The 15th Annual International Dose-Response Conference

PRECONDITIONING: IN BIOLOGY AND MEDICINE

MECHANISMS AND TRANSLATIONAL RESEARCH

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ABSTRACT BOOK

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Facilitating Preconditioning through Neurotechnology: A Paradigmatic Approach for Using New Tools to Optimize "Old Tricks"

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The techniques and tools of neurosciences have developed at ever increasing pace and sophistication. Recent progress reflects efforts of the United States' *Brain Research through Advancing Innovative Neurotechnologies' (BRAIN)* initiative, and other large-scale brain research enterprises world-wide. A significant portion of these projects' work is directed toward developing novel approaches to modulating neural substrates and mechanisms both operative in health, and as affected by neuropsychiatric disorders.

To do so, we believe that it will be important, if not essential, to encompass a broader scope of research, so as to examine both "high tech" and "low tech" approaches. This is certainly valuable to a more global orientation (i.e. - internationally relevant and viable) to/of health promotions.

Therefore, we call for a more encompassing perspective (and paradigm) that entails and seeks to obtain four principal goals:

First, is capitalization upon use of new neurotechnologies to foster improved understanding of (a) brain substrates and mechanisms of cognition, emotion and behavior in health and pathology, and (b) various treatments that show promise in affecting these brain structures and functions.

Second, is to use this information to develop more mechanistically-based, integrative paradigm of assessment, therapeutics, and prevention. We call for the complementary, and synergistic use of both newer "high tech" (e.g. - neurotechnologic) and older "low tech" (e.g. – preconditioning) approaches.

Third, is to employ such interventions within a bio-psychosocial framework, to insure evaluation and therapeutic targeting of multiple factors contributory – and correlated to – pathology and health.

This framework is not without potential technical and (neuro)ethico-legal problems. These include: relative novelty of neurotechnological approaches and potential for unknown (and/or unanticipated) effects; concerns regarding informed consent, and provision/continuity of care. Thus, a fourth goal is to address these issues to reduce if not resolve questions and challenges arising in/from the articulation of such an integrative, complementary paradigm.

It's Adaptation to Reactive Intermediates, But Not as We Know It: Time is of the Essence

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Adaptation to changing conditions is a vital part of life. In fact, health is currently defined as 'the ability to adapt'. We are constantly exposed to reactive toxic intermediates which are either formed in situ or are present in the environment.
Adaptation entails either prevention of the formation of these reactive compounds or detoxification of these molecules. Several mechanisms can be discerned over time in these adaptation processes. Some examples illustrate these processes.
Rapid inhibition of formation of reactive intermediates is nicely illustrated by the metabolism of the drug orphenadrine, which is used in the treatment of pain and muscle spasms of various etiologies. A reactive intermediate, the N-oxide radical of N-desmethylorphenadrine (tofenacine) a metabolite of ophenadrine, inhibits its own formation via an isozyme specific complexation of cytochrome P-450 thus preventing its own formation and providing product-inhibition in the clinical pharmacokinetics of orphenadrine. This metabolic intermediate or MI-complex formation occurs with many compounds. Metabolism can, in this way, be re-directed to other, for the organism, less harmful pathways. These are rapid adaptations.
Adaptations that take more time are exemplified by inducing processes of cytochrome P-450. Different processes of induction of P450 with a concomitant variation in time scale are apparent. It has even been suggested that P-450 played an early role in evolution to cope with slowly emerging oxygen in the anaerobic environment, which enabled anaerobic life forms to adapt to oxygen.
Reactive intermediates (also those formed by P450) can be neutralized via microsomal glutathione (GSH) S-transferase. Alkylating intermediates are able to rapidly activate this protective enzyme system. It is increasingly recognized that protection on a longer time scale of GSH-dependent processes also occurs through activation of specific transcription factors by reactive electrophiles.
Health, defined as 'the ability to adapt', is a dynamic and continuous process. Appropriate adaptability creates the essence of life. Time determines the mode of adaptability.

Stimulus Frequency and Consequent Duration of the Induced Phenotype: Further Characterizations of the Hormetic Dose-Response Relationship

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While many features of the hormetic dose-response relationship have been extensively characterized with respect to stimulus efficacy and response magnitude, and on the notion of "early" or "late" responses, relatively little attention has been focused on how the duration of the protective response might be subject to modulation. Our previous work in mouse models of CNS conditioning revealed that intermittent presentations of a stimulus, either physiologic or pharmacologic, can extend the resultant periods of neuroprotection from days to months (Zhu Y et al., *Invest Ophthalmol Vis Sci*, 2007; Zhu Y et al., *J Ocular Pharm Therap* 2008; Stowe AM et al. *Annals Neurol* 2011). That said, inducing such long-lasting changes in phenotype requires identification of not only the appropriate magnitude, duration, and stimulus frequency that provides such a 'cumulative' effect, but perhaps even some degree of intentional stochasticity and/or ongoing modification of these parameters to prevent potential tachyphylaxis. Such a dose titration challenge is made greater by the presence of comorbidities, and the lack of biomarkers predictive of conditioning efficacy. Nevertheless, from a translational perspective, it would seem the 'therapeutic window' of the adaptive hormetic response may be broader than initially realized. Theoretically, such a long-lasting response may provide protracted resilience against chronic disease. Indeed, we also demonstrated that both repetitive preconditioning, and repetitive postconditioning (initiated after disease onset), ameliorated retinal ganglion cell soma and axon injury in a mouse model of glaucoma (Zhu Y. et al., *Mol Med* 2012; Gidday JM et al., *NeuroTherapeutics* 2015). Other studies, not widely recognized, report that the incidence or recurrence of specific injuries/diseases can be prevented (creating a "lifespan" phenotype), and/or recovery metrics augmented, by repetitively-presented stimuli. In my presentation, I will highlight the provocative literature on this topic, briefly address the epigenetic mechanisms underlying these long-lasting adaptive responses, and explore some of its broader biomedical implications.

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Molecular Dissection of Hormesis

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Thousands of examples of hormesis abound in the literature and include stimulation and responses. Alternative names for the phenomenon include “preconditioning” among others. Obvious examples in mammals include the immune response, which leads to thousand-fold (and more) increases in resistance to a microbial or viral infection. Tanning is another example of such a response. Several molecular pathways have been identified that are involved in the response to stimulus and subsequent rebound. Short-lived species have been used in several studies designed to uncover the molecular mechanism underlying hormesis. *C. elegans* , a short-lived nematode has been the focus of several of these studies. In *C. elegans,* response to heat, oxidative stress, and toxic foods, life span and/or resistance to the toxin can be up-regulated several fold. However, not all stimuli cause a hormetic response. Our lab has studied the insulin-like signaling (ILS) pathway that involves the first metazoan anti-aging mutation, which we named *age-1*. In a typical hormetic response, a toxic stimulus results in activation of a signal transduction pathway that causes a transcriptional shift mediated by one or more transcription factors (in this case DAF-16/FOXO). Nuclear localization of DAF-16 can result in transcriptional alterations in as many as 6,000 transcripts, which individually contribute a very small fraction of the total hormetic response. In *C. elegans*, life span, as well as resistance to toxins, have been shown to have hormetic responses mediated by the ILS pathway. An interesting stochastic effect modulates the level of hormetic response; this variation can be visualized using a visible “reporter” of response to stress, and animals sorted into different bins that can be shown to have differential response to the hormetic signal.

Preconditioning Biomedical and Therapeutic Applications: Part I

Ethanol Ingestion Elicits an Anti-inflammatory Phenotype to Limit Ischemia/Reperfusion Injury by a Neutrophil-dependent Mechanism

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The Optimal Ischemic Postconditioning Protocol and Its Relevance to Clinical Cardiology

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Linking Mechanism with Clinical Findings: Preconditioning and Prevention of Myocardial Infarction Damage

Andrew Redington, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Exercise is Medicine in the 21st Century - Emphasis on Efficacy, Dosing, Safety/Toxicity

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Remote Ischemic Conditioning to Prevent Organ Injury following Hemorrhagic Shock

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Neuroprotective Mechanism of Preconditioning Against Intracranial Stenosis and Ischemic Stroke

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Stress-Induced Preconditioning in the Inner Ear

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Ethanol Ingestion Elicits an Anti-inflammatory Phenotype to Limit Ischemia/Reperfusion Injury by a Neutrophil-dependent Mechanism

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The aim of this presentation is to summarize a large volume of work indicating that antecedent ethanol ingestion at low to moderate levels induces the development of an anti-inflammatory phenotype that limits the extent of postischemic injury when tissues are exposed to ischemia/reperfusion (I/R) 24 hrs later, with a particular emphasis on the role of neutrophils in eliciting this protection. Work conducted in our laboratory and by others indicates that the anti-inflammatory and tissue-sparing effects of ethanol ingestion 24 hrs prior to I/R are triggered by transient-receptor potential vanilloid-1 (TRPV1) channel-dependent release of calcitonin gene-related peptide (CGRP) from capsaicin-sensitive sensory neurons. CGRP release is associated with the production of tumor necrosis factor alpha (TNFα). These proinflammatory mediators elicit the release and activation of matrix metalloproteinase-9 (MMP-9, and perhaps other proteases) from tissue resident neutrophils. The enzymatic activity of MMP-9 liberates matricryptins from the extracellular matrix. These proteolytic digestion products activate large conductance, calcium-activated potassium (BKCa) channels on endothelial cells, which in turn upregulate heme oxygenase-1 (HO-1) expression and activity by an Nrf2/ARE-dependent mechanism. The enzymatic activity of HO-1 produces the powerful antioxidants bilirubin and secondarily-derived biliverdin and the antiadhesive signaling molecule carbon monoxide, which act in concert to prevent postischemic expression of endothelial cell adhesion molecules, thereby limiting I/R-induced leukocyte infiltration and neutrophil-dependent tissue injury. The antioxidant actions of ethanol-induced HO-1 activity may also serve to protect soluble guanylyl cyclase from redox inactivation during reperfusion, thereby preserving arteriolar responses to endothelium-dependent vasodilators and limiting capillary no-relow.

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The Optimal Ischemic Postconditioning Protocol and its Relevance to Clinical Cardiology

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A heart subjected to prolonged coronary occlusion can be protected against infarction by postconditioning it with a series of very brief reperfusion/ischemia cycles (IPOC) at the beginning of reperfusion. Examining IPOC's mechanism allows one to design an optimal protocol. During preconditioning (IPC) ligands including adenosine, bradykinin and opioids occupy receptors which initiate signaling to cause K_{ATP} in mitochondria to open. This activates a complex signaling cascade that ultimately inhibits lethal mitochondrial transition pores (MPTP) through redox signaling. In IPC the introduction of oxygen following the short ischemic period fuels that redox signaling and puts the heart into a protected phenotype. In the naïve ischemic heart the protective pathway is stalled at the redox signaling step, but low pH inhibits MPTP opening. When the heart is reperfused, reactive oxygen species (ROS) open MPTP much faster than redox signaling can establish a protected state. In IPOC the staccato reperfusion limits blood flow just enough to keep pH low while supplying enough oxygen to complete redox signaling to inhibit MPTP. That means that no reperfusion cycle should be long enough to normalize pH (< I min) and the cycles must be continued until a protected state is established (>3 min) before full reperfusion can be established. Unfortunately, recent clinical trials of IPOC have been disappointing, and these failures coincided with the introduction of anti-platelet agent loading in patients with acute myocardial infarction (AMI) prior to percutaneous coronary intervention. We have discovered that these drugs are actually pharmacological postconditioning agents, and, therefore, IPOC can offer no additional protection. Although the anti-infarct effect of platelet inhibitors has reduced morbidity and mortality from AMI, they have not eliminated them. We are now identifying interventions which can add to the protection from a platelet inhibitor and hopefully further protect these patients.

Linking Mechanism with Clinical Findings: Preconditioning and Prevention of Myocardial Infarction Damage

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It has long been known that pre-infarction angina is associated with better outcomes after established myocardial infarction. This natural form of 'preconditioning' was investigated experimentally by Charles Murry in 1986, and so his discovery of the phenomenon of 'local ischemic preconditioning' (IPC) is reaching its 30th anniversary. While an incredibly potent, biologically conserved, natural mechanism of protection against ischemia-reperfusion injury that is active in almost all species and tissues, the clinical utility of local IPC is limited. The relatively recent discovery that a similar level of protection can be induced by a remote ischemic stimulus, such as transient ischemia of a limb, (RIPC) has led to an explosion of potential clinical applications. RIPC has an early cytoprotective effect, but appears to be more biologically inclusive than e.g. pharmaceutical preconditioning. Indeed, the modification of the early and late effects of myocardial infarction by RIPC involve modification of key components that drive ischemia-reperfusion injury (endothelial, platelet and neutrophil activation), the subsequent local inflammatory responses (cellular infiltration and pro-inflammatory signaling), and reparative mechanisms (autophagy). Consequently, the clinical application of RIPC may be beneficial in the immediate peri-infarct period (as an adjunct to percutaneous coronary intervention and reperfusion) as well as in the remodeling phase during the weeks after MI. The experimental underpinnings, and the early clinical data to support these concepts will be discussed in this presentation.

Exercise is Medicine in the 21st Century – Emphasis on Efficacy, Dosing, and Safety/Toxicity

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Substantial evidence has established the value of physical activity (PA), exercise training (ET), and overall cardiorespiratory fitness (CRF) in the prevention and treatment of cardiovascular diseases (CVD). The role of low PA as the fundamental cause of obesity will be discussed, as well as CRF explaining the obesity paradox. The potential benefits of PA/ET and increases in CRF to protect against CVD will be discussed, especially the impact on psychological risk factors and stress-induced mortality risk. Most of the evidence indicates that the ET benefits especially occur at low doses, whereas very high levels of ET (e.g. marathons and triathlons) are associated with potential cardiotoxicity. Exercise is Medicine and optimal dosing for this potentially beneficial therapy will be discussed.

Remote Ischemic Conditioning to Prevent Organ Injury Following Hemorrhagic Shock

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Systemic ischemia/reperfusion and activation of immune cells resulting from hemorrhagic shock and resuscitation contribute to organ dysfunction in trauma patients. Strategies directed at preventing ischemia/reperfusion injury and the onset of inflammation may lead to better outcome in this patient population. Remote ischemic conditioning (RIC), a simple non-invasive intervention consisting of brief occlusion of blood flow to the limb to induce transient ischemia/reperfusion, has been shown to prevent injury in multiple organ-specific models of ischemia/reperfusion. We hypothesized that application of RIC could also confer organ protection in a trauma model of hemorrhagic shock and resuscitation. In a murine model of hemorrhagic shock, we applied remote ischemic conditioning on the hindlimb, which consists of four cycles of 5-minute ischemia and 5-minute reperfusion, and evaluated liver and lung injury following resuscitation. We saw that hemorrhagic shock resulted in elevated release of liver enzymes, expression of inflammatory cytokines, neutrophil infiltration, and protein leakage in the lungs, all of which were prevented by application of RIC prior to hemorrhage. We further demonstrated that RIC when applied during shock (per-conditioning) and during resuscitation (post-conditioning) was able to prevent liver inflammation and injury. To examine the mechanisms of RIC, we evaluated the effects of plasma derived from ischemic conditioned mice on neutrophil migration *in vivo* using a transgenic zebrafish model of inflammation. Zebrafish pretreated with ischemic conditioned plasma or dialyzed ischemic conditioned plasma (fraction >14 kDa) had reduced neutrophil migration towards the site of injury following tailfin transection when compared to zebrafish pretreated with control plasma or dialysate. These results suggest a role of humoral factor(s) mediated systemic protection induced by RIC through alterations in immune cell function. The beneficial effects of RIC, performed during the shock or resuscitation phase of care, suggests a role for its application early in the post-trauma period.

Neuroprotective Mechanism of Preconditioning against Intracranial Stenosis and Ischemic Stroke

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Generally, minor physical or chemical stress stimulates biological systems to generate an adaptive response, which may be beneficial to the systems. Preconditioning methods vastly differ in terms of the properties of their respective stimuli. Despite their differences, varying stimuli, such as ischemia, exercise, hypothermia, hyperthermia and oxygen provide different values of potential clinical utility. Our group has studied the features and mechanisms underlying the cerebral protection that is conferred through the utilization of exercise and ischemia against intracranial stenosis and ischemic stroke.

Ischemic conditioning is a brief ischemia that protects against subsequent and concurrent severe ischemia. Clinically, upper limb ischemic preconditioning has been used to prevent recurrent stroke in intracranial arterial stenosis, including for octo- and nonagenarians. The ischemic preconditioning triggers endogenous neuroprotective mechanisms in cerebral ischemia. Previous experimental studies have demonstrated that remote ischemic post- or per ischemic conditioning reduced brain edema in ischemia/reperfusion injury. This reduced brain injury was attributable to diminished matrix metalloproteinase-9 (MMP-9) expression and attenuated extracellular matrix protein loss in rats. AKT/GSK3beta-dependent autophagy contributes to the neuroprotection of limb remote ischemic conditioning after transient cerebral ischemic stroke.

Pre-ischemic exercise induces neuroprotection in stroke by increasing expression of neurotrophic factors, the extracellular matrix (ECM) proteins, integrins and angiogenic factors, as well as tumor necrosis factor (TNF-α) and heat shock proteins (Hsp-70). These factors all directly enhance the neurovascular unit and alleviate the harmful effects following ischemia/reperfusion injury. Furthermore, exercise preconditioning decreases expression of MMP-9 and Toll-like receptor-4, inflammatory response and apoptosis following ischemic insult.

Taken together, the various effects of pre-conditioning on the neural response to ischemia/reperfusion injury not only demonstrate potential treatments for chronic or acute ischemic events, but also unearth necessary background information for potential therapeutic and pharmaceutical interventions in the future.

Stress-Induced Preconditioning in the Inner Ear

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Hearing loss is the most common sensory impairment in humans. Hearing loss is often caused by death of mechanosensory hair cells in the inner ear. These cells are sensitive to death from a variety of stresses, including noise trauma, aging, and exposure to therapeutic drugs with ototoxic side effects. While severely stressful stimuli result in hair cell death, moderately-stressful preconditioning stimuli can trigger a robust protective response in the inner ear. Examples of moderate stresses that induce this preconditioned state include heat stress, noise stress (“sound conditioning”), and treatment with low doses of ototoxic drugs. Each of these preconditioning stresses results in a period of resistance to hearing loss caused by exposure to traumatic noise. In addition, preconditioning noise can also protect against hearing loss caused by ototoxic drugs, suggesting that the preconditioned state is a generalized response that can protect the inner ear against a variety of stresses that would otherwise cause permanent hearing loss. The molecular and cellular mechanisms underlying these protective responses are poorly understood. Our data suggest that signals from surrounding cell types, including glia-like supporting cells and resident macrophages, play important roles as mediators of stress-induced preconditioning in the inner ear. Harnessing these intrinsic protective responses may allow the development of clinical therapies to reduce hearing loss and balance disturbances caused by noise trauma or ototoxic drug exposure.

Preconditioning Biomedical and Therapeutic Applications Part II

Fighting Neurotoxicity with a Double-Edged Sword: The Dual Role of Thrombin in Neuron Health

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Intermittent Hypoxia-Induced Spinal Motor Plasticity: Implications for Spinal Injury

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Hypoxia Induction of Vascular Remodeling in the Brain: Defining the Dose-Response Relationship

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Parameters of Hormetic Preconditioning Stress and Resilience to Trauma in Rats

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Is Hyperbaric Oxygen the Preconditioning Agent of Choice?

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Redox Modulation of Vitagenes by Hormetic Antioxidants: Relevance to Aging and Neurodegeneration

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Preconditioning for Traumatic Brain Injury

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Fighting Neurotoxicity with a Double-Edged Sword: The Dual Role of Thrombin in Neuron Health

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Like many mediators of inflammation, thrombin's role in the nervous system is not well understood. Under conditions of blood-brain barrier compromise (e.g., neurosurgery or stroke), thrombin can result in neuroapoptosis and the formation of glial scars. Despite this, preconditioning with thrombin has been found to be neuroprotective in models of cerebral ischemia and intracerebral hemorrhage. We investigated the effects of physiologically relevant concentrations of thrombin on cortical neurons using culture-based assays. We found that low concentrations of thrombin (1 nM) enhances neurite growth and branching, neuron viability, and protects against excitotoxic damage. In contrast, higher concentrations of thrombin (100 nM) are potentially detrimental to neuronal health as evidenced by inhibition of neurite growth. Lower concentrations of thrombin resulted in equivalent neuroprotection as the antifibrinolytic, aprotinin, and the direct thrombin inhibitor, argatroban. Interestingly, exogenous application of the species-specific thrombin inhibitor, antithrombin III, was detrimental to neuronal health; suggesting that some endogenous thrombin is necessary for optimal neuron health in our culture system. We conclude that an optimal concentration of thrombin exists to enhance neuronal health.

Intermittent Hypoxia-Induced Spinal Motor Plasticity: Implications for Spinal Injury

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Spontaneous spinal plasticity contributes to limited functional recovery of respiratory and non-respiratory motor function after incomplete spinal cord injury (SCI). Strategies to induce additional spinal motor plasticity have considerable potential to enhance functional recovery. An important model of spinal motor plasticity that has guided our development of new strategies to treat chronic SCI is phrenic long-term facilitation (pLTF), a long-lasting increase in phrenic motor following acute intermittent hypoxia (AIH). Repetitive AIH preconditioning enhances AIH-induced pLTF, indicating that AIH preconditioning elicits pLTF meta-plasticity, increasing the potential of repetitive AIH as a therapeutic tool to restore breathing capacity following chronic, incomplete cervical SCI. With moderate AIH, phrenic motor facilitation (pMF) is initiated by serotonin 2-receptor activation. In contrast, with severe AIH, adenosine 2A receptor activation predominates. Both pathways to pMF increase receptor tyrosine kinase (TrkB) signalling within phrenic motor neurons, thereby amplifying phrenic motor output. AIH-induced respiratory motor plasticity can be harnessed to improve breathing capacity in rodent models of cervical SCI and motor neuron disease (ALS). However, we have come to realize that AIH and AIH pre-conditioning also elicit similar mechanisms in **non-respiratory** motor neurons, improving limb/leg function in rodent models and humans with chronic, incomplete SCI. Intermittent hypoxia induced spinal motor plasticity may be a general feature of motor systems, reflecting an evolutionary coupling of hypoxia, breathing and movement (swimming) in aquatic vertebrates. We continue progress towards understanding cellular mechanisms of intermittent hypoxia induced motor plasticity, factors that amplify or constrain plasticity, its biological significance and clinical applications. Although research on intermittent hypoxia induced motor plasticity is still in its infancy, progress has been rapid, and there is considerable promise that it will lead to novel, safe and effective therapeutic approaches to treat devastating clinical disorders that compromise respiratory and non-respiratory motor function.

Reference

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Hypoxia Induction of Vascular Remodeling in the Brain: Defining the Dose-Response Relationship

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Severe cerebral hypoxia triggered by ischemic stroke leads to rapid neuronal death and loss of functional brain tissue. Interestingly, in animal models, pre-conditioning with mild hypoxia (8-10% O_2) confers protection against subsequent ischemic stroke, mediated in part through an extensive vascular remodelling response. In light of the therapeutic potential of hypoxic pre-conditioning, the goal of this study was to establish the dose-response relationship between level of hypoxia and extent of cerebrovascular modelling, and to define the mildest level of hypoxia that promotes remodeling. Mice were exposed to different levels of continuous hypoxia (8-21% O_2) for seven days before different aspects of vascular remodeling were evaluated, including endothelial cell proliferation, total vascular area, arteriogenesis (formation of new arteries), and endothelial expression of tight junction proteins (key components of the blood-brain barrier) and the angiogenic proteins fibronectin and $\alpha5\beta1$ integrin. For most events, the threshold level of hypoxia that stimulated remodeling was 12-13% O_2, though tight junction protein expression was upregulated by milder hypoxic levels of 14-16% O_2. Interestingly, many parameters displayed a biphasic dose-response curve, with peak levels attained at 10% O_2, but declined with increasing hypoxia. Further analysis in the 12-13% O_2 range suggested that vascular remodeling occurs by two separate mechanisms: (i) endothelial hyperplasia, triggered by a hypoxic threshold of 13% O_2, which leads to increased capillary growth, and (ii) endothelial hypertrophy, triggered by a more severe hypoxic threshold of 12% O_2, which leads to expansion of large vessels and arteriogenesis. Taken together, these results define the hypoxic thresholds for different parameters of vascular remodeling in the brain, and point to two separate mechanisms mediating this process.

Parameters of Hormetic Preconditioning Stress and Resilience to Trauma in Rats

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Hormesis is the process by which small stresses build resilience to large stresses. We pre-exposed rats to various parameters of mild-to-moderate preconditioning stress prior to traumatic stress in the present experiments to assess the potential benefits of hormetic training on resilience to traumatic, uncontrollable stress. Rats underwent varying stress pre-training parameters prior to exposure to uncontrollable traumatic stress in the learned helplessness procedure. The ability to prevent the exaggerated fear responding and escape deficits that normally follow experience with traumatic stress were used as a measure of the benefits of hormetic training. Four experiments examined the effects of number of training sessions, stressor severity and pattern of rest between pre-training stress sessions. Repeated exposure to mild restraint stress or moderate shock stress eliminated both the enhanced fear conditioning and shuttle-escape deficits that result from exposure to traumatic, inescapable shock. The pattern of rest did not contribute to resilience when the pre-exposure stressor was mild, but was vital when the preconditioning stressor was moderate, with an alternation of stress and rest being the most effective procedure. The data also suggest that the level of resilience may increase with the number of pre-exposure sessions. Two additional experiments demonstrated the efficacy of ineffective preconditioning procedures is dramatically increased when rats consume a concentrated glucose solution following each preconditioning session. Post-stress glucose ingestion has been shown to reduce the impact of stress and increase resilience in previous research.

Is Hyperbaric Oxygen the Preconditioning Agent of Choice?

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Complications associated with modern medical and surgical interventions detract from clinical outcomes, significantly reduce the patients' quality of life and add significant cost to an already burdened healthcare system. In an effort to reduce iatrogenic organ and tissue injury, preconditioning strategies have become popular. The technique of ischemic preconditioning (IPC) has received the most attention and confirms the potent protective effect that a sublethal stress can induce in complex tissues. IPC and related techniques of remote IPC (rIPC) and hypoxic preconditioning (HPC) are difficult to apply clinically and have had poor translational success in clinical trials. Hyperthermia (heat shock) and endotoxin administration likewise are effective, but are not clinically relevant, agents to achieve tissue level protection in humans. Hyperbaric oxygen therapy (HBOT) is a safe and widely available medical treatment used to heal diabetic foot ulcers, radiation ulcers and to treat carbon monoxide poisoning and decompression illness. HBOT at 1.5-3.0 atmospheres (1140-2280 mm Hg) has been reported to successfully precondition the heart, brain, kidney, spinal cord and liver against acute ischemia-reperfusion injury in multiple animal models. We have recently tested and confirmed the hypothesis that HBOT pretreatment (2.4 atm x 60 min) of human microvascular endothelial cells protects these cells from oxidant injury in vitro. This cytoprotected phenotype is associated with acute changes in more than 8,000 genes based on a genome-wide microarray analysis. Gene expression changes were dominated by genes regulating the cytoprotective chaperones as well as genes regulating pro-proliferative and anti-oxidant functions (Ingenuity Pathway Analysis). A limited number of human controlled trials have been completed and demonstrate successful protection of the heart and brain during coronary artery bypass surgery by the administration of preoperative HBOT. Hyperbaric oxygen is an attractive agent for testing in human preconditioning trials as it is a safe, convenient and widely available.

Redox Modulation of Vitagenes by Hormetic Antioxidants: Relevance to Aging and Neurodegeneration

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Alzheimer's disease (AD) is the most common form of degenerative dementia whose therapeutic strategy current pushes the development of drug targets on the basis of cell signaling pathways. Dietary antioxidants have recently been demonstrated to be neuroprotective through the activation of hormetic pathways, including vitagenes. Over the past decade there has been a remarkable increase of interest in hormesis as a result of more significance being given to low dose effects and the use of more powerful study designs which have enabled to identify rational approaches to detect hormetic biphasic dose responses in the low dose zone[1]. Given the broad cytoprotective properties of the heat shock response there is now strong interest in discovering and developing pharmacological agents capable of inducing stress responses. We will introduce the emerging role of exogenous molecules such as polyphenols capable to induce endogenous neuroprotective mechanisms through hormetic-based effects leading to regulation of fundamental processes such as mitochondrial function and resistance to oxidative stress. In addition, we will present and discuss the most current and up to date understanding of the possible signaling mechanisms by which polyphenols by activating vitagenes can modulate signal transduction processes enhancing defensive antidegenerative mechanisms[2,3].

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Preconditioning for Traumatic Brain Injury

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Ischemic preconditioning (IPC) has been shown to be both cardio- and cerebroprotective against subsequent ischemic insults. Insights into IPC mechanisms have been obtained with preclinical studies using stroke models. Little is known if such IPC knowledge can be used to mitigate traumatic brain injury (TBI). TBI treatment is now focused on the prevention of primary injury and reduction of secondary injury. However, no single effective treatment is available as yet for the mitigation of traumatic brain damage in humans. Both chemical and environmental stresses applied before injuries have been shown to induce consequent protection against post-TBI neuronal death. This concept termed “preconditioning” is achieved by exposure to different pre-injury stressors to achieve the induction of “tolerance” to the effect of the TBI. However, the precise mechanisms underlying this “tolerance” phenomenon are not fully understood. A summary TBI pathophysiology, existing animal studies presented here demonstrates the secondary mechanisms at work after TBI include ischemic-reperfusion (I/R). Therapeutic targeting of the I/R could promote preconditioning against chronic secondary mechanisms that underlie TBI. Thus IPC based approaches benefit diffuse and focal type of TBI. This led to the HOPES Trial (HypOthermia for Patients requiring Evacuation of Subdural Hematoma: A Multicenter, Randomized Clinical Trial. Such studies could help discover clinical targets in which pre-TBI preconditioning can be applied.

Chemical and Radiation Implications of Preconditioning

Age During Pre-Conditioning Hormesis Might be as Important as Dose for Improving Performance in insect models

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Low Doses, Adaptive Responses and Bystander Effects; Where are We Now?

Carmel Mothersill, McMasters University, Hamilton, ON

Radiation Induced Adaptive Protection

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Age During Pre-Conditioning Hormesis Might be as Important as Dose for Improving Performance in Insect Models

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The long-term effects of environmental stress are seldom studied and understood. While this is particularly true for the negative effects of abiotic stress, it is also the case for the positive effects that physiological conditioning hormesis can have. Using multiple insect models, I have shown that short (1 to 2 hour) exposures to conditioning treatments can improve organismal performance for weeks and even months. While it is clear that dose, whether intensity or duration of treatment, plays a crucial role in a hormetic framework, there is another factor that seems to be central to the repeatability and scale of these effects. That factor is the age of the animal. Generally, younger animals tend to a have a higher capacity for benefiting from conditioning treatments or for buffering the negative side-effects of stress. However, the developmental period that is key for achieving those long-term positive effects of conditioning may be different in different organisms and to be seriously considered during experimental design. My previous works shows that an hour-long treatment of anoxia (complete oxygen depletion) was not life-threatening to several species of insects; but also boosted their cellular defenses which were beneficial when challenge with a stronger stressor (i.e. ionizing radiation). In all cases, this led to an increase in male performance that lasted into advanced age. Ongoing work shows that the age at which the conditioning treatment is applied appears to be as crucial as the dose. The short anoxia treatment that can improve performance (flight), reproduction, and longevity can have zero effect if applied to early or too late and thus a type of sensitive period exists for the maximum benefit. These data suggest that additional work is warranted to understand this sensitive period and whether it can be extended.

Low Doses, Adaptive Responses and Bystander Effects; Where are We Now?

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The field of low dose radiobiology has advanced considerably in the last 30 years from small indications in the 1980's that all was not simple to a paradigm shift which occurred during the 1990's which severely dented the DNA centric theories which had dominated until then. However while the science has evolved, the application of that science in medicine and environmental health protection has not. A reason for this appears to be the uncertainties regarding the shape of the low dose response curve, which lead regulators to adopt a precautionary approach to radiation protection. However the recent advances in preconditioning research suggest that one sided application of a precautionary principle may actually be doing harm and that a more flexible approach based on sound knowledge of basic mechanisms and individual variation in response may need to be considered. This presentation will review low dose effects and mechanisms focussing on so called non-targeted effects which predominate at low doses. The aim will be to demonstrate just how variable low dose responses are, and how they are so dependent on context, underlying genetics, other environmental stressors and epigenetic responses. When aiming to protect, the approach is always to err on the side of caution which currently means reducing exposure using the ALARA principle but what if the low dose exposure is beneficial? How can this be accommodated in regulatory systems especially if it only applies to subsections of the population or if the dose of highest benefit (DHB) is on a spectrum determined by other factors? The idea will be explored in this paper, that lessons can be learned from radiation protection approaches to non-human biota where populations not individuals are the target of protection efforts. While clearly the target of protection for humans is the individual, some of the modelling approaches being used to derive system level risk factors, may yield new concepts deserving of exploration.

Radiation Induced Adaptive Protection

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The absorption of ionizing radiation by living cells produces chemical changes in macromolecules, including nucleic acids, proteins and lipids. As a result, different signaling cascades responding to these stress conditions are triggered. For example, adaptive responses encompassing DNA repair and antioxidation reactions may be induced following exposures to low doses of sparsely ionizing radiations such as X- and γ-rays. The protective mechanisms often over-compensate, resulting in stimulatory responses that enhance the well-being of the organism long after the exposure. A wealth of data on the stimulatory effects of radiation were described in a variety of living systems. Notably, *in vitro* and *in vivo* exposures to low doses of γ- or X-rays were protective to cellular DNA. Moreover, human cellular responses to low doses of radiation that are typical of certain occupational activities or diagnostic radiography were often shown to harbor lower levels of chromosomal damage than what occurred spontaneously at the basal level and were protected against subsequent challenge by radiation.

Using normal human cells maintained in culture, we have shown that exposure to low doses from ^{137}Cs, ^{60}Co γ-rays or energetic protons triggers signaling events that protect cells from endogenous oxidative damage or damage due to a subsequent challenge dose of ionizing radiation. DNA repair, oxidative metabolism and cell cycle checkpoints are implicated in the observed responses. Moreover, the induced adaptive effects were communicated to neighboring non-targeted cells and protected the latter against stress from a subsequent exposure to radiation. The effects were impacted by the rate of delivery of the radiation, and were mediated by molecular and biochemical changes that differ from those induced by high doses. Using mice, we have shown that mitochondria play a crucial role in induced adaptive responses, which were transient and organ-dependent.

Posters

Use of Low Oxygen Treatment to Reduce Symptoms of Parkinson's Disease in a Drosophila Model

Zachary L. Clifford, New Mexico State University, Las Cruces, NM
Giancarlo Lopez-Martinez, New Mexico State University, Las Cruces, NM

How the Conditioning Dose Mediates Protection: Dose Optimization within Temporal and Mechanistic Frameworks

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Preconditioning is Hormesis Part I: Documentation, Dose-Response Features and Mechanistic Foundations

Edward J. Calabrese, University of Massachusetts Amherst, Amherst, MA
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Finding Interventions that Reduce Infarct Size Beyond that from Platelet Inhibitors Alone

James M. Downey, University of South Alabama, Mobile, AL
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The Thermal and Radiological Stress Dichotomy: Adaptive Response in Lake Whitefish (*Coregonus clupeaformis*)

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Investigating the Contribution of L-Tryptophan to the UV Fluorescence Observed from Beta-Irradiated Cells

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Bionic Motion Platform to Increase Exercise-Induced Hormesis in Wider Population

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Hormesis Mechanism Based on Quorum Sensing: A Case Study on Sulfonamides to *Photobacterium phosphoreum*

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Alteration of the Immunological Parameters in Animals Pre-exposed to Radiofrequency Electromagnetic Fields before Infection with *Salmonella typhimurium* and *Klebsiella pneumoniae*
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Samaneh Nematollahi, Shiraz University of Medical Sciences, Shiraz, Iran

A Discrete Drug Dilution Model for Personalized Medicine Based on Non-Linear Threshold Philosophy
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A Novel Nanodosimetry Drug Quantification Model to Treat Chronic Diseases
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The Adaptive Response Induced by Chronic Radiation from ^{226}Ra in Fish Cells and Human Cells
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Examining The Effects of Low-dose Radiation on The Primary Cilium Biology in Human Epithelial Cells
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Evaluation of Radiotherapeutic Efficacy of Terpenes for Low Dose Irradiation
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Use of Low Oxygen Treatment to Reduce Symptoms of Parkinson's Disease in a Drosophila Model

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The pathological marker of Parkinson's disease, in both familial and sporadic cases, is alpha synuclein agglomerates known as Lewy bodies. While it is still an open research question as to whether Alpha-synuclein is a true cause of Parkinson's disease, the transgenic up regulation of alpha synuclein production in Drosophila has been kshown to produce Parkinson's like effects. Notably intraneuronal formation of Lewy bodies, disruption of locomotor activities, and loss of dopaminergic neurons. Conversely Drosophila which have been transgeneticly formed to up regulate both alpha synuclein and heat shock proteins show a marked decrease in lewy body formation and both improved locomotor function and longevity versus those which up regulate only alpha synuclein. We are investigating the induction of heat shock protiens via anoxia in Drosophila as a possible treatment modality. It has been shown that Heat shock proteins are inducible not only by high temperature, but in response to many different environmental stressors. We will be investigating multiple lengths of anoxia exposure in addition to response at different ages. By using anoxia we hope to reduce the symptoms of alpha synuclein over production in a method that mimics the human response to remote ischemic preconditioning, increasing HSP production in a non-invasive and drug free treatment.

How the Conditioning Dose Mediates Protection: Dose Optimization within Temporal and Mechanistic Frameworks

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The optimal conditioning (hormetic) doses of many agents are documented, cellular mechanisms and temporal profiles are examined from which the conditioning (hormetic) responses are elicited, and the optimal conditioning doses are compared to the levels at which optimal protection occurs in response to the toxic challenge dose. Entry criteria for study evaluation required a conditioning mechanism-induced endpoint response, an hormetic/biphasic dose response for the protective response following the challenging dose, and a mechanistic assessment of how the conditioning dose afforded protection against a toxic challenging dose. The conditioning dose that demonstrated the largest increase in a mechanism-related conditioning (hormetic) response (i.e., prior to administration of the challenging dose) was the same dose that was optimally protective following the challenging dose. Specific receptor antagonists and/or inhibitors of cell signaling pathways which blocked the induction of conditioning (hormetic) effects during the conditioning period abolished the protective effects following the application of a challenge dose, thus identifying a specific and essential component of the hormetic mechanism. Conditioning responses often had sufficient doses to assess the nature of the dose response. In each of the cases these mechanism-based endpoints displayed a hormetic dose response. The present analysis reveals that hormetic biphasic dose responses were associated with both the conditioning process and the protective effects elicited following the challenging dose. Furthermore, based on optimal dosage, temporal relationships and the known mediating actions of receptor-based and/or cell signaling-based mechanisms, the protective effects were shown to be directly linked to the actions of the conditioning (hormetic) doses. These findings indicate that the biological/biomedical effects induced by conditioning represent a specific type of hormetic dose response and thereby contribute significantly to a generalization of the hormetic concept

Preconditioning is Hormesis Part I: Documentation, Dose-Response Features and Mechanistic Foundations

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This is the first extensive documentation of the dose response features of pre- and post conditioning. Pre- and post conditioning studies with rigorous study designs, using multiple doses/concentrations along with refined dose/concentration spacing strategies, often display hormetic dose/concentration response relationships with considerable generality across biological model, inducing (i.e., conditioning) agent, challenging dose treatment, endpoint, and mechanism. Pre- and post conditioning hormesis dose/concentration-response relationships are reported for 154 diverse conditioning agents, affecting more than 550 dose/concentration responses, across a broad range of biological models and endpoints. The quantitative features of the pre- and post conditioning-induced protective responses are modest, typically being 30–60% greater than control values at maximum, findings that are consistent with a large body (>10,000) of hormetic dose/concentration responses not related to pre- and post conditioning. Regardless of the biological model, inducing agent, endpoint or mechanism, the quantitative features of hormetic dose/concentration responses are similar, suggesting that the magnitude of response is a measure of biological plasticity. This also provides the first documentation that hormetic effects account for preconditioning induced early (1–3 hour) and delayed (12–72 hour) windows of protection. These findings indicate that pre- and post conditioning are specific types of hormesis and occurs in a wide range of biological models.

Finding Interventions that Reduce Infarct Size Beyond that from Platelet Inhibitors Alone

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Today $P2Y_{12}$ receptor inhibitors (PI) are given to all patients presenting with acute myocardial infarction. If given prior to primary angioplasty, they greatly reduce morbidity and mortality. The assumption has been that they protected by preventing formation of recurrent thrombi in the coronary vasculature. However, we observed that PI were very cardioprotective in animals if present at the time of reperfusion, and that the same signaling inhibitors that block postconditioning also block protection from PI. None of these blockers interfered with PI's anti-platelet effect indicating that PI were actually protecting by conditioning the heart. Neither pre- nor postconditioning (IPOC) could offer any additional protection to that from PI in animals because the PI had already conditioned the hearts. Not surprisingly IPOC stopped being effective in all clinical trials conducted after PI became the standard of care. We have looked for interventions that could further limit infarct size and provide additional protection in animals receiving PI. Both mild hypothermia and cariporide were effective but required treatment prior to ischemia. Recent findings suggest that fragments of mitochodrial (mt) DNA released from necrotic myocardium are very pro-inflammatory and kill neighboring cells by pyroptosis (death by inflammation). We tested several interventions designed to prevent mtDNA toxicity: a mitochondrially-directed DNA repair enzyme (prevents release of DNA fragments), DNase I (degrades any extracellular DNA), and a caspase-1 inhibitor (prevents activation of interleukins). Each was tested in open-chest rats experiencing 60 min of ischemia and 2h of reperfusion. All were very protective individually and, most importantly, had an additive effect when used in the presence of the PI cangrelor. Untreated rats had 73±5% infarction of the ischemic zone. Cangrelor reduced that to 43±4% and combining cangrelor with the caspase 1 inhibitor further reduced infarction to 14±4%.

The Thermal and Radiological Stress Dichotomy: Adaptive Response in Lake Whitefish (*Coregonus clupeaformis*)

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There is growing evidence that mild hyper- or hypo- thermia can produce an adaptive response when combined with ionizing radiation treatment. One proposed mechanism is that the induction of a heat shock protein response infers genotoxic protection from subsequent ionizing radiation damage. Lake whitefish (LWF) (*Coregonus clupeaformis*) a commercially important species, has a considerable amount of information about the effect of each stressor individually but little is known about the combined effects. LWF embryos were treated with a 2 hour heat shock (HS) treatment at magnitudes of 3 and 9°C above control incubation temperature at the gastrulation or organogenesis stages of embryonic development. Embryos were subsequently treated with either 10 or 15 Gy 137Cs gamma irradiation 2, 4, 8, 16 or 24 hours post-HS. Based on preliminary results, HS-only controls at both developmental stages appeared to result in increased mortality. Radiation treatment alone induced mortality across all experiments. This effect was not observed when combined with HS treatment, providing evidence for decreased mortality when embryos were co-treated with HS and radiation relative to radiation-only treatments. Based on preliminary data, we can infer that this adaptive response may be dependent on developmental stage, as the decrease in mortality was only observed with stressor exposure at gastrulation but not at the later organogenesis stage. Future work includes studying heat shock protein expression profiles at various time points following HS to compare the timing of heat shock protein expression and observed adaptive response with radiation treatment Overall, this research is providing key insights into the mechanism of the reported adaptive HS response to irradiation with relevance to organisms in the wild that may experience low levels of radiation exposure from anthropogenic sources.

Investigating the Contribution of L-Tryptophan to the UV Fluorescence Observed from Beta-Irradiated Cells

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The current investigation aims to identify the sub-cellular source(s) of ultraviolet (UV) photon emission that are elicited by the beta-irradiation of cells. L-tryptophan was investigated due to the close coincidence of its emission peak with the UV emission wavelength range studied in our previous work. The contribution of L-tryptophan to overall cellular fluorescence was investigated via the exposure of various biologically-relevant L-tryptophan concentrations to tritium (3H), concurrent to the quantification of photon emission using a photomultiplier tube fitted with a band-pass filter (340±5 nm). An increase in tryptophan concentration proved to increase the photon count rate slightly, yet significantly, between the lowest (0.3 μM) and highest (3 mM) concentrations employed. The marked change in fluorescence intensity with changing L-tryptophan concentration can suggest that L-tryptophan is one of the factors contributing to the UV flux observed upon beta-irradiation of HaCaT cells in previous experiments. However, L-tryptophan is not considered a major contributor to the detected radiation-induced UV fluorescence since tryptophan's fluorescence intensity, even at its highest concentration, reached only a fraction (5%) of the intensity observed upon irradiation of a cell population with the same beta dose. Investigation was further extended to western blotting of tryptophan-rich sensory protein (TSPO) expression in 3H-irradiated HaCaT cells to determine if the observed photon emission could be used as a non-invasive method by which to measure a cell population’s response to radiation-induced stress. The results showed an increase in TSPO expression in response to irradiation up to 0.1 Gy and a decrease in expression with a further increase in dose up to 0.5 Gy. A weak correlation between TSPO expression and photon emission (R=0.453) indicates the inability to use photon emission as a non-invasive marker of TSPO-related cellular stress. Investigation of potential alternative sources of radiation-induced cellular UV emission is ongoing and includes candidates such as 5-hydroxytryptamine.

Bionic Motion Platform to Increase Exercise-Induced Hormesis in Wider Population

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Physical exercise (PE) is a front line therapy to ameliorate wide-ranging physical and neuropsychiatric debilities. Bringing about hormesis via PE aims for levels of mild stress stimuli that avoid damaging effects while eliciting responsiveness from adaptive capacities of cellular or systemic origin. With weight-bearing exercise generally, cumulative effects vary with individuals such that intolerant individuals may readily experience damaging effects, while individuals with more formidable endurance capabilities may require long duration exposure to improve upon their adaptive capacities. PE-induced hormesis entails tailoring of “the dose (that) makes the poison”, to the individual.

A ‘bionic’ motion platform for facilitating physical acceleration of a person’s center-of-gravity was developed to enable many PE intolerant individuals to accomplish weight-bearing PE, and to enable individuals undertaking endurance PE to accomplish longer duration PE activity without diverting their attention from work or leisure pursuits. The bionic platform provides for periodic reciprocating motion of the body center-of-gravity in the vertical dimension while a person is standing. Gravitational acceleration and deceleration of body weight in a head-to-toe direction results in forces exerted internally on circulatory vessel walls that cause shear stress on vessel walls and consequently lead to increased production of circulatory mediators, principally nitric oxide.[1] Performing gentle PE while standing on the bionic platform increases circulation and subsequent increase in oxidative phosphorylation leads to mild oxidative stress (hormesis). The bionic platform additionally provides for assistance to circulation from muscle contractions similar to ones associated with locomotion, walking. Retrograde shear stress arising in low doses from these contractions is another stimulus possibly leading to beneficial vascular adaptations.[2]

1. Low amplitude pulses to the circulation through periodic acceleration induces endothelial dependent vasodilatation, J Appl Physiol 106:1840-1847, 2009.
2. Exercise-induced Signals for Vascular Endothelial Adaptations: Implications for Cardiovascular Disease, Curr Cardiovasc Risk Rep . 6(4): 331–346, 2012.

Hormesis Mechanism Based on Quorum Sensing: A Case Study on Sulfonamides to *Photobacterium phosphoreum*

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During the past two decades, the phenomenon of hormesis has gained increasing recognition in environmental and toxicological communities. However, the mechanistic understanding of hormesis, to date, is extremely limited. Herein is proposed a novel parametric model with a mechanistic basis and two model-based parameters for hormesis that was successfully applied to the hormetic dose−response observed in the chronic toxicity of sulfonamides on *Photobacterium phosphoreum*. On the basis of the methods of molecular docking and quantitative structure−activity relationships (QSARs), we proposed a mechanistic hypothesis for hormesis that introduces for the first time the concept of quorum sensing in toxicological studies and explains the mechanism at the level of the receptors. The mechanistic hypothesis stated that (1) specific target binding like interaction with LuxR may contribute to transcriptional activation leading to enhanced luciferase activity at low dose exposure of sulfonamides, and (2) as the dose of sulfonamides increases, more sulfonamides competitively bind to dihydropteroate synthase, which inhibit the biosynthesis of folic acid and thus provoke toxicity. This mechanistic hypothesis, which explains both the dosedependent and time-dependent features of hormesis, could give new insight into the mechanistic study of hormesis.

Alteration of the Immunological Parameters in Animals Pre-exposed to Radiofrequency Electromagnetic Fields before Infection with *Salmonella typhimurium* and *Klebsiella pneumoniae*

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Substantial evidence now indicates that exposure to low levels of ionizing radiation can lead to enhanced immune responses. However, the question whether low levels of non-ionizing radiations such as radiofrequency electromagnetic fields (RF-EMF) can induce the same biopositive immune responses, cannot be answered easily. There are some of evidences which indicate the stimulatory effects of radiation on the immune responses. The aim of this study was to investigate the effects of RF-EMF on some parameters of immune system in an animal model following infection with *Salmonella enterica* subsp *enterica* serovar Typhimurium (*Salmonella* Typhimurium) and *Klebsiella pneumoniae*. The male BALB/c mice were exposed to RF-EMFs generated by a common GSM mobile phone 4h/day for 3 days. Animals were infected by *K. pneumoniae* or *S.* Typhimurium at day 4. At day 7 post injection, the blood samples were collected by cardiac puncture. The specific antibodies against bacteria were determined by agglutination method. The serum levels of cytokines were measured using ELISA method. The leukocytes count was measured by using a cell coulter and standard hematological techniques. The specific antibodies against bacteria were higher in non-irradiated mice as compared with irradiated mice. No significant differences were found between radiated and non-radiated mice with respect to the blood total leukocyte count. The mean serum levels of IFN- γ and IL-17 were significantly higher in *K. pneumoniae* infected-radiated than *K. pneumoniae* infected-non radiated mice ($p<0.001$). These findings showed that low levels of RF-EMF can stimulate the immune response in mice which exposed to radiation. Finding of this study provide further evidence supporting that immune system can be stimulated by exposure to certain levels of RF-EMF to show increased resistance against bacterial infection. These adaptive responses may have applications in different fields such as overcoming the increased susceptibility of astronauts who take part in deep space missions to infections.

A Discrete Drug Dilution Model for Personalized Medicine Based on Non-Linear Threshold Philosophy

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Formulation of an optimized drug dose to initiate a specific biological process in a living organism is highly desirable in routine clinical practice. A personalized dosimetry can be tailored to address different pathological conditions specific to age, gender and sickness stage of a patient. Stronger drug doses may be needed to eliminate bacteria and cancerous cells in a patient. Milder doses of a drug are required to enhance healing through immunotherapy or biotherapy. Diluted drugs are intended in immunizations and vaccinations to ward off epidemic diseases. In short, an ideal drug should be optimized to produce intended results without any compromise to the patient's wellbeing. A mathematical model to quantify drugs has been developed to formulate required dose. An intended drug dose, **D**, can be estimated from a drug solution by
$\mathbf{D} = [(\mathbf{N_A} \,.\, \mathbf{w_m})/(\mathbf{T} \,.\, \mathbf{A_m})]^{*}\mathbf{C_f}$, where $\mathbf{N_A}$ is Avogadro's number, $\mathbf{w_m}$ is the physical weight of the drug, $\mathbf{A_m}$ is atomic/molecular weight of the drug and **T** is the sample size. The parameter $\mathbf{C_f}$ is the correction factor for temperature, pressure, humidity and other effects. Any subsequent drug dose may be derived from the existing higher concentration by $\mathbf{S_n}=\boldsymbol{\lambda_n}(\mathbf{S_{n-1}})$ where $\boldsymbol{\lambda_n}$ is known as an adjustment parameter based on n=2,3,4,5,….p-1. The factor **n** is the desired dilution level and **p** is the upper limit or threshold point for standardization. $\mathbf{S_n}$ is the new drug quantization level derived from the previous $\mathbf{S_{n-1}}$ level. The adjustment parameter, $\boldsymbol{\lambda_n}$, is computed using an expert program that adjusts the dilution ratio at each step to meet the set objective. The model is based on nonlinear threshold philosophy i.e., drugs show therapeutic effects up to certain concentrations. The drug dilutions beyond effective dose are simply ignored which forms the threshold point. The simulation results suggest that any drug, with known atomic or molecular structures, can be standardized to a unique scale. It can be estimated for those drugs with unknown molecular structures and further research is needed in this direction.

A Novel Nanodosimetry Drug Quantification Model to Treat Chronic Diseases

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All chronic diseases evolve through different biological phases in a living system. The initial cellular insults are registered in the neurological networks that trigger various symptoms. These may include sensations, feelings, pains etc. Such systemic modulations produce anxiety, insomnia, loss of appetite, and other benign clinical conditions. A majority of such aberrant biological fluctuations are resolved through cellular adaptations over time. However, cells under continuous stimulations for a prolong time, that fail to resolve, develop into lesions. Lesions generally produce inflammations in a living organism. The unresolved inflammatory processes consequently lead to chemical productions. These chemicals include chemokines, cytokines, and tumor necrotic factors among others. Such chemicals form the roots of most of the chronic diseases. Some of these unresolved chronic inflammatory processes develop into malignancies and other degenerative diseases. A chronic inflammatory lesion can progress into different geometrical configurations based on the location of the insult and the structure of the target organ. The chronic inflammatory processes can be healed through cellular apoptosis - a biological mechanism in which deformed cells in a tissue are absorbed by neighboring healthy cells. Assume that a lesion is comprised on $\boldsymbol{n}$ defective cells, the number of drug molecules required to induce apoptosis is $\boldsymbol{d}$, and the drug uptake factor in the target is $\boldsymbol{p}$ then one can compute the total dose, $\boldsymbol{D}$, required to induce apoptosis as $\boldsymbol{D}=(\boldsymbol{n}\text{x}\boldsymbol{d})/\boldsymbol{p}$. The drug dose may be modified over time as the lesion is healed through apoptotic processes. Such healing processes shrink the lesion's surface area thus reducing the number of targets over time. This will result in dose deescalate with time. The repetition of dose is dependent on the cell cycles. For example, if the target cell's sensitivity lies in the *M* phase then the dose repetition time will be $\boldsymbol{T_m}=\boldsymbol{t_{2m}}-\boldsymbol{t_{1m}}$, where $\boldsymbol{t_{2m}}$ is the time when the target cell leaves the sensitive phase and $\boldsymbol{t_{1m}}$ is time when the target cell enters the sensitive phase. The duration of the treatment time depends on the size of the target lesion. Suppose a lesion has $\boldsymbol{l}$ layers and if the treatment time to heal a single layer is $\mathbf{r}$ then the total treatment time, $\boldsymbol{T_r}$, will be $\boldsymbol{T_r}=\boldsymbol{l}\text{x}\boldsymbol{r}$. Simulation studies based on different lesion sizes, cell cycles and target layers show reasonable time to heal chronic diseases. Administration of an appropriate dose of the selected drug in a latent chronic disease will yield optimal therapeutic effects with minimal side effects. The intended dose is meant to seek out the defective cells in a lesion without any risk of overdose or side effects to normal tissues. The model basically addresses four parts of the drug dosimetry: The initial quantity of the medicinal dose, repetition of dose, duration of dose and adjustment of dose over treatment time.

The Adaptive Response Induced by Chronic Radiation from ^{226}Ra in Fish Cells and Human Cells

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Purpose: To determine whether or not chronic low-dose α-particle radiation from ^{226}Ra over multiple cell generations can induce adaptive effect in CHSE-214 fish cells and HaCaT human cells.

Methods: CHSE-214 and HaCaT cells were exposed to ^{226}Ra in medium for multiple generations prior to being challenged by larger dose of radiation. Clonogenic assay was used to test the survival of cells with or without being pretreated by radiation from ^{226}Ra.

Results: The increased radiosensitivity can be induced in CHSE-214 cells by priming radiation from ^{226}Ra over 185 days. Compared to unprimed cells, CHSE-214 cells receiving 122mGy accumulated radiation prior to exposure to 0.39Gy challenging radiation had decreased survival from 99.99% to 91.78%, p=0.006, and the reduced survival also happened to cells exposed to 0.122mGy radiation prior to 0.78Gy challenge radiation, from 97.26% to 89.45%, p=0.009. On the contrary, the priming radiation from ^{226}Ra can induce a protective adaptive response in HaCaT cells. For HaCaT cells pretreated with ^{226}Ra-medium for 48 days, 0.316mGy priming radiation could significantly increase their survival after exposure to 0.5Gy challenging radiation, p=0.006, or exposure to 2Gy challenging radiation, p=0.033. For HaCaT cells cultured in ^{226}Ra-medium for 70 days, pretreatment with 0.046mGy radiation significantly increased their survival from 97.25% to 110.78% (p=0.001) after exposure to 0.1Gy challenging radiation, and the survival fraction of cells challenged with 0.5Gy dose radiation 6h after receiving 46.2mGy accumulated priming dose was 9.84% higher than unprimed cells, p=0.027.

Conclusion: Priming radiation of chronicα-particle radiation from ^{226}Ra can cause increased radiosensitivity in CHSE-214 cells to the subsequent challenging radiation, and can induce typical protective adaptive effect in HaCaT cells. Both of these two responses in cells could be a kind of adaptive effect from the aspect of genomic stability or survival ability.

Examining The Effects of Low-dose Radiation on The Primary Cilium Biology in Human Epithelial Cells

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Once thought to be an evolutionarily vestigial organelle, non-motile primary cilia (PC) are now known to be involved in many important cellular functions. PC regulate cell growth and differentiation and signal transduction via chemosensory communication between cells and their external environment. Thus the maintenance of PC architecture and the orchestration of PC responses are pivotal during proper human development and in tissue homeostasis. Increasing evidence suggest that there be a strong correlation between defective PC and many major human diseases such as polycystic kidney disease (PKD), congenital heart disease, pancreatic cancer, Bardet-Biedl syndrome (BBS), and diabetes. Exposure to radiation, usually in very low doses, exists in the natural environment, occurs during some human activities, and is used as a medical means to cure diseases or manifest the impairment of their progressiveness. Yet literally little to nil is understood about the plausible direct and bystander effects of low-dose radiation on the architecture and function of PC in human health. Previous work in our laboratory has demonstrated that radiation-induced bystander effects are a widespread biological phenomenon, most notably observed in human epithelial cells. Yet, the identity of radiation-induced bystander signals and how they are transmitted to unirradiated cells remain largely unknown. Inasmuch as PC are ubiquitous and can be found as a solitary appendage on the cell surface of many cell types including epithelial cells in the human body, further investigation into this channel of research is of relevant importance. In this study, we seek to present experimental evidence to construct a platform to delineate possible outcomes of low-dose radiation on the primary cilium biology in human epithelial cells.

Evaluation of Radiotherapeutic Efficacy of Terpenes for Low Dose Irradiation

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Therapeutic proposals have focused on the antioxidative capabilities of plant based compounds to rectify and restore mitochondrial function to cells exposed to low dose irradiation. Of particular interest are essential oils, called terpenes. Terpenes demonstrate potent anti inflammatory effects and low cytotoxicity, suggesting utility in responses to chronic stressors such as radionuclides. This study serves to examine whether administration of terpenes to affected cells would aid/degenerate the response to low dose irradiation as part of an interventional treatment. Specifically, HCT116 p53 +/+ cells were treated and optimized to various doses of terpene compounds; Curcumin (0.5, 1.0, 1.5, 2.0, 2.5 µg/mL) and D-Limonene (10, 20, 30, 40, 50 µg/ml) to assess cytotoxicity. Dose optimizations indicate a minimal growth inhibition concentration of 0.5 µg/mL of Curcumin and 30 µg/mL of D- limonene dosage. Values for minimal growth inhibition of terpenes were tested for radiotherapeutic efficacy via α – particle emission with various concentrations of Radium – 226 (10, 100, 1000, 10 000 mBq/mL). Cell cytotoxicity was analyzed as per the aforementioned dose optimizations. Preliminary data suggests no effect of low dose irradiation via Radium – 226 exposure (10, 100, 1000, and 10 000 mBq/mL) on clonogenic survival of HCT116 p53 +/+ cells with and without terpene dosage. Research implications are that the radionuclide doses are mild and not capable of significant effect, therefore further research will monitor and evaluate the significance of high doses of irradiation on these systems and final findings will be presented.