

Pushing the Frontiers



COSBID 2016



UNM HEALTH SCIENCES CENTER

presents:

COSBID's 18th scientific meeting

July 13-15, 2016
Albuquerque, NM, USA

COSBID 2016

Cooperative Studies on Brain Injury Depolarizations

¡Bienvenidos a Albuquerque!

We are excited to host this 18th scientific meeting of the *Cooperative Studies of Brain Injury Depolarizations (COSBID)* group!

We have assembled what we think will be another excellent program for this year's meeting. We are hoping to "push the frontiers" in many directions. Holding the meeting in our southwest frontier US city is emblematic of the expansion of the scientific conference to new centers and investigators around the globe. From the basic science perspective, we are reaching out to other related fields to determine how SD related concepts can apply to their work and what we can learn from them.

From the clinical perspective, we are excited to welcome new investigators just beginning with clinical monitoring as well as seeing the successful early clinical trial efforts from around the globe. We are rethinking some of the structure of this meeting to highlight some of the controversial topics and look forward to some exciting conversations and debates throughout the meeting.

As always, we are grateful to our industry partners and are especially excited to involve several new companies dedicated to ischemic and hemorrhagic stroke therapies.

Presenters are generally allotted 20 minutes total. 15 minutes of presentation time will allow for discussion after the presentations, which is vital to the spirit of the meeting.

We hope you have an enjoyable and stimulating time with us!

-Andrew P Carlson and Bill Shuttleworth
On behalf of the other members of the
scientific organizing committee:
Jed Hartings, Cenk Ayata, and K.C. Brennan

Program overview:

Wednesday, July 13th, 2016

Hotel Albuquerque

5:00- Registration

5:30- Keynote 1: Jed Hartings Opening Keynote

Thursday, July 14th, 2016

UNM HSC Nursing and Pharmacy Auditorium

8:00- Breakfast

8:30- Session 1: Basic Mechanisms and Models

10:30- Break with industry

11:00- Keynote 2: Daniela Pietrobon

11:45- Lunch and Industry presentations

13:30- Session 2: Clinical Recordings

14:50- Session 3: Trial and Center Updates

16:20- Session 4: Case discussion

18:30- Conference Dinner: Seasons Rotisserie & Grill

Friday, July 15th, 2016

UNM HSC Nursing and Pharmacy Auditorium

8:00- Breakfast

8:30- Keynote 3: Steven Schiff

9:30- Session 5: Animal Studies: Injury and Protection

12:10- Lunch

13:00- Concurrent Sessions

Session 6: Nuts and Bolts of Clinical Recording

Session 7: Standards for reproducibility in animal

15:00- Session 8: What's next for COSBID?

16:00- Closing remarks, Bus to closing reception

Detailed Program:

Wednesday July 13th

Hotel Albuquerque

5:00 Registration opens

5:30-5:35 Howard Yonas, MD: Chairman, UNM Department of Neurological Surgery

Welcome and Opening comments

5:33-6:20 **Keynote 1:** Jed Hartings- University of Cincinnati, Cincinnati, OH, USA

Perspectives on the COSBID Consortium: Mission, History, and Future.

6:30 Opening Reception

Notes:

Detailed Program:

Thursday July 14th

UNM HSC Nursing and Pharmacy Auditorium

07:45 Transportation from Hotels to UNM

08:00 Continental Breakfast

8:25 Corey Ford, MD: Senior Associate Dean for Research- *Welcome to UNM campus*

Session 1: Basic Mechanisms and Models

Chairs: Bill Shuttleworth and Cenk Ayata

08:30-8:50 R. Meldrum Robertson- Queens University Kingston, UN, Canada

Environmental stress and the insect CNS: a simpler systems approach to understanding evolutionarily conserved mechanisms of spreading depolarization.

8:50-9:10 David Chung- Neurovascular Research Unit, MGH, Boston, MA, USA

Optogenetic induction of spreading depolarizations

9:10-9:30 Anja Srienc- University of Minnesota, Minneapolis, MN, USA

Retinal spreading depression in the in vivo ischemic rat retina

9:30-9:50 Ning Zhouo China Medical University, Taiwan

Spreading depolarization promotes astrocytic calcium oscillations and enhances gliotransmission to hippocampal neurons.

9:50-10:10 Trent Anderson- University of Arizona, Phoenix, AZ, USA

Neurosteroids selectively alter cortical inhibition and facilitate cortical spreading depression.

10:10-10:30 Punam Sawant- University of Utah, Salt Lake City, UT, USA

Prodrome and aftermath of spreading depolarizations

10:30-11:00 Break and Coffee with Industry

Notes:

Detailed Program:

Thursday July 14th

UNM HSC Nursing and Pharmacy Auditorium

11:00-11:45 **Keynote 2:** Daniela Pietrobon- University of Padova, Italy
Mechanisms underlying facilitation of cortical spreading depression
in mouse models of hemiplegic migraine

Chair: K.C. Brennan

11:45-13:30 Lunch and **Industry Presentations**

Session 2: Clinical Recordings

Chairs: Jed Hartings and Jens Dreier

13:30-13:50 Johannes Woitzik- Charité University Medicine, Berlin, Germany
*Excitotoxicity and Metabolic Changes in Association with Cortical
Spreading Depolarization in Patients with Malignant Hemispheric Stroke.*

13:50-14:10 Alois Josef Schiefecker- Medical University Innsbruck, Austria
*Brain Temperature But Not Core Temperature Increases During Cortical
Spreading Depolarizations In Patients With Spontaneous Intracerebral
Hemorrhage.*

14:10-14:30 Edgar Santos- University of Heidelberg, Heidelberg, Germany
*Effects of ketamine on the incidence of spreading depolarizations (SD) in
subarachnoid hemorrhage.*

14:30-14:50 Andrew P Carlson- University of New Mexico, Albuquerque, NM,
USA
*Cortical spreading depolarizations occur in repetitive, distinct patterns in
human brain injury and stroke.*

14:50-15:20 Break and Coffee with Industry

Notes:

Detailed Program:

Thursday July 14th

UNM HSC Nursing and Pharmacy Auditorium

Session 3: Trial and Center Updates

Chairs: Oliver Sakowitz and Martin Lauritzen

15:20-15:40 Maren Winkler- Charité University Medicine, Berlin, Germany

DISCHARGE-1

15:40-16:00 Sebastian Major- Charité University Medicine, Berlin, Germany

Common COSBID database

16:00-16:20 Renan Sanchez-Porras- University of Heidelberg, Heidelberg, Germany

Center TBI

16:20-16:30 Jed Hartings

TRACK-TBI and SDII

Session 4: Interesting Cases/ Discussion

Chairs: Jed Hartings and Andrew Carlson

16:30-18:00 *How I Score: Moderators will bring or go over raw data samples, demonstrating the approach to setting up LabChart and Scoring data. Discussions of complex cases.*

18:30-21:00 Conference Dinner- Seasons Rotisserie & Grill

History and Folklore of Old Albuquerque

Notes:

Detailed Program:

Friday July 15th

UNM HSC Nursing and Pharmacy Auditorium

07:45- Transportation from Hotels to UNM

08:00- Continental Breakfast

08:30-9:15 **Keynote 3:** Steve Schiff- Penn State University, Pennsylvania, PA, USA

Unification of Neuronal Spikes, Seizures, and Spreading Depression.

Chair: Jed Hartings

9:15-9:30 Coffee and Break

Session 5: Animal studies: Injury and protection

Chairs: Sergei Kirov and Edgar Santos

9:30-9:50 Jason Hinzman- University of Cincinnati, Cincinnati, OH, USA

Continuum of Spreading Depolarizations in Rat Model of Acute Subdural Hematoma.

9:50-10:10 Renan Sanchez-Porrás- University of Heidelberg, Heidelberg, Germany

Ketamine Modulation of the Hemodynamic Response to Spreading Depolarization in the Gyrencephalic Swine Brain

10:10-10:30 Kate Reinhart- University of New Mexico, Albuquerque, NM, USA

Targeting the vulnerable phase of SD: Protective effects of ketamine and memantine.

10:30-10:50 Thad Nowak- University of Tennessee Health Science Center, Memphis, TN, USA

Anesthesia and other variables impacting peri-infarct depolarization during experimental stroke.

Notes:

Detailed Program:

Friday July 15th

UNM HSC Nursing and Pharmacy Auditorium

Session 5: Animal studies: Injury and protection

Chairs: Sergei Kirov and Edgar Santos

10:50-11:10 Anna Maslarova- University Hospital, Bonn, Germany

Altered Properties of Sharp -Wave-Ripples in the Subiculum of Mice that Underwent Kainate-induced Status Epilepticus.

11:10-11:30 Break and Coffee with Industry

11:30-11:50 Cenk Ayata- MGH, Boston, MA, USA

Mild and brief intracranial pressure spikes effectively trigger peri-infarct depolarizations.

11:50-12:10 Martin Lauritzen- University of Copenhagen, Copenhagen, Denmark

PSD-95 uncoupling from NMDA receptors by Tat-N-dimer ameliorates neuronal depolarization in cortical spreading depression.

12:10-13:00 Lunch

Notes:

Detailed Program:

Friday July 15th Concurrent Sessions

UNM Department of Neurosurgery

Session 6: Nuts and Bolts of Clinical Recording

13:00-14:30 Andrew Carlson, Kyna Seale, Mohammad Abbas

Clinical Recording from OR to Bedside to Data

Domenici Center Room B116

Session 7: Standards for Reproducibility and Rigor in Animal SD Studies

13:00-14:30 Bill Shuttleworth and K.C Brennan

Animal models from Single Cell to Slice to Swine

Session 8: What's next for COSBID?

Chair: Jens Dreier

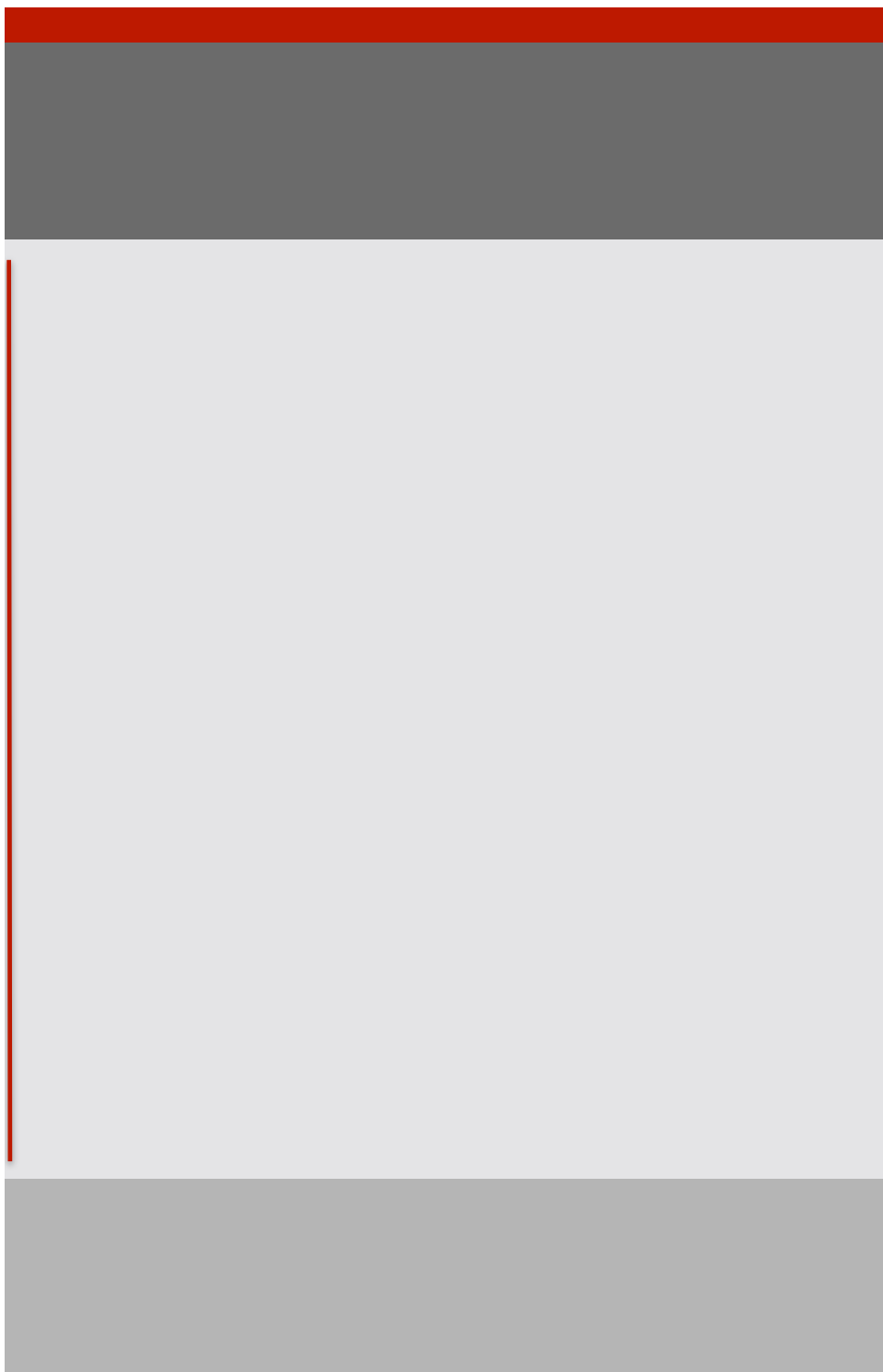
14:30-16:00

The next big challenges and controversies

16:00 *Announcement of 2017 meeting, Close of 2016 meeting*

16:15-20:00 *Bus to Closing reception*

Notes:



Abstracts:

Environmental stress and the insect CNS: a simpler systems approach to understanding evolutionarily conserved mechanisms of spreading depolarization.

R. Meldrum Robertson, Department of Biology and Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada

Many basic cellular mechanisms have been conserved during evolution and are present in animals as diverse as humans and fruit flies. Environmental stressors for insects are equivalent to physiological stressors that the mammalian CNS must endure under pathological conditions. For insects, survival in harsh environments depends critically on preserving neural function so that appropriate behaviours and physiological control mechanisms can still be carried out. Nevertheless, neural activity in the CNS is arrested under extreme conditions of temperature or oxygen availability at which point insects enter a protective coma. This is associated with a surge in potassium ion concentration in the CNS extracellular space and, when conditions improve, recovery is dependent on restoration of normal ion gradients. Preconditioning by prior exposure can alter the threshold conditions that trigger the potassium surge and the rate of recovery, suggesting that the neural shutdown is an adaptive mechanism to conserve energy, which can be modulated as prevailing conditions change. The mechanisms responsible for this phenotypic plasticity in the insect CNS are of considerable interest for predicting the ecological consequences of global climate change. In addition, because stress-induced neural shutdown in the insect CNS has all the hallmarks of mammalian spreading depolarization (SD), these results from the simpler systems of insects may have relevance for human health.

In locusts, prior heat shock causes trafficking of the Na^+/K^+ -ATPase into neuronal membranes, modulates neuronal K^+ conductances, modifies axonal excitability and speeds recovery from SD. In addition, activation of second messenger pathways involving cGMP-dependent protein kinase (PKG) or AMP-activated protein kinase is also able to modify the dynamics of SD and thus the timing of neural arrest. In *Drosophila*, genetic manipulations are able to modulate SD in the brain induced by ouabain application. Notably, flies genetically engineered to have low PKG activity are more resistant and less vulnerable to ouabain-induced SD. Future experiments using tissue-specific targeting in *Drosophila* will enable genetic dissection of the mechanisms regulating potassium ion homeostasis in the CNS in response to environmental stress and the relative roles of neurons and glia. By identifying intrinsic cellular signaling pathways capable of modulating the susceptibility of brain tissue to mass depolarization, this research could suggest therapeutic strategies for reducing the pathological impact of SD, from reducing migraine pain to limiting stroke injury.

Supported by the Natural Sciences and Engineering Research Council of Canada.

Abstracts:

Optogenetic induction of spreading depolarizations

David Y. Chung*, Homa Sadeghian, Tao Qin, Fumiaki Oka, Cenk Ayata

*presenting author

Background: Spreading depolarizations (SD) have a critical role in the pathogenesis of secondary damage after traumatic brain injury (TBI), ischemic stroke, intracerebral hemorrhage (ICH), and aneurysmal subarachnoid hemorrhage (SAH). Experimental studies targeting SDs continue to be important to develop new therapeutic approaches; however, current SD induction methods require invasive mechanical, electrical, or chemical stimulation of the brain through a burr hole in the skull. There is a need for better methods for the study of SDs in order to reduce confounders from direct tissue damage and to improve experimental throughput.

Methods: We sought to develop a non-invasive method for the study of SDs. Transgenic mouse lines expressing channelrhodopsin (ChR2) in cortical neurons were used to determine regional thresholds for optogenetic precipitation of SDs through intact skull. Laser speckle and Doppler flowmetry, bright field imaging, and electrocorticography were used to detect SDs. Additionally, dynamic local field potential shifts (LFP) in the area of light stimulation prior to an SD were measured using a glass microelectrode. Expression levels of channelrhodopsin were quantified at each of the stimulation sites using fluorescence immunohistochemistry.

Results: We observed regional differences in thresholds for optogenetically-induced SDs (from lowest to highest threshold): (1) whisker barrel, (2) motor, (3) sensory, and (4) visual cortex. SDs were reliably induced in whisker, motor, and sensory cortices for all tested stimulation paradigms; however, it was not always possible to predict whether an SD could be induced over visual cortex. Expression levels of ChR2 and LFP shifts corresponded to optogenetic SD susceptibility with the highest expression and potential shift in whisker barrel and the lowest in visual cortex.

Conclusions: SDs can be reliably induced using non-invasive optogenetic stimulation through intact skull. There are differences in regional thresholds which are likely due in part to differential expression of ChR2 in the mouse lines tested. Non-invasive optogenetic induction of SDs in ChR2 transgenic mice is a potentially useful method for the study of secondary brain injury after TBI, ischemic stroke, ICH, and SAH.

Abstracts:

Retinal spreading depression in the in vivo ischemic rat retina

Srienc A.I.*, Biesecker K. R., Shimoda A.M., Newman E.A.

*Presenting author

University of Minnesota, Department of Neuroscience, Minneapolis, MN

It has become apparent that cortical spreading depression (CSD) has important clinical consequences. Under pathological conditions, such as ischemia or traumatic brain injury, CSD correlates with neurological deficits and contributes to injury expansion. Spreading depression can also occur in the retina (retinal spreading depression, RSD), but previous observations have come only from ex vivo preparations. Using a photothrombosis model of ischemia, we show that acute occlusion of primary retinal arterioles and venules evokes RSD waves in the in vivo rat retina. Waves typically begin near the optic disc and spread peripherally, but a subset of waves originates at the periphery and spreads towards the optic disc. Waves propagate with a velocity of 3.0 ± 0.1 mm/min and are associated with a negative shift in DC potential, a transient cessation of neuronal spiking activity, and a drop in tissue oxygen tension. Wave frequency is reduced with the NMDA antagonist MK-801 and the 5-HT_{1D} receptor antagonist, sumatriptan. RSD could be an important therapeutic target for preventing cell death and vision loss following vascular occlusive injuries in the retina.

Abstracts:

Spreading depolarization promotes astrocytic calcium oscillations and enhances gliotransmission to hippocampal neurons

Dong Chuan Wu, Rita Yu-Tzu Chen, Ning Zhou*

*Presenting author

Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan

Objectives

While it is generally believed that neurons lead and astrocytes follow during spreading depolarization (SD), it remains unknown how astrocytic activities are modulated after SD and how the altered astrocytic signalings contribute to neuronal excitabilities. In the present study, we investigated changes of astrocytic Ca^{2+} activities in the SD recovery phase and the possible roles of astrocytes in regulating neuronal excitation.

Methods

SD was induced by focal ejection of KCl in hippocampal slices of mice. Astrocytic $[\text{Ca}^{2+}]_i$ changes were imaged with a two-photon laser scanning microscope directly coupled to a Mai Tai HP Ti:sapphire laser. Astrocytes were bulk loaded with the Ca^{2+} indicator Rhod-2 AM. Astrocytes were identified by their distinctive size and shape with small round soma ($<15\ \mu\text{m}$) and numerous thin radiating processes. The Rhod-2 fluorophores were excited at 820 nm and detected with PMT detectors with a 605-nm (70 nm bandpass) filter. Rhod-2 fluorescence signals were measured from astrocyte soma and primary processes. Whole-cell currents and slow inward currents were acquired by patch clamp recordings in CA1 pyramidal neurons.

Results

After the SD-concurrent Ca^{2+} wave, SD enhanced astrocytic activities by promoting a secondary period of Ca^{2+} oscillations. The SD-induced Ca^{2+} oscillations were originated from non-synaptic transmissions and were independent of metabotropic glutamate or ATP receptor activation. Different from the SD-concurrent Ca^{2+} wave, the Ca^{2+} oscillations likely resulted from enhancement of IP_3 receptor-dependent intrinsic activities in astrocytes. Furthermore, SD increased the number of NMDA receptor-mediated slow inward currents (SICs) in pyramidal neurons. The occurrence of Ca^{2+} oscillations in astrocytes and SICs in neurons had similar time courses. Selective inhibition of astrocytic Ca^{2+} signals reduced the incidents of SD-induced SICs.

Conclusion

Our data indicate that SD enhances activities of the astrocyte network that further promote gliotransmissions and neuronal excitabilities.

Abstracts:

Neurosteroids selectively alter cortical inhibition and facilitate cortical spreading depression

Alejandro Parga, Sharmila Venugopal, Chen Wu, Trent Anderson*

*Presenting Author

University of Arizona – College of Medicine Phoenix, AZ, USA

Migraine is one of the most common neurological disorders affecting over 36 million Americans and is characterized by severe headaches and sensory disturbances. For 20-30% of migraine patients, their symptoms are preceded by an aura that is often perceived as a visual disturbance of flashing lights or blind spots. Cortical spreading depression (CSD) is believed to cause migraine aura and may result in activation of the migraine pain pathway. Frequent triggers of migraine including stress, diet, the menstrual cycle and pregnancy are known to increase neurosteroid levels.

Neurosteroids, such as allopregnanolone, are brain-derived hormones which can be directly synthesized *de-novo* from cholesterol within individual neurons or glial cells in the brain. The aim of this study was to examine the role of neurosteroids on migraine using an *in-vitro* model of CSD using intrinsic optical signal (IOS) imaging combined with patch-clamp electrophysiology. Neurosteroids are potent allosteric modulators which are thought to preferentially act to increase tonic inhibition mediated by delta subunit containing GABAA receptors. However, we determined that application of endogenous and synthetic neurosteroids to brain slices paradoxically increased the probability of inducing CSD by up to 40%. This was in contrast to the GABA-A delta specific agonist THIP (gaboxadol) which failed to increase the probability of inducing CSD. To investigate the underlying mechanism we performed a detailed analysis of the action of neurosteroids on inhibitory cortical synaptic neurotransmission. We found that in contrast to THIP, neurosteroids preferentially act to increase phasic and tonic inhibition onto inhibitory interneurons while decreasing inhibition onto excitatory pyramidal neurons. These results suggest neurosteroids facilitate CSD by selectively disinhibiting the cortex which is predicted to lead to an increased incidence of attacks of migraine with aura.

Abstracts:

Excitotoxicity and Metabolic Changes in Association with Cortical Spreading Depolarization in Patients with Malignant Hemispheric Stroke

Alexandra Pinczolits^{1,2}, Anna Zdunczyk^{1,2}, Nora Dengler^{1,2}, Nils Hecht^{1,2}, Christina M Kowoll^{3,4}, Christian Dohmen^{3,4}, Rudolf Graf⁴, Maren K.L. Winkler^{2,5}, Sebastian Major^{2,5}, Jens P. Dreier^{2,5}, Peter Vajkoczy^{1,2}, Johannes Woitzik^{1,2}

¹Department of Neurosurgery, Charité - Universitätsmedizin Berlin, Berlin, Germany

²Center for Stroke Research Berlin, Charité - Universitätsmedizin Berlin, Berlin, Germany

³Department of Neurology, University of Cologne, Cologne, Germany

⁴Max Planck Institute for Neurological Research, Cologne, Germany

⁵Department of Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany

Cortical spreading depolarization (CSD) occurs in high frequency in patients with malignant hemispheric stroke and experimental data provides clear evidence that CSD significantly contributes to secondary brain damage. However, the mechanism for infarct progression due to CSD is still unclear. Here we studied extracellular brain glutamate and metabolites via two precisely implanted microdialysis probes in the peri-infarct tissue with a distance of 5 and 15 mm to the infarct. Simultaneously, CSDs were recorded by an overlying subdural strip electrode. During a total monitoring time of 2356.6 hours, 587 CSDs were assessed in 16 of 18 patients. 113 CSDs were classified as single, 362 as clustered and 112 as isoelectric depolarization (ISD). There was a trend towards fewer CSDs over time while a significant number of ISDs was only recognized during the first 36 hours post-surgery. Although the high number of ISDs was accompanied by a significant glutamate surge ($> 100\mu\text{M}$), we were not able to demonstrate significant excitatory or metabolic changes before or after single CSDs or in a grouped analysis when the hourly sampled excitatory or metabolic values during single or clustered CSD or ISDs were compared to control. Therefore, secondary damage due to CSD during this delayed monitoring period (mean time from stroke onset to surgery: 28 ± 12 hours) appears not to be significantly mediated by excitatory or metabolic mechanisms.

Abstracts:

Brain Temperature But Not Core Temperature Increases During Cortical Spreading Depolarizations In Patients With Spontaneous Intracerebral Hemorrhage

Alois Josef Schiefecker¹, Raimund Helbok¹

¹Department of Neurology, Division of Neurocritical Care, Medical University Innsbruck, Austria;

Introduction: Cortical spreading depolarizations (CSDs) commonly occur in patients with intracerebral hemorrhage (ICH) and may contribute to secondary brain injury. Fever is an independent predictor for unfavorable outcome after ICH and may trigger CSDs. Here, we investigated the dynamics of brain-temperature (T_{brain}) relative to CSDs and core-temperature (T_{core}).

Methods: Twenty comatose patients with ICH and multimodal electrocorticography (EcoG) monitoring were prospectively enrolled. A subdural EcoG strip was placed adjacent to the evacuated ICH. A combined intracranial pressure (ICP) and T_{brain} probe was inserted in the white matter ipsilateral to the ICH. Monitoring data were averaged to 5-minute-means for longitudinal analysis and to one-hour-means. Clusters of CSDs were defined as ≥ 2 CSDs/hour. Data were analyzed using GEE-models and are presented as median and interquartile range (IQR). Fever-burden was defined as % of temperature $>38.0^{\circ}\text{C}$ per 24-hours.

Results: During 3097 hours (173 hours [81-123] /patient) of EcoG monitoring, 342 CSDs were analyzed. 15% of CSDs occurred in clusters. Baseline T_{core} and T_{brain} were 37.3°C (36.9-37.8) and 37.4°C (36.7-37.9), respectively. T_{brain} but not T_{core} significantly increased 5 minutes preceding the CSDs by a median of 0.2°C (0.1-0.2; $p<0.001$) and returned to baseline 35min following CSDs. T_{brain} ($+0.4^{\circ}\text{C}$ [0.1-0.4]; $p<0.001$) but not T_{core} ($p=0.34$) was higher during clusters compared to episodes of single CSDs. CSDs probability was highest during $T_{\text{brain}} \geq 38.0^{\circ}\text{C}$ (23% probability; $n=150$), compared to 9% probability at $T_{\text{brain}} \leq 36.6^{\circ}\text{C}$ ($n=41$). Fever burden was predictive for the occurrence of CSDs (T_{brain} : $p<0.001$; OR=1.2 per %; T_{core} : $p<0.001$; OR=1.1 per %)

Conclusion: CSDs were triggered during episodes of fever. Our data suggest an association between CSDs and cerebral heat production, especially during clusters. Integration of EcoG monitoring in trials investigating prophylactic normothermia after ICH may help to understand the potential beneficial effect of this intervention.

Abstracts:

Effects of ketamine on the incidence of spreading depolarizations (SD) in subarachnoid hemorrhage

Edgar Santos¹, Arturo Olivares-Rivera¹, Sebastian Major², Renan Sánchez-Porras¹, Christian Stock³, Daniel Saure³, Alejandro Álvarez-Ayala¹, Daniel Hertle¹, Oliver W. Sakowitz¹, Jens P. Dreier²

1) Neurosurgery Department. University of Heidelberg, Heidelberg, Germany

2) Center for Stroke Research Berlin, Charité University Medicine Berlin, Berlin, Germany

3) Department of Statistics. University of Heidelberg, Heidelberg, Germany

Ketamine, a non-competitive NMDA receptor antagonist, has the capacity to block spreading depolarizations (SD) in metabolically uncompromised or mildly compromised tissue. However, in animal experiments, tolerance to ketamine was observed within about two hours; its SD-inhibiting effect was almost lost after several hours. The safety of ketamine doses of up to 150 mg/h has been established; higher doses are the discretion of the treating physician. We studied the effect of intravenous administration of ketamine on the susceptibility to SD in aneurysmal subarachnoid hemorrhage (aSAH) patients. 67 aSAH patients from a prospective observational study with multimodal cerebral monitoring including subdural ECoG requiring sedation were identified and independently included in this study. 24 patients required ketamine additionally to the standard sedatives to achieve good sedation, in doses from 40 mg/h to 400 mg/h. Patients who received ketamine displayed a total of 13.8 SDs/patient over a monitoring time of 10.12 days, while 16.9 SDs/patient were observed over a monitoring time of 10.21 days in patients not receiving ketamine. Ketamine was given first after a mean of 3.67 days of monitoring for a mean of 4.83 days. Compared to the day before administration of ketamine, there was a reduction of the incidence of SDs over the following 4 days by 70.37%, 90.74%, 81% and 74% respectively. During the ketamine administration, there was a mean rate of 0.85 SDs/day, with a significant difference compared to the rate in patients not being given ketamine (1.66 SDs/day, Wilcoxon, $p=0.002$). We found three cases with CT-proven delayed cerebral ischemia during the administration of ketamine at high doses (>150 mg/h), in which SDs were either not suppressed or they recurred in clusters after two days. The findings suggest that i.v. ketamine decreases the incidence of SDs at usual doses, but a fraction of SDs is not suppressed. This might depend on the tissue conditions but, in addition, it could be related to the development of tolerance.

Abstracts:

Cortical spreading depolarizations occur in repetitive, distinct patterns in human brain injury and stroke.

Andrew P Carlson, MD, MS-CR¹; Fares Qeadan, PhD²; Howard Yonas, MD¹; C. William Shuttleworth, PhD^{3,2}

Departments of Neurosurgery¹, Clinical Translational Science Center², and Neuroscience³, University of New Mexico.

Background: With the increased understanding that at least some CSD represent deleterious events after brain injury and stroke, a need for real time detection or prediction of these events is relevant. Anecdotal scoring of patient data has resulted in the observation that similar events recur within a patient over the course of monitoring. We sought to formally characterize and test this observation.

Methods: ECoG was monitored using the standard COSBID technique and a DC coupled amplifier in patients with TBI, SAH, and MHS. Standard scoring criteria of CSD were used initially. In a second pass of scoring, similar events were grouped as *types*. Descriptive characteristics for each CSD were measured including the duration of the event, the inter peak duration, the integral of each DC shift, and the voltage range in all leads at the time of the first two DC shifts (as a measure of the order of occurrence). In patients where there were >10 CSD of each of 2 or more *types*, formal statistical analysis was performed to determine 1) the similarity of all events of a certain *type* by evaluating the covariance structure **within** that *type*, and 2) the covariance structures were then compared **between** *types* using Box's M test to determine if different *types* displayed a statistically different covariance structure. Descriptive statistics were used to describe the whole group. Statistics were performed using the SAS system.

Results: All individual *types* of CSD were remarkably similar within *types* when each characteristic was plotted against the same characteristic of the other events within a given *type*; substantially high correlation measures were observed. The covariance structure was compared within each patient between *types* to determine if they were similar. All comparisons of covariance structure between *types* (n=8 comparisons in 3 patients) resulted in statistically different structure ($p < 0.05$). Overall, 16 strips in 15 subjects were found to have CSD (out of 18 monitored patients). Subjects were found to demonstrate up to 5 different *types* (though only the *types* with >10 events were statistically analyzed to ensure adequate power.) 78.4% of events were *types* 1 or 2 (ordered by frequency), and 91.8% of events were *types* 1, 2, or 3, demonstrating that most of the events were the commonly repeating. On subjective analysis, the recognition of repetitive *types* allowed for identification of additional events that would not have met the standard criteria due to artifact and allowed better characterization of more complex events such as intersecting events.

Conclusions: CSD occurs predominantly in repetitive, distinct patterns in human ECoG after stroke and brain injury. This allows for an additional consideration for scoring and characterization of events. Future automatic detection algorithms can therefore recognize repeated events more accurately or can predict as an event is beginning to occur to allow for early patient directed treatments to be initiated.

Abstracts:

DISCHARGE-1: progress report

Maren K.L. Winkler¹, Sebastian Major^{1,2,3}, Eun J. Kang^{1,2}, Viktor Horst^{1,4}, Michael Scheel^{3,4}, Johannes Woitzik^{1,5}, Jens P. Dreier^{1,2,3} for the DISCHARGE-1 study team
¹Center for Stroke Research Berlin, ²Experimental Neurology, ³Neurology, ⁴Radiology and ⁵Neurosurgery, Charité University Medicine Berlin, Germany

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening disease and the second most common type of hemorrhagic stroke. Mortality and disability rates of initial survivors reaching medical care are high and delayed cerebral ischemia (DCI) is the most prominent in-hospital complication. The prospective, multicenter, diagnostic phase III trial "Depolarizations in ISCHemia after subARachnoid HaemorrhAGE-1 (DISCHARGE-1)" aims at establishing the invasive neuromonitoring of spreading depolarizations for real-time diagnosis of DCI after aSAH and estimating a cut-off value with predefined sensitivity and specificity so that subsequently, spreading depolarizations can be used in future studies as a biomarker to facilitate treatment decisions.

Methods: Spreading depolarizations are recorded by electrocorticography (ECoG) with a subdural electrode strip placed on cerebral cortex for up to 14 days following aSAH. The development of delayed infarcts is assessed and verified by serial magnetic resonance imaging (MRI). Recruiting centers are Berlin (with two centers), Cologne, Frankfurt, Heidelberg, and Bonn. The analysis of secondary diagnostic variables such as partial pressure of tissue oxygen, brain metabolism, autoregulation, and perfusion constitutes different research modules that are nested in DISCHARGE-1.

Results: The first DISCHARGE-1 patient was recruited in September 2009. Until February 2016, 156 patients were recruited in the 6 recruiting centers: 103 in Berlin (2 centers), 17 in Cologne, 23 in Frankfurt, 13 in Heidelberg, and 2 in Bonn. Based on the number of patients allocated to the trial (n=200), it is estimated that the patient recruitment period will continue until the end of 2016. Blinded analysis of raw ECoG data (primary study variable) and MRI data (primary study endpoint) has been completed for 82 and 79 patients, respectively.

Conclusions: It is aimed at providing an update on the status quo of the study.

Abstracts:

Unification of Neuronal Spikes, Seizures, and Spreading Depression

Steven Schiff

The pathological phenomena of seizures and spreading depression have long been considered separate physiological events in the brain. By incorporating conservation of particles and charge, and accounting for the energy required to restore ionic gradients, we extend the classic Hodgkin–Huxley formalism to uncover a unification of neuronal membrane dynamics. By examining the dynamics as a function of potassium and oxygen, we now account for a wide range of neuronal activities, from spikes to seizures, spreading depression (whether high potassium or hypoxia induced), mixed seizure and spreading depression states, and the terminal anoxic “wave of death.” Such a unified framework demonstrates that all of these dynamics lie along a continuum of the repertoire of the neuron membrane. Our results demonstrate that unified frameworks for neuronal dynamics are feasible, can be achieved using existing biological structures and universal physical conservation principles, and may be of substantial importance in enabling our understanding of brain activity and in the control of pathological states.

Abstracts:

Continuum of Spreading Depolarizations in Rat Model of Acute Subdural Hematoma

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Introduction: Acute subdural hematomas (ASDH) occur frequently in severe traumatic brain injury (TBI), are the most common TBI indication for neurosurgery, and are associated with high rates of morbidity and mortality. ASDH is thought to induce lesions of cerebral tissue through ischemic compression due to mass effect. Here we sought to determine whether spreading depolarizations (SD) mediate the development of acute cortical lesions in a rat model of ASDH.

Methods: 27 Male Sprague-Dawley rats were anesthetized with isoflurane (30/70% O₂/N₂), mechanically ventilated via tracheostomy, maintained normothermic, and arterial blood pressure was continuously monitored. An L-shaped 25g needle was placed in the subdural space via a burr hole over occipital cortex, and fixed with dental cement. Two micropipettes for field-potential recordings were placed in ipsilateral cortex at ± 2 mm from bregma. ASDH was induced by injecting 0.3 ml of arterial blood through the subdural needle at 3.6 ml/hr. Recordings were performed for 4 hours after injection and cortical lesions were quantified with TTC staining.

Results: In eight animals, electrical silence followed by anoxic terminal spreading depolarization (ATSD) developed at both sites within 5 min of ASDH. These animals died spontaneously 122 (± 16 min) after ASDH. In the other 19 animals, ASDH induced an ATSD in the core and an initial prolonged SD (1005 \pm 159 s) in the periphery, followed by an additional 2.8 (± 0.5) transient SDs (80 \pm 4 s). TTC staining in 7 of these animals demonstrated cortical lesions of ASDH produced a cortical lesion of 133.5 (± 11.8) mm³ that accounted for 19.1 (± 2.1) % of the injured hemisphere.

Conclusions: These results demonstrate that ASDH is a risk factor and sufficient condition for the development of SD after TBI. These experimental results are further confirmed by our clinical data where 83.3% (5/6) of patients who developed secondary ASDH during ECoG monitor had SDs. The occurrence of the full continuum of short, prolonged, and terminal depolarizations is similar to that observed in focal ischemia from arterial occlusion, and suggests that SD mediates development of ischemic cortical lesions triggered by compressive mass effect. Further characterization is likely to yield a novel, clinically relevant model to study SD as a neuroprotection target and a diagnostic marker along spatiotemporal gradients of developing lesions.

Abstracts:

Ketamine Modulation of the Hemodynamic Response to Spreading Depolarization in the Gyrencephalic Swine Brain

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Spreading depolarization (SD) generates significant alterations in cerebral hemodynamics, which can have detrimental consequences on brain function and integrity. The mechanisms involved in these cerebrovascular changes during SD remain unclear. In animal models, inhibition of SD initiation and/or propagation, and decrease of SD incidence in patients has been obtained with ketamine, a NMDA receptor blocker. Theoretically, therapies targeting the noxious hemodynamic changes of SD in brain injury states could contribute to diminishing its pathological effects. However, the effect of ketamine on SD hemodynamic response is incompletely understood. We investigated the effect of two therapeutic ketamine dosages, a low-dose of 2 mg/kg/h and a high-dose of 4 mg/kg/h, on the hemodynamic response to SD in the gyrencephalic swine brain. Cerebral blood volume was assessed through laser-Doppler flowmetry, and cerebral blood flow and pial arterial diameter changes were assessed through intrinsic optical signal imaging. In intrinsic optical signal imaging a variety of hemodynamic responses after KCl stimulation were observed. We found that frequent SDs, with a time interval of 30 min between stimulations, caused a persistent increase in the baseline pial arterial diameter, which led to a diminished capacity to further dilate. Ketamine infused at a low-dose (2 mg/kg/h) reduced the hyperemic/vasodilative response to SD; however, it did not alter the subsequent oligemic/vasoconstrictive response. This low-dose did not prevent the baseline diameter increase and the diminished capacity of pial arteries to dilate. Only infusion of ketamine at a high-dose (4 mg/kg/h) suppressed SD and the coupled hemodynamic response. After medication infusion a lasting dose-dependent effect on the previously affected hemodynamic responses was found during the following 2 hours of stimulation. These results suggest that the hemodynamic response to SD can be modulated by continuous infusion of ketamine. Nevertheless, lower ketamine doses did not suppress the oligemic/vasoconstrictive components, only higher doses of ketamine (i.e., ~4 mg/kg/h) may be appropriate to completely hinder SDs and the coupled hyperemic and oligemic responses. Whether or not this might offer any clinical advantage is unknown. The use of ketamine in gyrencephalic pathological models needs to be explored to corroborate its possible clinical benefit. Hence, more work is needed before a potential therapeutic scheme can be suggested.

Abstracts:

Targeting the Vulnerable Phase of SD: Protective effects of ketamine and memantine

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Waves of spreading depolarization (SD) can be a key trigger for excitotoxic injury in metabolically-compromised brain. Recent work has emphasized the potential beneficial effects of blocking the initiation and/or propagation of SDs, including promising work with sedatives such as ketamine. However it may be difficult to completely prevent SDs in the clinical setting without deleterious side effects. We have been studying whether a complementary approach might be effective – targeting the deleterious consequences of SD with lower concentrations of NMDAR antagonists that do not block SD initiation/propagation. We have studied SD in murine brain slices, using microinjection of KCl as a stimulus. We have modeled conditions of healthy brain (where repetitive SDs appear benign) and metabolically compromised brain (where tissue remains viable until subjected to SD). Extracellular glutamate levels were detected using the glutamate-sensing fluorescent reporter (iGluSnFR). Virus containing the iGluSnFR construct was delivered *in vivo* via stereotaxic injection into the hippocampus of C57Bl/6 mice, and brain slices were prepared ~2-4 weeks post injection. Neuronal Ca^{2+} transients were assessed in brain slices from mice expressing the intracellular Ca^{2+} -sensitive fluorescent protein (GCaMP5G). SD was recorded with DC electrodes and progression tracked with IOS signals. In healthy tissues, SD resulted in large glutamate transients that returned to baseline levels within ~20s (n=8). In the same conditions, Ca^{2+} transients were longer, but still fully recoverable within ~55s (n=10). Intermediate metabolic compromise was achieved by reducing O_2 and glucose availability. Under these conditions, the majority of slices did not recover from SD generated by KCl microinjection (~14% survival; n=7). Here, glutamate transients were prolonged, but returned to baseline levels after SD. In contrast, Ca^{2+} transients were markedly extended and remained ~35% above baseline levels 2 minutes post SD (n=5). Under conditions of complete metabolic depletion (oxygen and glucose deprivation; OGD) SDs were generated spontaneously, with glutamate and Ca^{2+} transients both sharply increasing at the onset of SD, and were irrecoverable throughout the duration of recordings (~10 min). We next determined concentrations of ketamine and memantine that reduced did not block SD, but which effectively reduced the duration of the DC shift (30 and 100 μ M, respectively). In healthy slices, ketamine reduced Ca^{2+} transient duration ($P=0.01$; n=4). In intermediately compromised conditions, ketamine attenuated Ca^{2+} dysregulation after SD ($P<0.05$) and prevented tissue death (6/6). Similar results were obtained with memantine. These results demonstrate the influence of metabolic status influences both glutamate and Ca^{2+} accumulation during SD, and support potential utility of ketamine and memantine as interventions that do not block, but reduce deleterious consequences of SD.

Abstracts:

Anesthesia and other variables impacting peri-infarct depolarization during experimental stroke

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Anesthesia is one of many factors impacting the occurrence of peri-infarct depolarizations (PIDs) after experimental brain injury, potentially confounding the translation of acute pathophysiological studies in animals to the clinical situation. As a highly reproducible model of severe focal ischemia, distal middle cerebral artery occlusion (MCAO) in the Spontaneously Hypertensive Rat (SHR) is well suited to the quantitative evaluation of such effects. Whereas acute anesthesia impacts are well recognized, awake recordings in this model (Kudo et al., *Neuroscience* 325:142, 2016) identified a subtle effect of prior isoflurane anesthesia to reduce both infarct volume and PID number, persisting up to one week following surgery to place recording electrodes. This example of "anesthetic preconditioning" is therefore a practical issue to be considered in study design.

The limited collateral perfusion of the SHR also provides a useful comparison with previous awake recordings after intraluminal filament occlusions in Sprague-Dawley rats (Hartings et al., *J. Neurosci*, 23:11602, 2003). In that early study there was a generally similar pattern of PID incidence after permanent and transient occlusions, both exhibiting a biphasic time course during 24 h. In contrast, PIDs terminated within 4 h after permanent distal MCAO in the SHR, but persisted for up to 48 h after transient occlusions, consistent with the progress of infarction in the respective models.

PID number correlated with infarct volume, but the relationship could be dissociated. Maintained isoflurane anesthesia during the initial hours after permanent occlusion markedly reduced total PID number and prolonged their time course, indicating delayed infarct expansion, but there was no reduction in final infarct size. The already steep CBF gradient in the SHR may make it insensitive to further worsening of the perfusion deficit by PIDs. Rather, variations in penumbral territory with infarct size may determine the probability of triggering PIDs. Transient occlusions were more variable with respect to infarct size, as well as PID incidence and time course. Both PID number and infarct volume were inversely correlated with the delay in PID onset. This is remarkably consistent with earlier observations in the filament occlusion model. The final extent of injury after transient occlusion appears closely linked with early infarct expansion, as reflected in PID time course. This temporal component of PID incidence may be more informative than absolute PID number with respect to ongoing pathophysiology in experimental stroke. It remains to be seen how this could be applied to evaluating human brain injury.

Abstracts:

Altered Properties of Sharp -Wave-Ripples in the Subiculum of Mice that Underwent Kainate-induced Status Epilepticus

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Sharp-wave ripples (SWRs) are network oscillations in the hippocampus, which occur during rest/ slow-wave sleep and represent the replay of firing sequences of place cell assemblies, initially formed during exploratory behavior. SWRs therefore very likely are associated with memory consolidation in the hippocampus. Interictal epileptic events of similar duration and amplitude have been described in the subiculum of epileptic patients in an in-vitro slice preparation, implying a relation and possible transition between these two types of activities.

Using extracellular field potential recordings and intracellular sharp electrode recordings, we investigated the properties of SWRs in acute hippocampal slices from adult male black 6 mice that underwent status epilepticus, induced by a single injection of kainic acid in the dorsal CA1 region of the hippocampus. SWRs recorded in-vitro from the subiculum of these animals 8 weeks later maintained their usual incidence, duration and amplitude. Similarly to events from control mice, they were sensitive to pharmacological manipulation by glutamate- and GABA-receptor blockers. Other than described for epileptiform activity, they were only partially dependent on excitatory GABA transmission, as tested by the NKCC1 blocker bumetanide. However, compared to events from naïve mice, they were characterized by an increase in the number of ripples/SWR (2.1 vs 0.6 in control mice) and an increase in the ratio of pyramidal neurons that exhibited depolarizing potentials during SWRs (95% vs 70 % in control mice) or fired action potentials during SWRs (47% vs 17%). These results imply on the one hand side, that SWRs in epileptic specimens might be mistakenly regarded as interictal spikes. The findings may furthermore provide a partial explanation for the pathophysiology of memory impairment in temporal lobe epilepsy.

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Abstracts:

PSD-95 uncoupling from NMDA receptors by Tat-N-dimer ameliorates neuronal depolarization in cortical spreading depression

Krzysztof Kucharz, Ida Søndergaard Rasmussen, Anders Bach, Kristian Strømgaard and Martin Lauritzen*

*Presenting author

Cortical spreading depression is associated with activation of NMDA receptors, which interact with the postsynaptic density protein 95 (PSD-95) that binds to nitric oxide synthase (nNOS). Here, we tested whether inhibition of the nNOS/PSD-95/NMDA receptor complex formation by anti-ischemic compound, UCCB01-144 (Tat-N-dimer) ameliorates the persistent effects of cortical spreading depression on cortical function. Using in vivo two-photon microscopy in somatosensory cortex in mice, we show that fluorescently labelled Tat-N-dimer readily crosses blood-brain barrier and accumulates in nerve cells during the first hour after i.v. injection. The Tat-N-dimer suppressed stimulation-evoked synaptic activity by 2–20%, while cortical blood flow and cerebral oxygen metabolic (CMRO₂) responses were preserved. During cortical spreading depression, the Tat-N-dimer reduced the average amplitude of the negative shift in direct current potential by 33% (4.1 mV). Furthermore, the compound diminished the average depression of spontaneous electrocorticographic activity by 11% during first 40 min of post-cortical spreading depression recovery, but did not mitigate the suppressing effect of cortical spreading depression on cortical blood flow and CMRO₂. We suggest that uncoupling of PSD-95 from NMDA receptors reduces overall neuronal excitability and the amplitude of the spreading depolarisation wave. These findings may be of interest for understanding the neuroprotective effects of the nNOS/PSD-95 uncoupling in stroke.

Abstracts:

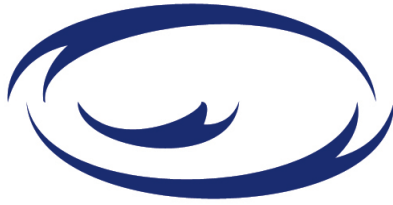
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