P0327 / #787

Topic: AS03 Stem Cells, Organoids, Neural Injury Neurotoxicity and Repair

FEAR EXTINCTION AND CORTICAL CIRCUITRY AFTER MILD TRAUMATIC BRAIN INJURY

Catherine Ubri [1,2]

[1] *Children's Hospital of Philadelphia, Department Of Anesthesiology And Critical Care, Philadelphia, United States of America*
[2] *University of Pennsylvania, Department Of Neuroscience, Philadelphia, United States of America*

Traumatic brain injury (TBI) is a leading cause of death and disability in children and adults in the United States. 10-15% of mild TBI (mTBI) survivors develop neuropsychiatric disorders such as posttraumatic stress disorder, making them a significant public health concern. Notably, an inability to suppress fear and override fearful memories lies at the core of many neuropsychiatric disorders. This ability, known as fear extinction, is essential to mental health. Fear extinction requires learning and remembering that a fear-evoking object or situation is nonthreatening (i.e., safe) after it is repeatedly presented without an aversive consequence, thereby creating a retrievable extinction memory. The ability to retrieve fear extinction memories relies on the infralimbic cortex (IL) subregion of the mPFC. Indeed, data suggests that the potentiation of IL neurons is necessary for fear suppression and the retention of fear extinction memories. While previous research shows fear extinction is impaired after mTBI in both humans and rodents, little is known of how the IL responds to mTBI. Using a well-established mouse model of mTBI, this work aims to determine whether mTBIs disrupt the IL neurocircuitry responsible for the capacity to extinguish fearful memories. Preliminary data suggests that during the fear extinction retrieval test session, injured mice freeze more than sham. We further predict injured mice will show reduced IL network activity, a failure to generate long-term potentiation, and reduced excitability in IL neurons after injury. This work begins to outline the mechanism of injury-induced fear-based neuropsychiatric disorders, and lays the groundwork for the development of a treatment for mTBI survivors.

Declaration of Interest Statement: None

https://doi.org/10.1016/j.ibneur.2023.08.332

P0328 / #4252

Topic: AS03 Stem Cells, Organoids, Neural Injury Neurotoxicity and Repair

PROTEOMIC PROFILING OF MESENCHYMAL STEM CELL SECRETOME AND ITS RESTORATIVE EFFECT IN MONOCROTOPHOS INDUCED TOXICITY IN NEURAL PROGENITOR CELLS

Pankhi Vatsa [1,2], Renu Negi [1,2], Uzair Ansari [2], Aditya Pant [1,2], Vinay Kumar Khanna [1,2]

[1] *CSIR-Indian Institute of Toxicology Research, Systems Toxicology And Health Risk Assessment Group, Lucknow, India*
[2] *Academy of Scientific and Innovative Research, Acsir, Ghaziabad, India*

The microenvironment of the cells governs their general physiology in both normal and diseased circumstances. Investigating the conditioned medium of any cell at a specific time point provides us with ample information about the cell's current state. Secretory chemicals released from the cell into the culture medium, mediate cellular communication between cells. Mesenchymal stem cells (MSCs) are multipotent cells that can self-renew and differentiate into various cell lineages and have thus been widely exploited in regenerative medicine. Evidence shows that the MSC secretome can improve healing by avoiding cell death, regulating the inflammatory response, and encouraging endogenous repair mechanisms such as neurogenesis. Considering all of this, we set out to characterize the MSC secretome using LCMS/MS in both unstimulated and stimulated (cellular pre-conditioning) conditions. We also looked at the restorative effects of mesenchymal stem cell (MSC) secretome on iPSC-derived neural progenitor cells (NPCs) exposed to 100 μM Monocrotophos, a widely used organophosphorus pesticide and a known neurotoxicant. The LCMS/MS data revealed that the MSC secretome mostly comprised proteins involved in glycolysis, oxygen transport, anti-inflammation, anti-fibrosis, neuroprotection, and cell proliferation pathways. We also discovered that exposing MCP-challenged NPCs to MSC secretome at a 1:1 ratio restored cell viability, oxidative stress, mitochondrial membrane potential, and apoptotic cell death. These connections imply that the MSC secretome greatly heals and rescues NPCs exposed to MCP. Identifying secretory components of the MSC secretome will shed light on the potential routes of the MSC secretome-mediated neuro-restorative effects on injured neuronal cells/tissues. These molecules may be used as a potential candidates involved in neuro-restorative therapies in the field of regenerative medicine.

Declaration of Interest Statement: None

https://doi.org/10.1016/j.ibneur.2023.08.333

P0329 / #1488

Topic: AS03 Stem Cells, Organoids, Neural Injury Neurotoxicity and Repair

GLUTATHIONE SYSTEM OF THE BRAIN: ROLE IN ENDOGENOUS NEUROPROTECTION AND SUBSTANTIATION OF PROMISING TARGETS FOR THERAPY

Olena Popazova [1], Ivan Yelozhenko [2], Igor Belenichev [3], Olena Aliyeva [4], Nina Bukhtiyarova [5], Victor Ryzhenko [6]

[1] *Zaporizhzhia State Medical University, Department Of Histology, Cytology And Embryology,, Zaporizhzhia, Ukraine*
[2] *Zaporizhzhia State Medical University, Department Of Pharmacology And Medical Prescription With A Course Of Normal Physiology, Zaporizhzhia, Ukraine*
[3] *Zaporizhzhia State Medical University, Department Of Pharmacology And Medical Formulation With Course Of Normal Physiology, Zaporizhzhia, Ukraine*
[4] *Zaporizhzhia State Medical University, Department Of Medical Biology, Parasitology And Genetics, Zaporizhzhia, Ukraine*
[5] *Zaporizhzhia State Medical University, Department Of Clinical Laboratory Diagnostics, Zaporizhzhia, Ukraine*
[6] *Zaporizhzhia State Medical University, Department Of Medical And Pharmaceutical Informatics And Advanced Technologies, Zaporizhzhia, Ukraine*

Introduction. The role of glutathione in neuron protection as an antioxidant and its participation in neuroplasticity due to NMDA

modulation is known. We put forward a hypothesis that an increase in endogenous glutathione through the use of pharmacological agents in ischemic neurodestruction may be a new direction in neuroprotection and treatment of cerebral strokes. This will also expand our understanding of the involvement of glutathione in the signaling of neuroapoptosis and its role in the formation of intimate mechanisms of endogenous neuroprotection. Materials and methods. A drop in the level of AHF was induced both by the administration of L-butionine-(S,R)-sulfoximine (BSO) and by modeling cerebral ischemia in Wistar rats. In the brain, ELISA, immunoblotting, PCR, and biochemistry were used to determine GSH forms, HSP70, HIF-1, and bcl-2 expression, neuron-specific enolase (NSE), and S-100 protein. GSH modulators were introduced: Ce-cysteine, Ce glutathione, glutoredoxin, lysinium 3-methyl-1,2,4-triazolyl-5-thioacetate. Results. The introduction of BSO and/or modeling of cerebral ischemia leads to a decrease in GSH and an increase in GSSG, an increase in nitrotyrosine, against the background of a decrease in HSP70 and the initiation of neuroaproptosis in the sensorimotor cortex and CA 1 of the hippocampus and neurological disorders. Administration of GSH modulators to animals had a neuroprotective effect (decrease in neurological symptoms, decrease in neuroapoptosis, and decrease in oxidative stress). The introduction of these substances led to an increase in GSH against the background of an increase in HSP70 and HIF-1. The greatest activity was demonstrated by glutoredoxin and lysinium 3-methyl-1,2,4-triazolyl-5-thioacetate. Conclusions. For the first time, we have obtained data on the initiation, implementation, and regulation of GSH/HSP70-dependent mechanisms of endogenous neuroprotection through the regulation of reduced glutathione levels.

Declaration of Interest Statement: None

https://doi.org/10.1016/j.ibneur.2023.08.334

P0330 / #3395

Topic: AS03 Stem Cells, Organoids, Neural Injury Neurotoxicity and Repair

A STUDY THAT INTEGRATES SPATIAL TRANSCRIPTOME AND METABOLISM ANALYSIS UNCOVERING THE METABOLIC DIVERSITY WITHIN THE INJURED HUMAN BRAIN

Ping Zheng [1], Ning Zhang [2], Cong Yu [1]

[1] *Shanghai Pudong New area People's Hospital, Neurosurgery, Shanghai, China*
[2] *Shanghai Fengxian Hospital, Neurosurgery, Shanghai, China*

Background: Single-cell transcriptomics is a powerful tool that can provide quantitative molecular signatures for a diverse range of cell types in the brain. However, with the increasing availability of multi-omics datasets, a significant challenge is to validate and integrate results in a biologically meaningful manner, particularly in relation to spatial organization and functional orientation.

Methods: In this study, we collected surgical samples from six brain trauma patients and generated transcriptomes and metabolite profiles.

Results: By integrating multiple datasets and quantitatively validating marker reproducibility, we identified spatial marker genes that are highly replicable across analysis methods, sequencing technologies, and modalities. These comprehensive molecular markers capture the diverse metabolic changes that occur in the injured human brain, including an area of lipid peroxidation resembling injured neurons.We also discovered imbalanced myo-inositol and myo-inositol phosphate levels and related spatial markers, providing insight into the complex transcriptomic regulation and metabolic alterations that occur in the injured brain.

Conclusions: These findings may facilitate the design of reagents that can target specific genes in the human brain for functional analysis, enabling a better understanding of the underlying pathophysiology.

Declaration of Interest Statement: None

https://doi.org/10.1016/j.ibneur.2023.08.335

P0331 / #2556

Topic: AS04 Neurons and Glia: Physiology and Inter-Cell Communication

ASTROCYTES GATE SPIKE TIMING DEPENDENT PLASTICITY IN THE NUCLEUS ACCUMBENS

Samuel Alberquilla [1], Carmen Nanclares [2], Rocio Gómez-Pastor [2], Paulo Kofuji [2], Rosario Moratalla [1], Eduardo Martín [1], Alfonso Araque [2]

[1] *Cajal Institute, Functional And Systems Neurobiology, Madrid, Spain*
[2] *University of Minnesota, Neuroscience, Minneapolis, United States of America*

The nucleus accumbens (NAc) is a pivotal locus for reward-related behaviours and addiction circuitry. It is mainly composed by medium spiny neurons that receive dopaminergic and glutamatergic afferents. The glutamate homeostasis in the NAc is regulated by the glutamate transporter 1 (GLT-1), a highly specific glutamate electrogenic transporter that is expressed on astrocytes. GLT-1 controls signal transmission uptaking glutamate from the synaptic cleft and thus controlling the time course of excitatory postsynaptic currents and potentials. Drugs of abuse causes glutamatergic dysregulation in the NAc and a downregulation of GLT-1 after prolonged drug-withdrawal. Although numerous studies show that GLT-1 regulate the synaptic plasticity triggered by different cell conditioning paradigms like spike timing-dependent plasticity (STDP). In STDP, the temporal coincidence of pre- and postsynaptic spiking activity leads to long-term potentiation or depression. However, the role of astrocytes in the regulation of NAc plasticity induced by drugs of abuse is poorly understood. In this study, we combined cell biology and electrophysiological approaches in brain slices, to test the hypothesis that dopaminergic activity alters the expression of astrocytic GLT1 and regulates the time course of glutamatergic synaptic transmission in the NAc. Astrocytic activation with opto-stimulation of dopaminergic axons, or with different drug abuse or with selective stimulation via DREADDs decreases GLT-1 functionality and glutamate synaptic currents in astrocytes. Furthermore, we found an increase in time and space of glutamate in the synaptic cleft modifying the kinetic of excitatory postsynaptic potentials. This phenomenon allowed us to find a temporal window between presynaptic activity and postsynaptic spikes in STDP paradigm in which the synaptic weigh was modified after drugs of abuse, adjusting the computational ability of the system during addiction.

Declaration of Interest Statement: None

https://doi.org/10.1016/j.ibneur.2023.08.336