference and thermal sensitivity data can be used to statistically differentiate between multiple variables. Sex differences in response to thermal stimuli clearly show male mice have a higher tolerance to cold temperatures than female littermates (TP_{female} = 34.59 °C, TP_{male} = 30.93 °C, p = 0.0004). CFA induced inflammatory pain increases thermal sensitivity and induces symptoms of cold allodynia when compared to baseline measures ($TS_{baseline}$ = 12.57°C, TS_{CFA} = 10.70°C, p = 0.009631; $TP_{baseline}$ = 30.93 °C, TP_{CFA} = 33.81°C, p = 0.1139). Treatment of pain due to CFA with morphine show not only a higher distance traveled ($Mean_{CFA}$ = 8.951 m, $Mean_{CFA+morphine}$ = 78.29 m, $p < 0.0001$) but also a significantly higher tolerance to low temperatures (13 °C - 22 °C, $p < 0.01$, 4 °C -13 °C $p < 0.05$) regardless of pain condition (4 °C -13 °C $p < 0.01$).

Conclusions: Using statistical differences in behavioral patterns quantified using the TGT, we can differentiate the behavioral patterns of multiple conditions. First, sex differences in response to thermal stimuli are clear in the TGT. Second, changes in behavior after inducing an inflammatory pain state are seen as changes to thermal sensitivity in the TGT. Finally, the TGT can identify behavioral changes due to the known analgesic morphine before and after CFA induced inflammation.

Significance: A noninvasive high-throughput test of quantifiable behaviors allows researchers to identify pain states and treatments of those pain states with a higher degree of confidence. Removing researcher subjectivity allows for fast and reliable discovery of novel analgesics.

Research Grant Support: This work is supported by R01NS122830 to YX.

Abstract 7

REGULATION OF ETHANOL CONSUMPTION BY THE LNCRNA *MALAT1*

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Introduction: Alcohol use disorder (AUD) is a chronic human condition caused by genetic and environmental factors that lead to system-wide changes in molecular pathways and cell-types. Understanding the underlying pathophysiology of AUD is essential for ameliorating this disorder and other co-morbid conditions. Non-coding RNAs are key regulators of molecular and cellular functions such as RNA transcription, RNA-protein interactions, and gene expression. In our previous studies we determined that the long non-coding RNA (lncRNA) metastasis associated lung adenocarcinoma transcript1 (*Malat1*) was significantly elevated in both human prefrontal cortex (CTX) postmortem tissue from AUD subjects and in the CTX of C57BL/6J mice chronically exposed to ethanol. Additional studies from our laboratories and others have further implicated *Malat1* in regulation of the neuroimmune system, suggesting *Malat1* may be a novel regulator of neuroinflammatory pathways associated with the development of AUD.

Hypothesis: *Malat1* global knockout in adulthood will result in decreased ethanol consumption in females but not males using the every other day two bottle choice (EOD-2BC) paradigm.

Methods: 5 week-old ethanol naïve homozygous *Malat1* floxed, hemizygous UBC-CreERT2a mice on a C57BL/6J background received an intraperitoneal (i.p) injection of 150 mg/kg tamoxifen to induce recombination. Matched control groups received an equivalent volume of corn oil. Following a 10-day washout period, mice were single housed and received alternating access to either ethanol and water, or only water for 29 consecutive days during the EOD-2BC behavior paradigm. Bottles were weighed every 24 hours to record total fluid consumed in each bottle. At the end of EOD-2BC, mice experienced a seven-day washout period before being given continuous two-bottle choice access to saccharin and quinine to determine changes in taste preference to sweet or bitter tastants. Total fluid consumption as well as ethanol and tastant behavior were analyzed using multi-factor ANOVA.

Results: Adult female, but not male, *Malat1* global knockout (KO) mice demonstrated a selective decrease in ethanol consumption and preference. These changes were not due to decreased ethanol consumption or altered preference in response to sweet and bitter tastants.

Conclusions: Our studies currently indicate that *Malat1* plays a sex specific role in EOD-2BC drinking behavior, suggesting a novel association for the lncRNA *Malat1* in sexual dimorphism of alcohol consumption and neuroimmune function.

Significance: Further understanding the biological role of *Malat1* in alcohol drinking behavior may provide a novel avenue for the design of rational pharmacotherapies for treating AUD and co-morbid disorders

Research Grant/Support: We gratefully acknowledge the support of NIH/NIAAA grants AA029942 (AMB), AA020889 (GEH/SPF), and AA030257 (SPF).

Abstract 8

PROGNOSTIC VALUE OF INTRAOPERATIVE LEFT VENTRICULAR GLOBAL LONGITUDINAL STRAIN IN LIVER TRANSPLANT RECIPIENTS

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Introduction: Cirrhotic cardiomyopathy, defined as cardiac dysfunction in patients with end-stage liver disease in the absence of prior cardiac disease, occurs in about 50% of patients with liver cirrhosis. Up to 21% of deaths following liver transplant are related to cardiovascular events. Left ventricular global longitudinal strain (LV GLS) can be used to detect worsening function of subendocardial longitudinal fibers before changes are noted in other measures, such as left ventricular ejection fraction (LVEF). LV GLS at rest has been shown to be an independent mortality predictor in liver transplant candidates.

Hypothesis: Intraoperative LV GLS measured with TEE can predict postoperative outcomes after liver transplant.

Methods: Single center, prospective study of 104 patients undergoing orthotopic liver transplant at a large academic center. Inclusion criteria were patients who were liver transplant recipients, aged ≥18 years, and had a diagnosis of cirrhosis. The primary outcome was postoperative occurrence of adverse cardiac events (defined as a composite of death, myocardial infarction, coronary revascularization, stroke, heart failure, or arrhythmia). Secondary outcomes were acute kidney injury, prolonged intubation (>24 hours), and prolonged hospital stay (>30 days). Intraoperative TEE images were obtained by a cardiac anesthesiologist prior to skin incision. Speckle tracking analysis was used to calculate LV GLS, and the biplane method of disks was used to calculate LVEF. Data were analyzed with logistic regression.

Results: 104 patients were included for analysis. LV GLS of -18% or greater was considered abnormal. There were 15 patients with abnormal LV GLS (≥-18%), of which 3 (20%) had a postoperative adverse cardiac event. Of the remaining 89 patients with normal LV GLS, 4 (4.5%) had a postoperative adverse cardiac event (OR 5.31, p=0.043). There were no significant differences regarding the secondary outcomes in patients with abnormal vs normal LV GLS: AKI [9(60%) vs 41(46%), OR 1.76, p=0.32), prolonged intubation [1(7%) vs 13(15%), OR 0.42, p=0.42], prolonged hospital stay [3(20%) vs 7(8%), OR 2.93, p=0.16]. None of the patients had LVEF < 50%.

Conclusion: Liver transplant recipients with intraoperative abnormal LV GLS (≥-18%) were at increased risk of postoperative adverse cardiac events (OR 5.31, p=0.043).

Significance: For liver transplant recipients, intraoperative LV GLS measured with TEE may be a helpful tool for identifying patients at risk of postoperative adverse cardiac events.

Research/Grant Support: N/A

Abstract 9

INTRANASAL ADMINISTRATION OF A NPY Y1 AGONIST FOR THE TREATMENT OF POSTSURGICAL PAIN

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Introduction: Chronic postsurgical pain (CPSP) is inadequately managed in over 80% of patients (Goldberg & McGee, 2011) due to a lack of efficacious and safe treatment options. A promising therapeutic target for CPSP is the population of interneurons that express the Neuropeptide Y (NPY) Y1 receptor. These neurons (Y1-INs) are a predominately excitatory, pronociceptive population under inhibitory control of Y1, a G_iPCR. A large body of evidence demonstrates that intrathecal administration of the Y1 agonist [Leu^{31}Pro^{34}]-NPY alleviates pain by inhibiting CNS Y1-INs. (Nelson & Taylor, 2021; Taylor et al., 2014). However, the intrathecal route of administration is highly invasive and risky, making it unideal for translation to humans. Furthermore, [Leu^{31}Pro^{34}]-NPY cannot readily pass the blood brain barrier (BBB) due to its size and lipophilicity, rendering systemic administration unable to deliver it into the CNS, where it exerts its analgesic effects. Intranasal administration has emerged as a groundbreaking route to deliver drugs directly into the brain, bypassing the BBB altogether (Lochhead & Davis, 2019). Our studies will test intranasal administration of [Leu^{31}Pro^{34}]-NPY in the incision model of CPSP.

Hypothesis: Y1 receptors in the brain can be pharmacologically targeted by intranasal administration to alleviate postsurgical pain.

Methods: All experiments were conducted using male and female C57BL/6 mice. All mice underwent plantar incision. Von Frey filaments of increasing forces were applied to the incised hindpaw to test mechanical threshold as a proxy for pain. Intranasal administration was performed with mice under light isoflurane anesthesia, during which approximately 5µl of drug or control (saline) was delivered into each nasal cavity. Doses of 0.3mg/kg, 1mg/kg, and 5mg/kg were tested. Time spent on an accelerating rotarod before falling was used to test for any unwanted side-effects on motor coordination 60 minutes after intranasal administration.

Results: 1. Plantar incision caused a robust decline in mechanical threshold, reflecting pain hypersensitivity. At the time of peak hypersensitivity (2-3 days post incision), intranasal [Leu^{31}Pro^{34}]-NPY dose-dependently alleviated hypersensitivity, with 5mg/kg proving to be optimal. 2. Intranasal [Leu^{31}Pro^{34}]-NPY had no effect on motor coordination compared to saline as measured by rotarod testing.

Conclusions: Intranasal [Leu^{31}Pro^{34}]-NPY at a dose of 5mg/kg effectively alleviates CPSP without causing sedation or ataxia.

Significance: Our data suggests that intranasal [Leu^{31}Pro^{34}]-NPY is a promising treatment option for CPSP to be researched further. Future studies include but are not limited to: 1. Coadministration of [Leu^{31}Pro^{34}]-NPY with a Y1 antagonist to test the hypothesis that [Leu^{31}Pro^{34}]-NPY exerts its analgesic effects by binding specifically at Y1 receptors 2. Immunostaining for the phosphorylated form of extracellular signal-regulated kinase (ERK) and cFos, which are molecular markers of neuronal activation in the spinal cord and brain. These studies will lead to an increased understanding of the mechanisms of intranasal [Leu^{31}Pro^{34}]-NPY induced analgesia.

Research/Grant Support: This work was supported by the NIH grant R01NS045954-18 (PI: Bradley K. Taylor, PhD)

Abstract 10

PATIENT AND PROVIDER PERSPECTIVES ON PAIN AND OTHER DIMENSIONS OF CESAREAN DELIVERY EXPERIENCE (PARTNER STUDY PART 1)

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Introduction: We currently lack insights on patient perspectives of pain and other aspects of clinical care in cesarean delivery as well as how these perspectives compare with provider perceptions.[1] The purpose of this study was to discover patient priorities for cesarean delivery anesthesia experience, to compare patient and provider perspectives, and to explore attitudes on shared decision-making around anesthesia choices for cesarean delivery.

Hypothesis: We hypothesized that patient priorities would differ from provider perspectives.

Methods: A prospective qualitative cohort study was conducted after IRB approval (STUDY23060017). Patients who recently experienced cesarean deliveries and clinical care providers for patients receiving cesarean delivery were enrolled using a purposive sampling strategy. Semi-structured interviews were conducted using an interview guide. Interview transcripts were independently coded by three coders and qualitatively analyzed for major themes. Participants were recruited and interviews continued until thematic saturation was achieved.

Results: 42 participants (20 patients and 22 providers) completed interviews. Five major themes emerged reflecting patient attitudes and beliefs toward cesarean delivery experience: (1) effective communication, education, and respect; (2) emotional support by care team to build trust; (3) intra-operative pain or discomfort; (4) contrasting acceptability around therapies for pain or discomfort; (5) stigma surrounding having a cesarean delivery. Five major themes emerged reflecting provider attitudes and beliefs toward cesarean delivery priorities: (1) complexity of pain responses and expressions; (2) multiple strategies for pain control; (3) effective communication and education surrounding an emergency cesarean delivery; (4) patient psychological well-being during cesarean delivery; (5) barriers to accommodating individualized birth plans.

Conclusion: Patients and providers alike prioritize pain management, psychological well-being, and effective communication during cesarean delivery experiences. Patients emphasize relationships and trust as influential in their cesarean experience, while clinicians emphasize clinical complexities and physical treatments. Key patient-centered priorities for cesarean anesthesia care were identified and can inform future patient-centered outcomes research on cesarean delivery experience.

Significance: There is a lack of insight into the patient's perspective, with limited data on the comparison of patient and physician perception of intraoperative pain. This study answers critical questions regarding patient centered priorities for cesarean delivery experience and informs future research to identify important patient centered outcomes for cesarean delivery.

Research/Grant Support: Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine

1 Mazzoni A. BJOG. 2011;118(4):391-9.

Abstract 11

DECODING THE IMPACT OF PREECLAMPSIA AND COGNITIVE FUNCTION USING CEREBROSPINAL FLUID PROTEOMICS BIOMARKERS

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Introduction: In the peripartum period, people with pre-eclampsia (preE) have worse cognition in subjective memory, attention, working memory and executive function domains. Elevated biomarkers in preE have been implicated in vascular remodeling, neuronal growth, and inflammation, suggesting a potential association with the early presence of cognitive deficits; however, the specific cerebrovascular molecular pathways have never been directly studied.

Hypothesis: We hypothesize that cognitive differences in preE reflect altered expression of cerebrospinal proteins related to inflammatory pathways and/or vascular remodeling.

Methods: This prospective cohort study evaluated cognition in the third trimester among preeclamptic (n=11) and normotensive (n=12) people paired with proteomics of third trimester peripartum cerebrospinal fluid (CSF) collected at neuraxial placement. CSF peptides were analyzed using an Orbitrap Eclipse Mass Spectrometer, querying MS spectra against the SwissProt database for high-confidence proteins. Limma-voom was used to normalize and perform differential expression for preE vs. normotensive or cognition scores covarying for age, body mass index, education, and magnesium administration at CSF collection. Pathway analyses was performed using GSEA on human MSigDB pathways.

Results: PreE individuals had higher rates of preterm delivery ($p<0.001$) and lower education ($p=0.004$). Seven proteins, including TAGLN, were differentially expressed between PreE and normotensive individuals after adjusting for covariates (FDR < 0.05). Enrichment analysis revealed four non-redundant clusters of pathways in preE CSF, highlighting dysfunction in coagulation, complement cascade, spontaneous abortion, and wound healing hemostasis. Cognitive tests, particularly WAIS IV Digit Span and Subjective Attention tests, correlated with CSF protein levels. Eight proteins, including HIST1H4A, ENO1, and brain related PTPRZ1, showed significant associations with cognition scores independent of PreE status. Pathway clustering identified stress response, cadherin binding, and blood micro-vesicle involvement.

Conclusion: Proteomics analysis found differences in CSF proteins between preE and normotensive individuals, suggesting early Alzheimer's disease features (e.g., TAGLN), with altered proteins linked to coagulation and complement pathways, possibly indicating blood-brain barrier disruption, such as increased PTPRZ1 expression may contribute to executive function deficits akin to small vessel disease dementia, warranting further study.

Significance: Identifying pathways related to cerebrovascular insults in preE will elucidate the mechanism(s) of peripartum cognitive decline and relation to long-term cognitive impairment.

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Abstract 12

DEEP MACHINE LEARNING USING LONG SHORT-TERM MEMORY NETWORK FOR GAIT ANALYSIS OF PAIN

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Introduction: Chronic pain is a tremendous burden to public health, affecting more than 116 million people in the USA annually. Treatment options are limited, and new analgesics with no or reduced abuse liability are desperately needed. Most of the conventional pain evaluation methods in pre-clinical animal studies rely on supraspinal reflex in response to noxious stimulations and are often subjective to experimenter's biases, which partially account for the failure of many drug candidates in human clinical trials. Objective and high-throughput pain evaluation methods based on non-provoked animal behaviors will facilitate analgesic drug discovery and development.

Hypothesis: We hypothesize that by training the Long Short-Term Memory (LSTM) networks, a machine deep learning algorithm, we will be able to detect and diagnose animals experiencing differing degrees of inflammatory or neuropathic pain.

Methods: Here, we report a fully automated gait analysis method using the Long Short-Term Memory (LSTM) networks, a deep machine learning algorithm, to detect and diagnose rodents experiencing differing degrees of inflammatory or neuropathic pain. We used a modern digital touch-recording technology with high spatial and temporal resolutions to collect gait data in an open field using the complete Freud's adjuvant (CFA) model of inflammatory pain and spared nerve injury model of neuropathic pain in mice, with naïve animals serving as the control. Gait features are extracted from the touch data to train an LSTM model to differentiate between painful and non-painful conditions. We extracted several features that demonstrate behavioral dichotomies between naïve and CFA mice. These features include the duration of individual steps, distance and latency of segments of a predefined size, the time and distance among four consecutive touches, the time an animal spends in the center of the field versus the periphery, angulation of steps, and speed of the animals' body movement.

Results: The model is accurate at predicting painful states from data not previously used in training but is only marginally accurate at predicting non-painful states.

Conclusions: Further refinement of the model is currently underway to achieve >90% predictability and reliability. Additional tests of our algorithm include differentiation between animals with and without pain under different pain treatments using known analgesics.

Significance: This approach will set a new platform for assessing pain and treatment efficacy of drug candidates.

Research Grant Support: This work is supported by R01NS122830 and T32NS073548.

Abstract 13

CROSS-GENERATIONAL TRANSCRIPTOMIC EFFECTS OF CHRONIC ALCOHOL EXPOSURE AND CANCER RISK: A TRANSLATIONAL STUDY

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Introduction: Ethanol is a carcinogen, but little is known about its role in cross-generational cancer risk. Previously, we found altered methylation of cancer-related genes *HRAS* and *TP53* in humans with multiplex alcohol dependence family history. We and others have also found in rodents that preconception chronic ethanol exposure results in offspring epigenetic alterations. However, these studies focused on paternal, not maternal or biparental preconception ethanol (PPE, MPE, and BPE, respectively) exposure. We conducted a translational study in mouse and human to characterize the cross-generational PPE, MPE, and BPE transcriptomes, focusing on immune- and cancer-related genes.

Hypothesis: PPE, MPE, and BPE result in unique, sexually dimorphic alterations in the offspring immune- and cancer-related transcriptome.

Methods: We exposed adult male and female C57BL/6J mice to chronic intermittent ethanol vapor– two bottle choice to induce ethanol dependence and measure drinking escalation. We bred these mice to produce offspring with PPE, MPE, and BPE exposure and controls (n=7-8/sex/group). We collected whole blood from adult, ethanol-naïve offspring for 3'Tag-based RNA sequencing (3'Tag-Seq). Brain punches from the medial prefrontal cortex and central nucleus of the amygdala are currently being processed for 3'Tag-Seq. We also performed 3'Tag-Seq on frozen lymphocytes from third-generation participants (n=72) from families at high and low risk for alcohol use disorder (AUD). Samples were collected in childhood before significant substance use, and analyses controlled for maternal prenatal substance use.

Results: In mouse, PPE, MPE, and BPE resulted in unique patterns of gene expression with strong sex differences. Differentially expressed genes (DEGs) shared between sexes within groups had opposing expression patterns. Less dramatic contrasts in shared DEG expression emerged within the sexes across groups. Ingenuity Pathway Analysis revealed enriched pathways related to innate immunity, growth, and metabolism across groups, with unique group terms; Notably, BPE resulted in the most cancer-related terms. Analysis of human data is ongoing; However, we found significant ($p<0.05$) overlap in pooled DEGs between species.

Conclusions: Chronic preconception ethanol exposure results in sexually dimorphic offspring gene expression, with distinct effects depending on the exposed parent. Immune- and cancer-related pathways are notably altered. Significant overlap of mouse and human DEGs bolsters the translatability of mouse models of preconception ethanol exposure.

Significance: This is the first study to directly compare PPE, MPE, and BPE outcomes. This work will uncover novel biomarkers of alcohol-induced disease risk across generations that could lead to novel therapeutic targets for AUD and comorbid diseases such as cancer.

Research/Grant Support: We gratefully acknowledge the award "Cross-generational effects of pre-conception alcohol use and cancer" from Bridging Connections in Addiction Research and the Pittsburgh Foundation (PI: Shirley Hill, PhD; Co-PI: Gregg Homanics, PhD; Co-I: Sean Farris, PhD) as well as NIAAA grants AA020889 (MPI: Sean Farris, PhD & Gregg Homanics, PhD), AA030257 (PI: Sean Farris, PhD), and AA031168 (PI: Rachel Rice, BS).

Abstract 14

COGNITIVE PERFORMANCE AND PAIN PERCEPTION WITH PROPOFOL, DEXMEDETOMIDINE, AND FENTANYL IN HEALTHY YOUNG ADULTS

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Introduction: This comparative analysis aims to investigate the differential effects of propofol, dexmedetomidine, and fentanyl on attention, memory, and pain perception in healthy young adults.

Hypothesis: We hypothesize that memory performance will be significantly reduced by propofol, and that reported pain will be significantly reduced by fentanyl.

Methods: Behavioral data was collected from volunteers under age 40 in a randomized single-blind crossover study comparing low doses of propofol (n=19), dexmedetomidine (n=25), and fentanyl (n=25) to saline. An effect-site concentration was targeted (propofol 1.0 mcg/ml, dexmedetomidine 0.15 ng/ml, or fentanyl 0.9 ng/ml). An electric nerve stimulator delivered a series of painful electric shocks (set in advance to a current level rated 7/10 intensity) and these were rated for intensity and unpleasantness. An image recognition task, free from shocks, was performed by showing a series of complex geometric colored shapes presented every 5 s. Attention was assessed with a 3-back task, and long-term memory was assessed by identifying new or old shapes presented > 60 s later. Performance was determined using the signal detection metric d´ compared across drug condition. Means and standard deviations were calculated to describe data. Mixed models were fit to test differences between drug groups.

Results: Preliminary analysis shows d´ averages for the 3-back task were saline= 2.6 propofol= 2.1, dexmedetomidine= 1.6, fentanyl= 2.5 [significant differences found between saline and dexmedetomidine (p-value<0.001)]. Average d´ for long-term memory were saline= 1.9, propofol=1.2, dexmedetomidine= 1.4, and fentanyl=2.0 [significant differences found between saline and dexmedetomidine (p-value=0.004) and saline and propofol (p-value<0.001)]. Average pain intensity scores were saline= 6.4, propofol=5.9, dexmedetomidine=6.2, fentanyl= 5.8 [significant differences found between saline and propofol (p-value=0.017) and saline and fentanyl (p-value=0.013)]. Average pain unpleasantness scores were saline=5.7, propofol=4.7, dexmedetomidine=5.5, fentanyl=4.8 [significant differences found between saline and propofol (p-value=0.023) and saline and fentanyl (p-value=0.042)].

Conclusions: These results suggest that dexmedetomidine most affected attention, while propofol most affected memory. Propofol was most effective at reducing pain perception, both intensity and unpleasantness.

Significance: In addition to added to our basic knowledge of cognitive effects of specific anesthetics, these findings could help guide anesthetic selection in settings where cognitive performance is intended to be retained, while alleviating pain (e.g. awake craniotomy).

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Abstract 15

THE DIURNAL DIVIDE: INVESTIGATING THE ASSOCIATION BETWEEN TIME OF INTUBATION AND OVERALL MORTALITY RATES IN THE INTENSIVE CARE UNIT

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Introduction: In the critical care setting, the decision to intubate requires a nuanced understanding of patient-specific and systemic factors, as well as a careful assessment of the risks vs benefits. There are a multitude of factors that can influence overall outcomes of an intubation procedure, including both intrinsic factors like the patient's medical history and current clinical course, as well as extrinsic factors like the availability of medical resources or location of procedure. The diurnal impact on overall outcomes has been demonstrated repeatedly across several domains within healthcare; including the composition of multidisciplinary care teams, the efficacy of rapid response systems, outcomes of ICU procedures, and worsened outcomes associated with overnight surgery. This demonstrates the need to determine whether temporal factors should be included in the clinical decision-making process for high-stakes interventions like intubation.

Hypothesis: Patients intubated during nighttime hours in the ICU exhibit a higher 30-day mortality rate compared to those intubated during daytime hours.

Methods: The study leveraged the MIMIC-IV database (version 2.2), a comprehensive repository of electronic health records from the Beth Israel Deaconess Medical Center. Data aggregation and analysis were facilitated through Google BigQuery and Python's Pandas library. Our statistical analysis framework included variable classification, survival analysis through Kaplan-Meier curves, comparative analysis using Chi-squared and Fisher's exact tests, odds ratio calculation for mortality outcomes, Welch's t-test for continuous variable comparison, logistic regression for survival outcome predictors, and Variance Inflation Factor (VIF) testing to assess multicollinearity and to demonstrate the level of independence between various factors.

Results: Of the 7,999 intubation events analyzed 5,362 occurred during the day (0700-1859) and 2,637 at night (1900-0659). There was a significant increase in 30-day mortality rates for nighttime intubations, with an odds ratio of 1.58 (95% CI [1.43-1.75]), z statistic of 8.712, and a significance level of $P < 0.0001$. Kaplan-Meier survival curves further supported these findings. A logistic regression model demonstrated that the time of intubation was no less predictive of overall outcome than several other markers of clinical condition (MELD, SOFA, APS3, SIRS scores). A variance inflation factor of <2 for each variable demonstrates limited multicollinearity.

Conclusions: Patients intubated overnight in the ICU had a higher 30 day mortality rate compared to patients intubated during the day. Nocturnal intubation was identified as an independent factor associated with increased overall mortality.

Significance: The observed disparity in mortality rates between daytime and nighttime intubations within the ICU sheds light on the influence of procedural timing and signals a pressing need for deeper investigation. Identifying specific factors that may underlie the increased mortality risk associated with nocturnal intubations could offer valuable insights into potential areas for intervention. Such research would aid development of strategies to help mitigate factors increasing overall mortality, ultimately enhancing the quality of care in critical settings. The study contributes to our understanding of diurnal influences on patient care while serving as a call to action for further analyses aimed at guiding medical decision making in the ICU to improve overall outcomes.

Research/Grant Support: None

Abstract 16

UNDERSTANDING THE ROLE OF CENTRAL MECHANISMS IN PAIN RELIEF FOLLOWING PERIPHERAL NERVE BLOCKS: A PILOT STUDY IN PATIENTS WITH CHRONIC LOW BACK PAIN

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Introduction: Lumbar medial branch blocks (MBB) are nerve blocks that involve a small amount of local anesthetic to block the medial branch nerves that supply the facet joints[1]. Even among patients with pain relief following a lumbar MBB, there is considerable variation in the trajectory of pain intensity over time. Offset analgesia is a sensory phenomenon which is likely mediated through descending inhibitory pathways in the central nervous system[2]. The sensory phenomenon of offset analgesia may contribute to the rapid reduction of low back pain in some individuals following the lumbar MBB.

Hypothesis: We hypothesize that individuals with a relatively high degree of offset analgesia will experience more rapid pain relief following their lumbar MBBs.

Methods: This is an ongoing mechanistic, prospective, observational study with one main study visit and one follow-up phone call. We are recruiting patients ≥ 18 years who have had daily chronic low back pain for ≥ 3 months. A sample of 30 will be powered to detect a moderate correlation between offset analgesia and change in low back pain (pre-post block), calculated with an alpha = 0.05, beta = 0.2 and r = 0.5 All data will be analyzed using Stata (v18) and MATLAB.

Results: Thus far, this study has collected data from four participants (two males and two females) with ages ranging from 48-71. Patients experienced a rapid decrease in pain immediately following the block as patient rating of procedural pain yielded a median score of 2 and a range of 2. Other categories analyzed included both minimum pain rating after the block over 24 hours (M=1, R=1) as well as maximum pain relief after the block over 24 hours (M=90%, R=20%).

Conclusions: Importantly, this study is still ongoing and actively recruiting participants. All four of the participants have interestingly reported a maximal pain rating of 1 in mere seconds of administration of the local anesthetic highlighting the importance of this research's aim to differentiate between central mechanisms of pain relief and pharmacologically induced pain relief.

Significance: This research is potentially relevant in the context of false positive lumbar medial branch blocks where the patient reports a positive pain relief, but the pain relief is not stemming from the pharmacological agent. Understanding the role of endogenous mechanisms in the presence of pain relief following a lumbar medial branch block could potentially decrease the rate of false positive lumbar MBBs.

Research/Grant Support: This study was supported by the University of Pittsburgh School of Medicine funds (DSRP, Department of Anesthesiology and Perioperative Medicine) as well as funds from the Foundation Anesthesia Education and Research (MSARF).

DEPARTMENT OF CRITICAL CARE MEDICINE

Oral Abstract O2

BLOOD-BASED BRAIN INJURY BIOMARKER LEVELS ARE ASSOCIATED WITH OUTCOME ACROSS ARREST LOCATION: A PERSONALIZING OUTCOMES AFTER CHILD CARDIAC ARREST SECONDARY ANALYSIS

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Introduction: The Personalizing Outcomes after Child Cardiac Arrest (POCCA) study showed that early blood-based brain injury biomarkers discriminated between favorable and unfavorable outcomes at 1 year. Biomarker performance by location of cardiac arrest (CA) is unknown.

Hypothesis: We hypothesize that patient and CA characteristics, outcomes, and biomarker prognostic accuracy will differ by location of CA.

Methods: This is a secondary analysis of POCCA, which evaluated children <18 years with pediatric intensive care unit admission after an in- (IH) or out-of-hospital (OOH) CA between 2017 and 2020 at 14 US centers. Patient and CA characteristics, Pediatric Index of Mortality-3 (PIM-3) scores were collected from the medical record. Glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal esterase L1 (UCH-L1), neurofilament light (NfL), and tau proteins were measured in blood samples on days 1 to 3 post-CA. The primary outcome was favorable (Vineland Adaptive Behavior Scale [VABS] ≥ 70) or unfavorable (death or survival with a VABS < 70) adaptive behavior at 1 year. Multivariate regression and area under the receive operating characteristic curve (AUROC) analyses were performed to determine the association of each biomarker with unfavorable outcome on days 1 to 3 by location of CA.

Results: Of 163 children, 90 (55%) had an OOH CA and 73 (45%) had an IH CA. Patients with OOH CA tended to be older (median [IQR], 35.5 [13.0-143.0] mo) vs IH CA (8.0 [2.0-42.0] mo). Sex, race, and ethnicity did not differ by location of CA. 58% of patients with OOH CA had an unfavorable outcome, vs 25% with IH CA. Patients with OOH CA had more asphyxia vs. cardiac etiology (83% vs 62%), longer duration of CPR (9.0 [3.5-21.5] min vs 6.0 [2-15.5] min), and more defibrillation (25.0% vs 10.5%) vs those with IH CA. Patients with an OOH CA had higher PIM-3 scores (18.5 [14.5-31.8]) vs those with an IH CA (14.2 [3.2-25.1]). All p-values <0.05. A total of 120 children with primary outcome data were available. 35/60 (58.3%) of children with an OOH CA vs 15/60 (25%) of children with an IH CA had an unfavorable outcome at 1 year. In both OOH and IH cohorts, levels of all 4 biomarkers (except GFAP at 24h for patients with IH CA) were increased in children with an unfavorable vs favorable outcome at 1 year. Univariate biomarker AUROCs for 1 year outcome did not differ by location of CA at any timepoint.

Conclusions: Children with OOH CA were older, were more likely to suffer from an asphyxia arrest, and had more unfavorable outcomes at 1 year than patients with an IH CA. Blood-based injury markers were associated with an unfavorable outcome at 1 year after pediatric CA, with no impact by location of arrest, strengthening the generalizability of biomarker performance found in the POCCA trial across a heterogenous cohort of children.

Significance: Blood-based brain-specific biomarkers may be helpful tools to aid clinicians and families to estimate long-term outcomes early after both IH and OOH pediatric CA.

Grant support: R01NS096714 (PI: Ericka L Fink, MD)

Abstract 17

METABOLOMIC CHANGES ASSOCIATED WITH ACETATE AND BUTYRATE SUPPLEMENTATION IN ADULT MALE MICE EXPOSED TO CONTROLLED CORTICAL IMPACT

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Introduction: Short chain fatty acids (SCFA) are produced by microbial fermentation of dietary fiber in the gut and can serve as energy substrate for glial cells and enter the TCA cycle. In the controlled cortical impact (CCI) model, SCFAs are reduced after CCI and supplementation of SCFAs is protective. We hypothesized that SCFAs may enter the TCA cycle after CCI and increase production of anti-inflammatory TCA metabolites itaconate and 2-hydroxyglutarate.

Hypothesis: Short chain fatty acid supplementation will increase itaconate through the citric acid (TCA) cycle.

Methods: TBI was performed in adult male C57BL6/J mice using the controlled cortical impact (CCI) model (6m/s, 2.0 mm depth). Sham mice received anesthesia and skin incision. Mice were randomized to short chain fatty acid supplementation with 0.067M of sodium acetate and 0.047M sodium butyrate prior to CCI and continued for up to 28 days after CCI/sham. Water was changed twice weekly. Mice (n=3/group/timepoint) were sacrificed at day 7 after injury. Pericontusional tissue was sent for analysis of TCA metabolites by liquid chromatography-mass spectrometry (LCMS) evaluation.

Results: In this exploratory study, CCI and SCFA supplementation were associated with multiple changes in TCA metabolites 7 days after injury. Itaconate level was decreased in pericontusional tissue after CCI. SCFA supplementation restored itaconate levels after CCI to sham levels. In addition, acetate supplementation with or without CCI increased production of the anti-inflammatory metabolite 2-hydroxyglutarate.

Conclusions: The concentration of TCA metabolites is altered in pericontusional tissue after CCI. SCFA supplementation can restore the level of the anti-inflammatory metabolites itaconate and 2-hydroxyglutarate. Further studies are needed to confirm these results, delineate the pathway implications, and identify whether this impacts neurologic outcomes.

Significance: Identification of beneficial adjunctive therapies in patients with TBI will improve patient outcomes.

Research/Grant Support: R01 NS127372

Abstract 18

ASSOCIATION OF HYPERTONIC SALINE TREATMENT WITH CHANGE IN CEREBRAL OXYGEN DELIVERY AFTER CARDIAC ARREST

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Introduction: Impaired cerebral oxygen extraction due to perivascular edema after cardiac arrest can increase jugular venous oxygen saturation (SjvO2), and treatment with hypertonic saline (HTS) may reduce this edema and thus the barrier to oxygen diffusion. Elevated SjvO2 may also occur when cerebral metabolic rate decreases due to mitochondrial failure. Electroencephalography (EEG) may differentiate between these etiologies of elevated SjvO2 and therefore could be used to identify patients for whom HTS treatment will improve oxygen extraction.

Hypothesis: We hypothesized post-arrest patients with elevated SjvO2 would have improved oxygen extraction after treatment with HTS. Secondarily, we hypothesized qualitative EEG could be used to predict treatment responsiveness.

Methods: We conducted a single center, retrospective observational cohort study including comatose survivors of cardiac arrest who had SjvO2 > 75%, were treated with HTS, and were monitored with EEG. Our primary outcome was SjvO2 and our primary exposure was HTS treatment status (pre-HTS vs post-HTS). We used mixed effects multivariable linear regression to test the association of HTS with SjvO2, adjusting for mean arterial pressure and partial pressure of both oxygen and carbon dioxide. We classified pre-treatment EEG patterns as benign or indicative of potential metabolic failure and tested for an interaction of EEG with HTS.

Results: We included 21 patients and 28 HTS treatments. We found an independent association of HTS with decreased SjvO2 (β = -3.8%; 95% CI, -6.4 to -1.2; p = 0.004). There was no interaction between pre-treatment EEG and HTS predicting SjvO2.

Conclusions: There was a decrease in SjvO2 following treatment with HTS, suggesting diffusion limited oxygen extraction secondary to modifiable perivascular edema. Pre-treatment EEG did not moderate the effect of HTS on SjvO2.

Significance: Mechanisms of secondary brain injury after cardiac arrest vary among patients, making a precision approach to treatment essential. We demonstrated that impaired oxygen extraction is a physiologically modifiable process but did not identify evidence to support the use of EEG to guide selection for treatment.

Abstract 19

SEIZURE PROPHYLAXIS IN YOUNG CHILDREN WITH ABUSIVE HEAD TRAUMA OR ACCIDENTAL TRAUMATIC BRAIN INJURY

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Introduction: Seizures occur frequently in patients with abusive head trauma (AHT). There are limited data on effectiveness of levetiracetam and fosphenytoin to prevent early post traumatic seizures.

Hypothesis: Fosphenytoin and levetiracetam will have equal efficacy in preventing early post traumatic seizures.

Methods: We performed a retrospective cohort study of children <3 years old admitted with AHT or accidental traumatic brain injury (aTBI) to the Pediatric Intensive Care Unit (PICU) at a Level 1 trauma center from 2011-2020. Our institutional guideline was for children with severe TBI to receive anti-epileptic drug (AED) prophylaxis. AEDs for mild or moderate TBI were used at the discretion of the treating physicians. Patient data were abstracted from the electronic health record. AHT was determined by the Child Protection Team; 'highly concerning' or 'diagnostic' injuries were included. Nonparametric tests were used to compare AED prophylaxis and TBI etiology.

Results: 693 patients (245 with AHT, 448 with aTBI) were included of whom 121 (17%) received fosphenytoin, 133 (19%) received levetiracetam, and 439 (63%) did not receive AED prophylaxis. Children with AHT were more likely to receive AED prophylaxis (AHT 59% vs aTBI 41%; $p<0.001$). Children with AHT were more likely to have ≥ 1 seizure during hospitalization vs. children with aTBI: AHT 66/245 [25%] vs aTBI 19/448 [4%], $p<0.001$. A difference in seizure frequency was observed between children that received fosphenytoin (43/121 [36%]), levetiracetam (24/133 [18%]), or no AED (13/439 [3%]; $p<0.001$). Multi-variable logistic regression controlling for mechanism and severity of injury (injury severity score (ISS), Glasgow Coma Score (GCS)) revealed that fosphenytoin (11.9 odds ratio [5.7, 26.4 95% confidence interval]), and levetiracetam (6.9 [5.7, 26.4]) were associated with seizure during admission. In the AHT patients, a multi-variable logistic regression controlling for severity of injury demonstrated that fosphenytoin (4.8 [2.4, 9.5]) was associated with seizure during admission while levetiracetam was not.

Conclusions: In children <3 years old with TBI admitted to our PICU, fosphenytoin prophylaxis had a higher risk of post-traumatic seizure than levetiracetam when controlling for mechanism and severity of injury.

Significance: Our study suggests a possible advantage to the use of levetiracetam in AHT seizure prophylaxis.

Grant Support: NICHD 5T32HD040686-20

Abstract 20

ABNORMAL POLYUNSATURATED FATTY ACID METABOLISM IS ASSOCIATED WITH A PHENOTYPE WITH MARKED SEPSIS-ASSOCIATED ACUTE KIDNEY INJURY IN PEDIATRIC SEPSIS

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Introduction: Pediatric sepsis has overall lower mortality than adult patients, but still a sizeable proportion of children die with progressive multiorgan failure. Preclinical and observational evidence show that modulation of linoleic acid (LA) metabolism, the major omega-6 polyunsaturated fatty acid in diet, influence inflammation. The first step in its metabolism and the rate limiting enzyme is delta-6-desaturase (D6D). LA metabolism has not yet been studied in human sepsis.
Sepsis-associated acute kidney injury (AKI) is characterized by abnormal energy metabolism, with animal models suggesting that functional recovery and survival is at least in part dependent on restoring the capacity of renal tubular epithelial cells to use fatty acid oxidation.

Hypothesis: We hypothesize that markers of higher exposure to LA and LA-derived oxylipins will be increased in pediatric sepsis phenotype D and will be associated with organ dysfunction.

Methods: We utilized ultra-performance liquid chromatography to analyze untargeted metabolomics in a cohort of 107 children with sepsis. We categorized sepsis phenotypes as previously described into phenotypes A-D. We built a heat map featuring comparisons between pairs of phenotypes. For this study we focused on the polyunsaturated fatty acid metabolic pathways.

Results: Phenotype D group showed higher incidence of AKI with creatinine increase between 2.60 and 3.47-fold compared with other phenotypes at 24h of admission to intensive care unit ($p < 0.05$). We found that LA was not significantly different in phenotype D compared with others. Conversely, arachidonic acid (AA) was lower in phenotype D compared with phenotypes A-C, with statistically significant difference when compared with phenotype C, along with lower AA metabolites such as 5-HETE. Metabolites of LA, both via non-enzymatic pathway (13-HODE, 9-HODE), and through CYP450 (12,13-DiHOME, 9,10-DiHOME) were significantly increased in phenotype D.

Conclusions: AKI is markedly increased in patients with pediatric sepsis phenotype D. While phenotype D showed no significant changes in LA levels, LA inflammatory metabolites were increased, and AA was decreased along with its metabolites. In summary, children with sepsis with phenotype D, a group with increase in AKI and mortality, showed polyunsaturated fatty acid metabolism abnormalities suggesting hyperactivation of an inflammatory pathway of LA metabolites independent of AA.

Significance: This constellation of results could be explained by changes in enzymes that metabolize LA to AA or by different dietary intake. Future studies should include analysis of D6D enzyme and relevant genotypes.

Research/Grant Support: NIH T32 (Saraiva IE); NIH GM108618 (Carcillo JA).

Abstract 21

ASSOCIATION BETWEEN NURSING WORKFORCE TURNOVER AND AGENCY USE ON PEDIATRIC INTENSIVE CARE UNIT CENTRAL LINE ASSOCIATED BLOOD STREAM INFECTIONS

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Introduction: During the COVID-19 pandemic, children's hospitals experienced staffing strain secondary to varied patient volumes coupled with increased staff turnover, including nurses.
Many hospitals utilized temporary agency workers to fill vacant positions. This study evaluated whether the proportion of nursing (RN) turnover or agency staffing in pediatric intensive care units (PICUs) were associated with mortality or complications such as patient safety and quality measures including central line associated blood stream infections (CLABSI).

Hypothesis: Did the use of agency staffing or nurse turnover in pediatric ICUs affect patient centered outcomes during the COVID-19 pandemic?

Methods: This IRB-exempt, retrospective cohort study linked data from the Pediatric Health Information Systems (PHIS) and PROSPECT Hospital Essentials (PROSPECT) databases from January 2019 to December 2022. Demographics, a severity of illness index, and outcomes of mortality and author derived ICU complications were extracted for all PICU admissions from PHIS to hospitals represented in both databases. The annual proportion of unit-level PICU agency staffing and PICU nurse turnover were extracted from PROSPECT. Data were analyzed by year with negative binomial regression with log-transformed offset terms for admissions (mortality model) and patient days (ICU complications models). Univariate and multivariate analyses controlling for a unit level random effect and severity of illness were completed using R v4.3.2.

Results: We included 222,154 admissions to PICUs from 21 hospitals. No association was found with percent agency or nurse turnover and mortality during the study years. Increased proportion of agency staffing and RN turnover were significantly associated with ICU complications in 2021 and 2022, respectively, but not 2019 or 2020. These associations remained significant after adjusting for illness severity and a random effect for hospital unit (all $P \leq 0.02$), such that a PICU with 10% agency staff per year was predicted to have 142 more ICU complications in 2021 compared to a unit with no agency staff. A PICU with 10% greater-than- average RN turnover was predicted to have 25 more ICU complications in 2022, compared to a PICU with average RN turnover for each year. In subgroup analysis, CLABSIs were notably associated with increased agency staffing during 2021 ($P=0.01$)

Conclusion: In this multicenter study of United States PICUs, mortality was not associated with RN turnover or percent agency use during the study. ICU complications, including CLABSIs, were significantly associated with the proportion of PICU agency staff and RN turnover in the years 2021 and 2022, respectively. More work is needed, including evaluating RN workload and PICU census, to better understand this relationship and guide RN staffing policies.

Significance: This data could assist hospital administrators in determining the use of agency staffing and RN staffing policies during periods of high turnover and resource limitations to prevent iatrogenic complications.

Research/Grant Support: NIH 5T32HD040686-23 (PI: Kochanek, Clark)

DEPARTMENT OF EMERGENCY MEDICINE

Oral Abstract O3

NALOXONE ADMINISTRATION IS ASSOCIATED WITH IMPROVED SURVIVAL AND ROSC IN PEA OUT-OF-HOSPITAL ARRESTS

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Introduction: The frequency of opioid-related out-of-hospital cardiac arrest (OHCA) is growing in the United States despite increased awareness of the epidemic. Several works have attempted to highlight identifying factors in these arrests, however no practical clinical tools have yet to be made. Thus, many OHCA cases due to opioid overdose go unidentified. In this work, we sought to compare rates of survival and ROSC between OHCA cases receiving any naloxone versus those that did not.

Hypothesis: Patients receiving naloxone during prehospital resuscitation have improved rates of ROSC and survival to hospital discharge compared to patients not receiving naloxone.

Methods: We utilized EMS records from a large, retrospective electronic health record database spanning over 1,300 agencies across the US between 2019-2020. Cases were stratified by presenting rhythm (VF/VT, PEA, asystole) for analysis. The outcomes of survival to hospital discharge and prehospital ROSC were compared by naloxone use status using propensity score matching and logistic regressions controlling for many factors known to predict OHCA outcomes.

Results: We analyzed 29,821 records, where 4,098 (13.7%) received naloxone but 1,304 (4.37%) were identified as having the etiology of OHCA as drug overdose. Rates of survival to hospital discharge was 8.04% and any prehospital ROSC was 20.8% in cases before matching. After propensity score matching, survival and ROSC were higher in the naloxone group for cases presenting in PEA (OR survival: 1.27-2.35, $p<0.001$; OR ROSC: 1.07-1.70, $p<0.01$). There were no differences in either outcome for patients presenting in VF/VT or asystole.

Conclusions: Naloxone administration was associated with survival and ROSC in OHCA cases presenting with PEA.

Significance: These findings suggest that empiric naloxone administration may improve outcomes for patients presenting with PEA arrests. Findings from this retrospective study should be corroborated with prospective, randomized work.

Research/Grant Support: n/a

Abstract 22

TIME-DEPENDENT ASSOCIATION OF GREY-WHITE RATIO ON EARLY BRAIN CT WITH OUTCOMES AFTER CARDIAC ARREST

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Introduction: Cerebral edema can be quantified by calculating the ratio of grey matter to white matter radiodensity (GWR). Overall, severe edema at any point is associated with poor outcomes after cardiac arrest, but the temporal dynamics of post-arrest edema formation are poorly characterized.

Hypothesis: We hypothesized that sensitivity and false positive rate of GWR predicting mortality change over time.

Methods: We performed a retrospective cohort study including comatose survivors of cardiac arrest treated at our hospital between January 2010 and December 2023 who had a brain CT performed within 24 hours of arrest. We divided patients into subgroups based on the hours from arrest to CT, then evaluated the association of GWR < 1.10 and GWR < 1.20 with mortality. Then, we identified the optimal threshold at which GWR predicted mortality to test for a non-linear association of GWR with mortality over time.

Results: We included 2,204 patients. Mean age was 58 (SD 16) years, 2,001 (91%) arrested out-of-hospital, and 346 (25%) survived to hospital discharge. Sensitivity of GWR < 1.10 and GWR < 1.20 for predicting mortality increased over the first four hours post-arrest, reaching a maximum of 25% at five hours. The false positive rate for GWR predicting mortality was <1% at all timepoints and both thresholds. The optimal threshold for GWR predicting mortality did not substantially change over time.

Conclusions: Sensitivity of early GWR predicting in-hospital mortality after resuscitation from cardiac arrest varies over the initial post-arrest period while maintaining a false positive rate of <1%.

Significance: Regardless of timing, severe reduction of GWR on brain CT in the first 24 hours after resuscitation is a highly specific marker of poor outcome, and the sensitivity at multiple cutoffs is low in the first three to four hours.

Research/Grant Support: NINDS R01NS124642 (PI: Jonathan Elmer, MD, MS) & NINDS R01NS119825 (PIs: Karen Hirsch, MD & Jonathan Elmer, MD, MS).

Abstract 23

PRECISION IDENTIFICATION OF BACTERIAL PULMONARY PATHOGENS USING NANOPORE SEQUENCING

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Introduction: Antibiotic resistance resulting from the overuse of antibiotics is a global health crisis with the potential to cause millions of deaths in the future. As bacteria continue to adapt and evolve, the effectiveness of modern antibiotics decreases. Plate-based microbial culture is commonly used but can take between 48-72 hours and has many limitations. Nanopore sequencing is a relatively new technology that can be used to rapidly provide pathological results which could help tailor specific antibiotics for patient treatment. We aim to investigate the comparative yield and agreement statistics between culture and Nanopore sequencing technology, and to characterize microbiome differences between post-cardiac arrest patients with and without pneumonia.

Hypothesis: We hypothesize that Nanopore sequencing can identify similar pathogens faster than standard microbiologic culture, as well as clinically important culture-negative pathogens, consistent with pneumonia.

Methods: This research project is a quantitative primary data analysis of post-cardiac arrest patients (preliminary data available for 101 subjects out of 212 enrolled) presenting in the UPMC Presbyterian Hospital ED. Bronchoalveolar lavage samples collected from these patients are processed and sequenced using the Nanopore MinION sequencer. The raw sequence data is then processed using a bioinformatics pipeline (EPI2ME, Nanopore Technologies) to prepare for analysis. Pneumonia diagnosis is adjudicated using a rigorous set of criteria adapted from the Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Thoracic Society guidelines for pneumonia diagnosis using medical record data. Percent positive agreement, percent negative agreement, and McNemar's test were performed to compare sequencing to culture results.

Results: This represents data from 101 subjects: average age of 62 years [SD=14.2], 39% female, 13% black, 77% Caucasian, 10% other race, 70% received antibiotics within the first 3 days of admission. Only 32% of subjects were diagnosed with early onset pneumonia. Nanopore sequencing technology (NST) and culture methods showed a percent positive agreement of 65% and a percent negative agreement of 33%, with a significant concordance discrepancy of -0.17 [95% CI: -0.30, -0.04; p = 0.011] by McNemar's test. NST identified potentially clinically significant culture-negative pathogens in 12 of 101 subjects and provided results approximately 12 hours post-sample acquisition, while culture results were not available before 24 hours. Preliminary beta diversity tests were performed on the first 92 subjects. Bray-Curtis PERMANOVA showed F=1.43 [p=0.05].

Conclusions: Pending completion of data analysis for the cohort, this study will offer insights into the use of Nanopore sequencing for rapid pulmonary bacterial pathogen identification in critically ill intubated patients. Our preliminary results demonstrate that Nanopore sequencing can identify pathogens similar to standard bacterial culture, as well as identify clinically important culture-negative pathogens. We noted differences in microbial composition between patients with and without pneumonia. Moreover, this research provides the proof-of-concept and foundational groundwork necessary for future studies that investigate the clinical use of Nanopore technology.

Significance: This study represents a step toward the application of Nanopore sequencing in real-time pathogen detection, paving the way for broader clinical adoption in the future.

Research /Grant Support: Zoll Foundation and Society for Academic Emergency Medicine Foundation (PI: Alexandra Weissman, MD MS MPH)

Abstract 24

WHAT'S WRONG? CLINICAL PROGNOSTICATION VIA PREHOSPITAL CHIEF COMPLAINTS

Sedor-Schiffhauer Z,[1] Weidman A,[1] Zikmund C,[1] Salcido D,[1] Weiss L,[1] Guyette F,[1] Pinsky MR,[2] Poropatich R[3]

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Introduction: A medic's ability to rapidly triage injured patients is paramount to providing efficient and effective care. The chief complaint, a concise description of the patient's most pressing medical concern, is often ascertained and recorded in the first moments of an interaction. While further information and workup is necessary for comprehensive patient care, analysis of the initial chief complaint text could be beneficial in rapidly triaging patients.

Hypothesis: Chief complaint text can be analyzed to help predict patient outcome parameters including necessity of lifesaving intervention (LSI) or mortality.

Methods: Records of 11,781 prehospital patients (mean age = 53.04, 64% men, 73% classified as trauma) transported via the STAT MedEvac air medical service from 2012-2021 were obtained for this study. These records yielded chief complaints and whether the patient required a LSI before or during transport to the hospital. Records from the UPMC Health System yielded mortality status for these same patients. Chief complaints were filtered for specific words or phrases (tokens) via manual misspelling correction (e.g., 'taruma' was changed to 'trauma'), manual medical synonym and abbreviation condensing ('vf' was changed to 'ventricular fibrillation'), and stop word removal/lemmatization, via the Natural Language Toolkit in Python. For the patients whose chief complaint was analyzed in this study, LSI rate was 31.6% and mortality rate was 7.6%.

Results: For 11,771 chief complaints, 1,896 tokens were accounted for in the chief complaint text by including only tokens found in at least 100 patients. The patients with the highest rate of LSI were those with tokens such as 'airway' (95.2%), 'cardiac arrest' (92.6%), and 'unresponsive' (86.3%). Those three tokens also accounted for the top three highest mortality rates at 25.6%, 53.1%, and 54.0%, respectively. Alternatively, the lowest prehospital LSI rate was related to stroke-like symptoms such as 'weakness face' (3.8%), 'face droop' (6.7%), and 'slurred speech' (7.4%). Many of the lowest mortality rates were associated with anatomical landmarks such as 'shoulder' (0.3%) and hip (0.3%).

Conclusions: Certain language markers can be utilized to forecast whether a patient will need LSI or their mortality rate based on the prehospital chief complaint. This can aid in more efficient triage in an emergency setting. Future steps will involve expanding predictive models to incorporate machine learning and natural language processing.

Significance: Identifying any early prognostic indicator of mortality or the need for LSI in the prehospital setting will promote more efficient and accurate triage of patients, and chief complaint stands as one of the very earliest portions of any medical interaction.

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Abstract 25

IMPACT OF COMA DURATION ON NEUROLOGIC OUTCOMES AT DISCHARGE AND LONG-TERM SURVIVAL AFTER CARDIAC ARREST

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Introduction: For many survivors of cardiac arrest, awakening from coma is a crucial step in recovery, though time to awakening can vary from minutes to weeks. Few data describe the impact coma duration has on long-term outcomes. The objective of this study is to test the association of time to awakening with long-term survival.

Hypothesis: We hypothesized that among patients who did not immediately awaken from cardiac arrest, coma duration was not independently associated with long-term survival.

Methods: In this retrospective cohort study, we identified patients resuscitated from cardiac arrest who were unresponsive to verbal commands on initial evaluation at our regional academic medical center. We excluded patients who never awoke before death or discharge. We prospectively recorded demographics and clinical characteristics, the calendar day each patient first followed verbal commands, and Cerebral Performance Category (CPC) at discharge in our registry. We used a Kaplan-Meier function to describe long-term survival for all patients included in the analysis. Finally, we used multivariable Cox regression to test the association of coma duration with survival, adjusting for age, arrest location, arrest rhythm, Charlson Comorbidity Index (CCI), and CPC.

Results: We analyzed 978 subjects and found that median time to awakening was 2 (IQR 1-4) days. We observed that the proportion of good neurologic outcome (CPC 1-2) at hospital discharge decreased as coma duration increased. In our analysis of long-term survival after hospital discharge, we observed 742 subjects for 3136 total person-years with an incidence of death of 68 per 1000 person-years. Finally, using a multivariable Cox proportional hazard model, we found that coma duration was not associated with hazard of death after hospital discharge (HR 1.00, 95%CI 0.97-1.03) after adjusting for age, arrest rhythm, CCI, and CPC at discharge.

Conclusions: In comatose patients resuscitated from cardiac arrest, longer coma duration is associated with lower proportion of good neurologic outcome at hospital discharge, but is not independently associated with long-term survival after hospital discharge.

Significance: Prolonged coma after resuscitation from cardiac arrest can often be discouraging for care teams and patient families alike, but our study suggests that prolonged time to awakening is not associated with an increase hazard of death after hospital discharge.

Research/Grant Support: This research is supported by a T-32 institutional training grant (5T32HL134615) from the National Heart, Lung, and Blood Institute.

Abstract 26

PREDICTING CORE TEMPERATURE CHANGES USING METABOLIC RATE AND TOTAL HEAT BALANCE

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Introduction: Measuring core body temperature requires invasive equipment that is impractical for long-duration spaceflight. We set out to develop noninvasive methods to estimate changes in core body temperature for monitoring health. Core body temperature is an index of the heat content of the head and torso, and heat content is determined by the balance of heat production (metabolic rate) and heat loss (heat flux).

Hypothesis: We hypothesize that total heat balance measured using heat flux sensors at key body sites along and metabolic rate can predict core temperature changes.

Methods: We conducted a laboratory study in healthy volunteers in which we placed heat flux sensors on the forehead, upper arm, anterior abdominal wall, and above the knee. We cooled participants with gel-adhesive circulating water pads. We measured energy expenditure in watts (W) by indirect calorimetry and gastrointestinal temperature (ºC) with an ingested telemetry capsule. Total body heat flux (W) was calculated from the sum of regional surface area x heat flux for arms, legs, torso, and head. We calculated net heat loss as the difference between total body heat flux and energy expenditure and calculated change in core temperature as ΔºC per 10 minutes. We used linear regression to estimate the association between change in temperature and net heat loss. We examined the time lag from heat loss to change in core temperature with lagged regression.

Results: Eight participants ranged from ages 21 to 51 with a weight and height range between 61 kg to 101.3 kg and 160 cm to 188 cm. The average (SD) energy expenditure during rest was 76.4 (16.2) W and the total heat flux was -69.9 (12.1) W. The present net heat loss of the participant had the best correlation with change in temperature 20-minutes later (lagged regression (**slope: 145,058 J/ΔºC; 95% CI: [107,879, 182,237]) (pseudo-R^2 = 15.93%).** Accounting for the skin surface temperatures at the measurement sites improved this association **(pseudo-R^2 = 16.98%)**.

Conclusions: In conclusion, we found that the heat balance measured through external sensors predicts temperature change with about 20-minute lag time. Our data imply that 145,058 ± 18,895 J of net body heat loss would lead to a 1ºC decrease in core body temperature 20 minutes later.

Significance: This work presents a method to non-invasively track core temperature changes in a resting individual. Applications include monitoring and managing core temperature of individuals in environments where space is limited, and where invasive core temperature monitoring equipment is impractical for long term use.

Research/Grant Support: TRISH BRASH 2101 award NNX16AO69A (PI: Clifton W. Callaway, MD PhD)

DEPARTMENT OF NEUROLOGICAL SURGERY

Oral Abstract O4

SYNAPTIC NEUROTRANSMISSION PROTEIN GENOTYPES ARE ASSOCIATED WITH POST-TRAUMATIC EPILEPSY AND LONG-TERM OUTCOME AFTER SEVERE TBI

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Introduction: Traumatic brain injury (TBI) dramatically increases the risk of epileptogenesis, occurring in one third of severe TBI patients (sTBI). Alterations in synaptic neurotransmission have been linked to the development of post-traumatic epilepsy (PTE), however underlying genetic etiology remains relatively unknown. Genes associated with regulation of synaptic neurotransmission are of particular interest given documented associations of gene variants with neurodevelopmental, psychiatric and neurodegenerative outcomes.

Hypothesis: We hypothesize that single nucleotide polymorphisms (SNP) of synaptic genes are associated with development of PTE as well as poor functional outcomes in patients with sTBI.

Methods: Participants were prospectively enrolled under an approved IRB, between 2002-2013, with corresponding PTE status extracted from the electronic medical record. SNPs from *AP2M1, CLTA, CLTC,* and *SYT1* were genotyped using the Human Core Exome v1.2 (Illumina). Outcome at 3, 6, 12 and 24 months post-injury was measured using Glasgow Outcome Scale (GOS) and Disability Rating Scale (DRS).

Results: 206 participants had DNA extracted and PTE analyzed (Mean Age: 38.57 ± 16.83, 80.63% male, Median GCS: 6). 28% (n=57) of patients had confirmed PTE, while 72% (n=149) did not. 38 SNPs across 4 genes were identified (*SYT1:* n=18; *AP2M1:* n=4; *CLTA:* n=2; *CLTC:* n=4). Multivariate logistic regression analysis, controlling for sex and age, found significant associations between 2 *AP2M1* SNPs and PTE status (rs8478 and rs2231224, $p<0.05$), specifically the minor allele variant increased the odds of PTE (OR= 2.16 and 2.12, respectively). Furthermore, the rs2231224 major allele variant reduced the odds of a poor outcome at 6 month DRS ($p=0.036$, OR=0.16). While no *Syt1* SNPs were associated with PTE status, 6 were significantly associated with 6 and 12 month GOS and DRS (rs1405499, rs1918193, rs1918191, rs1245804, rs1245824 and rs2272500, $p<0.05$), specifically that major allele variant reduced odds of a poor outcome (OR<0.5). rs1918193 major allele variant also significantly reduced odds of poor outcome at 24 month GOS ($p=0.046$, OR=0.37).

Conclusions: This study is the first to discover an association between synaptic neurotransmission genes *AP2M1* and *Syt1* SNPs and PTE and/or long-term outcome in a sTBI population.

Significance: Identification of these genetic variants may improve clinical care for patients at high-risk for PTE. Further work is needed to determine the implication of *AP2M1* and *Syt1* polymorphisms on protein function and pathological mechanisms.

Research/Grant Support: NIH R01-NS124730 (PI: Shaun W. Carlson, PhD)

Abstract 27

STEREOTACTIC RADIOSURGERY FOR BENIGN INTRADURAL SPINAL TUMORS

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Introduction: The role of radiosurgery in the treatment of benign intracranial tumors has been well established. However, there are limited long-term follow-up studies on the outcomes following spine stereotactic radiosurgery (SRS) for benign intradural extramedullary spinal tumors.

Hypothesis: Spinal SRS can offer long-term tumor control for benign extramedullary neoplasms.

Methods: Analysis of 184 patients (55% female) and 207 unique tumors in the cervical (37%), thoracic (28%), lumbar (28%), and sacral (7%) spine was conducted at the University of Pittsburgh Medical Center from 2001 to 2023. At the time of SRS, the median patient age was 52 years (range: 19 - 93) and the median Karnofsky Performance Score was 80 (range: 60 - 100). Tumor histology included schwannoma (78 lesions), meningioma (32 lesions), neurofibroma (43 lesions), hemangioma (18 lesions), hemangioblastoma (16 lesions), hemangiopericytoma (11 lesions), and paraganglioma (9 lesions). Twenty-three (11%) lesions were NF1 mutated and 17 (8%) were NF2 mutated. Thirty-four (16%) lesions underwent resection prior to radiosurgery. Common symptoms at SRS were pain (75%), sensory deficits (29%), and motor deficits (28%). Lesions were treated with single-fraction (82%), and multi-fraction (18%) regimens. The median gross tumor volume was 4 cc (range: 0.1 - 304) treated with a median prescription dose of 15 Gy (range: 11 - 25).

Results: The median follow-up period was 63 months (range: 1 - 258). For 196 (95%) tumors with available radiographic follow-up, tumors volumetrically regressed (15%), remained stable (77%), or locally progressed (8%, median duration of 20 months (range: 3 - 161)). Tumors that progressed were successfully managed with either repeat SRS (9 lesions) or open surgical resection (7 lesions). The 1-, 5-, and 10-year local control rates were 97%, 92%, and 90%, respectively. On multivariate analysis, NF1 status correlated with worse local control ($p = 0.027$, HR: 4.01, 95% CI: 1.17 - 13.8). The median overall survival was 251 months (range: 1 - 258) and rates of 1-, 5-, and 10-year overall survival were 95%, 85%, and 70%, respectively. On multivariate analysis, age ≤ 65 years ($p = 0.015$, HR: 4.60, 95% CI: 1.35 - 15.7) and KPS > 70 ($p = 0.002$, HR: 0.09, 95% CI: 0.02 - 0.40) were associated with improved overall survival. Tumor-associated neurologic symptoms improved (41%), remained stable (45%), or worsened (14%) at the time of last patient follow-up. Acute adverse-radiation effects included pain flare (8%), skin rash (2%), dysphagia (1%), vertebral compression fracture (1%), paresthesias (1%), and new neurologic deficits (1%).

Conclusions: Spine radiosurgery is demonstrated to be a safe and effective treatment for benign intradural spinal tumors with long-term follow-up. In select patients, including patients with an NF1 mutation, SRS offers a high likelihood of local control and overall survival.

Significance: SRS delivers cytotoxic doses of radiation to the tumor while sparing normal tissue tolerance to provide a better chance at significant palliation, durable local tumor control without the need for morbid resective surgery, and a potential cure for benign neoplasms.

Research / Grant Support: N/A

Abstract 28

KYPHOPLASTY TREATMENT PRIOR TO SPINAL STEREOTACTIC RADIOSURGERY OFFERS LONG-TERM TUMOR CONTROL WITH EFFECTIVE SYMPTOM RELIEF

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Introduction: In patients experiencing pain secondary to pathological compression fractures, combining kyphoplasty and subsequent spinal stereotactic radiosurgery (SSRS) may allow for stabilization of the fracture and irradiation of the underlying malignancy to control local disease progression. Both procedures can relieve pain associated with this condition to improve the patient's quality of life. This study aims to evaluate the safety and efficacy of kyphoplasty treatment prior to SSRS in patients with spinal metastases and benign tumors.

Hypothesis: Combined balloon kyphoplasty and SSRS will provide neurological symptom relief and long-term tumor control for patients with symptomatic pathological compression fractures.

Methods: Fifty-four patients (59% female, mean age 61 years) with pathological compression fractures of the thoracic (31 tumors, 57%) and lumbar (23 tumors, 43%) spine were prospectively analyzed at a single-institution (2002-2022). Histological diagnoses of 54 (18 breast, 13 lung, 6 renal, 4 melanoma, 3 prostate, 3 bladder, 2 multiple myeloma, 1 colorectal, 1 uterine, 1 thyroid, 1 hemangiopericytoma, and 1 leiomyosarcoma) tumors were recorded. Patient demographic and histological data, prior radiation and surgical treatment history, pain quality, treatment planning data and dosimetry, and outcomes after surgery were identified. The epidural spinal cord compression (ESCC) scale and the spinal instability neoplastic score (SINS) were calculated for 43 tumors using T2 weighted magnetic resonance imaging (MRI).

Results: The median time from kyphoplasty to stereotactic radiosurgery was 18 days (range: 2-119). Twenty (47%) tumors extended into the epidural space (ESCC >0) and the median SINS score was 9 (range: 4-15). Fifty-one tumors (94%) were treated with a single-fraction and 3 tumors with a multi-fraction regimen (3 fractions). The median gross tumor volume was 33 cc (range: 10-123) and the median prescription dose was 20 Gy (range: 13-27). No acute radiation-induced toxicities or new neurological deficits occurred during the follow-up period (median 13 months, range: 1-137). Pain improved in 49 (91%) patients. Four (7%) tumors locally recurred after a median duration of 9 months (range: 4-71). The 1-, 2-, and 5-year local control rates were 90%, 90%, and 75%, respectively.

Conclusions: For patients with pathological compression fractures, combined balloon kyphoplasty and SSRS provides effective symptom relief and long-term tumor control with limited instances of radiation induced toxicities.

Significance: This study is the largest consecutive series to date to report on patients undergoing combined balloon kyphoplasty and SSRS for the management of pathological compression fractures caused by spinal metastasis, showcasing that this treatment strategy is clinically safe, feasible, and effective in patients with symptomatic pathological fractures.

Research/Grant Support: None

DEPARTMENT OF PHYSICAL MEDICINE AND REHABILITATION

Oral Abstract O5

EXAMINING THE POTENTIAL EFFICACY OF CHRONIC GALANTAMINE ON ATTENTIONAL FUNCTION AND CHOLINERGIC NEUROTRANSMISSION AFTER PRECLINICAL TRAUMATIC BRAIN INJURY

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Introduction: Cholinergic disruptions underlie attentional deficits following traumatic brain injury (TBI). Yet, drugs specifically targeting acetylcholinesterase (AChE) inhibition have resulted in mixed outcomes.

Hypothesis: Our hypothesis posits that chronic administration of galantamine (GAL), a dual-action competitive AChE inhibitor and an α7 nAChR positive allosteric modulator that is FDA-approved for Alzheimer's disease, will improve sustained attention post-TBI (Experiment 1) and restore cholinergic tone by pharmacologically enhancing ACh efflux in the medial prefrontal cortex (mPFC), a critical brain region supporting cholinergic-driven attentional performance, as assessed by *in vivo* microdialysis (Experiment 2).

Methods: In experiment 1, adult male rats (n=10-15/group) trained in the 3 Choice serial reaction time test (3-CSRT) were randomly assigned to a cortical impact of moderate severity or sham injury and administered GAL (0.5, 2.0, or 5.0 mg/kg) or saline vehicle (VEH; 1 mL/kg) i.p once daily beginning 24-h post-surgery until sacrifice (day-28). During behavioral testing, GAL or VEH was injected 30 min prior to task onset. Measures of sustained attention (percent accuracy) and distractibility (percent omissions) were assessed on post-operative days 21-27 with the 3-CSRT. The rats were sacrificed on post-operative day-28 and cortical lesion volume and basal forebrain cholinergic cells were quantified. In experiment 2, the dose-dependent effect of GAL on *in vivo* ACh efflux in the mPFC was quantified. Briefly, adult male rats (n=3-4/group) were subjected to a moderate cortical impact then received daily GAL (0.5, 2.0, or 5.0 mg/kg) or saline vehicle (VEH; 1 mL/kg) i.p starting 24 h post-surgery. On post-operative day 14, a guide cannula was surgically implanted in the right mPFC. On post-injury day 21 (i.e., equivalent to the first day of behavioral testing from experiment 1), a microdialysis probe was inserted into the cannula and artificial cerebrospinal fluid (aCSF) with 50 nM Neostigmine was perfused at a continuous rate (2 µL/min). Baseline and post-injection (GAL or VEH) dialysate samples were collected, reflecting the 30-min post-injection delay and the 3-CSRT task duration (i.e., 30 min) from experiment 1. Concentrations of acetylcholine (ACh) from microdialysis samples were analyzed using reverse phase high performance liquid chromatography coupled to an electrochemical detector. On post-operative day 28, cortical lesion volume and serum AChE activity via ELISA were assessed. The ACh concentrations, cortical lesion volume, and AChE activity were subjected to ANOVA, followed by Newman-Keuls post hoc analysis for specific group comparisons.

Results: All TBI groups regardless of treatment had decreased sustained attention vs. SHAM controls [p's<0.05]. Moreover, the highest dose of GAL (5.0 mg/kg) exacerbated attentional deficits relative to the two lower doses of GAL and VEH [p's<0.05]. TBI significantly reduced cholinergic cells in the right basal forebrain, regardless of treatment condition vs. SHAM [p<0.05]. A significant reduction in cholinergic cells was observed in all TBI groups regardless of treatment vs. SHAM controls [p<0.05]. *In vivo* microdialysis revealed that prior to injection there were no differences in basal ACh in the mPFC; however, following drug injection GAL (5.0 mg/kg) significantly increased ACh concentration 30 min following injection compared to the VEH- and GAL- (0.5 and 2.0 mg/kg) treated groups [p<0.05]. In both experiment 1 and 2 there were no differences in lesion volume across groups [p>0.05]. In experiment 2, there were no differences in post-injection serum AChE activity between the GAL- and VEH- injury groups [p>0.05].

Conclusion and Significance: The lack of a GAL benefit in the 3-CSRT may suggest that a refined dosing paradigm that selectively modulates α7 nAChRs is necessary for more sophisticated cognitive tests. Furthermore, the utilization of *in vivo* microdialysis to assess drug-induced alterations in ACh tone offers real-time insights into the dynamic neurochemical changes associated with pharmacological interventions.

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Abstract 29

A NOVEL APPROACH FOR MORPHOLOGICAL ASSESSMENT OF CHOLINERGIC NEURONS FOLLOWING TBI IN FEMALE RATS

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Introduction: Cholinergic deafferentation and degeneration are pathogenic hallmarks of various neurodegenerative diseases, including traumatic brain injury (TBI). Numerous clinical and pre-clinical studies demonstrate a significant reduction in choline acetyltransferase positive (ChAT+) cells, a well-validated marker for cholinergic neurons, following TBI in brain regions involved in regulating cognition like the basal forebrain (BF). Despite this, cholinergic neurons exhibit diverse ultrastructure, encompassing soma morphology, dendrites, and synaptic connections, crucial for neurotransmission and neural signaling. Consequently, collateral damage to surviving cholinergic neurons in the BF post-TBI, marked by dendritic retraction, reduction in fiber density and length, and soma volume, might contribute to chronic cholinergic dysregulation, extending beyond ChAT+ cell quantity or density. Advanced analytical imaging software like IMARIS, enables the reconstruction of images into 3D visual representations, serving as a powerful tool for analyzing and quantifying complex changes in cellular morphology. We hypothesize that TBI will disrupt cholinergic projection morphology, as evidenced by reduced perikaryon volume, and projection length, volume, density, and branching points in the BF, correlating with deficits in functional, cognitive, and affective assessments.

Methods: Normal cycling female adult rats (6–8-month-old) received either a controlled cortical impact (CCI) of moderate severity or Sham injury. Motor function was assessed with beam-balance/beam-walk and spatial learning and memory were assessed in a well-established Morris water maze (MWM) on post-operative days 1–5 and 18-24, respectively. Adaptive and maladaptive-like coping was assessed via the protruding shock probe defensive burying task (SPDB) on post-operative day-31. Ipsilateral and contralateral cholinergic neuron ultrastructure in the BF was assessed using brightfield microscopy coupled with fluorescent immunolabeling of cholinergic neurons (ChAT+), on 35-µ thick free-floating sections. Z-stacked images, captured at 0.5 mm intervals, were deconvolved using a Landweber method, and reconstructed using IMARIS software with an automated seeding point reconstruction method. ChAT+ cell ultrastructure was analyzed via soma volume and projection volume, density, and branching, serving as markers of neuronal atrophy and complexity. Behavioral and histological statistical analyses included ANOVAs, nested analyses, and independent sample t-tests, with Newman-Keuls and Tukey post-hoc test, respectively.

Results: Consistent with previous findings from our laboratory, CCI significantly impaired both functional and cognitive performance in female rats, as demonstrated by deficits in the beam-walk and the MWM tasks (p's<0.05). In the SPDB, the CCI group exhibited significantly reduced number of stretch attends and time spent burying, indicative of maladaptive coping behaviors (p's <0.05). Initial analyses of ChAT+ ultrastructure revealed a reduction in soma and projection volume, suggesting injury-induced degeneration of cholinergic neurons in the BF. Furthermore, TBI showed a trend toward reduced cholinergic cell branching, reflecting potential dendritic degeneration. Future assessments of filament length and area will provide further insights into injury-induced effects on dendritic atrophy.

Conclusion/Significance: Preliminary findings suggest that TBI results in decreased soma and projection volume and complexity, indicative of an atrophy-like morphology in BF cholinergic neurons, alongside behavioral deficits observed in female rats. This study offers a novel approach utilizing advanced imaging software to reconstruct and analyze cholinergic neuron morphology, beyond traditional quantity-based assessments.

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**denotes first author contribution*

Abstract 30

PHARMACOLOGICAL AND NEUROREHABILITATION EFFECTS ON CHOLINERGIC TRANSMISSION, COMPLEX ATTENTION, AND SYSTEMIC INFLAMMATION AFTER CONTROLLED CORTICAL IMPACT INJURY IN MALE AND FEMALE RATS

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Introduction: Traumatic brain injury (TBI) is a leading cause of cognitive disability worldwide. Post-TBI attentional impairments lack proven treatments and can result from cholinergic dysregulation, which suggests that pharmacological strategies that amplify activation of acetylcholine (ACh) receptors may ameliorate behavioral deficits. To more closely mimic the clinical setting, combining a pharmacological therapy with noninvasive rehabilitation (i.e., enriched environment, EE, housing) may prove to be an efficient approach for cognitive recovery in both male and female rats, which is akin to the real world.

Hypothesis: We predicted that chronic administration of NS-1738, a novel α7 nicotinic ACh receptor (α7-NAChR) positive allosteric modulator (PAM), will improve sustained attention and brain markers of cholinergic transmission post-TBI in both sexes, alone and in combination with EE. Moreover, blocking α7-NAChRs with methylycaconitine (MLA) will attenuate the beneficial effects of NS-1738, confirming its mechanism of action.

Methods: Adult male and female rats were trained in the 3-choice serial reaction time task (3-CSRT), reaching stable pre-injury baselines prior to moderate-severity right parietal controlled cortical impact (CCI) or sham injury. First, male rats were randomized to NS-1738 (3 mg/kg intraperitoneally) or vehicle (1 mL/kg saline) starting post-injury day (PID) 1 and continued daily for 28 days. This chronic paradigm co-investigated daily NS-1738 administration with environmental enrichment (EE; 6h/d) housing, and subgroups were also subjected to daily concurrent α7-NAChRs blockade via MLA (3 mg/kg) injections. 3-CSRT retrials occurred on PID 14-24. Medial prefrontal cortex (mPFC) Western blots assessed cholinergic markers [acetylcholinesterase (AChE), choline acetyltransferase (ChAT), and α7-NAChR]. A microarray analysis examined serum inflammatory gene expression. Statistical analysis utilized ANOVAs, repeated measures when appropriate, with Newman-Keuls post hoc tests.

Results: TBI rats of both sexes exhibited impaired sustained attention and increased distractibility versus shams ($p<0.05$), the latter of which was improved by chronic NS-1738 administration in males ($p<0.05$). Daily EE was beneficial on 3-CSRT measures alone in male rats ($p<0.05$), while combining NS-1738+EE rendered an additive effect on lowering omissions and improving inflammatory markers ($p<0.05$) including TREM-1 (triggering receptor expressed on myeloid cells-1) and IL-1 RA (interleukin-1 receptor antagonist). Male TBI groups that received MLA demonstrated a reinstatement of performance deficits, as hypothesized, by reversing the beneficial effects of a slightly higher drug dose (5 mg/kg/day). Female TBI rats receiving daily NS-1738 displayed significant restorations of performance, whether drug was administered alone or in conjunction with EE. Again, NS-1738+EE rendered an additive effect on lowering omissions ($p<0.05$). Both male and female TBI rats reflected ChAT disruptions in mPFC and basal forebrain, which were improved by chronic NS-1738+EE housing in male rats ($p>0.05$).

Conclusions: Our findings support benefits of α7-NAChR type-I PAM and/or EE treatment after experimental TBI on sustained attention, cholinergic neurotransmission, and systemic inflammation.

Research/Grant Support: NIH NS110609 and Research Advisory Committee, Children's Hospital of Pittsburgh (COB), UPMC Children's Research Advisor Committee Dissertation Fellowship (EHM), and NS084967, NS121037 (AEK).

Abstract 31

RESCUING SUSTAINED ATTENTION CAPABILITY IN AGED MALE RATS USING A COMBINED THERAPY VIA A7 NICOTINIC ACETYLCHOLINE RECEPTOR ALLOSTERIC MODULATOR AND ENVIRONMENTAL ENRICHMENT AFTER EXPERIMENTAL BRAIN TRAUMA

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Introduction: Traumatic brain injury (TBI) poses significant challenges for elderly populations, often exacerbating existing age-related cognitive decline. Pharmacological strategies that enhance acetylcholine (ACh) transmission may ameliorate cognitive deficits, especially in conjunction with noninvasive rehabilitation, mirroring clinical approaches. We have shown before that a parietal cortex TBI induces sustained and significant deficits of complex attention in young adult rats, males and females.

Hypothesis: We predicted that parietal injury in aged (15-16 months old) male rats will augment sustained attention deficits compared to young adults. We then hypothesized that chronic NS-1738, a novel positive allosteric modulator (PAM) of the α7 nicotinic ACh receptor (α7-NAChR) will improve sustained attention post-TBI, alone and in combination with environmental enrichment (EE).

Methods: Aged male rats were trained in the 3-choice serial reaction time task (3-CSRT) prior to a right parietal controlled cortical impact (2.8 mm cortical deformation depth) or sham injury. Rats were randomized to NS-1738 (5 mg/kg) or vehicle (saline), as well as daily EE (24h) or standard housing for a month starting post-injury day (PID) 1. 3-CSRT retrials occurred on PID 17-27. Statistical analysis utilized repeated measures ANOVAs with Newman-Keuls post hoc tests. Assessment of cortical lesion volumes and choline acetyltransferase (ChAT) positive cells will be examined.

Results: TBI-induced cognitive deficits were pronounced in aged rats by way of impaired sustained attention ($p<0.05$) which were subsequently rescued by chronic NS-1738 ($p<0.05$). Moreover, NS-1738+EE rendered an additive effect on restoring accuracy and lowering omissions ($p<0.05$).

Conclusions: Our findings reflect the vulnerability of the elderly population following TBI and support benefits of α7-NAChR PAM and/or EE treatment after experimental brain trauma on sustained attention through cholinergic neurotransmission.

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Abstract 32

CHOLINERGIC NEUROTRANSMISSION DURING PERFORMANCE OF A SUSTAINED ATTENTION TASK AFTER TBI

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Introduction: Attentional deficits are prevalent following traumatic brain injury (TBI), and treatment options are limited due to an inadequate understanding of their etiology. Attentional functioning relies on an intact cholinergic network originating in the nucleus basalis of Meynert (NBM) and projecting to the medial prefrontal cortex (mPFC). Although *in vivo* microdialysis studies in non-TBI rats show task-evoked increase of ACh in the mPFC correlating with attentional performance, such studies are lacking in preclinical TBI models, where ACh circuitry is likely tampered by intrinsic pathological processes.

Hypothesis: TBI will decrease *in vivo* task-evoked release of ACh in the mPFC, correlating with impaired real-time performance on the 3-Choice serial reaction time test (3-CSRT), a validated behavioral measure of attention, and with cholinergic neuron morphology in the NBM.

Methods: Adult male rats (3-4 months old) trained in the 3-CSRT to the 2-second cue duration received either a moderate right parietal controlled cortical impact or a Sham injury (n=10/group). On post-injury day (PID) 14, a guide cannula was surgically implanted in the right mPFC. At PID 21 (i.e., first day of 3-CSRT testing), a microdialysis probe delivering artificial cerebrospinal fluid + Neostigmine (2 μL/min) was inserted into the cannula. Dialysate samples were collected at 15-min intervals for 3 h before and during 3-CSRT testing. Samples underwent analysis via high pressure liquid chromatography utilizing a reverse-phase column, followed by passage through an immobilized post-column enzyme reactor. The detection limit for ACh was 100 fmol/10ul injection. After completion of behavioral testing and dialysate collection, the probes were removed, and rats underwent subsequent daily 3-CSRT testing for five days. At PID 28, cortical lesion volume was quantified, and probe location verified following Cresyl violet staining. Cholinergic neuron ultrastructure in the NBM and mPFC was quantified using brightfield microscopy with ChAT+ immunolabeling on 35-μ coronal sections. Z-stacked images were deconvolved and reconstructed with IMARIS to assess ChAT+ soma and projection volume, length, and branch points as indicators of neuronal atrophy and plasticity. Statistical analyses included ANOVAs with Newman-Keuls post-hoc tests.

Results: TBI rats exhibited significant deficits in sustained attention compared to their baseline performance and the Sham group. There were no differences in basal ACh efflux between the Sham groups ($p>0.05$). After 3-CSRT onset, Sham rats showed a significant increase in task-related ACh release in the mPFC compared to both their baseline ($p<0.05$) and the TBI group ($p<0.05$). In contrast, the TBI group did not exhibit a comparable increase in ACh release during the task compared to their baseline. Linear regression analyses may reveal a potential correlative relationship between attentional performance and task-evoked ACh release. Preliminary findings of ongoing ChAT staining analyses suggest a decrease in soma and projection volume, as well as reduced branching in both the NBM and mPFC.

Conclusion and significance: The results suggest that observed attentional impairments are the result of phasic disruptions in behaviorally-evoked ACh efflux in the mPFC. To our knowledge, this is the first study in neurotrauma to conduct *in vivo* microdialysis in awake, freely moving rats performing a cognitive task. To date, our understanding of the cholinergic system following TBI has been widely derived from post-mortem analyses using semi-quantitative techniques such as immunohistochemistry. Comparatively, *in vivo* sampling techniques such as microdialysis, which is a quantitative approach, provide increased temporal resolution and when combined with real-time behavioral performance can elucidate the correlative relationship between behaviorally-driven chemical dynamics.

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Abstract 33

EPIGENETIC ASSOCIATIONS OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) AND NEUROBEHAVIORAL RECOVERY FROM PEDIATRIC TBI

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Introduction: Up to 50% of children with TBI experience lasting neurobehavioral impairments, however, the biological factors that affect recovery are unclear. The aim of this study is to evaluate *BDNF* DNA methylation (DNAm) as a potential biomarker of neurobehavioral recovery in children with complicated mild to severe TBI.

Hypothesis: We hypothesized that acute *BDNF* DNAm would be negatively associated with neurobehavioral outcomes in children 6 months and 12 months after TBI.

Methods: We recruited 208 children (3-18 years) hospitalized overnight at UPMC Children's Hospital of Pittsburgh with complicated mild to severe TBI (n=144, Glasgow Coma Scale of 3-12 or 13-15 with abnormal neuroimaging) and orthopedic injury controls (OI, n=65). DNA was extracted from acute blood samples (mean ± SD, 20.4 ± 8.16 hours post-injury). *BDNF* DNAm of 5 CpG sites across exons I and IV were measured via pyrosequencing. Cognitive function (NIH Toolbox-Cognitive Battery) and caregiver-reports of emotional/behavioral, executive, and adaptive functions were assessed. Associations between DNAm and injury group (TBI vs. OI) were determined using logistic regression, adjusting for age and sex. Associations between acute *BDNF* DNAm and neurobehavioral measures were determined using linear regression, adjusting for age, sex, and injury severity.

Results: BDNF was hypomethylated in children with TBI at two sites (Odds Ratio [95% CI], exon I site 2: 0.39 [0.17, 0.91], p=0.03; exon IV site 2: 0.52 [0.27, 0.98], p=0.04) and marginally hypermethylated at a third site (exon I site 1: 2.23 [0.98-5.09], p=0.055). Higher DNAm at exon 1 sites 1 and 3 were significantly associated with lower crystallized cognition (β [95% CI], 5.47 [-9.48, -1.46], p=0.009), and lower total cognition (β: -7.13 [-12.61, -1.64], p=0.01), respectively, at 6 months in children with TBI but not OI (n=53 TBI, n=15 OI). Lower DNAm at exon I site 2 was associated with greater adaptive function at 12 months (β: 13.33 [4.14, 22.52], p=0.005) in TBI but not OI (n=85 TBI, n=34 OI).

Conclusions: *BDNF* DNAm has potential as a biomarker of neurobehavioral recovery over the first year post-injury. Further exploration with greater sample sizes is required.

Significance: Dynamic and responsive biomarkers of neurobehavioral recovery are a critical aspect of precision medicine. These findings suggest *BDNF* DNAm may be useful to identify children at risk of poor recovery and guide future interventions.

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