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Short Communication

Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose–response framework

Edward J. Calabrese [a,*], Kenneth A. Bachmann [b], A. John Bailer [c], P. Michael Bolger [d], Jonathan Borak [e], Lu Cai [f], Nina Cedergreen [g], M. George Cherian [h], Chuang C. Chiueh [i], Thomas W. Clarkson [j], Ralph R. Cook [k], David M. Diamond [l], David J. Doolittle [m], Michael A. Dorato [n], Stephen O. Duke [o], Ludwig Feinendegen [p], Donald E. Gardner [q], Ronald W. Hart [r], Kenneth L. Hastings [d], A. Wallace Hayes [s], George R. Hoffmann [t], John A. Ives [u], Zbigniew Jaworowski [v], Thomas E. Johnson [w], Wayne B. Jonas [u], Norbert E. Kaminski [x], John G. Keller [y], James E. Klaunig [z], Thomas B. Knudsen [aa], Walter J. Kozumbo [ab], Teresa Lettieri [ac], Shu-Zheng Liu [ad], Andre Maisseu [ae], Kenneth I. Maynard [af], Edward J. Masoro [ag], Roger O. McClellan [ah], Harihara M. Mehendale [ai], Carmel Mothersill [aj], David B. Newlin [ak], Herbert N. Nigg [al], Frederick W. Oehme [am], Robert F. Phalen [an], Martin A. Philbert [ao], Suresh I.S. Rattan [ap], Jim E. Riviere [aq], Joseph Rodricks [ar], Robert M. Sapolsky [as], Bobby R. Scott [au], Colin Seymour [aj], David A. Sinclair [at], Joan Smith-Sonneborn [av], Elizabeth T. Snow [aw], Linda Spear [ax], Donald E. Stevenson [ay], Yolene Thomas [az], Maurice Tubiana [ba], Gary M. Williams [bb], Mark P. Mattson [bc]

[a] *School of Public Health, Morrill I, N344, University of Massachusetts, Amherst, MA 01003, USA*
[b] *University of Toledo, OH 43606, USA*
[c] *Miami University, FL 33124, USA*
[d] *US Food and Drug Administration, MD 20857, USA*
[e] *Yale University, CT 06520, USA*
[f] *University of Louisville School of Medicine, KY 40292, USA*
[g] *The Royal Veterinary and Agricultural University (KVL), Denmark*
[h] *University of Western Ontario, Canada*
[i] *Taipei Medical University, Taipei, Taiwan*
[j] *University of Rochester, NY 14627, USA*
[k] *RRC Consulting, LLC, TX 78727, USA*
[l] *University of South Florida, FL 33620, USA*
[m] *RJR Tobacco Company, NC 27101, USA*
[n] *Eli Lilly and Company, IN 46285, USA*
[o] *ARS, USDA, MD 20857, USA*
[p] *Heinrich-Heine-University Duesseldorf, Germany*
[q] *Inhalation Toxicology Associates, DC 20006, USA*
[r] *NCTR, US Food and Drug Administration (Retired), MD 20857, USA*
[s] *Harvard University, MA 02114, USA*
[t] *College of the Holy Cross, MA 01610, USA*
[u] *Samueli Institute for Information Biology, VA 22314, USA*
[v] *Central Lab for Radiological Protection, Warszawa, Poland*
[w] *University of Colorado, CO 80309, USA*
[x] *Michigan State University, MI 48824, USA*

* Corresponding author. Fax: +1 413 545 4692.
E-mail address: edwardc@schoolph.umass.edu (E.J. Calabrese).

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[y] Professional Consulting Services, USA
[z] Indiana University School of Medicine, IN 46202, USA
[aa] University of Louisville, KY 40292, USA
[ab] Air Force Office of Scientific Research, VA 22203, USA
[ac] European Commission, Joint Research Centre, Ispra, Italy
[ad] Jilin University Health Sciences Center, China
[ae] World Council of Nuclear Workers, Paris, France
[af] Sanofi-Aventis U.S. Inc., NJ 08807, USA
[ag] University of Texas Health Science Center (Emeritus Professor), TX 78712, USA
[ah] Toxicology and Human Health Risk Analysis, NM 87111, USA
[ai] University of Louisiana, Monroe, LA 71209, USA
[aj] McMaster University, Canada
[ak] RTI International, MO 63080, USA
[al] University of Florida, FL 32611, USA
[am] Kansas State University, KS 66506, USA
[an] University of California–Irvine, CA 92697, USA
[ao] University of Michigan School of Public Health, MI 48824, USA
[ap] University of Aarhus, Denmark
[aq] North Carolina State University, NC 27695, USA
[ar] ENVIRON Int. Corp., TX 77056, USA
[as] Stanford University School of Medicine, CA 94305, USA
[at] Harvard Medical School, MA 02114, USA
[au] Lovelace Respiratory Research Institute, NM 87108, USA
[av] University of Wyoming, WY 82071, USA
[aw] University of Tasmania, Australia
[ax] Binghamton University, NY 13902, USA
[ay] Dermigen Consulting Group, TX 78057, USA
[az] Institut Andre Lwoff, France
[ba] Centre Antoine Beclere, France
[bb] New York Medical College, NY 10595, USA
[bc] National Institute on Aging, MD 20877, USA

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Abstract

Many biological subdisciplines that regularly assess dose–response relationships have identified an evolutionarily conserved process in which a low dose of a stressful stimulus activates an adaptive response that increases the resistance of the cell or organism to a moderate to severe level of stress. Due to a lack of frequent interaction among scientists in these many areas, there has emerged a broad range of terms that describe such dose–response relationships. This situation has become problematic because the different terms describe a family of similar biological responses (e.g., adaptive response, preconditioning, hormesis), adversely affecting interdisciplinary communication, and possibly even obscuring generalizable features and central biological concepts. With support from scientists in a broad range of disciplines, this article offers a set of recommendations we believe can achieve greater conceptual harmony in dose–response terminology, as well as better understanding and communication across the broad spectrum of biological disciplines.

Keywords: Hormesis; Adaptive response; Conditioning; Preconditioning; Postconditioning; Stress response; Dose–response; Biphasic; U-shaped

A bewildering array of terms for similar biological phenomena

The biomedical sciences have long been concerned with how biological systems respond to and tolerate environmental stress (Seyle and Fortier, 1949). Such stresses have been broadly considered by researchers and may include hypoxia/ischemia, endogenous metabolic products such as certain lipid peroxides and other oxidant stressors, heat stress, radiation exposures, caloric restriction, exercise, toxicants, and psychologically induced stress. Of particular importance is that the response to a stressor does not monotonically increase or decrease with increasing dose, rather it is often characterized by nonlinear relationships commonly described as U- or J-shaped. For example, at low doses the response may be opposite to that at higher doses. In this situation, high doses that inhibit growth, decrease fecundity and reduce longevity often enhance these responses at lower doses (Calabrese, 2005c). In some, but not all cases, exposure to a low dose of an agent or condition that is toxic at higher doses induces an adaptive, potentially beneficial effect on the cell or organism if exposed to a subsequent and more massive exposure to the same or related stressor agent, a

phenomenon called preconditioning in the biomedical sciences. Such adaptive responses to low doses of a stressor that is toxic at high doses have been observed in essentially all organisms studied so far, including prokaryotes, fungi, plants, invertebrates and mammals, including humans.

Since many biological disciplines assess specific aspects of this general nonlinearity phenomenon, it is not unexpected that numerous terms have emerged to describe these biological responses to the plethora of possible stressors with respect to diverse endpoints in varied biological models. For example, some terms address the shape of the dose–response curve such as β-curve, biphasic, bell-shaped, U-shaped, inverted-U shaped, J-shaped, diphasic, bitonic, bimodal, bidirectional, sinusoidal, subsidy gradient, functional antagonism, dual response, nonmonotonic, stimulatory inhibitory, among others (Calabrese and Baldwin, 2002). Terms such as autoprotection, heteroprotection, adaptive response, preconditioning, hormesis, xenohormesis, paradoxical and others have characterized the shape of the dose–response patterns mentioned above when low doses elicit an adaptive response of the cell/organism. Others have referred to the above dose–response patterns in more grandiose and older historical terms such as the Arndt-Schulz Law and Hueppe's Rule stemming from the early decades of the 20th century and in the mid-1950s the Yerkes–Dodson Law for a broad range of psychological stressors (Calabrese and Baldwin, 2000a, 2000b, 2000c, 2000d, 2000e). Given this sea of terms for what appears to be a family of biological responses set within a dose–response framework, there is a need for convergent terminology that is consistent with the quantitative features of the dose–response and underlying molecular foundations. Lack of a commonly understood terminology is counterproductive in numerous ways, undercutting interdisciplinary understanding and collaboration, even leading to a failure to recognize the generalized significance of these dose–response patterns in the toxicological and biomedical sciences.

It is our opinion that the numerous biological disciplines that routinely deal with the concept of dose–response patterns have reached a point of terminological cacophony, as seen in the vast array of terms that describe similar features of the dose–response relationship. Here we propose a set of recommendations that can achieve some harmony in terminology, fostering better understanding and communication with respect to the dose–response relationship, while being sufficiently flexible to accommodate future scientific developments and refined understanding of the dose–response pattern (Table 1).

Historical perspective

Cognizance of historical developments is critical for framing a more unified terminology for dose–response relationships. The historical foundations of the terms preconditioning, adaptive response and autoprotection must be considered and their biological/toxicological relatedness evaluated. "Preconditioning" has been a widely used term to describe a low level initial stress (e.g., hypoxia) that provides protection against a subsequent more intense stress. This term was first employed in the biomedical sciences by Murry et al. (1986) who demonstrated that a brief series of hypoxic episodes (i.e., four cycles of 5 min of coronary occlusion with each followed by 5 min of reperfusion) would greatly reduce the magnitude and severity of subsequent induced myocardial

Table 1
Biological stress terminology summary[a,b]

Conditioning/Adapting dose	No conditioning/adapting dose	Stressor agent
Stressor/Agent	Stressor/Agent	Postexposure conditioning dose (i.e., low dose treatment after massive exposure)
Recommended terms	**Recommended terms**	**Recommended terms**
Physiological conditioning hormesis	Physiological hormesis	Physiological postexposure conditioning hormesis
Radiation conditioning hormesis	Radiation hormesis	Radiation postexposure conditioning hormesis
Chemical[3] conditioning hormesis	Chemical hormesis	Chemical postexposure conditioning hormesis

[a]Preconditioning, adaptive response and autoprotection represent examples of what is described here as "conditioning hormesis".
[b]Advantages: Standardized terminology provides information on the presence or absence of a conditioning dose, whether it is prior to or after the more massive challenge and the nature of the stressor agents. This terminology would establish a consistent and understandable framework across the spectrum of biological disciplines concerning dose–response and stress response.
[c]Chemical (e.g., xenobiotic, endogenous agents).

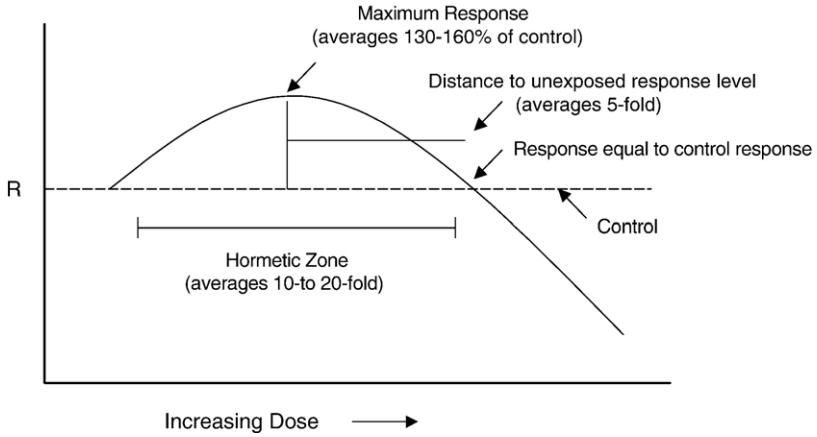

Fig. 1. Dose–response relation depicting the quantitative features of hormesis. The figure illustrates the average maximum stimulation range and the typical width of the stimulation range. This representation is based on data in the hormesis database (Calabrese and Blain, 2005) (source: Calabrese and Baldwin, 2002).

infarctions (i.e., resulting from a 40-min occlusion of a branch of a coronary artery) in a dog model. This observation was replicated and generalized to other animal models and then other biological systems including the central and peripheral nervous systems, liver, kidney, various muscular systems and intestines. By 2006, the term "preconditioning" had over 9200

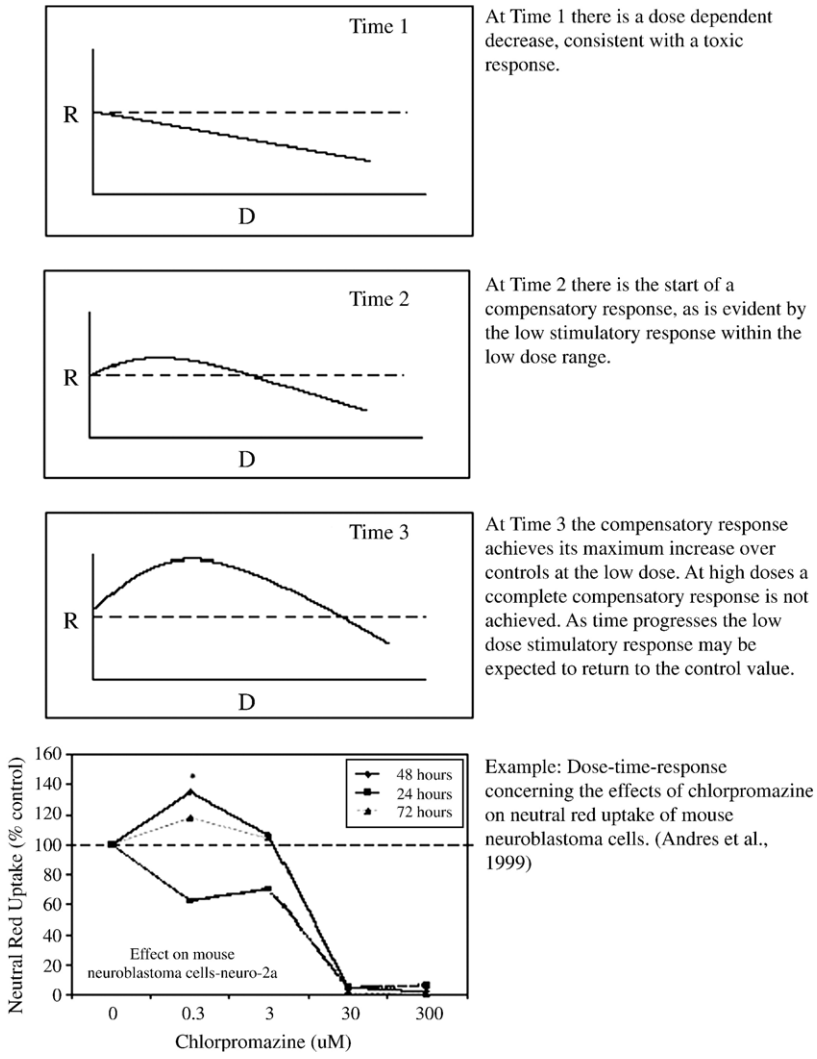

Fig. 2. Overcompensation stimulation (hormesis) within a dose–time–response relationship. Response (R) on the vertical axis, dose (D) on the horizontal axis (source: Calabrese and Baldwin, 2002; Andres et al., 1999).

citations in the Web of Science database while the original paper of Murry et al. (1986) had been cited nearly 2700 times. Despite the widespread use of the term "preconditioning", we prefer to call this process "conditioning". Exposure to an agent "conditions" the system to respond in some manner.

The same general concept applies when a small prior exposure to a mutagen reduces the response to a larger subsequent mutagenic exposure, a phenomenon first reported by Samson and Cairns (1977) in bacteria and subsequently named the "adaptive response" (Jeggo et al., 1977). As in the case of conditioning, the adaptive response concept was soon replicated, generalized to other biological models, and found to encompass both chemical mutagens and various types of radiation. A similar response was reported in the early 1970s for a nonmutational endpoint when a low dose of carbon tetrachloride was found to protect the liver against a very large subsequent exposure to this agent (Ugazio et al., 1972). This was called "autoprotection". It was soon generalized to cases where exposures to one chemical reduced response to other chemicals. The term heteroprotection was coined to describe such cases. The three types of observations (i.e., conditioning, adaptive response, and autoprotection) are quite similar even if different endpoints are measured.

The principal mechanism in common among conditioning, adaptive response and autoprotection is that low levels of stress activate or upregulate existing cellular and molecular pathways that enhance the ability of the cell and organism to withstand more severe stress. The optimal range of doses of autoprotective, adaptive or conditioning treatments is similar to that of the hormetic dose–response pattern. Based on the general adaptive nature of these responses and the shape of the dose–response pattern (i.e., adaptive/conditioning dose), these phenomena can be generalized as being specific cases of "hormesis", an adaptive response characterized by biphasic dose–response patterns of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced (Fig. 1) or the result of compensatory biological processes following an initial disruption in homeostasis (Calabrese and Baldwin, 2002) (Fig. 2). The term "hormesis" was coined in 1943 by Southam and Ehrlich (1943) and so predates the other commonly used terms for the same and/or similar phenomena.

Proposed unifying terminology

Biological systems do not "care" what term is used to describe their response to stress. When biological systems are exposed to a low dose of a toxicant or other mild stress, survival will typically be enhanced when physiologically existing mechanisms that protect against a similar but more severe stress are activated or upregulated. Since many different terms are used to describe this phenomenon, many of which are discipline-specific, we propose a unified terminology for use across the broad range of biological disciplines assessing dose–response relationships.

There are two well-established experimental frameworks within which hormetic dose–response patterns have been reported. The first includes examples of autoprotection, adaptive response, and conditioning, in which the toxicity of a more massive insult is reduced when a lower prior dose is administered. The second kind of hormetic response is observed when a subsequent large exposure is not included within the study design. Thus, the hormetic response occurs without the inclusion of separate conditioning and challenging doses. We propose that a common terminology should include the operational term *Hormesis*, which would be preceded by the type of inducing agent and whether or not conditioning was present. For example, in the case of a prior ischemic exposure induced by a metabolic technique (e.g., surgical occlusion of an artery) protecting against damage from a subsequent more massive threat (e.g., ischemia) we propose the phrase *physiological conditioning hormesis*. A similar example is the prior exposure to a chemical toxicant reducing the toxic effect of a subsequent more massive chemical or radiation insult. This would be called *chemical conditioning hormesis*. When hormesis occurs without the conditioning element, the term "*conditioning*" would simply be dropped (e.g., chemical hormesis, radiation hormesis). Likewise, if the adapting dose is administered after the larger, toxic exposure, the phenomenon would be an example of postexposure conditioning hormesis (Table 1). The postconditioning hormesis concept is a relatively new development, which was initially observed when a low level hypoxic stress following a myocardial infarction (MI) significantly reduced the magnitude of the damage from the induced MI. The degree of protection was similar to that observed with preconditioning (Zhao et al., 2003). The postconditioning phenomenon has been viewed as having possible important biomedical implications with respect to patient treatment.

Discussion

Hormesis-like biphasic dose–response patterns are also commonly observed with endogenous and synthetic agonists (e.g., numerous drugs, hormones, peptides) that activate and inhibit receptor-mediated signaling pathways that affect various biological functions (Calabrese, 2005a, 2005b; Calabrese and Baldwin, 2001). As one example, low levels of activation of receptors by the neurotransmitter glutamate engage stress response pathways in neurons that promote their survival and adaptive plasticity, whereas excessive activation of glutamate receptors kills nerve cells in a process called excitotoxicity (Jiang et al., 2005). Such intrinsic dose–response functions are regulatory in nature and, although they may not be classically viewed as "adaptive", they clearly belong to the same general "family" as those described above for exogenous stressors based upon the quantitative features of the dose–response relationship. Indeed, this general form of the dose–response relationship is evolutionarily based and therefore an "adaptive" regulatory response. Finally, since such hormetic dose–response patterns are independent of the biological model, endpoint and stressor agent/condition, the specific mechanisms responsible for this dose–response pattern are unique to the experimental

conditions. Thus, there is no common proximate mechanism to account for the vast array of hormetic dose–response patterns, but there is apparently a common and highly conserved downstream strategy yielding the generalized quantitative features of the hormetic dose–response pattern with its underlying and pervasive dose–response plasticity. This general pattern of response is commonly observed across the spectrum of biological models. Examples of well-established conserved hormetic pathways include those involving heat-shock proteins, antioxidant systems and anti-apoptotic proteins (Arumugam et al., 2006).

While our illustrations have emphasized molecular/biological applications, it is worth noting that this nonlinear pattern of response relative to stressor level is broadly observed. In ecology, the intermediate disturbance hypothesis posits that intermediate level of ecosystem disturbance will be associated with maximum species richness (Connell, 1978). This has led to empirical assessments designed to evaluate this hormetic pattern (see, e.g., Townsend et al., 1997). The nonlinear relationship between arousal and performance is commonly taught in introductory psychology classes. This relationship is still referred to as the Yerkes–Dodson Law in reference to Yerkes and Dodson (1908). Finally, while discussions of biphasic dose–response patterns may appear esoteric, the public health aspects of this pattern will capture the public attention on some occasions. Perhaps the most common illustration is the potential health benefits associated with moderate consumption of alcohol. Quantifying this U-shaped relationship along with examining potential mechanistic reasons for it has been the focus of much research (see, e.g., de Labry et al., 1992; Rehm et al., 1997). Integrating the understanding of dose–response relationships across disciplinary lines will enhance the capacity for practical application of the hormesis concept to the biomedical, clinical and environmental health science domains.

There are also exposures that induce hormetic-like biphasic dose–response patterns but where the response appears potentially harmful to both individual and species (e.g., autoimmune responses, endocrine modulation/disruption and psychomotor stimulation as a marker for addictive behavior as seen with numerous drugs such as amphetamine, cocaine, opiates, ethanol and other addictive agents, anxiogenic (i.e., anxiety enhancing) responses and cell proliferation with potential for tumor promotion). While these cases have typically been viewed as potentially harmful, the proposed terminology can incorporate such phenomena within its conceptual framework as potentially maladaptive changes depending on specific conditions. Even though the terminological framework proposed here can include situations that seem maladaptive, conditions such as a very low degree of neuronal autoimmunity may actually be adaptive (Schwartz and Kipnis, 2004). While there may not be complete unanimity regarding each of the specific examples and explanations described in this essay, we are convinced that the proposed framework is sufficiently flexible to explore the nature of the dose–response relationship in the low-dose zone. Moreover, we strongly concur that further exploration of these low-dose effects is important and that the framework proposed will facilitate the conduct of such work in a context of intellectual openness, regardless of the nature and characterization of the response.

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