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Awareness of Hormesis Will Enhance Future Research in Basic and Applied Neuroscience

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Abstract

Hormesis is defined operationally as responses of cells or organisms to an exogenous or intrinsic factor (chemical, temperature, psychological challenge, etc.) in which the factor induces stimulatory or beneficial effects at low doses and inhibitory or adverse effects at high doses. The compendium of articles by Calabrese entitled “Neuroscience and Hormesis” provides a broad range of examples of neurobiological processes and responses to environmental factors that exhibit biphasic dose responses, the signature of hormesis. Nerve cell networks are the “first responders” to environmental challenges—they perceive the challenge and orchestrate coordinated adaptive responses that typically involve autonomic, neuroendocrine, and behavioral changes. In addition to direct adaptive responses of neurons to environmental stressors, cells subjected to a stressor produce and release molecules such as growth factors, cytokines, and hormones that alert adjacent and even distant cells to impending danger. The discoveries that some molecules (e.g., carbon monoxide and nitric oxide) and elements (e.g., selenium and iron) that are toxic at high doses play fundamental roles in cellular signaling or metabolism suggest that during evolution, organisms (and their nervous systems) co-opted environmental toxins and used them to their advantage. Neurons also respond adaptively to everyday stressors, including physical exercise, cognitive challenges, and dietary energy restriction, each of which activates pathways linked to the production of neurotrophic factors and cellular stress resistance proteins. The development of interventions that activate hormetic signaling pathways in neurons is a promising new approach for the preventation and treatment of a range of neurological disorders.

COMMENTARY ON NEUROSCIENCE AND HORMESIS

The biphasic nature of responses to neurotransmitters, neurotrophic factors, cytokines, drugs of abuse, and treatments for a range of neurological disorders is underappreciated and often ignored in basic and applied neuroscience research. Calabrese demonstrates a broad understanding of basic principles of neuroscience, to which he applies his expertise in toxicology and hormesis to catalog hundreds of examples of “toxins,” pharmacological agents, intrinsic signaling molecules, and behavioral factors that exhibit biphasic dose responses. The focus throughout the series of articles in “Neuroscience and Hormesis” is on the results of cell culture and in vivo experiments in which the effects of increasing doses of exogenous agents (toxins, neurotransmitters, peptide, hormones, drugs of abuse, etc.) on neuronal survival or plasticity or on animal behavior has been investigated. Calabrese aptly explores the existence of hormesis in most of the major areas of the field of neuroscience, ranging from developmental mechanisms (cell survival and neurite outgrowth) to synaptic plasticity to behavior to

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psychiatric and neurodegenerative disorders. This unprecedented collection of dose response data will provide a valuable resource for the fields of neuroscience and neurology. Rather than comment on specific aspects of the information presented by Calabrese, which is accurate and very well presented, I will consider the reasons why hormesis is such a prevalent feature of neurobiology, and how a better understanding of neurohormetic mechanisms can advance the field.

WHY IS HORMESIS SO COMMON? AN EVOLUTIONARY PERSPECTIVE ON NERVOUS SYSTEMS

The theory of evolution by natural selection provides an explanation of why hormesis is a prominent feature of responses of organisms to their environments, and the biological processes underlying those responses. Life began in a harsh environment where cells were exposed to high levels of toxic agents including ultraviolet radiation, oxidizing agents, and metals. Therefore, the organisms that survived and reproduced successfully were those best able to cope with such environmental hazards. The evolution of nervous systems was particularly instrumental for avoiding and responding to environmental hazards—organisms developed sensory and motor systems to detect move away from noxious agents, as well as complex learning and memory and communication capabilities to avoid potentially damaging environmental exposures. Interestingly, in some cases cells and organisms actually took advantage of the physiochemical properties of toxic agents, using them (in low amounts) to their advantage. Indeed, oxygen, carbon monoxide, iron, and selenium are all toxic when present in high amounts, but are commonly used by cells—oxygen is used for the production of cellular energy (ATP), carbon monoxide is an intercellular signaling molecule in blood vessels and nerve cells, and iron and selenium are important for the proper functions of proteins such as hemoglobin and antioxidant enzymes (Benzie, 2000; Crichton and Pierre, 2001; Ryter and Otterbein, 2004; Hartl and Baldwin, 2006).

The evolution of nervous systems was shaped, in part, by the competition among individuals and species for limited amounts of energy in the form of food. Indeed, much of the sophistication of the nerve cell circuits and the organs they innervate (muscles, blood vessels and digestive systems, etc.) is the result of the need to locate, ingest, distribute, and store energy in the face of intense competition. The nervous system mediates the identification of food sources, their acquisition and allocation among members of families and communities, and the intake and assimilation of energy of the individual. Organisms with the ability to cope with the stresses associated with food deprivation (fasting), seeking and obtaining food (exercise), and “outwitting” other individuals and species (cognitive activity) held a survival advantage. These considerations suggest that nervous systems were shaped through evolution so as to respond to stress in ways that increase the resistance of the organism to more severe stress (i.e., hormesis). Such neurohormetic mechanisms are believed to be responsible for the well-known health benefits of exercise, dietary energy restriction, and intellectual and social engagement (Mattson et al., 2004a; Martin et al., 2006; Gomez-Pinilla, 2007; Radak et al., 2007). The nonlinear nature of the effects of many environmental stresses on survival is therefore a consequence of the evolutionary process (Parsons, 2003). For example, a family of histone deacetylases called sirtuins played pivotal roles in stress resistance through a vast expanse of evolutionary history (Lamming et al., 2004). The sirtuins are activated by various types of stress, and can protect cells against energy deprivation and oxidative stress. Two other types of stress resistance proteins are chaperones such as heat-shock protein 70 and glucose-regulated protein 78, and antioxidant enzymes such as Mn-superoxide dismutase and glutathione peroxidase (Macario and de Macario, 1999; Benzie, 2000).

In addition to the importance of the nervous system in sensing and responding to noxious environmental conditions at the time of exposure, learning and memory processes likely

evolved, in part, to permit organisms to avoid hazards such as toxic plants and prey, contaminated food, etc. Even higher cognitive functions and language can be considered as mediators of population-based hormesis in which one member of the family or community transfers information concerning environmental hazards to other members.

ENDOGENOUS NEUROTOXINS AND THE PATHOLOGICAL SECOND PHASE OF THE BIPHASIC CURVE

Many environmental neurotoxins act by binding to specific receptors or enzymes. Examples include the algal toxins kainic acid and domoic acid, which bind and activate glutamate receptors (Hampson and Manalo, 1998), and atropine (produced by the nightshade plant *Atropa belladonna*), which binds and inhibits muscarinic acetylcholine receptors (Lawrence and Kirk, 2007). It is therefore not too surprising that endogenous ligands for these receptors exhibit biphasic dose-response curves, with high doses being toxic. A prime example is glutamate, the major excitatory neurotransmitter in the brain. In low to moderate amounts that are released from presynaptic terminals during the normal activity of nerve cell networks, glutamate mediates processes such as learning and memory and sensory-motor behaviors (Mattson, 1988; Lessmann, 1998). Binding of glutamate to its receptors causes membrane depolarization and calcium influx through ligand-gated and voltage-dependent calcium channels (Mattson and Chan, 2003). The beneficial effects of low to moderate levels of glutamate receptor activation result from calcium-mediated activation of transcription factors such as nuclear factor (NF)-κB and CREB (cyclic AMP response element binding protein) that induce the expression of genes that encode proteins that promote the survival and plasticity of neurons including brain-derived neurotrophic factor (BDNF) and the anti-apoptotic protein Bcl-2 (Mabuchi et al., 2001; Mattson and Camandola, 2001). However, excessively high levels of glutamate can overwhelm any hormetic pathways and kill the neurons by a process called excitotoxicity (Mattson, 2003).

Carbon monoxide is well known as a toxic gas present in the exhaust of internal combustion engines. Interestingly, however, carbon monoxide and a related gas, nitric oxide, are produced by many different types of cells in the body, including vascular endothelial cells, macrophages, and neurons (Lowenstein et al., 1994). Carbon monoxide is produced in cells when the enzyme heme oxygenase-1 acts on heme; carbon monoxide then activates certain protein kinases, resulting in biological responses. Nitric oxide is produced during the conversion of L-arginine to L-citrulline, which is catalyzed by nitric oxide synthase (NOS). NOS is activated by calcium influx and/or release from inracellular strores. Because of their abilities to rapidly spread from the site of production to adjacent cells, and to activate a signal transduction pathway involving cyclic GMP and kinases, nitric oxide and carbon monoxide may have important roles in many different physiological processes, including relaxation of blood vessels, regulation of reproductive functions, learning and memory, and immune responses to pathogens. However, excessive production of nitric oxide is implicated in the pathogenesis of major diseases, including cardiovascular disease, diabetes, cancer, stroke and neurodegenerative disorders (Hofseth et al., 2003; Duncan et al., 2005; Pacher et al., 2005).

CO is generated during normal physiological process such as synaptic transmission and smooth muscle contraction (Wang et al., 1997; Zhuo et al., 1998). Low concentrations of CO (below 200 ppm) can inhibit apoptosis and inflammation, and can be protective in animal models of ischemia-reperfusion injury, hepatitis and vascular injury. In excitable cells such as neurons and smooth muscle cells, CO hyperpolarizes the plasma membrane by activating calcium-dependent potassium channels. CO may exert such biological effects by stimulating soluble guanylate cylase and by more directly activating potassium channels (Kaide et al., 2001). The involvement of CO in regulating blood pressure and its production in response to ischemic and metabolic stress suggest roles for CO in the pathogenesis of cardiovascular disease. Similarly,

the emerging evidence that CO plays roles in learning and memory and other behaviors (Zhuo et al., 1998) has led to investigations suggesting roles for CO in neurological disorders such as stroke and Alzheimer's disease (Schipper, 2004).

The increased production of CO under stressful conditions suggests the possibility that it functions in stress adaptation. In this regard, it has been shown that administration of CO can protect endothelial cells, smooth muscle cells, and neurons against apoptosis in models of ischemic injury (Dore et al., 2000; Neto et al., 2004). Conversely, blockade of HO activity can exacerbate injury in such animal models. Thus, beneficial actions of CO appear to be mediated by a hormesis response. The signaling pathways of CO-mediated hormesis are beginning to be elucidated and may involved cyclic GMP production and activation of the transcription factor NF-κB (Brouard et al., 2002). NF-κB is known to induce the expression of genes that help cells resist stress including Bcl-2 family members and antioxidant enzymes (Mattson and Camandola, 2001).

Another example of an endogenous signaling molecule that exerts beneficial effects at low doses but toxic effects at high doses is the cytokine tumor necrosis factor-alpha (TNF). TNF plays a key role in the killing and removal of infectious agents and damaged cells within the affected tissue, and TNF can prevent the death of cells that are not severely damaged. TNF exerts its beneficial effects by activating an adaptive stress response pathway involving the transcription factor NF-κB (Mattson and Camandola, 2001). However, excessive long-term production of TNF can damage and kill normal cells including neurons; such toxic actions may be mediated by stimulation of the production of toxic chemicals by inflammatory immune cells such as macrophages/microglia.

TRANSCELLULAR HORMESIS

In many instances only a subset of cells in an organism is exposed to a chemical agent or other environmental challenge. The affected cells then alert adjacent cells and, in some cases, cells throughout the body of the impending danger. Three classes of factors that function as intercellular mediators of hormesis responses in the nervous system are neurotransmitters, neurotrophic factors, and hormones. Examples of neurotransmitters involved in transferring information from sensory receptors (pain, olfactory and gustatory receptors, for example) that respond to noxious agents include glutamate and substance P. In response to exposure to a seizure-inducing toxin or in a stroke, the most affected brain cells produce and release BDNF and basic fibroblast growth factor (bFGF) which activate receptors on adjacent neurons, thereby engaging signal transduction pathways that result in increased production of cytoprotective proteins such as antioxidant enzymes and protein chaperones (Mattson et al., 2004a; Ren and Finklestein, 2005). Hormones that are produced in response to stress and act on many different cell types throughout the body include epinephrine, adrenocorticotrophin (ACTH), and adrenal glucocorticoids (Carrasco and Van de Kar, 2003).

In general, the signal transduction pathways activated by intercellular messengers during transcellular hormesis involve cell surface receptors coupled to the activation of protein kinases, which in turn activate transcription factors. For example, glutamate induces calcium influx, which activates calcium/calmodulin-dependent protein kinases and mitogen-activated protein (MAP) kinases; the kinases then activate transcription factors such as CREB (cyclic AMP response element-binding protein) and NF-κB (Hardingham and Bading, 2003; Mattson and Camandola, 2001; Camandola and Mattson, 2007). BDNF and insulin-like growth factors activate receptor tyrosine kinases coupled to the PI3 kinase–Akt–FOXO transcription factor pathway (Mattson et al., 2004c). Hormones that mediate adaptive stress responses may diffuse into cells (the steroid hormone cortisol, for example; De Kloet, 2004) and directly activate transcription factors, or they may activate cell surface receptors coupled to GTP-binding

proteins and the production of cyclic AMP (epinephrine and glucagon-like peptide 1, for example; Bloom, 1975; Mattson et al., 2003).

PHYSICAL AND MENTAL EXERCISE AND NEUROHORMESIS

There is considerable evidence from studies of animals and humans that regular exercise is beneficial for health. Both the peripheral and central nervous systems control the complex body movements involved in exercise, and also regulate the dynamic changes that occur during exercise in the cardiovascular, hepatic, renal, and other organ systems. The beneficial effects of regular moderate exercise on skeletal and cardiovascular systems provide a prototypical example of hormesis (Michaelides et al., 2003; Radak et al., 2007). During exercise, skeletal and cardiac muscle cells are subjected to considerable oxidative (superoxide and hydroxyl radical production), metabolic (increased ATP and NAD^+ consumption), and ionic (sodium and calcium influx) stress. This cellular stress activates multiple transcription factors that induce the expression of genes that encode proteins that protect the cells against damage. Examples of such exercise-stimulated transcription factors include myocyte enhancer factor 2 (MEF2), which induces expression of the glucose transporter GLUT4 (McGee and Hargreaves, 2006); NF-kB, which induces expression of the mitochondrial antioxidant enzyme Mnsuperoxide dismutase (Ji et al., 2004); and peroxisome proliferator-activated receptor delta (PPAR-delta), which regulates the oxidative capacity of mitochondria, switches fuel preference from glucose to fatty acids, and reduces triacylglycerol storage (Furnsinn et al., 2007). These kinds of hormetic signaling pathways activated by exercise result in increased insulin sensitivity and glucose uptake, thereby reducing the risk for type 2 diabetes.

Physical exercise also exerts hormetic actions on nerve cells in the central nervous system. Several biochemical and functional changes in the brain, resulting from exercise, have been elucidated. Rodents that exercise regularly exhibit enhanced synaptic plasticity and increased neurogenesis in the hippocampus, and improved performance in tests of learning and memory (van Praag et al., 2005; Cotman et al., 2007). The latter effects of exercise on cells in the hippocampus may be due, in part, to imposition of a mild stress on the nerve cell during exercise, because levels of several molecular markers of mild stress are increased in response to exercise, including BDNF and vascular endothelial cell growth factor (Cotman et al., 2007). Of course, motor neurons and neurons in the motor cortex, striatum, and cerebellum that effect and control exercise are themselves highly active (and therefore energetically, ionically, and oxidatively stressed) during exercise (Adkins et al., 2006). Neurons in many regions of the brain are “exercised” during cognitive processing of information and are therefore subjected to the same kinds of stress that motor neurons experience during physical exercise. Epidemiological studies have provided evidence that individuals who engage in cognitively challenging occupations are at reduced risk of developing Alzheimer’s disease (Wilson et al., 2002). When rodents are cognitively challenged they exhibit increased hippocampal synaptic plasticity and neurogenesis, and increased production of BDNF as well (Young et al., 1999; Mattson et al., 2004b), changes consistent with adaptive stress responses.

DIET AND NEUROHORMESIS

Dietary factors are increasingly recognized to influence the function of the nervous system and its vulnerability to aging and disease. One widely studied dietary intervention that exerts profound and quantitatively large beneficial effects on the nervous system and the organism as a whole is dietary energy restriction. Controlled caloric restriction and intermittent fasting each extend the life span of rats of mice by up to 40% and improve cardiovascular fitness and stress resistance (Wan et al., 2003; Mattson et al., 2004b; Martin et al., 2006; Speakman and Hambly, 2007). Dietary energy restriction apparently imposes a mild stress on neurons, as indicated by increased production of heat-shock proteins, BDNF, and mitochondrial

uncoupling proteins (Yu and Mattson, 1999; Lee et al., 2002; Liu et al., 2006). Specific dietary components may also benefit neurons and so organisms through hormetic mechanisms. Diets rich in vegetables and fruits can reduce the risk of cardiovascular disease, cancers, diabetes, and neurodegenerative disorders (Heber, 2004). Because vegetables and fruits have high concentrations of antioxidants such as vitamins E and C, it is believed that most beneficial chemicals in these foods act by decreasing oxidative stress. However, work in this and other laboratories suggest that some phytochemicals are toxins that serve the function of protecting the plants against insects and other predators (Groot and Dicke, 2002; Trewavas and Stewart, 2003; Mattson and Cheng, 2006). Such phytochemicals can induce a mild adaptive stress response in cells. Examples include resveratrol, a chemical in red wine that may protect against cardiovascular disease, which induces a stress resistance response mediated by a protein called Sir-2 (Tissenbaum and Guarente, 2001; Howitz et al., 2003); sulforaphane and curcumin, which are present at high levels in broccoli and curry powder, respectively, and activate the Nrf-2–antioxidant response element pathway resulting in the expression of phase 2 detoxifying and antioxidant enzymes (Faulkner et al., 1998); and allicin, from garlic, which activates transient receptor potential receptors, resulting in calcium influx and downstream signaling cascades that upregulate neurotrophic factor expression (Macpherson et al., 2005; Jia et al., 2007). Therefore, from both evolutionary and mechanistic perspectives, at least some beneficial effects of phytochemicals in the human diet may be mediated by hormetic mechanisms.

IMPORTANCE OF A RECOVERY PERIOD IN HORMETIC RESPONSES TO CHALLENGES

While the dose of an exposure to an agent is a critical determinant of whether or not it is beneficial or toxic, the frequency of exposure to the agent is also of major importance. The frequency of exposure is important because cells must have time to recover in order to benefit from the stress. This principle is well established in the case of exercise, where a recovery period is necessary for the accrual of the benefits of the exercise. Less well known is the importance of a recovery period for the beneficial effects of other hormetic stressors including dietary energy restriction, phytochemicals, and even certain drugs. Periodic fasting improves the health and function of many tissues and organs, including the brain and heart. The mild stress that occurs during fasting is important for its beneficial effects, as is a re-feeding recovery period to provide the nutrients necessary for maintaining tissue and organ functions. In the fields of pharmacology and medicine it is often assumed that a chemical is most effective when its concentration in the body is maintained constant. However, this notion may not apply to drugs and dietary components or supplements that act by hormetic mechanisms. Instead, many chemicals may provide an optimal therapeutic benefit when delivered in a pulsatile or intermittent manner that allows a recovery period for cells to respond adaptively to the stress induced by the chemical.

TRANSLATING KNOWLEDGE OF HORMESIS INTO INTERVENTIONS FOR THE PREVENTION AND TREATMENT OF NEUROLOGICAL DISORDERS

It is well established that a “couch potato” lifestyle is unhealthy, a fact that clearly demonstrates that our cells tissues and organs require a certain level and frequency of stress in order to function optimally and resist disease. Engagement in periodic exercise and intellectual activity and engagement in energetic stress (caloric restriction) activate adaptive stress response pathways in the nervous system and other organ systems. Recent findings suggest that beneficial effects of low to moderate levels of environmental stressors can also exert health-promoting actions through hormetic mechanisms. It therefore becomes essential to establish whether dietary chemicals and other environmental factors do exert biphasic dose responses in animals and humans. The elucidation of hormetic effects of low doses of some chemicals

that were initially known only as toxins (selenium, carbon monoxide, etc.), together with the fact that some hormetic phytochemicals function as natural pesticides in plants, suggests that the term "toxin" can be misleading if the dose is not defined. Therefore, the notion that the goal of environmental health should be to eliminate all "toxins" is archaic and not evidence based. Indeed, there are an increasing number of examples of chemicals initially identified as toxins at relatively high doses and that were subsequently shown to exert beneficial effects on health when consumed in low doses (selenium and copper, for example). The prominence of hormesis in biological systems should therefore be exploited by performing dose-response and frequency-of-treatment studies of the effects of specific chemicals in bioassays and animal models of various diseases. Promising candidate treatments should then be tested in clinical trials in humans. The existence of hormesis in biological systems was recognized as early as the 1500s when the Swiss physician and alchemist Paracelsus stated that "All things are poison and nothing is without poison, only the dose permits something not to be poisonous." Indeed, essentially all medicines are administered at doses that fall within the beneficial stimulatory first phase of the biphasic dose-response curve, and increasing the dose typically results in toxic actions. This fundamental concept of medicine should also be extended to dietary factors and environmental exposures..

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