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MIMETICS OF HORMETIC AGENTS: STRESS-RESISTANCE TRIGGERS

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◻ Mimetics of hormetic agents offer a novel approach to adjust dose to minimize the risk of toxic response, and maximize the benefit of induction of at least partial physiological conditioning. Nature selected and preserved those organisms and *triggers* that promote tolerance to stress. The induced tolerance can serve to resist that challenge and can repair previous age, disease, and trauma damage as well to provide a more youthful response to other stresses. The associated physiological conditioning may include youthful restoration of DNA repair, resistance to oxidizing pollutants, protein structure and function repair, improved immunity, tissue remodeling, adjustments in central and peripheral nervous systems, and altered metabolism. By elucidating common pathways activated by hormetic agent's mimetics, new strategies for intervention in aging, disease, and trauma emerge. Intervention potential in cancer, diabetes, age-related diseases, infectious diseases, cardiovascular diseases, and Alzheimer's disease are possible. Some hormetic mimetics exist in pathways in primitive organisms and are active or latent in humans. Peptides, oligonucleotides, and hormones are among the mimetics that activate latent resistance to radiation, physical endurance, strength, and immunity to physiological condition tolerance to stress. Co-activators may be required for expression of the desired physiological conditioning health and rejuvenation benefits.

Key words: mimetics, intervention, hormesis, trauma, exercise, aging

INTRODUCTION

Hormesis represents the biphasic dose-response patterns to toxic challenges that has been championed by Calabrese and colleagues (Calabrese and Baldwin 2000). Low doses of otherwise harmful agents are beneficial at threshold low levels. The beneficial hormetic response involves the adaptive stress response to the low dose toxic challenge as multiple conserved protective enzymatic and signaling systems are activated by stress (Smith Sonneborn 1992a,b). These fundamental survival pathways, when activated, confer plasticity to species longevity (Arking *et al.* 2004; Sonneborn 2005). Key regulators in these hormetic environmentally and chemically cued pathways are candidates as hormetic mimetics. Activation of these latent protective responses not only overcome the immediate challenge but may also repair previous damage and reduced vulnerability in the organism (Smith Sonneborn 1979). Natural detoxifying systems, activated by a wide range of physical and chemical

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hormetic agents with ROS (reactive oxygen species) activity, trigger manganese superoxide dismutase (MnSOD) and catalase, to neutralize superoxide anion and hydrogen peroxide, and DNA damage repair (Carter and Brunet 2007). In diverse species, transcription factors, like the forkhead-box (FOXO) transcription factor family in development and stress resistance, activate a broad suite of cellular genes, including those encoding enzymes involved in DNA repair and oxygen detoxification (Morris 2005) and are pro-longevity genes in invertebrates. The identification and use of molecular mimetics of stress to access ancient molecular pathways for survival represents a major strategy for resistance to stress, disease prevention and recovery, rejuvenation, and extended life quality.

The focus of the present study is on molecular mimetics known to induce entire or partial pathways in the stress response to specific hormetic agents. Candidate pharmaceutical agents that imitate the physical and environmental emergency signals to activate complete or partial molecular cascades common to heat, radiation, diet restriction, cell immunity, exercise and trauma have been identified (Smith Sonneborn 2008) and are reviewed here as drugs with potential for intervention in aging, disease and trauma. Evidence is accumulating that some protective inducible responses to stresses may require co-activators. Co-activators are metabolic switches, which together regulate metabolic pathways through their multiple interactions with nuclear receptors and other transcription factors (Feige and Auwerx 2007; Narkar *et al.* 2008). Activation of stress intervention may be effective prior, during and after the stress interval. The associated physiological conditioning and rejuvenation benefits include stimulated DNA repair, endogenous antioxidants, restoration of protein structure and function, immunoregulation and tissue remodeling, and central and peripheral neuronal systematic and metabolic responses to ischemia, and energy endurance. The conditioning benefits pose potential intervention in cancer, diabetes, infectious diseases, heart and kidney failure, inflammatory diseases including atherosclerosis and Alzheimer's disease, osteoporosis, and ischemic trauma injury from heart attack, stroke, and hemorrhage.

Candidate mimetics reviewed include ethanol, thiols and metals, isoprenoids, oltipraz, ferritins, oligonucleotides, conserved peptide sequences, biguanides, the sirtuin Resveratrol, AMPK and PPAR agonists, and Hibernation Induction Trigger (HIT)-like delta opioid receptor agonists, as examples of pharmaceutical triggers to stimulate the hormetic physiological conditioning. The conserved hormetic pathways that modulate heat-shock proteins, antioxidant systems, IGF-1 and homeostatic energy balance, accessed by mimetics of heat, radiation, caloric restriction, immunoregulators, exercise, and hibernation, are reviewed with their potential use in anti-aging, disease and trauma.

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Hormetic mimetics for health

HORMETIC HEAT MIMETICS

Molecular chaperones, the heat shock proteins (HSPs) are major defense responses that enable proper refolding of damaged protein structure induced by heat, alcohol, heavy metals, age, disease, oxidative and post ischemic stress. Proteins structural refolding with molecular chaperones avoids inactivation of proteins or abnormal aggregates (Morimoto 2006). A conserved DNA sequence in the promoter of all inducible heat shock genes provides an address of member genes for transcription factor activation of the coordinated cascade of targeted novel responsive gene expression when the cellular "911" signal is given. Restoration of protein function by the activated HSP chaperoned folding of proteins occurs in response to multiple protein denaturing agents from chemical, environmental, or age related stress. Protein rejuvenation of old cells may occur whenever the stressor activates the cascade by restoration of activity-required three dimensional protein structures. As is typical of hormetic agents, high doses of the stressing agent can overload the system and result in uncontrolled degradation of necessary regulatory molecules.

Elevated temperature increases lifespan in human fibroblasts and keratinocytes (Rattan and Ali 2007). Heat treatment results in increased basal levels of various chaperones, reduced accumulation of damaged proteins, stimulated proteasomal activities for the degradation of abnormal proteins, improved cellular resistance to ethanol, hydrogen peroxide, and UV-B rays, enhanced levels of various antioxidant enzymes, and increased phosphorylation-mediated activities of various stress kinases. Thus, heat confers cross-resistance to other hormetic agents. The effect of combination of heat and potential hormetic molecules, such as curcumin on aging, longevity, and differentiation of human cells in culture is under investigation (Rattan and Ali 2007). Stress response genes, particularly HSP70, are now the major candidates in the gene-longevity association studies (Singh *et al.* 2007). Enhanced survival and growth rate maintenance in bacteria after heat or cold shock, at 37° or 40° heat, or 12°C cold that results in expression of small HSPs (Fiocco *et al.* 2007). Small HSPs overproduction of these HSPs leads to an enhanced survival in the presence of butanol and ethanol.

Ethanol

Constitutive and inducible HSP70s are involved in oxidative resistance evoked by heat shock and ethanol (Su *et al.* 1998). In the brain, moderate ethanol pretreatment causes an almost 3-fold increase in brain levels of heat shock protein HSP 70, and can prevent beta-amyloid peptide (Abeta)-induced neurotoxicity and apoptosis in organotypic hippocampal-entorhinal slice cultures and suggest possible molecular

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mechanisms underlying the protective effect of moderate drinking against Alzheimer's dementia (Belmadani *et al.* 2004). Pretreatment of gerbils with ethanol ameliorates behavioral deficit, neuronal death, and protects the brain against Ischemia/Reperfusion (I/R)-induced delayed neuronal death, neuronal and dendritic degeneration, oxidative DNA damage, and glial cell activation (Wang *et al.* 2007). Ethyl alcohol evokes cross-resistance to hydrogen peroxide in rat myocytes (Su *et al.* 1998) and protection against the proinflammatory effects of I/R on the mesenteric artery and reactive oxygen species (Yamaguchi *et al.* 2002). The cardioprotective advantage of moderate consumption of ethanol in popular beverages "the so-called French Paradox" may result from ethanol induced favorable changes in lipid metabolism, antioxidant effects, changes in homeostasis and platelet aggregation, arterial vasodilatation mediated by NO release, expression of cardioprotective proteins, insulin sensitization and lower levels of inflammatory markers. The presence of resveratrol and quercetin in beverages are also partly responsible for some of the cardioprotective effects of alcoholic drinks (Providencia 2006).

Interestingly, in yeast, different doses of ethanol induce different responses. Over 4%v/v ethanol doses optimally induce heat shock promoters, while 6-8%, induce the same two major changes in integral plasma-membrane protein composition as sublethal heat stress. These changes include reduction in levels of the plasma membrane ATPase protein, and acquisition of the plasma membrane heat-shock protein Hsp30 (Piper *et al.* 1994). In humans, a beneficial induction of plasma antioxidants is achieved with one drink (5% v/v alcohol) while an increased pro-oxidant state occurs after three drinks from volunteers averaged over 360 minutes. One drink of red wine, beer, or stout provided equivalent increases in plasma antioxidant activity without induction of pro-oxidative stress (Prickett *et al.* 2004). Thus, at different doses, *different* physiological responses occur from benefit to harmful response.

Geranylgeranylactone (GGA)

GGA occurs naturally in herbs, may act as a defense mechanism in plants, is synthesized in bone in vitro and in vivo, is inducible by UVC, and participates in induction of apoptosis in a human hepatoma-derived cell line (Shidoji and Ogawa 2004, Wang *et al.* 2002). As a heat mimetic, this acyclic isoprenoid, is non toxic and safely induces HSP70 in cultured guinea pig gastric mucosal cells and rat gastric mucosa. Pretreatment of rats with GGA protects the liver, small intestine, or heart, and improves survival after 95% hepatectomy from ischemia-reperfusion injury or liver transplantation (Kawai *et al.* 2000). GGA apoptosis inhibition in normal cells correlates with inhibited activation of c-Jun N-terminal kinases, decline of mitochondrial membrane potential, and formation of apoptosome by binding with Apaf-1. GGA induces other protective pathways like

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thioredoxin and anti-viral genes that offer a generalized upregulation of disease immunity (Hirakawa *et al.* 1996). GGA also alleviates the pathological progression of atrophic gastritis with inflammation relief (Liu *et al.* 2007), promotes bone osteoblasts, and is a potential anti-osteoporosis agent (Wang *et al.* 2002).

Although low concentrations (1-100nM) of GGA reduce neurotoxicity in cultured spinal cord, higher concentrations produce neurotoxicity in spinal cord neurons (Kikuchi *et al.* 2002). This highly conserved molecule in plants and animals has multiple beneficial effects in humans, induces heat shock proteins, and intervenes in chronic and infective diseases at low doses. It may have protective potential for use in pandemic threats.

HORMETIC RADIATION MIMETICS

Mimetics of the beneficial effects of low dose radiation elicit resistance pathways of repair without the potential of radiation damage. Radiation tolerance, like heat tolerance, activate gene expression cascades that promote survival and longevity from bacteria to man (Gilchrest and Eller 2001). The DNA repair response is an ancient conserved fundamental survival and longevity induced gene expression cascade in cells and vertebrates (Hart and Setlow 1975; Gilchrest and Eller, 2001; Pollycove and Feinendegen 2001). In the single-celled protozoa, *Paramecium,* exposure to ultraviolet radiation and photoreactivation repair, accesses a 296% increase in remaining life span and reserve repair pathways (Smith Sonneborn 1979).

Oligonucleotides

Mammalian cells are more resistant to higher radiation doses, show enhanced repair, and correction of age related decline of repair in human cells when stimulated by DNA oligonucleotides without radiation (Gilchrest and Eller 2001; Goukassian *et al.* 2002). Thymidine dinucleotides (pTpT), imitating a damage product of UV, stimulate melanogenesis (tanning) in mammalian pigment cells and intact skin and increase DNA repair rate. The pTT effects occur in the absence of initial damage (Arad *et al.* 2007). UV oligonucleotide mimetics are capable of reducing mutagenesis and carcinogenesis even by topical application (Goukassian *et al.* 2004). Oligonucleotides, substantially homologous to the telomere 3-prime overhang sequence (T-oligos), increase DNA repair capacity in cultured human cells, decrease UV-induced mutation rate, and reduce photocarcinogenesis in mouse skin as well (Arad *et al.* 2006). The response efficacy depends at least crudely on their length and percent telomere homology. Using a homologous 9 base oligo, 40 µM was a maximally effective dose for induction of the protective p53 protein and DNA repair, roughly bioequivalent to damage by UV (Arad et al 2006).

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The oligonucleotides used imitate damage products produced by UV and senescence, and "trick" the cells into triggering a cascade of protective molecular responses, like the 911 call, to deal with medical emergency.

In contrast with the beneficial effects of t-oligos on normal cells, t-oligos induce death in cancer cells in a dose and time dependent manner (Aoki *et al.* 2007). T-oligos inhibit the proliferation of malignant glioma cells through induction of nonapoptotic cell death and mitochondria hyperpolarization, whereas normal astrocytes are resistant. The t-oligos trigger expression of a subset of genes for repair or apoptosis and type II programmed cell death with potential for cancer treatment (Aoki *et al.* 2007).

Since cancer cells are more sensitive to oligo cytotoxicity than normal cells (Aoki *et al.* 1007), oligo therapy may be a desired alternative or addition to radiotherapy, especially with the known differences in radiation sensitivity of normal cells among patients.

Thiols, Zinc, Selenium

Another strategy for protection against radiation damage, is the increase antioxidants levels at the endogenous and exogenous level, when ROS inducing agents activate an antioxidant subset of gene expression (Beani 2001; Hamilton 2007). Instead of increased repair of UV damage, antioxidants reduce the damage and therefore the need for repair. Antioxidant mimetics of low dose UV response, that target the cytotoxic ROS effects of UVA and UVB and reduce DNA damage, include thiols, zinc and selenium. ROS protection involves an increase in glutathione peroxidase activity. Their results show that thiols and selenium protect cells against UVA radiation with a synergic interaction. This protection acts though an increase in glutathion peroxidase activity. Zinc protects against cytotoxicity of UVA and UVB and against UVB induced DNA damages.Antioxidant thiols, including N-acetyl cysteine, glutathione, and thioproline, at doses 100-300 micro M, reduce gamma radiation damage to human lymphocytes DNA, and closely correlate with the reduction of cellular oxidative stress via multiple mechanisms (Tiwari *et al.* 2009). The higher the damage, the higher the dose of these antioxidants needed for benefit.

As DNA damages play a role in photocarcinogenesis, activation of antioxidant expression provides protection against UV or gamma induced oxidative damage. Cross-resistance is an under used strategy in biology and medicine in carcinogenesis, aging, and preservation of cell and tissue function. Since exercise can elevate antioxidant pathways (Hamilton 2007), exercise should provide cross-protection against radiation damage.

Antioxidant Response Element Activators-Oltipraz, and Ferritin agonists

Protection against carcinogenesis, mutagenesis, and other forms of toxicity mediated by carcinogens, is the induction of enzymes involved in their metabolism. Potent chemopreventive agents include the 1,2-dithiole-3-thiones (Kwak *et al* 2001). Oltipraz, a substituted 1,2-dithiole-3-thione, originally developed as an anti-schistosomal agent, possesses chemopreventive activity by transcriptional activation of a gene cascades involved in carcinogen detoxification and attenuation of oxidative stress (Kwak *et al.* 2001). Exposure of rodents to 1,2-dithiole-3-thiones trigger nuclear accumulation of the transcription factor Nrf2 and its enhanced binding to the "antioxidant response element" (ARE), that lead to transcriptional activation of a multiple genes involved in carcinogen detoxification, and attenuation of oxidative stress. The dose required for effectiveness depends on environmental challenges and severity.

Ferritins, an ancient family of protein nanocages, also participate in activation of the ARE responsive element. Ferritans concentrate iron in iron–oxy minerals for iron–protein biosynthesis and protection against oxy radical damage. The promoter of human ferritin-L, contains an overlapping Maf recognition element (MARE) antioxidant responsive element (ARE). The ferritin receptor is activated by *tert*-butylhydroquinone, sulforaphane, and hemin with responses comparable to thioredoxin reductase (ARE regulator) or quinone reductase (MARE/ARE regulator). The combination DNA and mRNA mechanisms of regulation, like those used for ferritin-L, illustrates the advantages of using two types of genetic targets to achieve sensitive responses to multiple signals (Hintze and Thiel 2005). This class of radiation mimetics represent triggers of protective responsive cascades by binding to a receptor element that activate antioxidant transcription that neutralize ROS damage produced by multiple physical and chemical hormetic agents. High doses of the antioxidant, butylhydroquionone, are neurotoxic (O'Donoghue 1985).

DIET RESTRICTION MIMETICS

Caloric Restriction (CR) is not simply a passive effect, but an active, highly conserved response to stress involving both central and peripheral effects of the ancient conserved signaling pathway, Insulin/IGF-1, important in aging, longevity, and cancer and as a hormetic agent (Sinclair 2005, Hayes 2008). Diet restriction as a hormetic agent is reviewed recently (Hayes 2008). The potential of antiglycation agents and cross-link breakers holds promise for correction of age related maladies delayed by CR and are recently reviewed (Smith Sonneborn 2008). Pharmaceutical mimetics could produce the beneficial health-promoting, anti-aging and anticancer effects of caloric restriction (McCarty 2004; Anisimov *et al.* 2005). Mimetics, even if only of partial benefit, range from

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glycolytic inhibitors, lipid regulating agents, antioxidants, sirtuin regulators, autophagic enhancers, insulin specific gene modulators, weight loss drugs(Roth 2005; Lane *et al.* 2007; Anisimov 2006), and cell energy regulators(Hardie 2007). Candidate CR mimetics used in treatment of diabetics have been effective in eliciting positive metabolic changes among the biguanides; the diabetic drug, phenformin and metformin stimulate activation of AMP-activated kinase (AMPK) that down regulates insulin secretion, suppresses IGF-1, and lowers blood glucose even in non-diabetics and embryos in high glucose(Zhou *et al.* 2001; Eng *et al.* 2007). However, high doses of some biguanides do induce especially lactic acidosis and renal toxicity (Chang *et al.* 2002).

Exercise can be a dramatic hormetic conditioner that can promote weight loss and provide the associated weight loss CR benefits. Changes in body weight (or CR) alter the response of an organism to chemical and physical agents, and can improve their ability to withstand chemical and physical challenges (Turturro *et al.* 2000). i.e., an altered hormetic threshold response.

AMPK agonist, AICAR, and PPARδ agonist, GW1516, are mimetics that alter cell energy regulation and are mimetics of CR and/or exercise described below. Resveratrol, a member of sirtuin family, shows promise as a CR mimetic as well, though the mechanisms of action are still under investigation.

AICAR-AMPK Agonist

The strategy to alter cell energy drugs as CR or exercise mimetics, targets AMP-kinase, an evolutionary conserved regulator of cell energy that interacts with the Insulin IGF-1 pathway (Zhou *et al.* 2001; McCarty 2004; Hardie 2007, Hardie and Carling 1997, Narkar *et al.* 2008). AICAR (5-aminoimidazole-4-carboxamide ribonucleoside) activates AMPK (Corton *et al.* 1995) and serves as an energy regulating mimetic of AMPK. AICAR is phosphorylated to form the AMP analog ZMP, creating an only "apparent" high AMP which "tricks" the activation of AMPK. The kinase is activated by high AMP and low ATP via a complex mechanism, which involves allosteric regulation, promotion of phosphorylation by an upstream protein kinase (AMPK kinase), and inhibition of dephosphorylation. This protein-kinase cascade represents a sensitive system, which is responsive to cellular stresses that deplete ATP, and thus acts like a cellular fuel gauge (Hardie and Carling 1997). AICAR may be beneficial for energy maintenance altered by unrelated illnesses, chemical toxins, trauma, and aging.

Activated protein kinase (AMPK), by metformin or mimetic AICAR, protects cells against environmental stress and hypoxia (Mu *et al.* 2001), and has antioxidant suppression of ROS (Kim *et al.* 2008). Activation of the kinase may be a key regulator of energy-related hormetic responses and AICAR may alter the toxicity of some energy disrupting hormetic

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agents. AMP-activated protein kinase contributes to UV- and H2O2-induced apoptosis in human skin keratinocytes (Cao et al 2008).The AMPK cross talk with the ancient FOXO pathway favors increased longevity seen with caloric restriction (Greer *et al.* 2007). In diverse species, transcription factors, belonging to the forkhead/winged helix box gene, FOXO subfamily, used in fly eye development, are crucial in downstream suppression of the life-shortening effects of insulin/insulin-like growth factor-I receptor. The FOXO pathway suppresses increased generation of ROS and promotes increased longevity in nematodes (Greer *et al.* 2007). Several age-related diseases, including hypertension, atherosclerosis, type 2 diabetes, cancer, and Alzheimer's disease, could be counteracted by the AMPK-FOXO activated pathways (Morris 2005). AICAR inhibits cancer cell proliferation via the AMP-activated pathway (Ratten *et al.* 2005). AICAR treatment increases oxygen consumption and endurance in untrained adult mice in part by stimulating PPARδ-dependent oxidative genes (Narkar *et al.* 2008). AICAR mimics the antioxidant upregulation, decreased apoptosis, anticancer and anti-toxicity response as well as an altered glucose uptake seen with caloric restriction. AMPK is a key regulator of stress response, and when activated by AICAR, promises multipurpose application potential. Other applications include reduction of intracellular pH by AMPK inhibition pH (Ségalen *et al.* 2008), anti-inflammatory/anti-oxidant and neuroprotective functions possibly useful in treatment of Alzheimer's disease (Ayasolla *et al.* 2005), and potentiating chemotherapy cytotoxicity by promoting influx of an anti-folate drug used to eliminate leukemic cells (McGuire *et al.* 2006).

In human toxicity studies, 10-100mg/kg AICAR dosages were non-toxic (Dixon *et al.* 1991). In rat cell cultures, non toxic doses and time dependent increase of P-AMPK correlates with increase in AICAR doses, indicating activation of the enzyme (Galardo *et al.* 2007). Only beneficial dose ranges are available in these studies.

GW1516-PPARδ (Peroxisome Proliferators Receptors) Agonist

The evolutionary conserved, PPARs are ligand-activated nuclear transcription factors that play important roles in lipid and glucose homeostasis. The PPARδ receptor plays a key role in the reversal of any tendency toward the development of insulin resistance by modulation of whole-body lipid homeostasis as well as in insulin sensitivity. PPARδ activates a transcriptional program in skeletal muscle leading to a switch in fuel usage from glucose/fatty acids to solely fatty acids, thereby drastically increasing its oxidative capacity and verified in humans. The inducible control of fuel use by PPARδ is pivotal in metabolic adaptation of skeletal muscle to a greatly increased oxidative capacity by switching from glucose/fatty acids to solely fatty acids during energy stresses of fasting or physical challenges and therefore as a caloric restriction hormetic agent

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(de Lange *et al.* 2008). The PPARδ agonist GW1516 (2-[2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl)-1,3-thiazol-5-yl]methylsulfanyl]phenoxy]acetic acid) induces activation of PPARδ and reduces glucose utilization in skeletal muscle through a switch in mitochondrial substrate preference from carbohydrate to lipid (Brunmair *et al.* 2006). The GW1516 regulates glucose metabolism and insulin sensitivity, as a partial mimic of caloric restriction (Lee *et al.* 2006).

The toxicity of different ligands, like GW1516 for PPAR activation, reveal organ specific benefit or toxicity; ie., potentiating hepatic toxicity is possible (Peraza *et al.* 2006). As a benefit, in the liver, the liver X receptors (LXRs) are established mediators of lipid-inducible gene expression and also participate in inflammation and immunity. In vivo, LXR agonists, including GW1516, reduce inflammation in a model of contact dermatitis and inhibit inflammatory gene expression in the aortas of atherosclerotic mice, linking lipid metabolism and inflammation (Joseph *et al.* 2003). The use of PPAR ligands as mimetics for diet restriction hold promise for reduction of age related diseases, but require caution. The roles of PPARδ and GW1516 in exercise are described below.

Resveratrol

Resveratrol, a plant derived polyphenol, sirtuin activator, and phytoestrogen (Gehm *et al.* 1997) is another candidate mimetic of diet restriction, though the exact mechanisms of the beneficial activation are unknown. As a phytoestrogen, resveratrol can inhibit the binding of labeled estradiol to the estrogen receptor and activate transcription of estrogen-responsive reporter genes transfected into human breast cancer cells, and that may not be appropriate in combination with other drugs.

These ancient NAD+ dependent sirtuins (Silent Information Regulators), are a class of proteins which possess either histone deacetylase or mono-ribosyltransferase activity and are found in organisms ranging from bacteria to humans (Zhao *et al.* 2004; North and Verdin 2004). These deacetylases increase organ, tissue and organism survival, especially under conditions of stresses of nutrient deprivation, and physical and chemical toxicity (Yang and Sauve 2006). Pharmacological approaches that target sirtuins offer attractive drugs to enhance toxicity resistance, especially the FOXO regulatory gene expression cascades and survival benefits of caloric restriction (Guarente and Picard 2005). Resveratrol has antioxidant protection against UV- and H_2O_2-induced cell death (van der Horst *et al.* 2004). In mammals, SIRT1 utilizes FOXO and other pathways to achieve their beneficial effects on health lifespan (Morris 2005). In humans the Sir2p homolog, SIRT1, deacetylates transcription factors and mediates stress resistance, apoptosis, and inflammatory responses in response to toxicity using FOXO (Brunet *et al.* 2004; Kobayashi *et al.* 2005), p53 (Luo *et* al. 2001; Langley *et* al. 2002) and NF-KappaB-dependent transcription (Yeung *et al.*

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2004; Chen *et al.* 2005). Activation of these pathways connects Sir2, caloric restriction, and radiation hormetic cascades that have cross-reactive benefits from their specific known mimetics.

The concentration and cell type can influence the dose responses to resveratrol and influence pro-oxidant properties that lead to oxidative breakage of cellular DNA in the presence of transition metal ions such as copper. The pro-oxidant properties provide a potential anticancer therapy (de la Lastra and Villegas 2007).

EXERCISE MIMETICS

Interaction between the quality of the environment and the health of the exposed population, determines the survival response of living organisms. The phenomenon of induced tolerance, by exposure to hormetic agents at threshold levels, stimulates natural defense mechanisms that have potential therapeutic value (Smith Sonneborn 1992 a,b). Exercise, heat and oxidative stress are hormetic agents (Sonneborn and Barbee 1998; Radak *et al.* 2008). The induction of heat shock proteins and the ubiquitin pathways are key regulators of stress response are seen from yeast to humans. Ubiquitin and heat shock pathways are involved with peroxisome biogenesis, AMPK pathways, cell cycle control, DNA repair, differentiation, sporulation, and in response to hormetic agents (Finley *et al.* 1987; Fornace *et al.* 1989; Ryan *et al.* 1991;Salo *et al.* 1991; Thompson and Scordilis 1994, Ciechanover 1994;Skidmore *et al.* 1995;Locke *et al.* 1996; Locke 1997; Sonneborn and Barbee 1998). Using moderate exercise as the stressor, human blood shows a significant increase in abundance of inducible polyubiquitin genes. The molecular cascades of gene expression induced by exercise are multiple and document exercise as a hormetic agent with therapeutic potential for benefit and energy upregulation. The mimetics of exercise show how a drug, AICAR, can imitate the energy benefit. Cross talk between major caloric restriction hormesis induced pathways especially AMPK/PPARδ and IGF1 reveal the linking of caloric restriction and exercise mimetics (Narkar *et al.* 2008).

AICAR AMPK Agonist

The use of mimetic drugs to replace the "hormetic exercise physical agent" has obvious health benefits for voluntary and involuntary sedentary populations and athletic performance. Investigation of pathway-specific drug mimetics of key regulators of cell energy reveals that the orally active AMPK agonist AICAR, improved endurance capacities using mice treadmill running test even in sedentary animals (Narkar *et al.* 2008). Remarkably, this oral active AMPK kinase agonist mimetic, overcomes the exercise requirement. Only 4 weeks of AICAR treatment alone induces metabolic genes and enhances running endurance by 44%. ACIAR-only treated mice ran longer (123%) and further (144%)

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than did vehicle-treated mice, revealing mimetic induced endurance without exercise. The other candidate exercise mimetic, the PPARδ agonist, GW1516, alone, could not increase running endurance despite the fact that transgenic mice with overexpression of activated PPARδ, maintain high basal endurance capacity to adult and exhibit 100% increase in endurance in untrained mice (Wang *et al.* 2004). In these transgenic mice, overexpression of a constitutively active PPARδ (VP16-PPARV δ) in skeletal muscles preprograms an increase in oxidative muscle fibers, enhancing running endurance by nearly 100% in untrained adult mice. Only the combination of Exercise training with GW1516, could increase running time by 68% and distance by 70% over vehicle-treated trained mice (Narkar *et al.* 2008). Thus, increased running endurance and myofibers induced by GW1516 require synergistic co-activation of Exercise and the GW1516, though AICAR alone is a sufficient inducer of energy endurance. Their studies reveal that gene expression signatures of AICAR only versus Exercise plus GW1516 share about 40% of gene expressions that function in oxidative metabolism, angiogenesis, and glucose sparing, pathways in muscle performance modification. Simultaneous AICAR AND GW1516 treatment creates a unique gene expression signature that shares 40% of the genes in common with Exercise plus GW1516, mostly oxidative metabolism genes that reprogram skeletal muscle. AICAR Only, induces a subset 32 genes, linked to oxidative metabolism, also upregulated in transgenic mice overexpressing PPARδ. Their supposition, that stimulation of oxidative genes by AMPK, depends on the PPARδ receptor, is consistent with the observation that AICAR is ineffective in PPARδ null mutant cells. Thus, AICAR induced transcription of oxidative genes requires an active PPARδ receptor. Transgenic over-expression as well as knockout studies have identified PPARδ and AMPK as key co-regulators of type I fiber specification, mitochondrial biogenesis, endurance adaptations and performance enhancement during exercise. A "muscle endurance gene signature" involves molecular crosstalk and perhaps a physical association between exercise-activated AMPK and PPARδ receptors (Narkar *et al.* 2008). Their study provides a novel pharmacologic strategy to reprogram muscle endurance by targeting AMPK-PPARδ signaling axis with orally active drugs and elegantly correlates molecular expression with physical response. The mimetics induce gene expression both common as well as unique with the hormetic agent exercise. The increased endurance effect requires the key regulator of cell energy, the AMPK kinase agonist. The PPARδ receptor agonist, GW1516, operated only in synergy with exercise pathways. As a model study of hormetic mimetics, the exercise experimental results reveal that a mimetic targeting AMPK can imitate the "hormetic agent gene expression signature" sufficiently to gain a biomedical advantage of exercise; endurance and energy. Co-activations

were required to achieve the geroprotective or athletic advantages using the PPARδ mimetic alone. Interestingly, the mimetics induce their own unique gene expression patterns, not found in the original hormetic agent exercise, and long term effects of these "extra gene expression signatures" are unknown with respect to benefit or harm.

In a different arena, the toxicity of pollutants, known to interfere with PPAR nuclear receptors, like phthalates and organotins (Casals-Casas *et al.* 2008), may be diminished by regulators of metabolic homeostasis, AICAR and/or GW1516 or HIT mimetics.

In the classic exercise experiments by Narkar *et al.* 2008, the concentration of mimetics used was only 5mg/kg, sufficient to induce replacement of exercise requirement and/or increase endurance. Whether higher concentrations of these mimetics, in these protocols, would increase or decrease the benefits are unknown. Dose dependent effects of AICAR or GW1516 in other biological arenas appear in the Diet restriction section above.

IMMUNOREGULATION

The immune response, though essential for survival, can participate in autoimmune diseases. Thus, like hormetic agents, can be beneficial or harmful. The beneficial elements include highly conserved peptides and oligos.

CDR1 Peptide and CpG Oligos

A preserved ancient immune response T cell immunoregulator of sharks is effective in higher organisms ((Marchalonis *et al.* 1998; Marchalonis *et al.* 2005). Sharks possess the genes essential for mounting the adaptive or combinatorial immune response involved in homeostasis, immunoregulation and response to infection. All three shark species possess constitutive antibodies to shared idiotypes defined by the CDR1 segment of the T cell receptor beta chain variable domain (Adelman *et al.* 2004). Certain TCR Vb CDR1 peptides can reverse the negative effects of immunosenescence on normal TH1 and TH2 T cell subsets and restore resistance to cardiopatholgy in mice. The TCR peptide itself restores balance between TH1 and TH2 and stimulated cells remodeling defective heart tissue implicating a role for immune system in cardiac repair (Yu *et al.* 2005). Net collagen synthesis increases by downregulation of matrix metalloproteinase and altered fibroblast expression and enzymatic activity. The natural immunomodulatory system enhancement, by administration of peptides (CDR1) to reduce cytokine dysfunction in immunosuppressed individuals and upregulate inflammatory activities mediated by TH2-type helper cells, is likely. There is an adaptive role of T cells from peptide treated mice in remodeling damaged hearts by increasing net collagen synthesis by cardiac fibroblasts as postexposure physiological conditioners and restoration of declined immunity typical of aging populations.

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Synthetic CDRs, from unrelated murine and human monoclonal Abs, show differential in vitro and in vivo antifungal (Candida albicans), antiviral (HIV-1) and antitumor (melanoma cells) activities (Magliani *et al.* 2009). Candidacidal activity can be optimized by alanine replacement of a single residue containing the first three amino acids of CDR1, to show dose dependence with a 50% inhibitory concentration of 0.056 µM (Polenelli *et al.* 2003).

Multiple roles to repair or provide anti-infective protection emerge from use of peptides conserved from primitive immune systems. The effective dose required depends on the desired benefit and optimized peptide sequence. Unmethylated CpG motifs are prevalent in bacterial but not vertebrate genomic DNAs.

Oligodeoxynucleotides containing CpG motifs activate host defense mechanisms leading to innate and acquired immune responses. The recognition of CpG motifs requires the Toll-like receptor. CpG-induced activation of innate immunity protects against lethal challenge with a wide variety of pathogens, and has therapeutic activity in murine models of cancer and allergy. CpG motifs also enhance the development of acquired immune responses for prophylactic and therapeutic vaccination (Krieg 2002).

When used as an adjuvant, the dose of CPG 7909 for the highest antibody response depends on the saturation concentration to the Alhydrogel (Mullen *et al.* 2007). Thus, defense peptides and oligonucleotides, used in lower organisms, are of benefit to humans for a variety of infectious and disease states. The dose response is dependent on the synthetic form, and desired strategy for the intended therapeutic target, i.e., direct or adjuvant therapy.

HIBERNATION

Hibernation is a biological strategy used to tolerate stress of depleted energy stores, intracellular acidosis, hypoxia, hypothermia, cell volume shifts, and inactivity induced muscle wasting (Harlow *et al.* 2001). Multiple stresses share the same toxic physiological responses ameliorated by hibernation. Hibernation therefore, or the trigger that activates its protective mechanisms, may be an intervention for multiple stresses including environmental toxins, disease states, trauma, and aging. Hibernation Induction Trigger (HIT) is an 88 residue opioid-like peptide from hibernating woodchucks (Horton *et al.* 1998). HIT protects skeletal muscles from hypoxia/reperfusion injury, and preservation of graft tissue (Hong *et al.* 2005), cardiac ischemia (Sigg *et al.* 2002; Smith Sonneborn *et al.* 2004;) and neuroprotection in a physiological preconditioning hormesis pattern (Govindaswami *et al.* 2008). The delta 2 opioid receptors, DADLE, and Deltorphins are mimetics of HIT.

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DADLE

HIT mimetics are delta opioid peptide receptor agonists that show ischemia resistance potential in both physiological conditioning and postexposure conditioning hormesis. DADLE. [D-Ala(2)-D-Leu(5)-Enkephalin] DADLE is protective against neurotoxins, ameliorates the neuronal damage induced by ischemia-reperfusion following a transient middle cerebral artery occlusion, induces hibernation in hela cells, and activates the beneficial recompensatory phase (Hayashi *et al.* 2002; Borlongan *et al.* 2004; Vecchio *et al.* 2006).

Deltorphins

Deltorphins are found in epidermal secretions of *Phyllomedusa bicolor*, a South American frog, that is used topically by Peruvian tribes to increase physical strength, heighten senses, resist hunger and thirst and promote fearless emotion before a hunt (Erspamer *et al.* 1993). The delta 2 specific variant (Tyr-d-Ala-Phe-Ala-Asp-Val-Ala-Ser-Thr-Ile-Gly-Asp-Phe-Phe-His-Ser-Ile-NH2), (Delt D), mimicks the HIT-Winter containing blood serum by cardioprotection from pretreatment of surgically induced left coronary artery occlusion, that restricted blood flow to the heart (Sigg *et al.* 2002; Smith Sonneborn *et al.* 2004;) and is neuroprotective during ischemia (Govindaswami *et al.* 2008). The physiological conditioning hormesis cardioprotection in rodents is associated with activation of KATP channels (Sigg *et al.* 2002; Smith Sonneborn *et al.* 2004). Delt D var but not DADLE, inhibits LPS proinflammatory cytokine production by macrophages and suppress LPS-induced p38 MAPK activation and expression of TNFalpha and MIP-2 (Husted *et al.* 2005). Thus, deltorphin has anti-inflammatory activity.

Postexposure physiological conditioning hormesis with Delt D var facilitates recovery from moderate (~30%) hemorrhage after blood pressure crash in conscience rats (McBride *et al.* 2005) by activation of Mean Arterial Pressure (MAP) and Heart Rate (HR) recovery through disinhibition of sympathetic drive and increased baroreflex sensitivity. By resetting baroreflex sensitivity animals are able to respond to decreases in arterial pressure by increasing heart rate after moderate hemorrhage (McBride *et al.* 2005). Delt D var also stimulates effective physiological conditioning hormesis. Treatment 24 hr *prior* to hemorrhage facilitates recovery from severe (~53%total blood loss) hemorrhagic shock during the recompensatory phase by improving hemodynamic stability and survival with activation of both nitric oxide and KATP channels during hemorrhage (Oeltgen *et al.* 2006). Delt-Dvar-induced tolerance to cardiac ischemia involves protein kinase C, NO synthase, KATP channels, and the autonomic nervous system (Maslov *et al.* 2009). MAP recovery correlates

with retardation of the anaerobic glycolytic pathways inducing metabolic depression similar to that seen in hibernation.

Delt E, (Tyr-D-Ala-Phe-Ala-Ile-Gly-Asp-Phe-Ser-Ile-NH2) another novel peptide mimic of HIT is δ2 opioid receptor agonist effective in postexposure conditioning hormesis. Within a stimulatory dose range, Deltorphin E restores hemodynamic stability after severe hemorrhage (~50%) treatment using behaving rodents (Rutten *et al.* 2008). Our recent studies show that this peptide was effective in maintenance of Mean Arterial pressure without fluid replacement and increased post hemorrhage survival time. The dose dependent reduction of lactic acid acidosis in the stimulatory range after hemorrhage predicted survival time. Comparison of Delt-E mediated survival time versus lactic acid post hemorrhage shows a significant ($R^2 = 0.969$) dose response correlation between the decrease in lactic acid and increase in survival time. For every 0.1 mmol/L decrease in lactic acid there is a 12.5 minute increase in survival time (2.9 mg/kg, 4.3mg/kg and to 5.5mg/kg Delt E. However, 14mg/kg Delt E exacerbated the stress and was lethal. Thus, Delta E opioid is beneficial within a low dose range and toxic at the high dose tested. Our results show that protection from ischemic shock, without fluid replacement is dose dependent, effective in a lower dose range, while toxic at the higher dose used (Rutten *et al.* 2008).

Altered energy metabolism by Delt E may be a candidate alone or in combination with anti-diabetic drugs to provide stable metabolic states and to reduce posttraumatic syndromes. Since heat stress alters the metabolic state, DeltE may be an intervention strategy.

Thus, mimetics of HIT, DADLE, DeltD and DeltE can elicit physiological conditioning or postexposure physiological conditioning hormesis. The mechanisms of the conditioning responses, though not yet fully characterized, depend on the extent of severity and the specific mimetic. These opioids provide a potent potential for use in emergency trauma setting i.e. in wartime, natural disasters, accidents, or in anticipated critical surgical procedures with risks of ischemic stress and in combination with other hormetic agents.

CONCLUSIONS

Conserved pathways in diverse species identify latent reservoirs of guardian mechanisms that when activated can improve intervention in human diseases, survival, rejuvenation, and longevity (Table 1, 2). Remarkable progress in the recent decades reveal the powerful potential, and proven success of mimetics of physical and chemical hormetic agents to trigger these pathways. Mimetic drugs of hormetic agents activate gene expression signatures that imitate heat, radiation, diet restriction, exercise, immune response and hibernation for treatment and/or prevention of diseases including diabetes, Alzheimer's disease, cancer, inflammatory

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TABLE 1: Conserved survival and longevity hormetic inducible pathways*

ANCIENT PATHWAY	HORMESIS
Genetic Stability/DNA Repair	Heat, Radiation,
Metabolic Control/IGF1, AMPK	Diet Restriction, Hibernation
Antioxidant	Diet Restriction, Radiation, Heat, Exercise
FOXO/AMPK	Energy Disruptors; CR, Exercise, Toxic chemicals
Heat Shock Response	Heat, Exercise
Hibernation	Cold, Hunger, Ischemia
Immunity	Infectious Agents
Regulators	
Sirtuins	Diet Restriction
Ubiquitin	Exercise, Diet Restriction

  *See text for explanations and references.

TABLE 2: Mimics of environmental hormesis and disease intervention*

Disease	Hormetic Agents	Hormetic Mimics
Diabetes	Heat, Exercise	Ethanol, GGA
	Diet Restriction	Biguanides, Resveratrol
		Metabolic Inhibitors
		AICAR, GW1516
	Exercise	AICAR, GW1516
Heart Attack	Heat, Exercise, Ischemia	Ethanol, GGA
	Cold, Hunger	HIT, Deltorphins
Heart Failure	Heat	CDRI peptide, GGA
Hemorrhage or Stroke	Cold, Hunger, Ischemia	HIT, Deltorphins
Cancer	Radiation	Small Nucleotides, T oligos
	UV Damage Products	
		Thiols, Zinc, Selenium, Oltipraz and ferritin agonists
Alzheimer's	Heat	Ethanol, GGA
Fatigue	Exercise	AMPK Agonist AICAR
Infection	Heat	GGA, CDR1, CpG Islands
Inflammatory	Heat, Immune Response	GGA, AICAR, Deltorphins**
Diseases:		
Rheumatoid arthritis		
Osteoarthritis		
Lung,Bowel disease		
Atherosclerosis		
Psoriasis		
Alzheimer's		
Post Traumatic Syndrome		Deltorphin E**
Hypertension, Atherosclerosis,	Diet Restriction	AICAR (AMPK-FOXO)
Osteoporosis	Heat	GGA

  *See Hormesis Sections in text for more information and references. The mimetics may induce common, partial, and unique physiological responses found within the hormetic agent beneficial dose range.

  **Speculation here on the basis of dramatic shock response found in our studies

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diseases, infection vulnerability, atherosclerosis, organ function, acute ischemic events like heart failure, heart attack, stroke, vessel obstructions and immune diseases (Table 2). The common denominator for hormetic benefit is the conservation of metabolic pathways that assure survival, stress resistance, and longevity throughout evolution. Major pathways include IGF-1, DNA repair, immunology, heat and cold shock proteins, antioxidants, and metabolic energy switches. The role of chromatin remodelling, translation regulation, and small RNA induction, contribute to the coordinated cellular response observed following the stress of hypoxia (Kenneth and Rocha 2008).

A major toxic response to environmental challenges is oxidative damage, a fundamental and universal denominator that regulates survival, species longevity, and stress tolerance (Martin *et al.* 1996). Survival depends on antioxidant induction pathways, responsive to a wide range of hormetic agents and their mimetics, that act as natural detoxifying systems. In diverse species, transcription factors, like the forkhead-box (FOXO) transcription factor family, activate a broad suite of cellular genes, including those encoding enzymes involved in DNA repair, oxygen detoxification and downstream suppression of the life-shortening effects of insulin/insulin-like growth factor-I receptor. The unique additions and removal of phosphorylations, acetylations, and ubiquitinations of FOXO for example, under specific environmental conditions provides specificity in the regulation of subsets of FOXO target genes (Carter and Brunet 2007). FOXO factors may regulate responses by facilitating different patterns of gene expression at threshold low doses but pro-apoptotic genes when the intensity of stress stimuli increases beyond a certain threshold (Carter and Brunet 2007) and thereby explain a basis for some paradoxical hormetic responses. Deacetylases, like the sirtuins, activate transcription of protective pathways. Diversity of interactions regulating function may explain diversity of outcomes, including the apparent dose low dose dependent benefit, versus high dose toxicity typical of hormetic responses to the same agent. The balance in favor of benefit increases when a key regulator of the desired effect is amplified by the mimetic, like AMPK by AICAR (Narkar *et al.* 2008).

The mimetics of hormesis may intervene in acute and chronic and acute diseases, inflammatory diseases, trauma, pandemics, metabolic disorders, and toxicity of oxidizing and metabolic pollutants. These include;

1. Health benefits from exercise and diet restriction mimetics of hormetic agents may cross-react since both share involvement of the FOXO-AMPK and IGF-1 pathways for intervention in energy related diseases especially diabetes.
2. Antioxidant pathways and triggers of repair pathways represent anti cancer pathways.

3. Antiinflammatory mimetics promise treatment strategies for inflammatory diseases.
4. Trauma recovery using the deltorphins peptides facilitates tolerance to shock of heart attack, stroke, hemorrhage, or surgical procedures. Post-traumatic syndrome may be treatable by Deltorphin D or E.
5. Toxicity of pollutants, known to interfere with PPAR nuclear receptors, like phthalates and organotins may be diminished by regulators of metabolic homeostasis, AICAR and/or GW1516 or HIT mimetics.
6. Immunity boosters, derived from ancient immune strategies, including heat shock inducer, GGA, CpG islands found in bacteria, and CDR1 sequences found in sharks promise aid in infection tolerance with Deltorphins.
7. Different doses of the same mimetic agent induce unique physiological changes that may explain some non-linear responses or hormetic effects. The harmful effects can be useful as anticancer therapies when differences in responses exist between normal and cancer cells.

In general, the mimetics of physical and chemical hormetic agents can "trick" or trigger a beneficial response by activation of key regulators of the stress response at the level of transcription, post transcriptional modifications, and regulation of energy metabolism. The dose responses are complex and reflect activation of different pathways at different doses and in different cells; a complexity useful in chemotherapy especially with agents that act differently in normal versus cancer cells.

SUMMARY

Elegant studies in lower organisms reveal strategies for survival in plants, bacteria, paramecia, yeast, nematodes, flies, frogs, sharks, rats, mice, woodchucks, and bears and offer the promise of relief from numerous painful and debilitating diseases for healthy aging. The secrets to survival lurk in our genes, awaiting access triggers in our conserved pathways and epigenetic modification potentials. The hormetic mimetics reviewed here are small nucleotide emergency signals, dipeptides, ethanol, thiols and metals, and conserved peptide sequences or energy regulators found throughout evolution that regulate cytokines, cellular immunity, central and peripheral neuronal pathways, and metabolic pathways. Engineered mimetics to target key regulators of metabolism imitate the environmental agents as well. Activation of these ancient cascades accesses prevention and treatment of disease, infection, aging, and trauma. Different doses of mimetics may activate different physiological cell, tissue, and organ specific responses in normal and cancer cells. A complex response, like survival, therefore, may be non-linear.

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