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Effects of Surgery, Traumatic Brain Injury and Anesthesia Interact to Induce Neurological Abnormalities in Young Adult Male Rats and their Future Unexposed Male Offspring

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Abstract

Introduction: Preexisting neurodegenerative diseases, perioperative stress, and inflammation play an essential role in accelerated neurocognitive decline after general anesthesia (GA) and surgery, termed perioperative neurocognitive disorder (PND). PND is an important public health problem potentially affecting millions of patients. Because neurodegenerative diseases prevail and worsen with age, PND is most readily detectable and studied in the aging population. Traumatic brain injury (TBI), with >50 million cases/year, is a dominant cause of disability in young adults. Similar to PND, the pathophysiology of TBI involves lasting dysregulation of stress response systems, neuroinflammation, and cognitive decline. Patients with a history of TBI may also require GA/surgery or sedation to treat conditions unrelated to TBI, or injuries sustained at the time of TBI. Here we tested whether the effects of GA/surgery, TBI, and subsequent repeated exposure to the general anesthetic sevoflurane (SEVO) interact to induce neurological and neuroendocrine abnormalities in the exposed young adult male rats (an animal model of PND) and/or in their future offspring (intergenerational PND).

Methods: All animal procedures were approved by IACUC. Sprague-Dawley male rats (F0 generation) underwent a moderate TBI via a midline fluid percussion injury on postnatal day 60 (P60) that involved craniectomy (surgery) under 3% sevoflurane for 40 min followed by anesthetics (2.1% SEVO for 3 h) on P62, P64, and P66 (injury group). Rats in the SEVO group had only SEVO exposure on P60, P62, P64, and P66. Rats in the surgery group had a craniectomy and injury hub implantation but not TBI on P60. They also had SEVO exposure on P62, P64, and P66. Rats in the control group were placed in a new cage and housed one per cage for an equivalent amount of time on P60, P62, P64, and P66. A subset of F0 male rats was sacrificed 1 h after recovery from SEVO anesthesia on P66 or at an equivalent timepoint in the control group to study acute effects. The remaining F0 males were mated with control females on P90 to generate male and female offspring (F1 generation). The F0 and F1 rats were sequentially evaluated in the elevated plus maze (EPM), for prepulse inhibition (PPI) of acoustic startle, in the Morris water maze (MWM) and for resting and stress levels of serum corticosterone starting on ~P125 (F0) and ~P60 (F1), followed by tissue collections for further analyses.

Results: Acutely, F0 injury rats exhibited the greatest increases in serum corticosterone, interleukins 1 β and 6, and activation of the hippocampal microglia. Long term, compared to controls, F0 injury rats had the most exacerbated corticosterone levels at rest and after restraint, increased interleukins 1 β and 6, and reduced expression of hippocampal glucocorticoid receptor (Gr) and brain-derived neurotrophic factor genes. They also exhibited greater behavioral deficiencies. A similar (more profound) pattern of abnormalities was evident in their male offspring, while female offspring were not affected. The reduced Gr expression in F1 male, but not female, hippocampi was accompanied by matching Gr promoter hypermethylated CpG sites in F0 spermatozoa and F1 male, but not female, hippocampi.

Conclusions: The findings of this study demonstrate that in young adult male rats, the effects of surgery and TBI, interact with the effects of subsequent repeated SEVO exposure to induce abnormalities in hypothalamic-pituitary-adrenal (HPA) axis functioning, inflammatory markers, and some, but not all, behavioral tests. The findings of this study also demonstrate that F1 male offspring of injury sires can develop the same types of abnormalities, i.e., an intergenerational PND. Matching hypermethylated CpG sites in the Gr gene in the spermatozoa of F0 injury rats and in the hippocampi of their male but not female offspring,

reduced Gr expression in the F1 male but not female hippocampi, and exacerbated GR-dependent HPA axis responses to stress in F1 males but not females support the involvement of epigenetic mechanisms in the intergenerational transmission of adverse effects of paternal surgery, TBI, and SEVO exposure.

The Neuroprotective Effect of a miR-96-5p Inhibitor: Delivery to Brain via the Blood-brain Barrier

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Abstract

Glutathione (GSH) is one of the most important antioxidants in the brain, which plays a critical role in neuroprotection. Decline in GSH level in the brain, followed by an increase in reactive oxygen species (ROS), induces oxidative stress and thereby aggravates cellular damage, which in turn is regarded as a hallmark of the early stage of neurodegenerative diseases. The neuronal GSH levels are mainly regulated by cysteine transporter EAAC1 and its inhibitory factor, GTRAP3-18. Recently we have shown that microRNA, miR-96-5p, could be a regulator of the GSH level via EAAC1 to control the ROS level in the brain. We have also found that the GTRAP3-18 levels were increased by up-regulation of miR-96-5p. Although microRNAs interact with 3'-UTR region of target genes in the most cases, GTRAP3-18 lacks the consensus sequence for miR-96-5p, so that we have speculated that an unidentified protein should be responsible for the intermediate regulation of GTRAP3-18 expression by miR-96-5p. Here we discovered that RNA-binding protein NOVA1 functions as an intermediate protein for GTRAP3-18 expression via miR-96-5p. Moreover, we show that intra-arterial administration of a miR-96-5p-inhibiting nucleic acid to living mice by a drug delivery system using microbubbles and ultrasound technology decreased the level of GTRAP3-18 via NOVA1 and increased the levels of EAAC1 and GSH in the dentate gyrus of the hippocampus. These findings suggest that the delivery of a miR-96-5p inhibitor to the brain would efficiently increase the neuroprotective activity by increasing GSH levels via EAAC1, GTRAP3-18 and NOVA1.

Progressive Microvascular Failure after Revascularization: A Meta-analysis

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Abstract

Introduction: The role of perfusion imaging in acute ischemic stroke (AIS) management is an area of intense research. While significant gains have been made with respect to utilization of advanced perfusion imaging to aid identification of optimal revascularization targets little is known about the time course of reperfusion dynamics of post-revascularized tissue, and the probability of secondary injury. Progressive microvascular failure (PMF) downstream of the revascularized large vessel occlusion may contribute to poor post-recanalization recovery. Our metanalysis aims to advance our understanding of the existence and relevance of PMF following mechanically revascularized human stroke.

Methods: We performed a systematic review and meta-analysis searching PubMed and Embase databases. Key search terms included vocabulary associated with acute ischemic stroke, revascularization, assessment of reperfusion, reperfusion failure, no-reflow.

Results: Results were combined across 554 patients pooled from 14 studies characterizing impairments in perfusion post revascularization. An exponential function was fit to the percentage of patients with microvascular failure weighted by number of patients included in each study with an average of 38% of revascularized patients demonstrating perfusion features suggestive of PMF ($p = 0.013$), with 75% occurring within the first 76-hours post revascularization.

Conclusion: Impaired reperfusion despite complete recanalization is common. Understanding the temporal evolution of cerebral microvascular changes after macrovascular recanalization will provide important insights into reperfusion pathophysiology that may aid in the identification of novel avenues to enhance treatment efficacy, provide prognostic information about early functional outcome, and ultimately allow for greater personalization of post-reperfusion therapy.

The Synaptic Phenotype of Male and Female Transgenic Mouse Models of Autism Spectrum Disorder. What is the Difference?

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Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder causing lifelong disability. Synaptic abnormalities are essential contributors to ASD pathology. Therefore, ASD is even referred to as “developmental synaptopathy”. It has been widely accepted that the estimated prevalence rate of male individuals diagnosed with ASD prevails over females in a proportion of 4:1. Consequently, males remain the main focus in ASD studies both in clinical and experimental settings. Meanwhile, several recent works point to an underestimation of this disorder in females. In this work, we studied the sex differences in the synaptic phenotype of ASD mouse models.

Methods: 6 to 8-week-old male and female Shank3^{Δ4-22} and Cntnap2^{-/-} mutant mice, representing well-established models of ASD, were employed in the experiments. Their wild-type (WT) littermates were used as controls. The animals were euthanized, and cortices and striata were used for the evaluation of the synaptic phenotype. Levels of glutamic acid decarboxylase 67 (GAD1), N-methyl-D-aspartate receptor subunit 1 (NR1), vesicular glutamate transporter (VGAT), and synaptophysin (Syp) were measured by Western blots. Coronal sections of the brain were used for Golgi staining followed by the dendritic spine density (SD) assessment using confocal microscopy.

Results: SD and levels of GAD1, NR1, VGAT, and Syp were all significantly reduced in Shank3^{Δ4-22} and Cntnap2^{-/-} mice compared to control indicating the impaired synaptic development in the mutant mice. However, no sex differences in these parameters were found.

Conclusion: Female ASD mice undergo similar synaptic aberrations as their male counterparts and need to be studied along with the male animals.

Synergistic Effect of SARS-CoV-2 and APOE Variants in Human Cerebral Organoid

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Abstract

The long-term effects of SARS-CoV-2 (SCV2) infection are not understood. SCV2 infection has demonstrated increased severity in those with apolipoprotein-E (APOE) variants, a genetic risk factor for Alzheimer's Disease (AD). Following SCV2 infection, there have been reported cognitive and neurological implications in individuals. SCV2 has been reported to cause AD-like pathology in post-mortem brain via dysregulation of the calcium signaling pathway. However, the potential effects of SCV2 on advancing AD pathology requires further understanding. To investigate the synergistic effects of genetic predisposition to AD and SCV-2 infection, human induced pluripotent stem cell (hiPSC) assembloids derived from APOE-ε alleles, including APOE-ε4/4, APOE-ε4/3 and APOE-ε3/3 cell lines were developed. The assembloids generated were novel in the types of brain cells and connections formed consisting of excitatory and inhibitory cortical neurons, astrocytes, oligodendrocytes, microglia, vascular endothelial cells and pericytes. The hiPSCs assembloids developed provide an important development in investigating the implications of infection on the brain and will be an insightful avenue of research regarding the SCV2 infection on neuronal function. In our study, we used these models to understand the mechanism of SCV2 infection on the brain. First, hiPSCs were infected with SCV2 after 3 months of culture. Then, samples were analyzed post infection using biochemical and molecular techniques to measure AD markers including amyloid-beta (aβ) and tau in insoluble and soluble fractions, and markers of SCV2 infection including SCV2 nucleocapsid and spike protein. In our results, we found that post-infection of

SCV2, there was a significant increase in a β and tau proteins in the insoluble and soluble fractionations of the APOE variants, specifically in the APOE- ϵ 4/4 and APOE- ϵ 4/3 insoluble fractionations. Overall, our data shows an increase in AD biomarkers in an isoform dependent manner following SCV2 infection. Further research will investigate downstream markers of the calcium signaling pathway as a possible mechanism of synergistic interaction in progressing AD pathology. Understanding the biochemical mechanisms that may be implicated by SCV2 infection in the brain, specifically for those predisposed to AD via APOE variants, can provide insight into AD pathology of the brain and avenues of treatment options for those with SCV2.

Hypoplasia of Dopaminergic Neurons by Hypoxia-induced Neurotoxicity is Associated with Disrupted Swimming Development of Larval Zebrafish

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Abstract

Hypoxic injury to the developing brain increases the risk of permanent behavioral deficits, but the precise mechanisms of hypoxic injury to the developing nervous system are poorly understood. In this study, we characterized the effects of developmental hypoxia (1% pO₂ from 24 - 48 hours post-fertilization, hpf) on diencephalic dopaminergic (DA) neurons in larval zebrafish and the consequences on the development of swimming behavior. Hypoxia reduced the number of diencephalic DA neurons at 48 hpf. Returning zebrafish larvae to normoxia after the hypoxia (i.e., hypoxia-recovery, HR) induced reactive oxygen species (ROS) accumulation. Real-time qPCR results showed that HR caused upregulation of proapoptotic genes, including p53 and caspase3, suggesting the potential for ROS-induced cell death. With HR, we also found an increase in TUNEL-positive dopaminergic DA neurons, a persistent reduction in the number of diencephalic DA neurons, and disrupted swimming development and behavior. Interestingly, post-hypoxia (HR) with the antioxidant N-acetylcysteine partially restored the number of DA neurons and spontaneous swimming behavior, demonstrating potential recovery from hypoxic injury. The present study provides new insights for understanding the mechanisms responsible for motor disability due to developmental hypoxic injury.

Breaking the Silence: Communicating with Photo Elicitation

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Abstract

Communication is key to life, relationships, and achieving our hopes, dreams, and aspirations. For individuals with intellectual disability, communication can be difficult and have a negative influence on one's quality of life. The use of photo elicitation can help individuals with disability access and express memories, emotions, feelings, and thoughts changing an abstract concept into a concrete concept. The result of this access and expression can result in a multitude of stories, details of events, personal emotions, and ideas from the individual giving others insight to his/her perception of quality of life which are often unknown to families, service providers and society.

This session explores the use of photo-elicitation with adults with Intellectual Disability to understand the individual's perceptions of personal development, career development, and self-determination as prompted by a series of photos over the course of 5 months to represent his/her lived experiences. These case studies provide insight to the thoughts and perceptions of adults with intellectual disability on their quality of life, a story that has been historically undocumented.

R-loop-mediated Neurodegeneration in Neuromuscular Disorders

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Abstract

R-loops are naturally occurring nucleic acid structures formed during the transcription. R-loops consist of three nucleic acid strands, nascent RNA hybridized to transcribing DNA strand (RNA:DNA hybrid) and a complementary DNA strand. Defects in R-loop resolution are associated with neuromuscular disorders, including spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis 4 (ALS4), characterized by spinal motor neuron degeneration. Mutation in the survival motor neuron 1 (SMN1) gene causes autosomal recessive SMA. Mutation in the senataxin (SETX) gene causes an autosomal dominant ALS4. The molecular mechanism of R-loop resolution is unclear. We report that the zinc finger protein ZPR1 binds to RNA-DNA hybrids, recruit SETX onto R-loops and is critical for the integrity of R-loop resolution complexes (RLRC) and R-loop resolution. To uncover the mechanism of R-loop resolution, we examined ALS4 and SMA disease models with low and high R-loop levels, respectively. The low levels of SETX-ZPR1 complexes onto R-loops result in decrease of R-loop resolution causing an increase in R-loop levels in SMA. ZPR1 overexpression increases recruitment of SETX onto R-loops, decreases R-loops and rescues SMA phenotype in neurons and patient cells. Interestingly, interaction of SETX with ZPR1 is disrupted in ALS4 patients that have heterozygous SETX (L389S) mutation. ZPR1 fails to recruit mutant SETX homodimer but recruits heterodimer with partially disrupted SETX and ZPR1 interaction. Notably, disruption of SETX-ZPR1 complexes causes an increase in R-loop resolution activity leading to fewer R-loops in ALS4. Modulation of ZPR1 levels regulates R-loop accumulation and rescues the pathogenic R-loop phenotype in ALS4 patient cells.

The Sensory Accommodation Framework for the Design of Accessible and Assistive Technologies for Autism

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Abstract

Autism is complex. Designing accessible and assistive technologies for autism is also complex. As more and more interventions look for digital solutions to deliver sustainable support, the need to bridge human-centered technology design guidelines with emerging intervention practices also increases. Many innovative technologies do not get adopted because of constraints on their usability. My decade of research as an assistive technology interventionist has recently culminated in the Sensory Accommodation Framework for the design of assistive technologies for autism. This presentation will present the framework for technology design from an interdisciplinary perspective so that teams of designers and interventionists can build technologies that can be acceptable and impactful. The Sensory Accommodation Framework addresses key tensions between therapeutic goals and quality of life for the end users. Applying a decade of research in the development of innovative technologies for autism, I review technology design mechanisms derived from theory as well as my user-experience studies. These technology guidelines support skill areas affected by the neurology of autism as: Sensory Integration (occupational therapy), Visual Nonverbal Communication (speech therapy, behavior therapy), and Hierarchical Visual Processing (cognitive neuroscience, vision). As a previous clinician, now professor of Interaction Design and Computer Science, I blend epistemologies from each group to make space for all stakeholders to come together.

Insulin Growth Factor Works Synergistically with Dopamine to Attenuate Diabetic Retinopathy by Downregulating Vascular Endothelial Growth Factor

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Abstract

Background: Diabetic retinopathy (DR) involves neurodegeneration accompanied with vascular damage leading to vision loss. Angiogenesis characterizes the disease progression from the Non-Proliferative Diabetic Retinopathy (NPDR) into the advanced stage known as Proliferative Diabetic Retinopathy (PDR). Dopamine (DA) deficiency in addition to low levels of insulin like growth factor (IGF-1) marks the NPDR stage and increasing IGF-1 manifests into PDR. Although IGF-1 proved to be proangiogenic manifesting neovascularization in the PDR stage but regulation of IGF-1 levels with adequate DA may delay the onset of angiogenesis.

Materials and Method: A group of 40 Wistar rats were maintained for a period of 8, 12 and 16 weeks after induction of diabetes with streptozotocin (STZ) and subsequently treated with DA and DA with IGF-1 in combination. The cytotoxicity of the combination is tested in retinal pigment epithelium (ARPE-19) cell line. The retinae from treated animals were assessed for morphological changes through H & E staining and TEM, DA level analyzed by HPLC, antiangiogenic mechanism of action confirmed through tube formation assay in HUVEC cell line and protein expression patterns of Akt, pAkt, Erk, and pErk, receptor levels by RT-PCR and immunofluorescence.

Results: Improved retinal morphology were observed in response to 10 mg/kg body weight of rats, DA as well as combination of DA and 2 µl/eye of IGF-1. DA levels were significantly lower in 16 weeks as compared to 12 weeks in retina and these levels were supported by DA levels in serum. The levels of angiogenic markers VEGFR1 and VEGFR2 were enhanced in 16 weeks compared to 12 weeks which was supported by tube formation assay in HUVEC cells. Consequently, Dopamine receptors DR1, DR2, DR4 and insulin growth factor-1 receptor, IGF-1R were also decreased in these time points which could be augmented by administration of DA in combination with IGF-1. Increased expression of pAkt and pErk indicates involvement of phosphoinositol pathway. The synergistic antiangiogenic effect of DA and IGF-1 was also established in an alternate CAM model. Inhibition of angiogenic factors causing vascular proliferation needs to be well timed in order to prevent the progression of NPDR to PDR stage.

Conclusion: L-DOPA at concentrations of 10 mg/kg body was able to attenuate IGF-1 induced hypervascularization as visible through H & E staining and TEM. The symptoms of PDR like onset of neovascularization due to disruptions in dopaminergic neurons and increased IGF-1 levels could be prevented by combination of DA and IGF-1.

Non-invasive Approaches to Promote Functional Recovery in a Preclinical Model of Cortical Stroke

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Abstract

Background: Stroke represents one of the most common causes of death and long-term disability, so strategies promoting post-stroke functional recovery are urgently needed. Several studies have shown that early treatment of ischemic stroke may reduce complications, disability, and death in the long term.

Objectives: Our study aims at: (i) evaluating the impact of non-invasive approaches, namely, transcranial direct current stimulation (tDCS) and intranasal administration of exosomes derived from human bone marrow mesenchymal stem cells (hMSCs), on forelimb motor function recovery and (ii) to clarify underlying mechanisms.

Methods: Experiments were performed in mice subjected to focal ischemia of the motor cortex induced by photothrombosis. Results showed that tDCS applied once per day for 3 consecutive days, starting 72 h after stroke increased the rate of motor recovery, anticipating it at the early subacute stage. In this window, tDCS enhanced BDNF (brain-derived neurotrophic factor) expression and dendritic spine density in the peri-infarct area, along with increasing functional connectivity between motor and somatosensory cortices.

Results: The efficacy of intranasal administration of exosome on forelimb motor performance - treatment started 48 h post-stroke and consisted in: a single dose/day, twice a week for 4 consecutive weeks. Mice subjected to stroke and treated with exosomes performed significantly better than vehicle-injected mice in the grid walking test since week 2 after stroke. Four weeks after stroke, reduction of initial deficit was about 63% in exosome-treated mice vs. 13% in vehicle injected mice. Histopathological assessment revealed reduced infarct size in exosome-treated mice, supporting neuroreparative effects of exosomes.

Neuroradiological Signature of Moderate Perinatal Hypoxia in the Rat Brain: Volumetric and Microstructural Changes Detected by *In Vivo* MRI

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Abstract

Multimodal *in vivo* magnetic resonance imaging (MRI) was used to disclose brain injury in juvenile rats after moderate perinatal hypoxia. The neuroradiological examination focused on volumetric and microstructural diffusion alterations. The observed changes were cross-referenced with histological and immunohistochemical data to understand the injury’s cellular and extracellular substrate. Wistar Han (RccHan: WIST) rats were subjected to either moderate hypoxia (8% O₂, 92% N₂/2h, n = 14) or normoxia (21% O₂, 79% N₂/2h, n = 14) on postnatal day one (P1). At P15, rats underwent *in vivo* structural and diffusion MR scanning protocol. Data were preprocessed and co-registered to a template, and volumetric and diffusivity parameters were measured in the whole brain and anatomical regions of interest. No differences in body or brain mass between hypoxic and control rats were detected at P15. However, MRI results comparing hypoxic rats to controls revealed widespread changes in regional brain volumes, particularly an increased volume in the colliculi and posterior sensory cortices of post-hypoxic rats at P15. Additionally, an elevation in fractional anisotropy (FA) values was observed in the A24a, A24b, and A33 of cingulate cortex in hypoxic rats. Alterations in FA values correlated with the emergence of myelinated axons, as evidenced by indirect immunohistochemical staining for myelin basic protein. The observed regional volume and diffusivity changes confirmed the cerebral cortical damage, predominantly in areas of primary myelination. Further research is required to elucidate the molecular mechanisms and pathophysiological implications underlying these demonstrated changes.

Future Treatment of Neurodegenerative Diseases; Why Multi-target Drugs

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Abstract

In Parkinson’s disease (PD) no drugs that are currently approved or being developed possess disease-modifying activity. PD subjects have a predisposition to depressive illness and a significant percentage also have dementia. Novel therapeutic approaches for the treatment of PD comprise drug candidates designed specifically to act on multiple CNS targets, rather than a single “receptor” as has been done with present drugs. At best the present mono-target drug therapy has symptomatic activity. Due to the complex etiology of PD, no “magic bullet” is expected to be developed to prevent the various cascade of neurotoxic events associated with the disease. Thus, we have hypothesized and developed an innovative novel approach toward neuroprotection and neurorestoration in PD with the development of multi-target drugs, which target an array of pathological pathways, each of which is believed to contribute to the cascade that ultimately leads to neuronal cell death. The compounds discussed originate from synthetic chemistry. The presentation will discuss examples of novel multi-target ligands (e.g., M30, M30P, and HLA-20) that combine cholinesterase (ChE) and monoamine oxidase (MAO) inhibitory moieties into an iron chelator-radical scavenger compounds that also possess neuroprotective and neurorestorative activities. They have the potential as disease-modifying therapeutics in PD. We have determined their neuropharmacological activities in cell cultures and in several established animal models of PD. M30 and M30P are brain-selective MAO-A and B and possess anti-depressant and anti-Parkinson’s activities. The major actions of these drugs are their ability to induce HIF1 (hypoxia-inducing factor) which regulates the cell cycle at G0 G1, resulting in neuronal differentiation and increase of endogenous neurotrophins BDNF, GDNF, VEGF, and erythropoietin. Both M30 and HLA-20 induce the biogenesis of mitochondria via activation of the PGC-1 α mitochondria nuclear transcription factor.

Physical Exercise Therapy for Autoimmune Neuroinflammation: Application of Knowledge from Animal Models to Patient Care

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Abstract

Background and Aims: Physical exercise (PE) impact various autoimmune and neurodegenerative diseases. Accordingly, clinical trials demonstrated the safety of PE in multiple sclerosis (MS) patients and indicated beneficial outcomes. There is also an increasing body of research on the beneficial effects of exercise on experimental autoimmune encephalomyelitis (EAE), the animal model of MS, and various mechanisms underlying these effects were suggested. However, despite the documented favorable impact of PE on our health, we still lack a thorough understanding of its effects on autoimmune neuroinflammation and specific guidelines of PE therapy for MS patients are lacking.

Methods: To that end, current findings on the impact of PE on autoimmune neuroinflammation, both in human MS and animal models are reviewed. The concept of personalized PE therapy for autoimmune neuroinflammation is discussed, and future research for providing biological rationale for clinical trials to pave the road for precise PE therapy in MS patients is described.

Results: PE modifies the pathogenesis of disease mainly due to modulation of encephalitogenic T cell responses, though direct neuroprotective mechanisms mediated by PE can also be involved. Research in animal models indicates that the effects of PE depend on several factors, particularly the intensity and the training paradigm.

Conclusions: In-depth understanding of the cellular and molecular mechanisms underlying the beneficial effects of exercise training on EAE and elucidating the training parameters that induce the optimal immunomodulation and/or neuroprotection are essential for designing effective clinical treatments in MS patients and other patients with autoimmune diseases.

Newborn Screening for Duchenne Muscular Dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) is one of the ten most severe and common pediatric genetic diseases and affects an estimated 1 in every 5000 male births. While DMD is a 100% fatal disease, the clinical community has demonstrated that immediate identification and early clinical interventions can add years, even decades to an individual's life span. As the landscape for the treatment of DMD has expanded, a DMD newborn screening (NBS) pilot study was conducted in New York State (NYS) to evaluate the feasibility and acceptability of NBS for DMD and to provide early diagnosis of screen positive babies. In NY, 36,781 newborns were screened for CK-MM. Forty-two newborns (25 male, 17 female) were screen positive and referred for diagnostic testing. Deletions or duplications in the *DMD* gene were detected in four male infants consistent with DMD or BMD. One female DMD carrier was identified. In addition, ethical issues were raised by NBS for DMD: 1) in an X-linked disorder, the potential burdens and benefits are very different for males and females: DMD has variable expression in females, and carrier females have available preconception options, and 2) NBS for a condition where only a portion of identified patients would qualify for treatment. However, these studies demonstrated that the infrastructure and screening technologies used are feasible to perform NBS for DMD. With an increasing number of available treatment options, the clinical utility of early detection for the newborns and their families lends greater support for NBS for this severe disease.

MRI Findings and the Occurrence of Posttraumatic Epilepsy – A Ten-year Cohort in Central Norway

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Abstract

Background: In a cohort of patients with moderate and severe traumatic brain injury (msTBI) with early MRI performed, we explored the role of lesion location and size in the development of posttraumatic epilepsy (PTE).

Methods: Patients >7 and <70 years old admitted between 01.10.04 - 01.01.14 to the St. Olav Hospital, Trondheim University Hospital with msTBI were prospectively included. MRI was performed ≤6 weeks post-injury and patients were followed-up for 5 years. Patients with preinjury epilepsy and patients who died before 5 years, without developing PTE were excluded. Fluid attenuation inversion recovery, diffusion weighted imaging and T2*gradient echo sequences were used to evaluate the presence and location of any lesions, and volume of brain contusions. Time from injury to first seizure was estimated in months. Covariates in the adjusted analysis were Glasgow Coma Scale (GCS) score, traumatic axonal injury grade, total volume of contusions in the frontal and temporal lobe.

Results: From 191 included patients, 13% developed PTE during the follow-up period. The median time from injury to first seizure was 12 months. Patients with PTE had more contusions in the frontal, temporal lobe, and larger total contusion volume than patients without PTE. From the adjusted analysis, we observed that lower GCS score and greater volume of contusions in the frontal and temporal lobe were independently associated with PTE.

Conclusion: Patients with lower GCS score, larger total contusion volume and larger contusions in frontal and temporal lobe were at particular risk of developing PTE and these patients might be informed about current precautions.

Perioperative Management of Spine Infections and Tumors

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Abstract

Spine infections and tumors are typically domains of neurosurgeons and orthopedic spine surgeons. However, over the years, it was proved to be beneficial to involve hospitalists (internal medicine trained physicians) in their management. Currently, co-management by spine surgeons and hospitalists is common. Typically, neurosurgery and orthopedic spine remain to be primary teams. However, a new model was currently developed at Thomas Jefferson University, where the primary team is led by a hospitalist, and surgeons remain in the consultative role. Thus, the perioperative management is primarily done by the hospitalist. This brief lecture highlights the multiple roles of the hospitalist in the perioperative management of spine infections and tumors, and experience and expertise gained in the process.

The Efficacy of Hyperbaric Oxygen Therapy in Traumatic Brain Injury Patients: Literature Review and Clinical Applications

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Abstract

Introduction: The application of hyperbaric oxygen therapy (HBOT) for patients with both acute and chronic traumatic brain injury (TBI) has been suggested for over five decades. In the past decade, the design and quality of studies were more detailed and thorough leading to an improved understanding of the uses of HBOT.

Objectives: A comprehensive literature review of HBOT application for patients with acute, and chronic TBI including persistent-post-concussion-syndrome (PPCS).

Methods: Literature search from 1969 to 2022 within the following databases: Cochrane Library, PubMed, Google Scholar, and Web of Science. Articles were first categorized into acute and chronic TBI and further classified into low, medium, or high-level quality.

Results: There was high level evidence including nine randomized controlled trials (RCT), one meta-analysis and two prospective study evaluating the effects of HBOT in acute settings. Mortality was significantly reduced, while functional outcomes in survivors showed mixed results. In chronic severe TBI, there were low to moderate evidence data including two uncontrolled prospective studies, two cohort studies and eight case reports suggesting improved outcomes. In chronic mild-moderate TBI (PPCS), there is high level evidence including eight RCT and five prospective studies suggesting significant improvement in cognitive function, symptoms, and quality of life.

Conclusions: HBOT may be recommended in acute-moderate-severe-TBI (Type-2a recommendation). However, further studies are needed to determine the optimal treatment protocols. HBOT can be recommended in chronic-TBI for a selected group of patients suffering from PPCS who have evidence of metabolically dysfunctional brain regions (Type 2a recommendation).

Infrared Microscopy of White Blood Cells based Machine Learning Methods: Differentiation between Alzheimer's Diseases and Dementia with Lewy Bodies

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Abstract

Introduction: Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are the two most well-known types of dementia. These types share similar symptoms and traits, particularly in the early stages, which might cause DLB to be mistaken for AD and vice versa. Although neither of these neurological disorders can be specifically treated with medicine, accurate and objective diagnosis of DLB and AD is of great clinical importance since it gives the doctors a routine, objective test to back up their diagnoses and enable them to targeted therapy that can delay the onset of these dementias' symptoms over time, thereby enhancing patients' quality of life.

Methods: The objective is to assess the potential of mid-infrared (IR) spectroscopy-based machine learning algorithms as a sensitive method to detect small changes in the biochemical structures that accompany the onset of AD and DLB using a straightforward peripheral blood test. White blood cells and plasma from 56 individuals—26 controls, 20 AD patients, and 10 DLB patients—were measured using IR microscopy, and the measured spectra were analyzed using a support vector machine.

Results: Our encouraging results show that it can distinguish between dementia (AD and DLB) and controls with a success rate of 86%, and yields a success rate higher than 93%, to discriminate between DLB and AD patients. The encouraging success of this method enables us to suggest a novel, simple, and useful tool for mental health practitioners that can improve the precision and objectivity of diagnoses of AD and DLB.

Regulation of NO/ROS Redox Signaling via 8-nitro-cGMP Formation by nNOS Splice Variants and Its Potential Involvement in Parkinson's Disease-like Neurotoxicity

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Abstract

We previously demonstrated different expression patterns of the neuronal nitric oxide synthase (nNOS) splicing variants, nNOS- μ and nNOS- α , in the rat brain; however, their exact functions are not fully elucidated. To investigate the role of NO/reactive oxygen species (ROS) redox signaling regulated by nNOS splicing variants in Parkinson's disease-like neurotoxicity, we used 1-methyl-4-phenylpyridinium (MPP⁺) treatment (a model of Parkinson's disease). *In vitro* studies using recombinant nNOS enzymes demonstrated that nNOS- μ produced NO, as did nNOS- α , in the presence of tetrahydrobiopterin (BH₄), an important cofactor for enzymatic activity. However, nNOS- μ generated more NO and less superoxide than nNOS- α in the absence of BH₄. MPP⁺ treatment induced more ROS production in nNOS- α -expressing PC12 cells than in those expressing nNOS- μ , which correlated with the intracellular production of 8-nitroguanosine 3', 5' -cyclic monophosphate (8-nitro-cGMP), a downstream messenger of nNOS redox signaling, and apoptosis in these cells. In rat cerebellar granule cells, MPP⁺ treatment enhanced 8-nitro-cGMP formation and subsequently induced S-guanylation and activation of H-Ras, following the elevation of extracellular signal-regulated kinase (ERK) phosphorylation. Pretreatment with a mitogen-activated protein kinase inhibitor attenuated MPP⁺-induced ERK phosphorylation and neurotoxicity. In conclusion, we demonstrate for the first time that NO/ROS redox signaling via 8-nitro-cGMP formation is involved in MPP⁺-induced neurotoxicity and that 8-nitro-cGMP activates H-Ras/ERK signaling. Our results indicate a novel mechanism underlying MPP⁺-induced neurotoxicity, and therefore contribute novel insights to the mechanisms underlying Parkinson's disease.

Some Structural Modifications to Donepezil to Improve Inhibitory Activity Against AChE and *In Silico* Medicinal Evaluations

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Abstract

In the current study, we designed new donepezil-derived molecules to enhance the inhibitory effect against AChE. By modifying some fragments of the donepezil, 16 new molecules were created. The designed molecules were docked to AChE, and the docking scores were determined. It was found that seven of the sixteen molecules studied had higher scores than donepezil. Besides that, the physicochemical properties and toxicity analyses of the seven molecules were studied using *in silico* tools, and they were compared to donepezil. We obtained satisfactory results with the new candidates (M3, M10, M12, M13, M14, M15, and M16) for AChE inhibitory activity. We recommend organic chemists to synthesize them and test these new molecular structures *in vivo* and *in vitro* activities.

Ischemic Stroke during Bevacizumab Treatment

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Abstract

A 25-year-old female presented with periodical right upper limb hypoesthesia and the radiological imaging revealed the presence of an extended AVM in the right frontoparietal region (Spetzler-Martin grade IV). The patient underwent two partial embolisms and received antiepileptic medication. Four years later, due to a significant increase in the frequency of seizures which did not respond to antiepileptic medication, the patient underwent gamma-knife radiosurgery. Eight months post operatively, there was a significant increase in the frequency of seizures and brain MRI revealed the presence of radiation necrosis and severe cerebral edema for which the patient received corticosteroids for three months and additional antiepileptic treatment was prescribed. Due to the absence of both clinical and radiological improvement, the patient received 4 cycles of therapy with bevacizumab. In-between the 3rd and 4th cycle the patient was presented with left hemiplegia. Brain MRI revealed the presence of ischemic stroke in the acute-subacute phase, located at the periventricular and deep white matter of the right frontal lobe. Bevacizumab is a monoclonal antibody which is being largely used in oncology for the treatment of several cancers. The use of bevacizumab in oncological patients has been related to an increased risk of stroke. According to the bibliography, the treatment of severe post radiation cerebral edema with bevacizumab is highly efficient and it is not associated with an increase in the risk of stroke in these patients. However, we present the case of a non-oncological patient who suffered a stroke while being treated with bevacizumab.

Tele-rehabilitation Project in Patients with Severe Brain Injuries Outcome Using Khymeia Virtual Reality Programs

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Abstract

Background and Aims: The American Thomas Bird, in the 70s, introduced the term “telemedicine” to indicate the practice of medicine without physical contact between doctor and patient, using an interactive and multimedia communication system. On 17 December 2020, the state-regions conference drafted a document “National guidelines for the provision of tele-rehabilitation benefits and services by health professions”, which regulates telemedicine and telerehabilitation in the Italian territory. TR replaces the traditional face-to-face patient-rehabilitator approach. In the present study, we propose the analysis of 15 clinical cases of patients with GCA, attending the Adelphi Day Center, Pad 12 Hosp. Santa Maria della Pietà, ASL ROMA 1, included in the home motor and cognitive telerehabilitation program, highlighting the benefits of these structured treatments. In the cases examined in the Adelphi Center, in the period between February 2021 and December 2022, tele-rehabilitation in GCAs proved to be one of the therapeutic pathways capable of producing greater results in the short/medium term. In our study, the 15 selected patients, 13 males and 2 females, aged between 40 and 60 years, with injuries of traumatic origin, had access to telerehabilitation 5 times a week for one hour of individual treatment, for a total of 3 months of rehabilitation cycle, assisted by a team composed of a physiotherapist, a psychologist, and an educator. The aim of this study is to demonstrate how the use of information technology can enable, restore, or improve the psychophysical functioning of people with GCA outcomes of any age with disabilities or disorders of various entities.

Methods: The technology used for Tele-rehabilitation interventions consists of (1) Home-kit case containing sensors, tablet, touch pen and (2) Telecockpit station for remote monitoring. The program makes use of virtual environments with software created for the execution and monitoring of physiotherapy and cognitive exercises specifically selected for the individual patient who is evaluated before the start of the project and at its conclusion through a battery of neuropsychological tests (MMSE; ENB-2; ASQ; CDQ) and physiotherapy (BERG; Asworth; Tinetti). The patients made daily connections of 1 hour, for a period of 3 months, carrying out 2 physiotherapy accesses, 2 cognitive accesses and one psychological access per week.

Results: The TRZ protocol has shown promising results in improving the health and quality of life of patients and their caregivers. The home location of the trainings guarantees the patient the serenity of being in a familiar context, the absence of distractors, the absence of the increase in stress due to getting ready and leaving the house to reach the place of rehabilitation. The one-to-one relationship with the therapist allows for greater concentration and motivational commitment on the part of the patient. In the analysis of the motor data, we found a significant increase in the degrees of flexion, extension, and lateral inclination in the movements of the trunk and in the stability of the upper limb subjected to training. As regards the cognitive data recorded by the machine itself and the analysis of the neuropsychological retests, we have found an improvement in attention, memory, praxic skills, speed of execution, and reduction of the average error. From a psychological point of view, the patients reported an absence of a sense of abandonment, a reduction in performance anxiety, higher levels of attention and an improvement in performance.

Conclusions: The use of TRZ technology in rehabilitation and maintenance of residual capacities for GCA patients provides multiple functional factors for a planned and structured use. Tele-rehabilitation allows the use of a personalized approach to care, since the whole protocol is created specifically on the needs, abilities and needs of the individual patient. It allows the reduction of the costs of the National Health Service, encouraging the continuity of care and the reduction of the time spent in hospitals. It provides the patient and his family with centrality in the rehabilitation process, as well as continuity of care. The innovative home tele-rehabilitation model of the ASL ROMA 1 integrates traditional home assistance and rehabilitation activities with those provided through new information technological solutions.

Evaluating Frontoparietal Network Topography for Diagnostic Markers of Alzheimer's Disease

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Abstract

Numerous prospective biomarkers are being studied for their ability to diagnose various stages of Alzheimer's disease (AD). High-density electroencephalogram (EEG) methods show promise as an accurate, economical, non-invasive approach to measuring the electrical potentials of brains associated with AD. These event-related potentials (ERPs) may serve as clinically useful biomarkers of AD. Through analysis of secondary data, the present study examined the performance and distribution of N4/P6 ERPs across the frontoparietal network (FPN) using EEG topographic mapping. ERP measures and memory as a function of reaction time (RT) were compared between a group of ($N = 63$) mild untreated AD patients and a control group of ($N = 73$) healthy age-matched adults. A concurrent cross-modal associative memory test and 128-channel high-density EEG facilitated data collection. By targeting select frontal and parietal EEG reference channels based on N4/P6 component time windows and positivity; our findings demonstrate statistically significant group variations between controls and patients in N4/P6 peak amplitudes and latencies during cross-modal testing, though there was no interaction effect. Our results also support that the N4 ERP might be stronger than its P6 counterpart as a possible candidate biomarker. We conclude by visually mapping FPN integration existent in healthy controls yet absent in AD patients during cross-modal memory tasks. The implications and limitations of these findings are discussed, as are foundations for future research in exploring processes and strategies that lead to identifying clinically useful biomarkers for the detection and treatment of AD.

Effect of Fitness Qigong on Gait of Patients with Parkinson's Disease

Betchy

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Abstract

Background and Purpose: Parkinson's disease (PD) is a neurodegenerative disease commonly seen in the elderly, which can lead to gait disorder and depression, and seriously affect the quality of life of patients. As a non-drug intervention for the adjuvant treatment of Parkinson's disease, exercise has a good effect on the improvement of gait disorder, balance loss and fall in patients with Parkinson's disease. Fitness Qigong is a traditional Chinese health exercise, which belongs to aerobic and slow exercise and is easy to learn and practice. This study intends to test the gait characteristics of Parkinson's disease patients before and after fitness Qigong exercise, so as to explore the effect of fitness Qigong exercise on the improvement of movement symptoms of Parkinson's disease patients.

Methods: In this paper, the influence of fitness Qigong exercise on Parkinsonism gait was analyzed by the method of literature data.

Results and Discussion: Fitness Qigong exercise can help improve the stride length and walking speed of patients with Parkinson's disease, increase stride time and reduce stride length variability, improve walking function, prevent fall, and increase walking safety. Panic gait was significantly reduced, and walking ability was improved, thus reducing the risk of falling.

Conclusion: Fitness Qigong exercise can improve the gait disorder of PD patients to a certain extent. It can effectively improve the walking ability and movement ability of PD patients in daily and emergency situations and improve their movement disorder symptoms.

A Pooled Analysis of Preoperative Inflammatory Biomarkers to Predict 90-day Outcomes in Patients with an Aneurysmal Subarachnoid Hemorrhage: A Single-center Retrospective Study

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Abstract

An inflammatory response after an aneurysmal subarachnoid hemorrhage (aSAH) has always been in the spotlight. However, few studies have compared the prognostic impact of inflammatory biomarkers. Moreover, why these inflammatory biomarkers contribute to a poor prognosis is also unclear. We retrospectively reviewed aSAH patients admitted to our institution between January 2015 and December 2020. The 90-day unfavorable outcome was defined as modified Rankin scale ≥ 3 . Independent inflammatory biomarker-related risk factors associated with 90-day unfavorable outcomes were derived from a multivariate anal-

ysis. ROC curve analysis was conducted to identify the best cut-off value. Then, patients were divided into two groups according to each biomarker's cut-off value. To eliminate the imbalances in baseline characteristics, propensity score matching (PSM) was carried out. A total of 543 patients were enrolled in this study and 96 (17.7%) patients had unfavorable 90-day outcomes. A multivariate analysis showed that the white blood cell count, the systemic inflammation response index, the neutrophil count, the neutrophil-to-albumin ratio, the monocyte count, and the monocyte-to-lymphocyte ratio were independently associated with 90-day unfavorable outcomes. The WBC count showed the best predictive ability (area under the curve (AUC) = 0.710, 95% CI = 0.652 - 0.769, $p < 0.001$). After PSM, almost all abnormal levels of inflammatory biomarkers were associated with a higher incidence of pneumonia during hospitalization. The WBC count had the strongest association with poor outcomes. Similar to nearly all other inflammatory biomarkers, the cause of poor prognosis may be the higher incidence of in-hospital pneumonia.

Pharmacotherapy of Schizophrenia According to Single Nucleotide Polymorphisms of Risk Genes in Schizophrenia

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Abstract

Schizophrenia has a genetic etiology in about 80% of patients concerned. Table 1 summarizes some important risk genes, the SNPs of the risk genes and an improved therapeutic effect or a lack of efficacy regarding a specific antipsychotic drug. The rs 165599 SNP of the COMT gene is connected with a higher therapeutic efficacy of risperidone, whereas another SNP of this risk gene is linked with a pharmacotherapy resistance. The GAD 67 gene is associated with a disturbed GABAergic neurotransmission, and in the hippocampus, GABAergic neurons which coexist with CCK weakly inhibit D2 dopaminergic neurons. The neuregulin-1 gene is linked with a glutamatergic dysfunction via NMDA receptors and an increased activation of the D2 receptor. The DAOA gene encodes as well, a glutamatergic dysfunction via NMDA receptors. The SNPs of the D2 receptor (rs 1801028) and D3 receptor (rs 6280) genes are correlated with a better therapeutic efficacy of risperidone, whereas the SNPs (rs 4680 and rs 1800497) of the D2 receptor gene are more frequently found in patients with a pharmacotherapy resistance. In this review, the neural networks in the mesolimbic system, hippocampus and prefrontal cortex are updated. In the future, it is of importance to examine the SNPs of schizophrenic patients in order to differentiate patients with a better response to a specific antipsychotic drug and patients with a pharmacotherapy resistance. The latter patients could be treated with the antipsychotic drug clozapine and an additional therapy with cariprazine, a partial D2 and D3 receptor agonist.

Association between Inflammatory Conditions and Alzheimer's Disease Age of Onset in Down Syndrome

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Abstract

Adults with Down syndrome (DS) have an exceptionally high prevalence of Alzheimer disease (AD) with an earlier age of onset compared with the neurotypical population. In addition to beta amyloid, immunological processes involved in neuroinflammation and in peripheral inflammatory / autoimmune conditions are thought to play important roles in the pathophysiology of AD. Individuals with DS also have a high prevalence of autoimmune / inflammatory conditions which may contribute to an increased risk of early AD onset, but this has not been studied. Given the wide range in the age of AD onset in those with DS, we evaluated the relationship between the presence of inflammatory conditions and the age of AD onset. We performed a retrospective study on 339 adults with DS, 125 who were cognitively stable (CS), and 214 with a diagnosis of AD. Data were available for six autoimmune conditions (alopecia, celiac disease, hypothyroidism, psoriasis, diabetes, and Vitamin B12 deficiency) and for one inflammatory condition, gout. Gout was associated with a significant delay in the age of AD onset by more than 2.5 years. Our data suggests that inflammatory conditions may play a role in the age of AD onset in DS.

GABRB2, a Key Player in Neuropsychiatric Disorders and Beyond

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Abstract

The GABA receptors represent the main inhibitory system in the central nervous system that ensures synaptogenesis, neurogenesis, and the regulation of neuronal plasticity and learning. GABA_A receptors are pentameric in structure and belong to the Cys-loop superfamily. The *GABRB2* gene, located on chromosome 5q34, encodes the β_2 subunit that combines with the α and γ subunits to form the major subtype of GABA_A receptors, which account for 43% of all GABA_A receptors in the mammalian brain. Each subunit probably consists of an extracellular N-terminal domain, four membrane-spanning segments, a large intracellular loop between TM3 and TM4, and an extracellular C-terminal domain. Alternative splicing of the RNA transcript of the *GABRB2* gene gives rise at least to four long and short isoforms with dissimilar electrophysiological properties. Furthermore, *GABRB2* is imprinted and subjected to epigenetic regulation and positive selection. It has been associated with schizophrenia first in *Han* Chinese, and subsequently validated in other populations. *Gabrb2* knockout mice also exhibited schizophrenia-like behavior and neuroinflammation that were ameliorated by the antipsychotic drug risperidone. *GABRB2* was also associated with other neuropsychiatric disorders including bipolar disorder, epilepsy, autism spectrum disorder, Alzheimer's disease, frontotemporal dementia, substance dependence, depression, internet gaming disorder, and premenstrual dysphoric disorder. Recently, it has been postulated that *GABRB2* might be a potential marker for different cancer types. As *GABRB2* has a pivotal role in the central nervous system and is increasingly recognized to contribute to human diseases, further understanding of its structure and function may expedite the generation of new therapeutic approaches.

Effects of Traditional Chinese Exercise on the Physical and Mental Health of Stroke Patients: A Meta-analysis based on Randomized Controlled Trail

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Abstract

Purpose: In recent years, traditional Chinese exercise has gradually become a means of exercise rehabilitation for stroke patients, and this study aims to systematically patients. the impact of traditional Chinese exercise on the physical and mental health of stroke patients.

Patients and Methods: Using computer searches PubMed, Web of Science, EBpatients.na National Knowledge Infrastructure (CNKI), Wan Fang Database, China Science and Technology Journal Database to obtain published randomized controlled Trails (RCT) related to stroke patients with traditional Chinese exercise that meet the evaluation criteria from the establishment of the database until September 2022. After a literature quality evaluation, RevMan5.4 was used for data processing.

Results: A total of 28 RCTs were included. The results of meta-analysis showed that the motor function [MD = 5.69, 95% CI (4.88, 6.49), $p < 0.001$], the equilibrium function [MD = 5.25, 95% CI (4.92, 5.58), $p < 0.001$], mental health [MD = -3.46, 95% CI (-3.96, -2.98), $p < 0.001$] were better than the control group.

Conclusion: The soothing traditional Chinese exercises based on Tai Chi and Health Qigong can improve the physical and mental health of stroke patients at the same time, and it is recommended to increase such exercises in the rehabilitation of stroke patients in the future.

Down Syndrome and Dementia: Monitoring Cognition and Clinical Change

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Abstract

Down syndrome (DS; trisomy 21) is a genetic neurodevelopmental condition that predisposes individuals to develop dementia due to Alzheimer and other pathologies, generally at a much younger age than is seen in typically developing individuals. This presentation will review historical and recent work to study the contributions of neuropathology to dementia in the context of DS, current issues in measurement and monitoring of cognition and dementia status in the DS population, and ongoing multi-site efforts to identify early biomarkers of cognitive and functional decline in parallel cohorts of adults with DS. Specifically presented will be highlights from the Alzheimer's and Down Syndrome (ADS) cohort study at the Sanders–Brown Center on Aging at the University of Kentucky, as well as the multi-site Alzheimer's Biomarker Consortium—Down Syndrome (ABC-DS).

Mitochondria Transfer for Intercellular Communication and Stroke Therapy

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Abstract

Mitochondria actively participate in the regulation of cell respiratory mechanisms, metabolic processes, and energy homeostasis in the central nervous system (CNS). Because of the requirement of high energy, neuronal functionality and viability are largely dependent on mitochondrial functionality. In the context of CNS disorders, disruptions of metabolic homeostasis caused by mitochondrial dysfunction leads to neuronal cell death and neuroinflammation. Therefore, restoring mitochondrial function becomes a primary therapeutic target. Recently, accumulating evidence suggested that active mitochondria are secreted into the extracellular fluid and potentially act as non-cell-autonomous signals in CNS pathophysiology. Here, we will present our findings that implicate the presence of cell-free extracellular mitochondria and the critical role of intercellular mitochondrial transfer from astrocytes to adjacent damaged neurons in stroke. We also discuss isolated mitochondrial transplantation as a novel therapeutic intervention in stroke and the future perspectives.

Oropharyngeal Dysphagia as the Main Expression of Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease. Only about 10% of ALS patients survive more than 10 years. Clinical studies show that multidisciplinary care statistically significantly improves survival compared to neurological care. ALS tends to manifest as limb weakness, but some patients present with bulbar symptoms, such as dysphagia and dysarthria. In rarer cases, the main symptom of ALS is oropharyngeal dysphagia. Respiratory muscle weakness is a relatively rare symptom at the onset of this disease and may lead to a fatal outcome due to aspiration pneumonia within about 1.4 years. These reasons led to a particularly complicated diagnosis of ALS in a 66-year-old Caucasian female patient complaining of dyspnea and coughing while drinking water. Notably, dyspnea is only present in one out of four treatment-seeking patients, and the course of ALS is non-specific. For these reasons, the diagnosis took an entire year while the patient underwent many tests and visited many specialists. However, the diagnosis was only made at a late stage of the disease. At present, the patient is almost unable to swallow food, water, or saliva, and is at a very high risk of aspiration, but refuses to have a percutaneous endoscopic gastrostomy performed. The objective of this case report is to highlight the fact that a symptom as simple as difficulty swallowing may be the result of severe disease, a frequent outcome of which is death.

Relationship of Length of Disease and Levels of Anxiety and Depression in Persons with Multiple Sclerosis during the COVID-19 Pandemic

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Abstract

Multiple sclerosis (MS) is a chronic neurological illness that impacts approximately 2.8 million individuals worldwide. The early age of onset (20 - 30 years), as well as the reduced quality of life related to the extended timeline of MS often leads to anxiety and depression. In 2020, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) caused a widespread infectious disease leading to the COVID-19 pandemic. The Centers for Disease Control and Prevention in the United States announced that individuals on immune-modulating drugs, such as those frequently prescribed for MS, are at increased risk for SARS-CoV-2. The combination of high SARS-CoV-2 risk status and unknowns related to immunotherapy and long-term disease outcomes was postulated to lead to increased anxiety and depression in persons with MS (PwMS). This study was undertaken to determine whether there were relationships between length of disease and the levels of anxiety and depression in a small population of PwMS in central Pennsylvania. The study protocol (#9784) was approved by the Penn State University College of Medicine Institutional Review Board, Human Subjects Protection Office; data were collected between January 2021 and July 2022. Participants completed a single page of demographics and 2 surveys on anxiety or depression. Anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS), which provides a reliable self-assessment for indicators of anxiety (HADS-A) or depression (HADS-D) in the previous one week. In addition, the Multiple Sclerosis Specific Beck Depression Inventory (MS-BDI) that queries specific qualities associated with depression including sadness, pessimism, sense of failure, and loss of interest specific to PwMS was included. Data were analyzed by two-tailed t-test, ANOVA, or chi-square using GraphPad Prism software. In this study based on 150 returned surveys, the gender ratio was 3.6:1 female to male, the age range was 41 to 75 years, and the mean length of disease (LOD) was 16.8 years (range 1-50 years). There was a significant difference ($p=0.009$) in mean HADS-A scores for PwMS with LOD of less than or equal to 15 years (7.1 ± 0.48) in comparison to PwMS who had the disease for longer than 15 years (5.24 ± 0.55). Scores on the depression-related surveys, HADS-D or MS-BDI, did not differ based on LOD. Of the respondents that had MS for 15 years or less, 53 were female and had HADS-A scores of 7.0 ± 0.6 , a value that did not differ from male PwMS (score = 6.7 ± 1.0). In conclusion, the length of disease has an impact on anxiety scores for both male and female PwMS suggesting that shorter period of time with MS resulted in greater levels of anxiety relative to those PwMS who had the disorder for greater than 15 years. More studies are needed to determine how specific durations interface with treatment, age, and sex.

Prevention of Dementia, Alzheimer's Diseases, Solid Water Particles, and Quantum Chinese Medicine

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Abstract

As a person gets older, his brain shrinks, and heats up. It can be seen as inflammation of the brain and is measured numerically by infrared imaging device at acupoints SJ 21 at the center of the ear, and GB14, at the forehead. A new high-tech product Solid- Water- Particles (SWP) that derived from the synthesizing Chinese Medicine with quantum physics is found to be constituents of Meridians. Drinking SWP will repair blockage of the meridians and enable qi and blood flow freely. When organs get sufficient nutrients, they will return to normal. Inflammation of organs will be reduced, and the shrinking of the brain will stop. Dementia and Alzheimer's diseases will be prevented. Twenty cases have been studied, the reduction of the brain from drinking SWP are shown in infrared images of the brain at acupoints SJ 21 and GB 14.

Non-pharmacological Therapeutic Strategies for Alzheimer's, Parkinson's, and Huntington's Diseases

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Abstract

Given the challenges in producing effective, disease-modifying drugs for the major neurodegenerative conditions, such as Alzheimer's, Parkinson's, and Huntington's diseases (AD, PD, and HD), nonpharmacological procedures may offer alternative curative approaches. Magnetic resonance-guided focused ultrasound has emerged as a noninvasive surgical tool for treatment of various brain diseases. It allows controlled opening of the blood-brain barrier, reduces amyloid and tau pathologies, and enhances hippocampal parenchyma in AD. Deep brain stimulation (DBS) is an approved procedure for treatment of PD and some other neurological conditions. Around 15 clinical trials of DBS on AD subjects have shown improvement in cognition and memory and enhancement of social performance. Stimulation by photo- or acoustic- oscillations of 20 - 50 Hz frequencies reduced amyloid and tau pathologies and improved the memory of AD mouse models, and at least one AD clinical trial is underway. Antisense oligonucleotide-based technologies are on the rise for treatment of neurodegeneration. An antisense drug HTT_{Rx}, i.e., DNA oligonucleotide that binds to disease-related mRNA and promotes its degradation by endogenous RNase, proved successful in HD clinical trials. Antisense therapy, as well as gene silencing strategies, hold promise for neurodegenerative disorders. Pluripotent stem cell (PSC) therapy has shown promise in treating PD. Grafting of human PSC-derived dopaminergic progenitor cells into the forebrain of primate or rodent models of PD resulted in significant behavioral improvement. Mesenchymal stem cells are able to differentiate into a variety of cell types, including neurons, and currently active clinical trials are aiming to use these cells for treatment of neurodegeneration.

Long COVID: Literature Review and Comparison of Impacts, and Pathophysiology, to Neurological Disorders Including Chronic Fatigue Syndrome/Myalgic Encephalitis, Multiple Sclerosis, and Dementia

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Abstract

Theories and proposed mechanisms for Long COVID (LC) development from COVID-19 (C-19), (previously called Encephalitis Lethargica with other entities) include: (1) Viral-induced auto-immunity and immune reaction impacting the neurovascular unit/Blood Brain barrier, microglia and CNS receptors, (2) Direct invasion by the virus via the olfactory epithelium and/or nervus terminalis ACE2 receptor uptake, and (3) reactivation of the Epstein Bar or other Viruses with SARS-CoV-2 infection. LC is reported to occur in up to 30% of patients who contract C-19. The majority of LC individuals were not hospitalized. LC impacts include: symptoms of dementia, obsessive compulsive disorder, anxiety, suicidality, post-traumatic stress disorder, and depression as well as post-exertional malaise and reduced occupational productivity. These symptoms have resulted in the formation of LC clinics to treat patients. This significant negative impact upon people's lives however has the potential to improve insight into other neurological disease processes.

In this talk will be discussed current literature and probabilities of these mechanisms including the lack of disease visualization on magnetic resonance imaging (MRI). Also discussed are similarities between LC and other neurological diseases clinically and at cellular levels including chronic fatigue syndrome/myalgic encephalitis, multiple sclerosis, neurocognitive/psychiatric illnesses, and dementia. These disease processes have underlying immunological similarities and underlying genetic markers including, but not limited to APOE4. There will also be discussed presumed and known impacts upon the glymphatic system, immune cellular markers (CSF/serum), cells/receptors that underlie these processes and how current LC therapy/ methods of prevention are related to these pathophysiological mechanisms.

G2019S-LRRK2 Induces Neurovascular Abnormalities in a Mouse Model of Parkinson Disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disease characterized by motor impairments resulting from mid-brain dopamine (DA) neuron loss. Mutations in LRRK2 cause genetic PD and contribute to sporadic PD. Here, we used LRRK2-G2019S transgenic mouse model to investigate abnormalities in arteriolar cerebral blood volume (CBVa) in various brain regions using the inflow-based vascular-space-occupancy (iVASO) MRI technique. CBVa was measured in the substantia nigra (SN), olfactory cortex and prefrontal cortex. Alterations in the blood volume of small arteries and arterioles (CBVa) were detected in the G2019S-LRRK2 mouse model of PD. Compared to non-transgenic mice, G2019S-LRRK2 mice at clinical stage showed decreased CBVa in the SN, but increased CBVa in olfactory and prefrontal cortex in both male and female groups. On contrast, WT-LRRK2 mice showed no change in CBVa in the SN (male and female), the olfactory (female) and prefrontal (female) cortex, but a slight increase in CBVa in the olfactory and prefrontal cortex in the male group only. These changes in CBVa in the SN and the cortex in G2019S-LRRK2 mice were corresponding with PD pathology. Our results suggest the potential value of CBVa as a marker for clinical PD studies.

Mechanism of Curcumin in Mitigating Oxygen-glucose Deprivation/Reperfusion-induced Endothelial Cell Injury through JAK/STAT3 Pathway

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Abstract

Reperfusion is the only approved therapy for acute ischemic stroke; however, it can cause deteriorated responses to aggravate brain damage, including declined infarction volume, brain edema and blood brain barrier (BBB) disruption. Endothelial layer is the primary defense of BBB, the dysfunction of endothelial cells is the hallmark of BBB disruption in cerebral ischemia/reperfusion (I/R) injury. In our previous study we demonstrated that curcumin supplementary could significantly alleviated cerebral I/R injury by attenuating BBB disruption, which related with anti-inflammation and anti-oxidative stress properties of curcumin in middle cerebral artery occlusion rat. To further explore the mechanism of curcumin, protect the BBB integrity against cerebral I/R injury *in vitro*. This study was conducted to detect the action of curcumin in alleviating oxygen-glucose deprivation/reperfusion (OGD/R) induced injury in human brain microvascular endothelial cells (HBMVECs). The OGD/R cell viability, and ROS levels were examined by CCK8 and flow cytometry. IL-1 β , IL-6, and TNF- α level were measured by ELISA. JAK/STAT3 pathway-related protein levels were measured by Western blotting. OGD/R treatment triggered oxidative stress and inflammatory responses, manifested as raised ROS and inflammatory factor levels, weakened cell viability, while curcumin attenuated the above OGD/R-induced injury. Meanwhile the OGD/R-induced activation of the JAK/STAT3 pathway was significantly inhibited by curcumin. Conjointly, curcumin probably impeded the JAK/STAT3 pathway to suppress oxidative stress and inflammatory response, thereby palliating OGD/R-induced HBMVEC injury. Furthermore, to perform its protective effect of against cerebral I/R induced BBB disruption.

Effect of Health Qigong Exercises on Heart Rate Variability in Patients with Parkinson's Disease

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Abstract

Background and Purpose: Parkinson's disease (PD) is a common neuronal degeneration disease, whose patients presented clinically with rigidity, muscle tremors, slowness of movement and postural instability. There are many medical treatment methods that can be used to prevent and treat Parkinson's disease, but they do not cure it and may cause the dependency of PD patients on these methods. In recent years, physical exercise as an adjuvant therapy and relief method is becoming mainstream. This paper is aimed at analyzing the influence of Health Qigong on Heart Rate Variability in PD treatment, and tries to provide a feasible adjuvant therapy for PD patients, to relieve and help treat PD.

Methods: 41 mild-to-moderate PD patients were randomly placed into experimental and control groups. The experimental group included 28 patients (male 11, female 17), with medication plus Health Qigong exercise; the control group had 26 patients (male 14, female 12) treated only with drugs. Two groups based on the general information of differences had no statistical significance ($p > 0.05$). 10 movements were chosen from Health Qigong. Led by a professional, participants did the exercise 5 times per week, 60 minutes every time, and the whole process lasted for 10 weeks. The data of Heart Rate Variability (HRV) was tested and studied before, during, and after intervention. Heart Rate Variability (HRV) involves a total of two indicators, one is the time domain (SDNN, RMSSD, and PDD50), and the other is the frequency domain (LF and HF). The experimental results of the experimental and control groups were compared using repeated measures ANOVA and independent samples t-test.

Results and Discussion: Compared with before in time domain, the values of SDNN between the experimental group and the control group had significant differences in the pre-test and interim test. In the experimental group, SDNN had very significant differences in the post-test ($p < 0.01$). RMSSD, PNN50 increased than before, but there was no significant. In the frequency domain, the two groups had significant changes. After the 8-week Health Qigong exercise, LF (MS2) significantly increased than before. It had significant differences between pre-test and post-test ($p < 0.05$). All other indices of experimental group increase than before, but there was no significant difference ($p > 0.05$).

Conclusions: In conclusion, after 10 weeks of Health Qigong exercises can improve HRV of PD patients at both elementary and middle stages. Health Qigong exercise can be added as one method of rehabilitation therapy.

Modeling Alzheimer's Disease Utilizing Human iPSC-cortical Neurons on MEA

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Abstract

Human-based functional cortical neural models are highly desired for investigating numerous neurological diseases. The use of induced pluripotent stem cells (iPSCs) provides a promising avenue for *in vitro* modeling due to its unique advantages: physiological relevance to human system, pluripotency and potentially inexhaustible source supply. We aimed to develop a functional human iPSC-derived cortical neuron (CN) system for investigating neurological disorders. One focus is modeling of cognitive dysfunction which is impaired in Alzheimer's disease (AD) and other dementia. First, we developed a protocol for differentiating cortical neurons from human iPSCs, accompanied by systematic characterization for their identity, maturity and functionality by immunocytochemistry and patch clamp electrophysiology. These neurons were then integrated onto microelectrode array (MEA) system, with the neurons cultured on circuit-encouraging surface patterned with lithographic technology. This CN-MEA system was analyzed for the functional maturation and synaptic formation. Then, a protocol was developed in this system to induce long term potentiation (LTP), the cellular base of learning and memory. To model AD, the neurons were treated with A β 42 and Tau oligomers, which caused damage of neuronal function analyzed by patch clamp, and impairment of synaptic plasticity demonstrated by the loss of LTP. These deficits were alleviated by AD drug treatment. Additionally, by integrating the cortical neurons differentiated from familial AD patient iPSCs, this CN-MEA model reproduced the AD-relevant phenotypes. In summary, a human-based functional cortical system was developed for the analysis of cognitive function, which can be applied to the modeling of different AD and other dementia.

Effect of Health Qigong Exercise on Lower Limb Flexibility of Patients with Parkinson's Disease

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Abstract

Background and Purpose: Parkinson's disease is characterized by rigidity and slow movement, difficulty in starting walking movement and frozen gait, and its limited range of motion will seriously affect the quality of daily life. Therefore, this study takes Health Qigong exercise as a means to observe the effect of exercise intervention on improving the lower limb function of patients with mild and moderate Parkinson's disease through Health Qigong exercise, providing valuable theoretical basis and reference basis for formulating exercise prescription for Parkinson's disease.

Methods: Twenty patients with mild Parkinson's disease were randomly divided into body-building Qigong intervention group and control group. The experimental group was treated with conventional drugs for 12 weeks. Three times a week, 60 minutes each time (preparatory activities, fitness Qigong exercises, and relaxation). The evaluation standard is the sitting body flexion test.

Results and Discussion: There was a significant difference between the two groups in the post-test, and the test results of the sitting body forward bending in the experimental group showed a significant effect ($p < 0.05$).

Conclusion: Fitness Qigong exercise has a positive effect on improving the flexibility of lower limbs of patients with Parkinson's disease.

Nuclear Receptor Corepressors in Autism and Intellectual Disability

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Abstract

Intellectual disability and autism spectrum disorders (ASD) have broad genetic bases. Nuclear receptor corepressor NCOR1/2 forms protein complexes with common ASD-causing genes and is a key regulator in hormonal actions or xenobiotics-induced responses. We found several pathogenic genetic variants in NCOR1/2 in sporadic ASD patients. NCOR1/2 recruits and activates histone deacetylase 3 (HDAC3) for epigenome modification. We found that abolishing NCOR1/2-HDAC3 interactions in mice led to social avoidance and memory deficits. Specific depletion of NCOR1/2 in GABAergic neurons caused cognitive dysfunction and downregulated gene expression of several GABAA receptor subunits in the hypothalamus, leading to hyperexcitation of GABAergic neurons. The excitatory-inhibitory (E/I) imbalance impaired long-term potentiation (LTP) formation in the hippocampal CA3 region through a hypothalamic-hippocampal circuit. Chemogenetic and optogenetic repression of the circuit rescued hippocampal synaptic plasticity and cognitive functions in mice with NCOR loss-of-function. We constructed a humanized NCOR1 knock-in mouse model (nKI+) containing the heterozygous NCOR1 c.2182+2T>G mutation identified from an autistic patient. nKI+ mice show ASD-like behaviors and memory deficits. snRNA-seq analysis of the hypothalamus from hnKI+ showed dysregulation of multiple genes related to neurotransmission, including neuregulins and GABAA receptor subunits. Pharmaceutical targeting of neuregulin or GABAA signaling with FDA-approved drugs rescued the memory defects. These results delineate molecular mechanisms underlying NCOR-mediated regulation of cognitive functions and lay the intellectual foundation for treating NCOR-related neurological disorders through drug repurposing.

Research on the Influence of Aerobics on the Static Balance Ability of People with Moderate Intellectual Disability

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Abstract

Objective: The health problems of people with intellectual disabilities can cause obstacles to motor development and basic motor skills, which is manifested by low balance ability or physical control ability. Good balance ability is particularly important for their healthy life, so this study aims to study the influence of aerobics on the static balance ability of people with moderate intellectual disabilities.

Methods: Sixteen people with moderate intellectual disability were randomly divided into control group (8 people) and experimental group (8 people). In the whole process of intervention, the control group did not do any project intervention to keep a normal life state, while the experimental group conducted aerobics intervention training for 13 weeks, three times a week, 90 minutes each time. Before and after the intervention for 13 weeks, the test of standing on one foot with eyes closed was performed.

Results: There was no significant difference in the data of the control group before and after the experiment ($p > 0.05$), but there was significant difference in the data of the experimental group before and after the experiment ($p = 0.025$). There was no significant difference between the pre-test data of the control group and the experimental group ($p > 0.05$), but there was significant difference between the post-test data of the control group and the experimental group ($p = 0.028$).

Conclusion: Aerobics can improve the static balance ability of people with moderate intellectual disability.

Effect of Health Qigong Combined Dance on Exercise-induced Emotion of Middle and Old-aged Women

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Abstract

Purpose: The purpose of this thesis is to study the effect of Health Qigong Combined Dance on exercise-induced emotion of middle and old-aged women.

Patients and Methods: In this study, 25 middle and old-aged women were intervened for 15 weeks (3 times per week, once using 60 min), electing The Exercise-induced Feeling Inventory (EFI) as statistical analysis and observation of the experimental results.

Results: Health Qigong Combined Dance has a relatively good effect on the exercise-induced emotion of middle and old-aged women in the dimension of vitality stimulation ($p < 0.01$); In the dimension of physical and mental calm, the effect was relatively good ($p < 0.01$); In the dimension of physical fatigue ($p > 0.05$) indicates that it will not bring too much physical fatigue to middle and old - aged women. In the dimension of positive investment ($p > 0.05$), the difference between groups was not statistically significant, indicating a very good effect from beginning to end.

Conclusion: Health Qigong Combined Dance has a positive effect on the emotional exercise of middle and old-aged women. It is suggested to carry out Health Qigong Combined Dance in the middle and old-aged people to bring happy and relax positive emotions to the practitioners.

Trauma-induced Onset of Non-intractable Epilepsy in a Patient with ACC: A Case Study

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Abstract

Case report of a 60-year-old patient with congenital corpus callosum agenesis (ACC) and interictal epileptiform discharges (IED) from the left anterior temporal region. No neurological deficits were present until a seizure occurred after a head-on motor vehicle collision while driving. This case report provides insight into the role of altered connectivity in individuals with ACC and non-intractable epilepsy. This case report underscores the importance of vigilance for potential deficits associated

with ACC, particularly in patients who present without any initial symptoms. Furthermore, it suggests that individuals with ACC and non-intractable epilepsy may benefit from dual therapy with Eslicarbazepine and Brivaracetam in the management of seizures. This case report highlights the impact of external factors such as trauma on the presentation of deficits associated with ACC and emphasizes the importance of understanding the varied clinical manifestations of this disorder. This case report considers the role of altered connectivity in individuals with ACC and non-intractable epilepsy, which can ultimately contribute to improved diagnosis and management of individuals with this disorder. This case highlights that though ACC is a congenital disorder, deficits associated with ACC can appear later in life due to external factors such as trauma. Additionally, it shows that while many patients with ACC present with variable neurological symptoms including seizures, this particular patient did not show any deficits until experiencing trauma leaving them with only non-intractable epilepsy. Third, this case also sheds light on the management of seizures in individuals with ACC through dual therapy using Eslicarbazepine and Brivaracetam.

Two-point Discrimination Test in the Oral Cavity

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Abstract

Background: The two-point discrimination test (TPD) is one of the most widely used neuro-testing methods that provides information of subject's spatial acuity.

Aim: Providing norms regarding the two-point discrimination values in the oral cavity among Jordanians.

Methods: Seven hundred and two (702) subjects were included in this study. The subjects were dental patients attending the dental clinics at the ministry of health in Jordan. All patients provided a signed written informed consent before including them in the study. The Institutional review board at Jordan University of Science and Technology approved the study. For every subject, a TPD of the hard palate, was performed using spring caliper with blunt tips. Five points were examined in the hard palate mucosa, two points opposing the right and left first molar, two points opposing the right and left canines, and one point in the incisive papilla region.

Results: The mean value of TPD was 1.649 mm (SD 0.803 mm) in the incisive papilla region, 1.767 mm (SD 0.798 mm) in the right canine region, 1.746 mm (SD 0.765 mm) in the left canine region, 1.726 mm (SD 0.790 mm) for the right molar region, and 1.678 (SD 0.825 mm) for the left molar region. Statistical analysis revealed significant differences between these regions and between males and females for the same region.

Conclusions: The study provided norms in the Jordanian population regarding the TPD values of the palatal mucosa. This might help neurological assessment of patients after oral surgeries.

Microarray Profiling Identifies Novel Circulating Noncoding RNAs in MCI

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Abstract

Mild Cognitive Impairment (MCI) is an intermediate state between normal aging and dementia and the identification of MCI subjects who will progress to AD (MCI-AD) is crucial for early diagnosis. Actually no one test represents the gold standard confirming that someone has MCI, but several works highlighted the role of ncRNAs in development and/or progression of neurodegenerative diseases. In the study, through microarray technology, we found an overexpression of lncRNAs and microRNAs and we did an enrichment analysis of lncRNAs/mRNA /microRNA coexpression network, from which is emerged what pathways are involved in MCI onset.

ASM-targeting ISU203 Improves Cognitive Memory via the Combined Effect by Affecting Both Microglial Cells and Th17 Immune Cells Indirectly in APP/PS1 Mouse Model

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Abstract

The activity of secretory acid sphingomyelinase (S-ASM) that hydrolyzes sphingomyelin to ceramide in the plasma membrane, increases in Alzheimer's disease (AD) patients. Importantly, it was reported that the inhibition of the S-ASM activity improves the AD pathologies including Amyloid- β plaque, neuroinflammation, and cognitive impairment. To develop a novel antibody therapeutics targeting ASM, we identified an ISU203 (#9104 clone) by phage display screening. Next, to demonstrate the in vivo efficacy of ISU203, repeated dose of ISU203 was administered in APP/PS1 mouse model. The ISU203 treatment clearly reduced ASM activity in plasma. Interestingly, deposition of amyloid- β plaque also decreased in both cortex and hippocampus of ISU203-treated mice significantly compared with control. Moreover, we confirmed the improvement of cognitive function using two behavioral tests: Morris water maze and Fear conditioning test. To understand the mechanism of action of ISU203, we further studied the effect of ISU203 on neuroinflammation in APP/PS1 model. We found that IL-17 production significantly decreased upon ISU203 treatment, resulting in the reduction of Th17-mediated inflammation. In addition, phagocytic function of microglia increased in ISU203-treated group. Therefore, ISU203 relieves two major causes of AD, neuroinflammation and amyloid- β plaque removal, by Th 17 inhibition and microglia phagocytosis respectively. In conclusion, ISU203 is suggested as a novel antibody therapeutic for AD patients through the combined indirect effect of both microglia and Th 17 cells.

3D Virtual Reality Prism Adaptation Simulation System for Hemispatial Neglect

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Abstract

Objective: Prism glass adaptation training is a treatment for hemispatial neglect syndrome. The aim of the study is to develop a 3D VR prism adaptation simulation system and to evaluate the effects of the VR training with the simulation system for hemispatial neglect.

Methods: The 3D VR prism adaptation simulation system was developed to implement the prism adaptation treatment. The VR prism training program consisted of 3 sessions, 10 times over 2 weeks. In the first session, the subjects were instructed to move their virtual hand straight to a midline target in the VR. The first session finished when the subjects succeeded the task 20 times continuously. In the second session, the virtual hand path was programmed to move 10° deviated rightwards, simulating the prism glass applied condition. The subjects missed the target to the right side initially. After adaptation to the deviation condition, the third session started, in which the deviation was eliminated. The subjects showed left side target missing initially, which was similar to 'the after effect' of prism glass training. Neglect tests (star cancellation test, line bisection test and Albert's test) were performed before and one week after the intervention.

Results: Ten subjects (M: F = 7: 3) with hemispatial neglect due to right brain lesion were recruited. All neglect test scores became improved after the virtual prism adaptation simulation training (Star cancellation 41.25% → 59.82%, Line bisection 48.51 → 64.76%, Albert's 62.75 → 92.50%) (p < 0.01).

Conclusions: Hemispatial neglect improved significantly using the 3D VR prism adaptation simulation program.

Identification of Tau Nucleation Core and Its Roles for Driving Tau Pathology in Alzheimer's Disease

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Abstract

In tauopathic conditions, such as Alzheimer's disease (AD), highly soluble and natively unfolded tau polymerizes into an insoluble filament; however, the mechanistic details of this process are not clear. In AD brains, only a small segment of tau forms β -helix-stacked protofilaments, while its flanking regions form disordered fuzzy coats. Here, we demonstrated that the tau AD nucleation core (tau-AC) sufficiently induced self-aggregation and recruited full-length tau to filaments. Unexpectedly, phospho-mimetic forms of tau-AC (at Ser324 or Ser356) showed markedly reduced aggregation and seeding propensities. Bio-physical analysis revealed that the N-terminus of tau-AC favored the fibrillization kinetics, while its phosphorylation induced conformation changes, sterically shielding the nucleation motif. Tau-AC oligomers, but not the monomers, were efficiently internalized into cells via endocytosis and induced endogenous tau aggregation. In addition, tau-AC-infected primary neurons showed abnormal axon initial segment (AIS) plasticity upon depolarization and retained mislocalized tau in dendritic spines. Furthermore, we observed significantly increased anxiety-like behavior and impaired memory retrieval in mice intracerebrally injected with tau-AC fibrils. These behavioral phenotypes corresponded to the neuropathological staining results and neuronal loss in the brain. These findings identified tau-AC species as a key neuropathological driver in AD, suggesting novel strategies for therapeutic intervention.

Recollection of Inaccessible Memories Among Patients Suffering from PTSD Receiving Hyperbaric Oxygen Therapy

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Abstract

Objective: Post-traumatic stress disorder (PTSD) is characterized by peritraumatic amnesia. Recent studies show that hyperbaric oxygen therapy (HBOT) can improve brain activity, microstructural integrity, and clinical symptoms of PTSD. A unique phenomenon of recollection of amnesic memories along the HBOT course, previously described, may reflect hippocampal neuroplasticity. The study aimed to characterize memory recollection during HBOT course among patients with PTSD.

Methods: A cohort of veterans with treatment resistant PTSD that participated in a prospective study that evaluated the effect of HBOT. The treatment consisted of 60 daily hyperbaric sessions. Each session includes exposure to 100% oxygen at pressure of 2ATA. The rate and course of memory surfacing among twenty-eight patients that completed HBOT protocol was analyzed.

Results: In 10 (35.7%) patients, recollection of new memories was reported during the HBOT course. Memory recollection mainly during the 2nd month of the 3-month course, with mean session of 30.5 ± 13.2 . In 9 of the 10 cases, prodromal symptoms such as distress, anxiety or worsening depression were documented, and in 4 cases somatic pain was reported prior to memory surfacing. The pain involved body regions that were later part of the surfacing memory and may be related to the somatic part of the memory. The pain and distress resolved after memory surfaced in a course that lasted 1 to 10 days.

Conclusions: Recollection of inaccessible memories accompanied by emotional distress and somatic pain is common during HBOT among patients with PTSD. This phenomenon may be related to a direct effect HBOT on the hippocampus previously reported.

Association between Complex Treatment of Oropharyngeal Dysphagia and the Risk of Aspiration Among Geriatric In-patients

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Abstract

Introduction: Oropharyngeal dysphagia (OD) is one of the most common geriatric syndromes with multiple complications. The most important task in the treatment of OD is to reduce mortality due to aspiration pneumonia. The aim of this study was to find the association between complex treatment of OD and the risk of aspiration in geriatric in-patients.

Methods: Permission was obtained by Bioethics center (No. BEC-2-12). 56 geriatric in-patients of the Geriatric department of LSMU Kaunas Hospital suffering from OD were enrolled. The Lithuanian version of the EAT-10 was used. All patients have been investigated using endoscopic evaluation of swallowing (FEES) twice – before and after complex treatment of OD: modified diet, physical training, and electrostimulation of swallowing muscles. Aspiration-Penetration (AP) scale was used for aspiration risk (AR) evaluation. Data was analyzed with Pearson coefficient and Wilcoxon test.

Results: The mean age of patients was 77.7 ± 9.2 years, 60.7% were women. The mild OD was in 19.6%, the medium – in 51.8 %, and severe – in 28.6% patients. The low AR was in 30.4%, the medium – in 39.3%, and high – in 30.4% patients. The EAT-10 score median was 13, the A-P score median was 4 points before and decreased to 10.5 and respectively to 3.7 points after complex treatment (p < 0.001). EAT-10 score >20 was observed in 17.9% patients before and decreased to 5.6% after treatment (p = 0.046).

Conclusions: About 30% of geriatric in-patients suffering from oropharyngeal dysphagia had severe OD and high aspiration risk. Complex treatment of oropharyngeal dysphagia was associated with lower risk of aspiration.

Innovative Stereoelectroencephalography-guided Radiofrequency Ablation System - *In Vivo* Swine Evaluation

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Abstract

Background: Drug-resistant epilepsy (DRE) impacts 30% of more than 50 million epilepsy patients worldwide. Stereoelectroencephalography (sEEG), where sEEG/depth electrodes are implanted into the brain to monitor seizure activity, is routinely performed to identify seizure onset zone(s)/networks. sEEG-guided radiofrequency ablation (RF) uses the already implanted electrodes to deliver electric current at high frequency (above 250 kHz) to raise the temperature between the active contacts sufficiently to destroy the seizing tissue.

Objective: Currently, the temperature at which sEEG-guided RF ablations are performed cannot be monitored. Here we evaluate a new RF ablation system, which uses FDA-cleared sEEG electrodes equipped with a unique temperature control accessory designed to monitor and maintain the temperature at which ablations are performed, in an *in vivo* swine model.

Methods: sEEG electrodes (n = 13) were implanted into the brain of two pigs. Monopolar and bipolar (between two adjacent sEEG contacts) RF ablations (n = 35) were performed using different temperature (70 - 90 °C) and time (30 - 600 s) settings. MRI and histology were used for lesion characterization.

Results: Lesions with diameter and/or length ranging from 4 - 10 mm were clearly identified in MRI and histology as spherical (monopolar) or ellipsoidal shape (bipolar). For most lesions, size was proportional to temperature and time. Histological

examination (n = 4) showed a necrotic center surrounded by neuropil vacuolation and intramyelinic edema. The adjacent neuroparenchyma was intact.

Conclusions: The RF system delivered clinically relevant RF energy to ablate porcine brain *in vivo*. The ability to precisely monitor and regulate temperature during the ablation has the potential to increase safety during epilepsy treatment.

Neuroprotective Agents based on RNA m6A Regulation

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Abstract

N6-Methyladenosine (m6A) is the most common cellular modification that occurs in the mRNA of eukaryotes, but also in microRNAs and some small nuclear RNAs. There is increasing evidence about mRNA m6A methylation dysregulation in the case of neurodegenerative diseases such as PD, AD and ALS, and neuropsychiatric disorders. By using *in silico*-based discovery, chemical synthesis, and biochemical studies, we had discovered unique small-molecule ligands that bind to and activate RNA m6A methylation through catalytic RNA m6A methyltransferase METTL3/METTL14/WTAP complex. In addition, we have identified several inhibitors of RNA m6A demethylases FTO and ALKBH5. The best compounds from each of these classes at 10 nM support the survival of 6-OHDA lesioned DA neurons in culture. Remarkably, the methyltransferase complex METTL3/METTL14/WTAP activator M4 improved motor behavior and protected DA neurons in rat 6-OHDA model of PD much more efficiently than neurotrophic factor GDNF. This is the first demonstration that RNA m6A regulators can protect DA neurons *in vitro* and *in vivo*. Furthermore, we have also discovered that the systemically administered METTL3/METTL14/WTAP activators are behaviorally active in preclinical *in vivo* tests for anxiolytic and antidepressant activity, and also displaying a profile of strong anti-apathy action. The strength of the compounds is their unique mode of action and high efficacy. Thus, our studies provide preclinical support for the use of compounds regulating the RNA m6A methylation as candidates for the further drug development against PD and neuropsychiatric disorders. 1 targets related to cancer and different viruses.

DNA Glycosylases Regulating Neuroinflammation in Alzheimer's Disease

Milena A. Egiazarian^{1*}, Paulina Schnur¹, Andreas Abentung^{1,2}, Mirta M. L. de Sousa¹, Magnar Bjørås^{1,3} and Katja Scheffler^{1,2}

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disease leading to dementia, triggering a neuroinflammatory response in the brain. Additionally, oxidative DNA damage is an important pathological factor in AD, and DNA glycosylases, enzymes that initiate DNA damage repair, have previously been shown to be involved in AD pathogenesis. Here, we investigate how different families of glycosylases affect neuroinflammation in the brain during AD progression in a mouse model of AD. Our results indicate that glycosylases alter both microglial and astrocytic function throughout the brain and already at early stages of the disease. Interestingly, depending on which type of glycosylase was depleted from the AD mouse model, the inflammatory response was either up- or downregulated. This highlights the importance of oxidative DNA damage repair in regulating neuroinflammation in AD.

Behavioral Symptoms in Patients with Mild Cognitive Impairment – Preliminary Results of Cohort Study

Nikita Cherkasov* and Igor Kolykhalov

Federal State Budgetary Scientific Institution “Mental Health Research Center”, Russia

Abstract

Study: Objective was to determine whether certain late-onset behavioral impairments are associated with conversion from MCI to dementia.

Methods: Participants were prospectively enrolled in an outpatient clinic of a specialized Alzheimer’s disease department and underwent clinical and psychometric assessment. Inclusion criteria: age of 60 and older; CDR total score of 0.5. Exclusion criteria: diagnosis of dementia; history of stroke; alcohol/substance abuse. All participants gave informed consent. Participants were reassessed 1 year after the initial visit. Statistical analysis was performed with RStudio, Wilcoxon-Mann-Whitney criteria was used to compare non-parametric data.

Results: 59 patients were included, of which 23 (39%) had no late-onset behavioral changes, 27 (45,8%) had affective symptoms (depression, apathy, anxiety), 9 (15,3%) demonstrated inappropriate behavior and irritability. Over 1-year follow-up 10 patients (“decline group” – DG) converted to dementia. DG was compared to a group of non-converted patients – “control group” (CG) matched by age (DG: 70.5 ± 9.5 vs CD: 71.9 ± 7.5) and initial MoCA score (DG: 21.8 ± 4.4 vs CD: 22.7 ± 4.6). FCSRT-IR performance showed predominance of the amnesic type of MCI (aMCI) in DG. Assessment of behavioral symptoms demonstrated higher prevalence of depressive and anxiety symptoms, apathy, lack of social norms in DG (MBI-C score in DG: 17.5 ± 6.5 vs CG: 6.0 ± 4.1). Patients converted to dementia in a 1-year follow-up were more likely to have mild behavioral impairment.

Conclusions: Our study reveals possible influence of mild behavioral impairment on the course of mild cognitive impairment.

Chronic Fipronil and Pyriproxyfen Exposure Leads to Short-term Effects on Anxiety and Locomotor Activity in a Zebrafish Model for Autism Spectrum Disorder

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Abstract

Autism spectrum disorder is a neurodevelopmental disorder known for its impairments in the social domain, communication, and repetitive and restricted behaviors or interests. The cure for this disorder is far from being discovered. Therefore, the use of animal models is one of the methods to investigate certain disorders. Zebrafish (*Danio rerio*) is a popular organism model used in biomedical research due to its most important features. In our study, we aimed to observe the effect of a chronic pesticide mixture treatment on zebrafish anxious behavior and locomotor activity. In order to accomplish this goal, 3 groups of animals were randomly selected from the housing tank with a number of 10 animals per group. During the treatment period, 2 of the 3 experimental groups were exposed to 50 µg L⁻¹ and 100 µg L⁻¹ fipronil and pyriproxyfen, and the last one was taken as control. Fish were daily tested in the light-dark box, and recorded for 4 minutes. The data was quantified through the EthoVision software. Regarding the anxious behavior, the control group did not exhibited strong preference for one zone as it was also seen for the 50 µg L⁻¹ group compared to the 100 µg L⁻¹ group which recorded the highest value spent in the light area. Significant changes were also obtained for the locomotor activity. The present findings provide evidence of the effect that pesticides can have on an organism even in a small amount, beside the possible involvement in triggering neurodevelopmental anomalies.

Cognitive Care Education: An Updated Cognitive Care Education First Edition

Russell Porter

Texas A&M University–Central Texas, Texas, USA

Abstract

This is an updated presentation to our Cognitive Care Education – First Edition Book – Published in 2020 by Cambridge Scholars. Specific updates include, but not limited to, literature support for each chapter, with an increased focus on compassionate care.

The Potential Use of Golgi Staining Method to Study Neurological Disorders

Sami Zaqout

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Abstract

Most neurological disorders are associated with alternations in neuronal morphology. Documenting such alternations in *in vivo* brain samples has always been challenging for the researchers. This is mainly due to the fact that the brain has millions of overlapped neurons. Different techniques have been used to visualize few numbers of neurons or even single neuron. Camillo Golgi, an Italian scientist, has discovered Golgi staining more than a century ago. Different modifications of the original method have been conducted afterwards. However, many researchers avoided this technique due to lack of details on critical steps that can be time-consuming and frustrating. Here we show samples of neurons stained by our well-established step-by-step protocol that has been used world-wide. This non-invasive method facilitates the analysis of neuronal morphology, dendritic arborization and dendritic spines. This can add great value to various studies on neurological disorders both in human and experimental animal models.

Motor Performance at Three Months Post Stroke Predicts Cognitive Functioning up to Two Years Follow-up

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Abstract

Introduction: Motor and cognitive impairment are prevalent consequences of stroke with long-lasting impact on daily functioning and both need to be addressed in rehabilitation. However, since cognitive deficits are less obvious than motor impairment, the focus is often on physical rehabilitation. The current study explored whether there is a link between cognitive and motor functioning in the first two years after stroke and whether measures of motor performance would predict cognitive functioning post-stroke.

Methods: Gross (Berg Balance Scale (BBS), 10-meter walk test) and fine motor (Stroke Upper Limb Capacity Scale (SULCS), Purdue Pegboard Test (PPT)) and cognitive functioning (information processing speed, cognitive flexibility) were evaluated in stroke patients (n = 47) at three months, one- and two-years post stroke, by computing correlations as well as predictive modelling.

Results: Measures of motor and cognitive functioning were correlated in the first two years post stroke. In the final prediction models PPT and BBS scores at three months post stroke contributed significantly to the prediction of the four cognitive tasks separately at all points in time.

Discussion: Both gross and fine motor measures were correlated to performances concerning information processing speed and cognitive flexibility up to two years after stroke and balance and fine motor dexterity contributed significantly to the prediction of cognitive performance. We conclude that evaluation of motor functioning in the acute phase of stroke could facilitate the

recognition of patients at risk for cognitive impairment. Focusing on both would improve stroke rehabilitation, patient care, and wellbeing.

Keywords: Stroke, motor and cognitive functioning, predictive modelling

Exogenous A β 1-42 Monomers Improve Synaptic and Cognitive Function in Alzheimer's Disease Model Mice

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Abstract

Growing evidence has suggested the poor correlation between brain amyloid plaque and Alzheimer's disease (AD). Presenilin1 (PS1) and presenilin2 (PS2) conditional double knockout (cDKO) mice exhibited the reduced 42-amino acid amyloid- β peptide (A β 1-42) level and AD-like symptoms, indicating a different pathological mechanism from the amyloid cascade hypothesis for AD. Here we found that exogenous synthetic A β 1-42 monomers could improve the impaired memory not only in cDKO mice without A β 1-42 deposition but also in the APP/PS1/Tau triple transgenic 3 \times Tg-AD mice with A β 1-42 deposition, which were mediated by α 7-nAChR. Our findings demonstrate for the first time that reduced soluble A β 1-42 level is the main cause of cognitive dysfunction in cDKO mice and support the opinions that low soluble A β 1-42 level due to A β 1-42 deposition may also cause cognitive deficits in 3 \times Tg-AD mice. Therefore, "loss-of-function" of A β 1-42 should be avoided when designing therapies aimed at reducing A β 1-42 burden in AD.

Keywords: Presenilins, A β 1-42, α 7-nAChR, Memory, AD

NPTX2 Loss of Function and Schizophrenia

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Abstract

Schizophrenia is a polygenetic disorder whose clinical onset is often associated with behavioral stress. Here, we present a model of disease pathogenesis that builds on our observation that the synaptic immediate early gene NPTX2 is reduced in cerebrospinal fluid of individuals with recent onset schizophrenia. NPTX2 plays an essential role in maintaining excitatory homeostasis by adaptively enhancing circuit inhibition. NPTX2 function requires activity-dependent exocytosis and dynamic shedding at synapses and is coupled to circadian behavior. Behavior-linked NPTX2 trafficking is abolished by mutations that disrupt select activity-dependent plasticity mechanisms of excitatory neurons. Modeling NPTX2 loss-of-function results in failure of parvalbumin interneurons in their adaptive contribution to behavioral stress and animals exhibit multiple neuropsychiatric domains. Since the genetics of schizophrenia encompasses diverse proteins that contribute to excitatory synapse plasticity, the identified vulnerability of NPTX2 function can provide a framework for assessing the impact of genetics and the intersection with stress.

DNA Glycosylases Regulating Neuroinflammation in Alzheimer's Disease

Milena A. Egiazarian^{1*}, Paulina Schnur¹, Andreas Abentung^{1,2}, Mirta M. L. de Sousa¹, Magnar Bjørås^{1,3} and Katja Scheffler^{1,2}

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disease leading to dementia, triggering a neuroinflammatory response in the brain. Additionally, oxidative DNA damage is an important pathological factor in AD, and DNA glycosylases, enzymes that initiate DNA damage repair, have previously been shown to be involved in AD pathogenesis. Here, we investigate how different families of glycosylases affect neuroinflammation in the brain during AD progression in a mouse model of AD. Our results indicate that glycosylases alter both microglial and astrocytic function throughout the brain and already at early stages of the disease. Interestingly, depending on which type of glycosylase was depleted from the AD mouse model, the inflammatory response was either up- or downregulated. This highlights the importance of oxidative DNA damage repair in regulating neuroinflammation in AD.

Matrix Metalloprotease-9 Inhibition Attenuates Ischemic Stroke Damage in Rodents When Given at the Time of Reperfusion: An Adjunct to Mechanical Thrombectomy?

Robert Singer

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Abstract

Objective: Matrix metalloprotease-9 (MMP-9) plays a critical role in infarct progression, blood-brain barrier (BBB) disruption, and vasogenic edema. While systemic administration of MMP-9 inhibitors has shown neuroprotective promise in ischemic stroke, there has been little effort to incorporate these drugs into endovascular modalities. By modifying the rodent middle cerebral artery occlusion (MCAO) model to allow local intraarterial delivery of drugs, one has the ability to mimic endovascular delivery of therapeutics. Using this model, the authors sought to maximize the protective potential of MMP-9 inhibition by intraarterial administration of an MMP-9 inhibitor, norcantharidin (NCTD).

Methods: Spontaneously hypertensive rats were subjected to 90-minute MCAO followed immediately by local intraarterial administration of NCTD. The rats' neurobehavioral performances were scored according to the ladder rung walking test results and the Garcia neurological test for as long as 7 days after stroke. MRI was also conducted 24 hours after the stroke to assess infarct volume and BBB disruption. At the end of the experimental protocol, rat brains were used for active MMP-9 immunohistochemical analysis to assess the degree of MMP-9 inhibition.

Results: NCTD-treated rats showed significantly better neurobehavioral scores for all days tested. MR images also depicted significantly decreased infarct volumes and BBB disruption 24 hours after stroke. Inhibition of MMP-9 expression in the ischemic region was depicted on immunohistochemical analysis, wherein treated rats showed decreased active MMP-9 staining compared with controls.

Conclusions: Intraarterial NCTD significantly improved outcome when administered at the time of reperfusion in a spontaneously hypertensive rat stroke model. This study suggests that supplementing endovascular revascularization with local neuroprotective drug therapy may be a viable therapeutic strategy.

Keywords: BBB = blood-brain barrier; DMSO = dimethyl sulfoxide; ICA = internal carotid artery; IV = intravenous; MCA = middle cerebral artery; MCAO = MCA occlusion; MMP-9; MMP-9 = matrix metalloprotease-9; NCTD = norcantharidin; VEGF = vascular endothelial growth factor; intraarterial therapy; ischemia reperfusion injury; neuroprotection; norcantharidin; stroke; tPA = tissue plasminogen activator; vascular disorders

Acceleration and Induction of Alzheimer's Neuropathology as an Effect of the Western Type of Nourishment

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Abstract

Introduction: Bad diet is known as a risk factor for Alzheimer's disease (AD), but the mechanisms remain not fully elucidated. The aim of the present study was to compare the effect of western diet (WD) on insulin signaling in the brain and its impact on the development of AD in familial and sporadic AD (FAD and SAD), i.e., in the presence of FAD mutation and in an unaltered genetic background.

Methods: To this aim, the WD effects on the formation of pathological amyloid- β (A β) and tau protein phosphorylation in the brain were investigated in the FAD mice model Tg2576 (APP^{swe}) compared with wild type C57BL/6 mice. Tg2576 and C57BL/6 males were fed WD or standard chow from the 3rd month of age and divided into 4-, 8-, 12- and 16-months old groups. Two brain structures were analyzed: the entorhinal cortex and hippocampus. Protein levels of p-IRS1(Ser616), IDE, p-Tau (Thr231) and APP were assessed by immunoblotting, while changes in neuronal location of p-Tau (Thr231) and A β formation were identified in brain sections by immunofluorescence.

Results: Under WD, early cerebral insulin resistance and altered p-Tau compartmentalization followed by A β formation were observed in wild-type mice. WD accelerated the onset of A β formation and p-Tau changes in Tg2576 mice, but independently of insulin signaling. The results showed differential sensitivity of hippocampal and cortical neurons to WD-related impairments.

Conclusion: Such findings are important for the development of personal strategies to prevention and therapies in FAD and SAD patients.

Funding: Polish National Science Center grant 2018/29/N/NZ7/01724, 2014/15/D/NZ4/04361.

Identifying Preclinical Alzheimer Disease and Correlation with Blood Brain Barrier Breakdown and Reduced Glymphatic Flow Using 3D ASL MRI

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Abstract

Introduction: The promise of disease modifying treatments for Alzheimer disease, the most prevalent form of neurodegenerative disease, is on the horizon. Early identification of patients in the most cost-effective, least invasive manner is necessary. By exploiting the early pathophysiology of the disease process, specifically blood brain barrier leak of small molecules, associated prolonged mean capillary transit time (cMTT) and glymphatic flow dysfunction (GFD), 3D Arterial spin labeling MRI provides a method to indirectly identify these changes noninvasively.

Methods: Our method uses 7 consecutive 3D TGSE (turbogradient spin echo) PASL (pulsed arterial spin labeling) sequences at 200 ms intervals beginning at 2800 ms post labeling to 4000 ms. No exogenous contrast agent is used. Scan time including reference FLAIR sequence is 19 minutes. Signal averages are obtained in identical large regions of interest within homologous bitemporal, bifrontal and biparietal regions across all 7 sequences. Results are transferred and graphed signal average vs. time on a spread sheet. The slope of the line is the regional clearance rate of signal.

Results: This technique has shown significant and reliable differences in AD subjects vs controls in our pilot study, as well as demonstrating transition in a patient presenting with MCI transitioning over 15 months to progressive dementia (manuscript in review). With further validation, this patient friendly, noninvasive technique will serve as a marker of MCI transition to progressive dementia pattern of clearance which precedes associated cognitive decline. The potential benefit will be more timely intervention, and reliable outcome measurement.

Effect of 660/850 nm LED on the Microcirculation of the Foot – Neurovascular Biphasic Reflex

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Abstract

Phototherapy (LED) can be used to stimulate the healing of chronic ulcers of the lower limb, as it affects healing cells and neurons. In this way, this study has sought to know if the heat stimulus of 660/850 nm contact LED is sufficient to trigger the response in the peripheral sympathetic nervous system of normal volunteers. The LED was applied on the right foot to forty-two normal volunteers followed by serial infrared images. After the stimulus, a biphasic hyperthermia curve was observed synchronously in both feet, in the right and left halluxes, while hyperthermia was attributed to the redistribution of postural blood flow in the plantar region, which may indicate independent neurovascular mechanisms. Thus, periodic thermographic analysis can be used in the evolution of the LED treatment.

Cerebrolysin Reduces the Risk of Conversion from aMCI to Dementia in First-degree Relatives of Patients with Alzheimer's Disease: A Prospective Comparative Study

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Abstract

Aims: The aim of the study was to evaluate the long-term effects of annual courses of Cerebrolysin therapy (2.5 years study) on cognitive functioning and the risk of conversion to dementia in first-degree relatives of patients with Alzheimer's disease (AD) diagnosed as amnesic mild cognitive impairment (aMCI) in comparison with a similar group of untreated relatives.

Study participants: The cohort included 88 first-degree relatives of AD patients with a MCI aged from 50 to 82 years (average age 65.0 + 9.9 years): 46 patients received Cerebrolysin therapy and 42 patients were not treated.

Study design: A prospective comparative study of the long-term effects of 3 annual courses of Cerebrolysin therapy (20 intravenous infusions of 20.0 ml Cerebrolysin in 100 ml 0.9% normal saline) and 3 months follow-up period in comparison with the cognitive functioning dynamics of the control group for the same period.

Methods: Clinical, neuropsychological, statistical. The following scales and tests were used to assess the dynamics of cognitive functioning: the Clinical Global Impression-Global Improvement scale – CGI-I [G. William, 1976], Mini-Mental State Examination – MMSE [M. Folstein et al., 1975]; Montreal Cognitive Assessment – MoCA [Z.B. Nasreddine et al., 2005]; test of 10 words memorization [A.R. Luria, 2002]; Boston naming test – BNT [E.H. Kaplan, H. Goodglass, Weintraub, 1983]; subtest 6 of Wechsler Memory Scale-Revised – WMS-R [D. Wechsler, 1955]; Clock Drawing Test – CDT [K. Shulman, 1986]; test of 5 geometric shapes memorization [E.D. Chomskaya, 2007]; Benton Visual Retention Test – BVRT [A.L. Benton, 1952]; subtest “sound” and “categorical” associations of Mattis Dementia Rating Scale – DRS [S. Mattis, 1976] and the Hugo Munsterberg test [H. Munsterberg, 1934]. The assessment was performed on a date before treatment, by the end of 1, 14, 27 and 30 months of the study.

Results: In the therapeutic group by the end of the 3rd course of Cerebrolysin therapy in 95.7% of cases was achieved a marked and moderate improvement on the CGI-I. According to all scales and tests, a significant improvement of the initial average group scores was found after each course of therapy. In the control group there was a significant deterioration of the average group scores of most of the cognitive scales and test by the end of the observation. The annual conversion from aMCI to dementia due to probable AD was 9.5% only in the control group. The average group indicators of all scales and tests significantly worsened starting from the 14th month of observation in the control group.

Conclusion: The absence of cases of aMCI conversion to dementia in the treated patients for 2.5 years of observation can serve as confirmation of a disease-modifying effect in Cerebrolysin. In a similar group of untreated relatives during the same period, 10 out of 42 people (23.8%) were diagnosed with dementia due to AD, which corresponds to the established population indicators of conversion from MCI to dementia (Petersen R.C. et al., 1999). These results confirm the previously reported data of multimodal preventive effects of the drug due to the impact on multiple neuropathophysiological mechanisms of the primary neurodegenerative process development (Gavrilova S.I., Alvarez A., 2021). The obtained results indicate the need for broader

clinical studies of the preventive effects of Cerebrolysin and to study the possibility of including such therapy in the programs of drug prevention of AD dementia in people at the highest risk of this disease.

Keywords: Alzheimer's disease, mild cognitive impairment, the first-degree relatives of patients with Alzheimer's disease, therapy, Cerebrolysin

Gene Therapy for Granulocyte-colony Stimulating Factor Against Global Ischemia

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Abstract

Exogenous G-CSF is neuroprotective in focal ischemic stroke. Despite exogenous G-CSF's extensive therapeutic potential, its plasma half-life is only 4 hours, limiting G-CSF clinical use. Therefore, G-CSF's efficacy needs to be re-evaluated, using approaches that would produce a lasting effect of G-CSF protein. This study tests the hypothesis that encoding human G-CSF (hG-CSF) in adeno-associated virus (AAV) would be efficacious against global ischemia. Global ischemia was induced via bilateral occlusion of the common carotid arteries (BCAO) for 30 mins. A single dose of either AAV-CMV-GFP or AAV-CMV-hG-CSF was dropped into the left eye of male Swiss Webster mice 30-60 mins post-BCAO. Four days post-BCAO, qRT-PCR and western blotting were performed for hG-CSF mRNA and protein expression. Western blotting was carried out 4-and-7 days post-BCAO for endoplasmic reticulum stress markers, GRP78 and CHOP, for autophagy markers, Beclin 1 and p62 and mitochondrion fission protein DRP1 and fusion protein OPA1. Immunofluorescence staining of glutamic acid decarboxylase (GAD) was performed 4-days post-BCAO. Double immunofluorescence for BrdU and Doublecortin was performed 14-days post-BACO on mice given BrdU (50 mg/kg). The mRNA and protein expression of hG-CSF was significantly increased ($p < 0.001$) in the AAV-CMV-hG-CSF. GRP78, CHOP, Beclin1 and p62, were downregulated ($p < 0.05$) by hG-CSF gene treatment. Mitochondrial fusion OPA1 was upregulated, while mitochondrial fission DRP1, was downregulated ($p < 0.05$) and a significant increase in GAD-positive cells in AAV-CMV-hG-CSF mice. A rise in colocalized BrdU+Doublecortin positive cells was also observed in AAV-CMV-hG-CSF mice. This study has shown that hG-CSF gene therapy is efficacious against global ischemic stroke.

Neuroprotective Effect of Argon, Krypton Inhalation in Photothrombosis Stroke

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Abstract

In our study, we performed 2-hour inhalation with argon and krypton for 3 days. Animals were randomly divided into 3 groups: control group with stroke + N₂ inhalation n = 10; experimental group with stroke + Ar inhalation n = 8; experimental group with stroke + inhalation Kr n = 10. Neurological status was assessed using the protocol described by De Rieck et al. (1989) and modified by J. Jolkkonen et al. (2000) An MRI study and euthanasia of the animals were performed on the 14th day after the stroke. The degree of brain damage was assessed by analysis of MRI images. The rat brain was sent for histological examination. Inhalation with argon and krypton had a significant impact on the studied parameters. The mean damage volume in the stroke + iAr group and the stroke group was 11.3 (8.8;16.6) mm³ and 20.7 (16.7;23.79) mm³, statistically significant differences between the groups ($p = 0.01$). Histological examination in the Stroke group on the 14th day shows typical changes in ischemic damage. In the nitrogen group, a shaft of glial cells is pronounced, destroying dead and damaged cells, in addition, a large number of foam cells are noted in the tissue structure, which absorb altered cells, trigger apoptotic mechanisms and then, at a later date, die, forming fibrous tissue, which underlies scar formation. Also in this group, newly formed vessels are visible, which are located on the periphery. There are no signs of capsule formation at this stage yet. In the Stroke + iAr and Stroke + iKr groups, signs of encapsulation are already noted, the newly formed vessels are already located in the thickness of the necrosis area, and not on the periphery. All this indicates the acceleration of tissue repair processes after ischemic injury.

Oropharyngeal Dysphagia as the Main Expression of Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease. Only about 10% of ALS patients survive more than 10 years. Clinical studies show that multidisciplinary care statistically significantly improves survival compared to neurological care. ALS tends to manifest as limb weakness, but some patients present with bulbar symptoms, such as dysphagia and dysarthria. In rarer cases, the main symptom of ALS is oropharyngeal dysphagia. Respiratory muscle weakness is a relatively rare symptom at the onset of this disease and may lead to a fatal outcome due to aspiration pneumonia within about 1.4 years. These reasons led to a particularly complicated diagnosis of ALS in a 66-year-old Caucasian female patient complaining of dyspnea and coughing while drinking water. Notably, dyspnea is only present in one out of four treatment-seeking patients, and the course of ALS is non-specific. For these reasons, the diagnosis took an entire year while the patient underwent many tests and visited many specialists. However, the diagnosis was only made at a late stage of the disease. At present, the patient is almost unable to swallow food, water, or saliva, and is at a very high risk of aspiration, but refuses to have a percutaneous endoscopic gastrostomy performed. The objective of this case report is to highlight the fact that a symptom as simple as difficulty swallowing may be the result of severe disease, a frequent outcome of which is death.

A Plea for Implementing the Use of Sex and Gender Variables in Biomedical and Health Research

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Abstract

Neurological and neuropsychiatric disorders affect men and women differently. Multiple sclerosis, Alzheimer's disease, anxiety disorders, depression, meningiomas and late-onset schizophrenia affect women more frequently than men, but it is the reverse for Parkinson's disease, autism spectrum condition, attention-deficit hyperactivity disorder, Tourette's syndrome, amyotrophic lateral sclerosis and early-onset schizophrenia, which are more frequent in men. The underlying biological reasons for sex and gender differences in the development of such devastating diseases are currently poorly understood because most pre-clinical research uses male rodents for cell or whole animal disease models and rarely studies both sexes, while women have been historically under-recruited or excluded from clinical trials. Hormones and epigenetic regulators are thought to be the main pathophysiological contributors to these sex-biased differences, but additional biological and non-biological influences may also be involved. We will present some evidence for the role of the sex chromosome complement, X chromosome inactivation, and environmental influences in differences in the vulnerability to brain disease between sexes. A pressing need for a better understanding of the genetic, epigenetic, and environmental mechanisms sustaining sex differences in neurological and neuropsychiatric disorders remains. We make a plea for implementing the use of sex and gender variables in biomedical and health research, which will be critical to the development of a precision medicine approach based on sex-tailored prevention and treatment.

Selective PPAR Activation Improves Behavioral Deficits and Pathology in Alzheimer's Disease Animal Model

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Abstract

The continuously increased association of Alzheimer's disease (AD) with the increased aging population and mortality rates indicates an unmet medical need and the critical need for establishing novel molecular targets for therapeutic potential. Peroxisomal proliferator activating receptors (PPAR), belong to the class of nuclear hormone receptors that are known to regulate energy in the body. There are three members of this class (delta, gamma and alpha), with PPAR-gamma being the most studied, as these pharmaceutical agonists offer promise for AD because they reduce amyloid beta and tau pathologies, display anti-inflammatory properties, and improve cognition. However, they display poor brain bioavailability, thus requiring high dosing and are associated with several adverse side effects on human health, thus limiting their clinical application. Methods: We have developed a novel series of PPAR-delta- PPAR-gamma agonists *in silico* with AU9 our lead compound that displays selective amino acid interactions focused upon avoiding Tyr-473 epitope in the PPAR-gamma AF2 ligand binding domain. Results: This design helps to avoid the unwanted side effects of current PPAR-gamma agonists and improving behavioral deficits, synaptic plasticity while reducing Amyloid-beta levels and inflammation in 3xTgAD animals. Our innovative *in silico* design of PPAR-delta/gamma agonists may offer new perspectives for this class of agonists for AD.

A Perspective Study on Applying the Science of Spaceflight in the Rehabilitation of Post Stroke Patients: Insights About the TheraSuit Method®

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Abstract

The microgravity exposure experienced by astronauts causes physiological changes that are debilitating, similar to the changes patients experience with brain disorders, such as stroke. Patients who are post-stroke, experience physiological changes that occur to the human body when exposed to bed rest, sedentarism and inactivity. These observed changes also include social isolation, confinement, muscle atrophy, bone density loss, cardiovascular weakness, alteration of the sensory motor system, vestibular disturbances, and alteration of vision. Space medicine has advanced in the translation of space technologies to terrestrial medicine, positively impacting daily clinical practice, mainly in the study of technologies used to counteract the deleterious effects of microgravity. The similarities between astronauts and post-stroke patients have provided a common challenge to the medical community regarding neurorehabilitation. However, the neural mechanisms underlying the effects of microgravity on stroke as well as how the use of a method based on space technology might contribute to stroke treatment, have not yet been discussed. Astronauts have been using an axial loading suit and resistive exercises to elicit proprioception to their body to counteract the detrimental effects of exposure to microgravity. In this sense, the TheraSuit® Method has been developed to provide proprioception and strengthening exercises to facilitate muscle activation against gravity. By using the garment TheraSuit® and resources simulating the spatial environment. In this review, we focus on recent evidence derived from animal studies and human trials, which implicate the deleterious effects of microgravity and bed rest on the human body, human brain structure and function, seeking a better understanding of the pathophysiology associated with these deleterious effects. And so, to understand how terrestrial therapeutic methods based on space medicine, such as the TheraSuit® Method, can effectively treat neurological patients with severe motor disorders and significant brain damage for thus, open new understandings, discussions and identify possible future directions for neurorehabilitation.

Multiprong Targeting with a Combination of Water-soluble CoQ10 and Ashwagandha Extract to Halt Progression of Neurodegenerative Diseases

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Abstract

Despite very good progress in understanding the mechanisms in the development of Alzheimer's and Parkinson's disease pathology, there is hardly any success in developing therapeutic or preventative modulators for these diseases. There are some general biochemical etiologies associated with the development of neurodegenerative diseases: (i) increased oxidative stress and accumulation of defective proteins, (ii) impaired proteasome system and autophagy, (iii) mitochondrial dysfunction, and (iv) inflammatory activation of microglia/astroglia. These interrelated/interdependent mechanisms could be triggered by amyloid β peptide oligomerization, tauopathy and/or by age-related decrease in anti-oxidative defense. Thus, AD and PD development are a multifactorial phenomenon leading to progressive neuronal loss. Any chemical interference targeting any one of the pathways may not be successful for treatment of these diseases. Furthermore, using chemo-modulators as therapeutics for AD patients over a long period could have severe toxic/psychological side effects. Natural health product, Ashwagandha extract in combination with water soluble coenzyme Q10 could target all these mechanisms and provide robust neuroprotection. Using rodent models of AD and PD, we have shown that oral delivery this combination leads to amelioration of behavioral and histochemical symptoms of these diseases. The exciting findings include resumption of autophagy, activation of pro-survival astroglia function, inhibition of oxidative stress and inflammation in the brain following treatment with this combination. These preclinical observations indicate that this combination treatment has a great potential for safe and successful therapy for AD and PD.

Experimental Rat Model of Neurocysticercosis: New Perspectives for the Control of Inflammation

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Abstract

Neurocysticercosis is an endemic disease in non-developed countries worldwide. The most frequent presentation is when the parasite is in the central nervous system. Two forms of NCC with different severity and response to treatment are distinguished. Parenchymal NCC, which generally does not compromise the patient's life and is susceptible to treatment, and the extra-parenchymal form (EXP-NCC), which is the most severe and frequently requires several cycles of cysticidal treatment and the concomitant use of glucocorticoids to prevent death from intracranial hypertension.

In our research group, we established an experimental murine model of EXP-NCC by injecting *Taenia crassiceps* cysticerci into the cisterna magna. The implantation and evolution of the infection were monitored by detecting the HP10 antigen and antibodies in the serum and CSF of the infected rats. The presence of parasites in the CNS has been confirmed by histological analysis and nuclear magnetic resonance. We have shown that chronic infection is associated with reduced lymphocyte proliferation resembling what occurs in human EXP-NCC. This model will allow us to evaluate new alternatives for the control of inflammation induced by cysticidal treatment and immunomodulatory treatments that restore and improve specific anti-cysticercal immunity.

Effects of Polystyrene Microplastics on Protein Expression of BDNF/TrkB and Survivability of HEK-293 cells

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Abstract

Contamination caused by the accumulation of plastic-derived microparticles has been an ever-evolving environmental issue for years caused by massive plastic production worldwide. This has enabled their introduction to our food web and daily-use products. Research has explored the implication of microplastic exposure at a cellular and molecular level. However, little attention has been focused on its effects during early-stage human development. Brain-derived neurotrophic factor (BDNF), along with its receptor TrkB, are proteins vital for neurodevelopment and neuronal survival. They play a role in fetal growth and posterior

maintenance of physiological and plasticity processes. BDNF has been targeted as a biomarker for early developmental disorders. Thus, our current project focuses on both BDNF and TrkB expression and cellular survival in response to physiologically relevant polystyrene microplastic (PS-MP) exposure using a human embryonic kidney cell line (HEK293). Cell cultures were subjected to PS-MP at a concentration of 4.8 µg/ml (5 ppm) for 48 h and compared to naïve preparations, during immunocytochemistry assays. Overall expression of either BDNF or TrkB was not affected. However, there was a significant decrease in BDNF expression specifically within the nucleus, suggesting possible subcellular BDNF translocation due to stress in response to PS-MP exposure. BDNF is known as an important transcription regulator and thus, based on our current results, future research will focus on significant changes in gene expression due to lack of BDNF regulation which may contribute to neurological and psychiatric disorders in response to early life PS-MP exposure.

Bisphenol-A Effects on BK Channels Surface Expression in HEK-293

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Abstract

Previous studies on the toxicity of Bisphenol-A (BPA) have revealed a variety of hazardous effects on human health especially in comorbid neurological pathologies like acute depression and anxiety disorders. BPA is a pollutant produced in large quantities that is commonly used as a plasticizer representing a threat not only to aquatic ecosystems but to human health. We have previously shown that physiologically relevant concentrations of BPA in C57 mice cause significant extinction deficits during contextual fear association experiments correlated to the development of anxiety disorders. However, the specific targets of BPA toxicity leading to this behavior anomaly are not fully understood. In the current study, we measure BPA effects on the surface expression of the large potassium calcium- and voltage-dependent channel (BK) involved in establishing key parameters for neural signaling mediating neuronal intrinsic excitability associated to fear learning. To achieve this, we used a stably transfected ZERO BK channel isoform fluorescently tagged expressed in human embryonic kidney (HEK-293) cells to monitor both overall and surface expression. Using confocal microscopy, we further quantified the expression FKBP5 in response to BPA treatment. Results show a significant linear increase in BK channel and FKBP5 expression as a function of BPA concentration. These results are consistent with the behavioral phenotype we have observed in response to BPA and its link to the development of anxiety disorders.

Clinical Application of Vasodilators in the Acute Phase of Ischemic Stroke

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Abstract

Ischemic stroke is a kind of disease of brain tissue dysfunction and necrosis due to a variety of reasons leading to cerebral blood flow deficiency, which is one of the most common causes of death in the world. The treatment of acute phase of ischemic stroke should put emphasis on early diagnosis, early treatment, early rehabilitation, and early prevention. Current drug treatments mainly include the thrombolytic drugs, anticoagulants, antifibrinogenic drugs and antiplatelet drugs, which can improve the circulation. But the efficacy of vasodilators is still lacking evidence-based support. This article reviewed the clinical application of vasodilators in the acute phase of ischemic stroke and suggested that using vasodilators to treat acute phase of ischemic stroke should be cautious, as they can cause intracranial steal phenomenon and aggravate cerebral edema, which is of referential significance in reasonably selecting proper diagnosis and treatment regimens for ischemic stroke, and further standardizing and perfecting the guidelines for the disease.