Hormesis provides a generalized quantitative estimate of biological plasticity

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Abstract Phenotypic plasticity represents an environmentally-based change in an organism's observable properties. Since biological plasticity is a fundamental adaptive feature, it has been extensively assessed with respect to its quantitative features and genetic foundations, especially within an ecological evolutionary framework. Toxicological investigations on the dose-response continuum (i.e., very broad dose range) that include documented evidence of the hormetic dose response zone (i.e., responses to doses below the toxicological threshold) can be employed to provide a quantitative estimate of phenotypic plasticity. The low dose hormetic stimulation is an adaptive response that reflects an environmentally-induced altered phenotype and provides a quantitative estimate of biological plasticity. Analysis of nearly 8,000 dose responses within the hormesis database indicates that quantitative features of phenotypic plasticity are highly generalizable, being independent of biological model, endpoint measured and chemical/physical stress inducing agent. The magnitude of phenotype changes indicative of plasticity is modest with maximum responses typically being approximately 30–60% greater than control values. The present findings provide the first quantitative estimates of

biological plasticity and its capacity for generalization. **Summary** This article provides the first quantitative estimate of biological plasticity that may be generalized across plant, microbial, animal systems, and across all levels of biological organization. The quantitative features of plasticity are described by the hormesis dose response model. These findings have important biological, biomedical and evolutionary implications.

Keywords Adaptive response · Biphasic · Hormesis · Hormetic · Phenotype · Plasticity

Introduction

Phenotypic plasticity is a basic concept in biology, being applied to and explored with regularity within evolutionary biology, genetics, ecology, neurosciences, developmental biology, stem cell biology and biogerontology, among others. It has been the subject of technical monographs (Schlichting & Pigliucci 1998) and more recently books for the general non-scientific reader (Begley 2007). As expected, it has its theoretical foundations, biomathematical models, genetic components and numerous specific applications in biological disciplines (Fig. 1) concerned with the problem of adaptation to heterogeneous environments ((Simons & Wagner 2007; Huey & Kingsolver 1989; Izem & Kingsolver 2005; De Jong 1995); Gomulkiewicz and Kirkpatrick (Gomulkiewicz & Kirkpatrick 1992; Scheiner & Lyman 1991; Scheiner & Lyman 1989; Scheiner et al. 1991; Van Tienderen 1991; Falconer 1990; Bierzychudek 1989; Bull 1987; Via 1987; Via & Lande 1987; Via & Lande 1985; Schlichting & Levin 1986; Schlichting & Levin 1984; Scheiner & Goodnight 1984; Freeman 1973; Bradshaw 1965)).

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Fig. 1 Biological plasticity: A key to survival

Phenotypic plasticity has been defined as an environmentally-based change in the phenotype (Via et al. 1995). Within this context, it is generally accepted that the degree of phenotypic adaptive change across environments can vary amongst measurable traits, and that the magnitude and type of phenotypic alternative reported is contingent on environmental conditions. While the plasticity changes in the phenotype are likely to be adaptive, this may not always be the case.

In studies of phenotypic plasticity, models are often recommended for the assessment of graded responses in continuous environments (e.g., polynomial model), while the use of other models are often recommended for the assessment of responses to discrete environmental parameters (e.g., Character State model) (Via et al. 1995). While there are important theoretical differences and similarities between these models that merit consideration, the goal of this paper is not to re-examine historical and/or ongoing debates in evolutionary ecology. Instead we suggest that the fields of toxicology and pharmacology offer an experimental system for quantitatively assessing aspects of phenotypic plasticity that may have widespread generalizability.

Toxicology/pharmacology and phenotypic plasticity

Experimental toxicology and pharmacology via the use of highly controlled experiments create the equivalent of environmental gradients of a single variable, often a chemical or physical stressor agent. A low dose exposure to numerous agents has often been reported to protect against a subsequent and more massive exposure. This is the case for radiation, heavy metals, hepatotoxins such as carbon tetrachloride, numerous oxidants, hypoxia and other agents and stressful procedures. This phenomenon is referred to as preconditioning in many biomedical disciplines and the adaptive response in radiation biology, toxicology and environmental mutagenesis (Calabrese et al. 2007). The prior

exposure is generally recognized as producing an environmentally induced alteration in phenotype that displays an enhanced adaptive response to the subsequent higher dose. Of further significance is that by altering the magnitude of the pre-conditioning dose a wide range of altered phenotypes may be created. When these phenotypes are subsequently exposed to the more massive dose the response generally follows an inverted U-shaped dose response indicating that the change in plasticity is both qualitatively and quantitatively described by the hormetic dose response. It therefore follows that a detailed description of the quantitative features of the dose response, especially when assessed over a broad dosage range, with appropriate dose-spacing, may provide a data-based foundation for quantifying treatment group variability, that is, a quantitative estimate of phenotypic plasticity which quantifies response variability.

Hormesis: providing a quantitative estimate of biological plasticity

Over the past 15 years we have assessed the quantitative features of the entire dose response continuum with particular emphasis on experiments which include low doses, that is, doses that both approach and are lower than toxicological and pharmacological thresholds as well as being above threshold (e.g., toxicity) responses (Calabrese 2008a). A relational retrieval database has been created based on the strength of the study design, statistical evaluation, magnitude of the low dose stimulation, reproducibility of the findings, and other parameters in order to assess biological changes in a broad range of biological models (e.g., plants, microbes, invertebrates or vertebrates, in vitro and in vivo). Nearly 8,000 dose responses have now been incorporated into this database (Calabrese & Blain 2009; Calabrese & Blain 2005).

The findings reveal that the most common and fundamental dose response relationship is the hormetic dose response which is characterized by a low dose stimulation and a high dose inhibition (Calabrese 2010; Calabrese & Baldwin 2003; Calabrese & Baldwin 2001; Calabrese et al. 2008; Calabrese et al. 2006). The dose at which the response crosses from stimulation to inhibition is the zero equivalent point or threshold. The stimulatory response is believed to represent an adaptation to the low (i.e., below threshold) dose, with affected organisms/cells in the stimulatory zone characterized as having acquired an altered/new phenotype. The quantitative features of the dose response in the hormetic stimulatory zone are proposed to represent a quantitative index of phenotypic plasticity, as well as a measure of biological performance. In general, the hormetic response (i.e., plasticity estimate) is modest with the maximum stimulation being typically less than twice as great as the control value, with an average

maximum response being about 30–60% greater than the control (Calabrese & Blain 2009; Calabrese & Blain 2005) (Fig. 2a, b). The width of the stimulatory response zone is more variable being generally less than 100-fold, and is likely affected by the heterogeneity of the sample population (Calabrese & Baldwin 2002).

The hormetic dose response measures the types of biological response that represent: (1) an overcompensation to a disruption in homeostasis (Calabrese 2001) and (2) a direct stimulation which typically occurs following receptor pathway activation (Calabrese & Baldwin 2002). Regardless of the means by which the response occurs (i.e., overcompensation or direct stimulation) the quantitative features of these dose responses are similar. The hormesis dose response is independent of the biological model (i.e., plant, microbe, invertebrate, vertebrate, in vitro, in vivo), endpoint measured (e.g., growth, fecundity, tissue repair, cognition, lifespan) and chemical class/physical agent (Calabrese & Blain 2005). The substantial generalizability of these observations suggests that the plasticity response is consistent across all forms of life, under an extremely broad array of stress-inducing conditions and is modest in magnitude, being in the percentage rather than in the fold range. Thus, whether the response occurs following exposure to toxic substances,

endogenous agonists, synthetic agonists, a broad spectrum of psychosocial/physical stressors (Calabrese 2008b; Calabrese 2008c), or is receptor-mediated or independent of receptor involvement, the quantitative features of the plasticity response are similar. This broadly based biological strategy indicates a previously unrecognized general biological principle.

This extensive set of observations is relevant to the long-disputed issue of whether phenotypic plasticity is a genetic character of its own with the capacity to evolve independently of trait means ((Bradshaw 1965; Schlichting & Levin 1986; Schlichting & Levin 1984; Schlichting 1986; Jinks & Pooni 1988); Scheiner and Lyman (Scheiner & Lyman 1989; Scheiner & Lyman 1991)), or whether it is due to selection toward different phenotypes in different environments ((Via & Lande 1987; Via & Lande 1985; Via 1987; Van Tienderen 1991); Gomulkiewicz and Kirkpatrick, (Gomulkiewicz & Kirkpatrick 1992)) without the need for separate genes for plasticity. Since the magnitude of the hormetic stimulation is a function of the mean across model, endpoint and stressor agent it does not support a conclusion that plasticity may be selected independently of the mean treatment, thus an argument against the independent plasticity gene hypothesis.

Generalizability of the hormesis concept

Numerous examples of hormetic-like dose responses are seen in a broad variety of biological sub-disciplines including pharmacology, aging, immunology, cancer cell biology, neuroscience [e.g., memory (Calabrese 2008d), neuronal tissue repair (Calabrese 2008e), neuronal growth (Calabrese 2008f), modulation of seizure threshold (Calabrese 2008g), anxiety (Calabrese 2008h), pain (Calabrese 2008i), and others], plant biology (Calabrese & Blain 2009), including the animal-plant interfaces of herbivory and plant compensatory responses (Agrawal 2000), plant-insect pheromone interactions, as well as responses from bacteria, yeast and fungi, amongst others (Calabrese & Blain 2009; Calabrese & Blain 2005; Calabrese 2005a; Calabrese 2005b; Calabrese 2005c) (Fig. 3). Processes in each of these disciplines display hormetic dose responses with similar quantitative features, that is, similar plasticity, while also being independent of model, agent and chemical class. These findings are also generalizable, quantitatively consistent across different levels of biological organization (i.e., cell, organ, organism) lifespan (i.e., early development, mature periods and old age) and, in both sexes, are independent of health status, and are accommodating of multiple chemical/agonist interactions; accordingly, potentiation/synergy/additivity is achieved within the quantitative features of the hormetic dose response (Calabrese 2008a).

Fig. 2 **a** Toxicologically based hormetic dose response. **b** Application of hormetic dose response to plasticity concept in toxicology

Toxicology/pharmacology and ecological approaches for assessing phenotypic plasticity: convergent concepts

The toxicological/pharmacological methodology to assess phenotypic plasticity as proposed here is similar to that reported for the use of thermal performance curves (TPC) in the assessment of phenotypic plasticity in ecological research (Huey & Kingsolver 1989; Izem & Kingsolver

2005). In fact, the TPCs are similar to hormetic dose response relationships, with performance (i.e., growth rate) enhancement increasing with temperature, achieving a maximum (i.e., optimal) at some intermediate temperature and then declining rapidly with higher temperatures. Assessment of such data has typically involved assessments of vertical shifts (maximum enhancement), horizontal shifts (i.e., variation in the position across temperature), and a

Fig. 3 Selected examples of hormetic dose responses reflecting its occurrence across various biological models, endpoints, and chemical stressor agents

Fig. 3 (continued)

third feature called generalist—specialist that have been characterized representing variation in the width of the TPC and the resultant trade-off between width and maximal performance (Izem & Kingsolver 2005). The incorporation of experimental toxicological data with large numbers of

properly spaced doses can substantially increase the types of stressors that can affect the formation of continuous reaction norms (i.e., altered phenotypes) by the selection of agents that affect specific target organs, and act via a broad range of mechanisms.

Fig. 3 (continued)

Estimating plasticity: why the plastic response is modest

Several potential explanations that may account for the modest size of the hormetic response and therefore the quantitative features of biological plasticity are presented below.

Resource allocation

Limiting a response magnitude as seen in the hormetic dose response has the capacity to provide a resource management plan in biological systems that maximizes efficiency to ensure that resource imbalances or system

Fig. 3 (continued)

disruptions do not occur. At the same time, there is flexibility to permit limited variable increases up to approximately twice that observed in the control, although the maximum increases are usually only about

50% greater than that value. This type of quantitative response management strategy operates on the level of cell, organ, whole organism and even ecologically (Calabrese 2005a).

Fig. 3 (continued)

Response redundancy

There are numerous examples of biological redundancies, such as with receptors which activate multiple independent pathways that reduce anxiety or grow axons, amongst a host of other endpoints. These redundant

pathways also act via similar hormetic dose response relationships. A possible explanation for independent pathway endpoint redundancy is built-in protection in case of a pathway malfunction due to lack of substrate, metabolic poison, mutation, oxidative damage or other possibility. However, another reason may be because it

Fig. 3 (continued)

would enhance system efficiencies by allowing for possible interactions of independent agonists and thereby the use of less biological resources. Evidence to support this is seen when assessing pharmacologically based agonist interactions. Synergies can occur at low concentrations, leading to a response that approximates the

hormetic maximum, that is, the ceiling effect (Flood et al. 1985; Flood et al. 1984; Flood et al. 1983; Flood et al. 1982). As the dose increases, the magnitude of the response decreases from that of potentiation to additivity to less than additive at even higher doses as the maximum response potential is approached.

Fig. 3 (continued)

Quantitative features of plasticity are highly conserved

Since the hormetic response is a function of the baseline value, there is a methodological requirement to establish what the baseline is in order to quantitatively explore plasticity characteristics. With hormesis there is a generally similar increase in the maximum stimulatory response above the control group in most experimental settings. Whatever the “selected” baseline response is, and it may vary widely in different species and strains for the same trait and across different traits within the same species/strains, the “plasticity” magnitude relative to the controls remains the same. This suggests that the “plasticity” trait, whatever its genetic foundation may be, is highly conserved and therefore a basic and primitive biologically selected characteristic.

Plasticity of the brain: hormetic principles in the most complex biological system

To illustrate how multiple hormetic mechanisms operate at multiple levels of organization in a highly orchestrated

manner to achieve a precise adaptive response, we consider nerve cell networks in the human brain. We focus on the nerve cell circuits in a brain region called the hippocampus, which has been intensively studied in humans and rodents because it plays pivotal roles in learning and memory (Silva et al. 2009). Sensory information received by the cerebral cortex is processed and transmitted into the hippocampus where the electrochemical impulses are transferred through and between three major populations of neurons—dentate granule neurons, CA3 pyramidal neurons and CA1 pyramidal neurons. Information is then transferred from the hippocampus to various regions of the cerebral cortex resulting in the long-term storage of the information and/or an acute response to the environmental factor sensed by the individual. The excitatory neurotransmitter deployed at the synapses on the dentate granule neurons and the pyramidal neurons is glutamate. Much as occurs in muscle cells during exercise, electrochemical neurotransmission (Na^+ influx, activation of glutamate receptors and Ca^{2+} influx) imposes a mild stress on neurons: as their energy demand increases (to restore ion gradients), free radical production is elevated. The activa-

tion of glutamate receptors not only transfers electrical impulses between neurons, but also stimulates the production of brain-derived neurotrophic factor (BDNF). BDNF is then released from the neurons and mobilizes an array of biochemical processes that help the neurons respond adaptively to the electrochemical signal-associated stress (Mattson et al. 2004).

Among the hormetic responses that occur in hippocampal neurons in response to cognitive challenges are: 1) growth of postsynaptic (dendritic) spines to increase the size of the active synapses; 2) production of stress resistance proteins including neurotrophic factors (BDNF, fibroblast growth factor and insulin-like growth factors), protein chaperones and cell survival proteins such as Bcl-2; 3) stimulation of neural stem cells located in the dentate gyrus to divide and then form new neurons which can then replace or cooperate with existing granule neurons. These adaptive changes in the structure and durability of hippocampal circuits, in addition to being critical for learning and memory, are also believed to be at least part of the reason why cognitively challenging lifestyles (and physical exercise as well) may protect the brain against cognitive impairment and Alzheimer's disease (Mattson 2008).

The description above is an oversimplification of the hormetic mechanisms involved in homeostatic (maintenance) and progressive (storage and retrieval of memories) responses of nerve cell circuits to environmental demands. Indeed, there is evidence for the involvement of many major subcellular organelles (nucleus, mitochondria and endoplasmic reticulum), structural proteins (actin and tubulin), kinases (Ca^{2+} /calmodulin-dependent kinases and mitogen-activated protein kinases) and transcription factors (AP1, CREB and NF- κ B) in "neurohormesis" (Mattson 2008). Interestingly, some of these same hormetic mechanisms are activated in response to dietary energy restriction and physical exercise, consistent with their playing fundamental roles in the evolution of the mammalian brain (Mattson 2010). Thus, under conditions of limited resources the brain evolved the ability to respond adaptively to conditions of low energy (food) availability, developed novel strategies to catch prey and escape predators, and evolved the cognitive abilities to understand the world and invent technologies that improve survival (agriculture, medicine, etc.). Much of the complex organization of the nerve cell circuitry in the nervous system was therefore sculpted by hormetic mechanisms.

Biphasic plasticity

Plasticity changes can reflect complex and diverse processes. In the case of various behaviors it may be important to have the capacity to modulate expression to exceed normal

Application of Hormesis-Based Biphasic Plasticity Concept to Animal Behavior

Fig. 4 Application of hormesis-based biphasic plasticity concept to animal behavior. • This example of hormesis-based plasticity indicates that a spectrum of behaviors (e.g. passivity, cautiousness, non-exploratory to aggressiveness, exploratory, boldness, "bravery") can be adaptive and that these are modulated and expressed within the context of the hormetic dose response relationship. It would also be expected that some responses may be adaptive within a stimulatory and inhibitory mode. • In some cases one would expect an inverted U-shaped response with the high dose not having a response going below the control group (Calabrese 2008a; Zoladz and Diamond 2009)

background (i.e., control) values or to suppress such responses. A rodent, for example, may need to modulate behaviors such as aggression, exploration, and what humans call bravery, while at other times such behaviors may need to be restrained below that of normal (Fig. 4). These behaviors follow the hormetic biphasic dose response with survival-preserving changes occurring on either side (i.e., above and below) of the control value. In the case of humans, anxiolytic drugs likewise act to decrease anxiety at low doses while at higher doses the anxiety response may increase beyond that of the normal background following a standard hormetic dose response (Fig. 5). In the case of humans the patient is typically being treated for an "anxiety" condition and seeks

Application of Hormesis-Based Plasticity Concept to Pharmaceutical Use of Anxiolytic Drugs

Fig. 5 Application of hormesis-based plasticity concept to pharmaceutical use of anxiolytic drugs

to have it reduced. However, anxiety can modulate above and below background normal levels and would have been selected for.

Discussion

An assessment of the quantitative features of plasticity has been predominately focused on ecological—genetic—evolutionary biology interactions along with the neurosciences, especially the molecular foundations of memory including synapse involvement. However, plasticity is a general biological concept that is incorporated into all organisms, tissues and cells. It defines the capacity of such levels of biological organization to adapt to environmental signals and stressors. In the case of molecular signaling the dose response is often seen as a direct stimulation whereas in the toxicity realm the stimulatory response is observed following an initial disruption in homeostasis, as a component of a dose-time-response. Regardless of the cause of the dose response their quantitative features are similar, reflecting the constraints placed on system plasticity. Therefore, the quantitative features of plasticity regardless of whether they result from either a direct or overcompensation stimulation are described by the hormetic dose response.

While the hormesis database was initially designed to evaluate the nature of toxicological and pharmacological dose response relationships its utility became more broadly generalizable. The most remarkable feature of the findings of the database has been the consistent observation that the maximum stimulation response was quite limited averaging about 30–60% greater than control values (Calabrese & Baldwin 1997). The modest response also makes hormesis more difficult to replicate since the signal to noise ratio is small. This places far greater need for stronger study designs (i.e., more doses and careful dose spacing) with markedly improved statistical power, and improved mechanistic understandings. Marked advances have been achieved in each of these areas over the past decade. This was especially assisted by advances in cell culture which has permitted the use of many concentrations in an inexpensive manner, and continued molecular advances which have improved mechanistic understandings.

The remarkable consistency of the observations across models, endpoints and chemical classes suggest that similar plasticity strategies and constraints are the rule throughout the biological sciences. That the quantitative features of biological plasticity could be reliably revealed via the development and assessment of the hormetic dose response reflect the value of integrated and cross disciplinary assessments that can help to clarify basic biological concepts.

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