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HORMESIS PERVERSIVENESS AND ITS POTENTIAL IMPLICATIONS FOR PHARMACEUTICAL RESEARCH AND DEVELOPMENT

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□ This mini-review illustrates that hormesis is not only confined to the areas of biochemistry, radiation biology and toxicology, where it is traditionally known, but illustrates, by citing published scientific literature, that it is found across a wide range of biomedical science and clinical medicine such as neuroscience, cardiology and oncology. The use of techniques and technology, including high through-put screening, micro-dosing or phase 0 studies, pharmacometrics and adaptive trial design in the clinic, are proposed to illustrate how acknowledging the potential impact of hormesis throughout different stages of drug discovery and development, including hurdles related to efficacy and safety, could help the pharmaceutical industry address some of its major and frequently mentioned challenges.

Keywords: dose response, hormesis, drug discovery, drug development, research and development, pharmaceutical industry

1. HORMESIS IS PERVERSIVE ACROSS SCIENCE AND MEDICINE

Traditionally, hormesis was confined to the areas of biochemistry, radiation biology and toxicology. Over the past twelve years, however, the publication of J-, U- or inverted U-shaped dose-response curves has exploded illustrating the presence of hormesis across many fields of biological sciences and clinical medicine.

The volume of literature published in this area each year has grown 10-fold in large part due to single, original papers in a variety of high impact factor, scientific, peer-reviewed international journals, but also due to entire volumes of journals which have been devoted to hormesis. Some of the various areas include aging, benign prostate enlargement, biochemical and physiological cellular responses, caloric restriction, cardiovascular function, cancer and tumor development, chemo-sensitization, chemotherapy, dermatology, drug binding, hair growth, sexual dysfunction, ocular diseases, osteoporosis, oxidative stress, prion diseases and synaptic plasticity (Calabrese 2008a, Maynard et al. 2008). Four special volumes concentrated on neuroscience, including neuronal survival, neurite outgrowth, glial adaptive responses to neurotoxins, p-glycoprotein efflux transporter activity, anxiety and anxiolytic drugs, epilepsy, traumatic brain injury, stroke, addiction, memory and Alzheimer’s Disease (Calabrese 2008b).
The examples below illustrate the caliber of scientific inquiry and diversity of disciplines where hormesis is exemplified across a broad range of biological science and clinical medicine.

2. SPECIFIC EXAMPLES OF HORMESIS

2.1 Neuroprotection

Since 1999 a series of original papers have been published in various journals and from various laboratories showing that nicotinamide (NAm, vitamin B3) is neuroprotective in models of stroke. U-shaped dose-response neuroprotection as shown by reduction in cerebral infarction volume was found in a model of focal cerebral ischemia using permanent middle cerebral artery occlusion in male Wistar rats at 500 mg/kg NAm, but not at 50 mg/kg or 1000 mg/kg (Ayoub et al. 1999). In separate studies, NAm was also shown to be neuroprotective in a model of transient middle cerebral artery occlusion, in female Wistar and Sprague Dawley rats (Sakakibara et al. 2000) as well as in Fischer 344 control and diabetic rats (Sakakibara et al. 2002).

From a rigorously scientific perspective, what is convincing about the NAm-induced hormetic response with regard to the neuroprotection is its consistency across different strains of both male and female rats and mice, different models of stroke and original studies published from different laboratories, each consistently showing the U-shaped neuroprotective effect of NAm.

NAm is a poly-ADP ribose polymerase (PARP) inhibitor and other PARP inhibitors such as 3-aminobenzamide exhibit U-shaped neuroprotection (Ayoub et al. 1999). PARP activation leads to the repair of DNA damage, which may be caused by ischemia. However, excessive PARP activation leads to neuronal injury through augmentation of nitric oxide (NO) - and glutamate-induced excitotoxicity and depleted energy (ATP) therefore adding insult to injury, since it is the initial energy imbalance that initiates the various ischemic cascades leading to neuronal and glial cell death. It was therefore speculated by Ayoub and colleagues (Ayoub et al. 1999) that the U-shaped dose-response curve may have been due to optimal PARP regulation. A review of the literature at that time, 1999 – 2001, revealed U-shaped dose-response neuroprotection reported not only by PARP inhibitors, but by a variety of agents representing many potential neuroprotective mechanisms (Table 1). Thus, it is true to say that at least in models of cerebral infarction, but perhaps in other models of central nervous system injury as well, the hormetic protection illustrated by reduction in cerebral infarction volume transcends a wide variety of mechanisms of action, and may perhaps point to a more generalized phenomenon, which is not yet currently understood. This is further evidenced by a later review of dose-response features of neuroprotective agents (Calabrese 2008c).
2.2 Chronic Heart Failure

In the 1990s, there was a major turn around of our understanding of the usefulness of beta-adrenoceptor blockers in the treatment of chronic heart failure (CHF). Beta-adrenoceptor blockers were originally contraindicated in the treatment of CHF until it was understood that the initial negative agonistic ionotropic effect was transient, eventually to be reversed, leading to improvement of CHF symptoms.

Agonists of beta-2-adrenoceptors acutely activate the receptor resulting in a reduction in the cardiac output. However, chronic treatment with inverse agonists such as metoprolol and carvedilol, have been shown in clinical trials to lead to improvement of cardiac output and a reduction in mortality. It is believed that this reciprocity due to receptor desensitization is the mechanism of action accounting for the temporal hormesis observed with selective beta-2-adrenoceptor inverse agonists (Dudekula et al. 2005). In this case, the hormetic effect is not due to a concentration/dose effect, but based on the duration of exposure to the drug which leads to the reversal of the initial drug response over time with chronic treatment.

2.3 Angiogenesis and Tumor Growth

The pharmacology of a 5 amino acid, anti-angiogenic peptide, ATN-161, which binds to integrins has been shown to illustrate U-shaped dose-response curves in various models of angiogenesis and tumor growth (Doñate et al. 2008). Using the Matricel plug model of angiogenesis and the Lewis lung carcinoma model of tumor growth, studies have shown a U-
shaped dose-response with 1 to 10 mg/kg, but not higher or lower doses being optimal ATN-161. Interestingly, a biomarker of the anti-angiogenic action using levels of viable circulating endothelial cells identified by flow cytometry also exhibited the hormetic response within the same dose range and can therefore be used to identify optimal dosing in the clinic. The potential mechanisms of action proposed by Doñate and colleagues (Doñate et al. 2008) for the hormetic response included a crossover of drug action from antagonist to agonist due to a lower affinity receptor, down-regulation of receptors for a particular ligand after exposure saturation and an up-regulation of clearance mechanisms at high concentrations of ligand that feedback to modulate the drug activity.

3. CHALLENGES FOR THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry is currently facing a variety of hurdles which may be positively impacted by hormesis, even if in the short term the concept may require adjustments. Some of these include:

1. A lack of preclinical systems that accurately predict clinical outcomes (e.g., toxicity and therapeutic efficacy)
2. A high failure rate at all stages of research and development (R&D), some of which is due to
   a. Inappropriate target – during the Discovery phase
   b. Toxicity – during the Preclinical phase
   c. Lack of efficacy – during the Clinical phase
3. Long R&D timelines from bench to bedside and associated increasing costs
4. Added hurdles of regulatory agencies/health authorities and payers (e.g., health insurers, health management organizations, Medicare/Medicaid)

The pharmaceutical industry has responded to these challenges in part by at least two ways:

1. Trying to reduce the R&D time and costs by sampling large (e.g., over 1 million) chemical libraries, but
   a. Assumptions are made such as linear or threshold concentration-response relationships
   b. In vitro - narrow concentration ranges are examined or a wide range is tested, but sampling many concentrations is reduced or unrepresentative of the targeted effect
   c. In vivo – the same as above for doses, duration or population sampling of studies tested in animals and humans, i.e., either narrow ranges or few samples are tested
2. Focusing R&D on novel mechanisms, molecularly targeted drugs, biologics and first-in-class molecules, sometimes using advancing technologies such as computer-assisted models with added risks, which could result in termination of projects at later and more costly stages of R&D

Many of these challenges could be positively affected if it is understood that hormesis:

1. Is found widely across many areas of biomedical science and clinical medicine, thus assumptions of linear and threshold drug-response relationships should not be made
2. Pertains not only to toxicity, but also to efficacy
3. Requires comprehensive sampling of data for successful characterization of drug effects, in vitro and in vivo

4. FDA: PHARMACEUTICAL GUIDELINES AND FINDINGS

The Food and Drug Administration (FDA) has dose-response guidelines for the pharmaceutical industry to support drug registration (International Conference on Harmonization (ICH)-E4, November 1994). In this guidance, various points are made which are particularly critical in the light of hormesis and are excerpted below:

1. Identify reasonable, response-guided titration steps, and the interval at which they should be taken, again with appropriate adjustments for patient characteristics. These steps would be based either on the shape of the typical individual’s dose-effect curves (for both desirable and undesirable effects) .... and the time needed to detect a change in these effects
2. Dose-response data for both beneficial and undesirable effects may provide information that allows approval of a range of doses that encompass an appropriate benefit-to-risk ratio. A well-controlled, dose-response study is also a study that can serve as primary evidence of effectiveness
3. Several dose levels are needed, at least two in addition to placebo, but in general, study of more than the minimum number of doses is desirable. A single dose level of drug versus placebo allows a test of the null hypothesis of no difference between drug and placebo, but cannot define the dose-response relationship. Similarly, although a linear relationship can be derived from the response to two active doses (without placebo), this approximation is usually not sufficiently informative. Study designs usually should emphasize elucidation of the dose-response function, not individual pair-wise comparisons
4. Dose-response data should be explored for possible differences in subsets based on demographic characteristics, such as age, gender, or race

It has been documented that between the period of 1980 and 1999, 1 in 5 drugs approved underwent significant post-approval dose adjustments by the FDA. Of these cases, 20% had the dose increased and 80% had the dose decreased (Cross et al. 2002).

In the light of hormesis, careful adherence to these guidelines could lead to fewer post-approval adjustments. More importantly, it may also result in a more successful R&D process leading to increased drug approvals, rather than missed opportunities due to unclearly characterized safety, toxicity and efficacy due to potential hormetic effects.

5. HORMESIS: PROVIDING SOLUTIONS IN THE R&D PROCESS

5.1 Discovery – High Through-put Screening

High through-put screening (HTS) is a process in which a large number of compounds can be tested in cellular and biochemical assays conducted in an automated fashion using large commercial machines capable of screening e.g., 1,536 and 2,080 wells per plate. The data can provide statistical hit-identification/confirmation, IC50 profiling, secondary testing, structural verification of the hit compounds and structure activity relationship (SAR) information. Thus, typically large libraries of compounds can be screened against drug targets automatically and rapidly (e.g., receptors) therefore saving time. The focus of using HTS can therefore also be used to focus on the thorough elucidation of a full concentration-response curve for each compound being tested, so that any potential hormetic responses which are now known to be very common can be discovered, rather than only examining many thousands of compounds with few data points for each so that many compounds can be tested. Therefore, the range and sampling of data can be increased to provide a more thorough understanding of the safety, toxicity and efficacy of each compound tested.

5.2 Preclinical – Microdosing/Phase 0

Microdosing (as it is called in Europe) or Phase 0 (as it is called in the USA) studies drug behavior in humans at ultra-low (100 µg) doses unlikely to produce whole-body effects, but allows the study of cellular responses. It helps to predict if a potential drug is viable for phase I testing and is aimed at reducing animal testing and non-viable drugs early in clinical development. As written by Graul (2008), “Microdosing also directly addresses the ethical problems of administering full human doses of a drug or biologic to healthy volunteers based only on available animal and in vitro data, as well as the
extreme inaccuracy of predicting humans doses based on animal data, as has been the standard procedure until now.”

Ultra-low doses are unlikely to produce whole-body effects, but it allows the study of cellular responses and as such, can be used to improve our understanding of human safety, toxicity and efficacy. However, one of the challenges of microdosing is that there might also be non-linearity or hormesis in extrapolating between a microdose and therapeutic dose observed in terms of pharmacokinetics and pharmacodynamics (Lappin and Garner 2008).

Thus, microdosing can be used in the light of hormesis to focus on obtaining thorough data related to the therapeutic index or margin of safety by not assuming that (a) the highest dose tolerable is the most efficacious dose and (b) that massive doses are the most toxic. Toxicity or efficacy may also be seen at lower, rather than higher doses as is readily seen in hormetic-type responses. It may also help in alleviating the challenge that despite the fact that receptors may often be highly homologous across species, animal models of toxicity and disease are frequently not highly predictive of the clinical outcome in humans.

If re-focused, therefore, the concept of micro-dosing can be used to save time and money in drug R&D by eliminating testing large amounts of compounds in toxicity and efficacy animal models by testing micro-doses directly in humans.

5.3 Phase I – Pharmacometrics

Pharmacometrics is an emerging science that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions. Drug models describe the relationship between exposure (or pharmacokinetics [PK]), response (or pharmacodynamics [PD]) for both desired and undesired effects, and individual patient characteristics. The typical focus of pharmacometrics has been on drug models, also referred to by terms such as: concentration-effect, dose-response, PKPD relationships.

The single-most important strength of such analyses is its ability to integrate knowledge across the development program with regard to the compounds, and biology.

Dose-response data should be explored for possible differences in subsets based on demographic characteristics, such as age, gender, or race as suggested in the FDA guidance.

5.4 Phase II/III – Adaptive Trial Design

Adaptive trial design (ATD) is defined as a study design that includes a sequence of interim analyses to enable modification of the course of the clinical trial dynamically (e.g., used by Drug Monitoring Committees
(DMCs) to stop trials early due to overwhelming evidence of efficacy. Possible adaptation of late phase clinical trials includes sample size re-estimation by dropping or adding treatment arms (e.g., different doses), therefore enabling the thorough examination of many doses in a clinical study (Phillips and Du Mond 2007). Although the complexity of an adaptive trial will be higher than a traditional one, it permits multiple objectives to be addressed in a single trial, e.g., identifying the dose-range as well as the patient population likely to get the maximum drug benefit, whilst potentially reducing the overall costs. Currently, there is a draft guideline from the FDA, and their Critical Path Opportunities highlights ATD as one way of speeding up drug development while reducing costs.

6. CONCLUSION

Hormesis is found not only in biochemistry, radiation biology and toxicology, but there are many examples of hormesis across a wide range of biomedical science and clinical medicine. The concept of hormesis could help the pharmaceutical industry address major concerns, even though short-term it could add to its challenges, which we have tried to rectify by reducing R&D timelines and costs via reducing the amount of data obtained.

Having understood the significant role that hormesis plays in R&D, it requires a major change in our mindset to focus more on providing more comprehensive datasets with regard to safety and efficacy all along the R&D process. In the long-term, this will provide more and better quality drugs. The use of existing techniques, tools and resources can be used to our advantage to help ensure that drugs with better safety and efficacy do not necessarily require major additional R&D costs, but rather carefully re-allocated resources.

A re-examination of our past failures is needed, since it is likely that many compounds in R&D were stopped, for example, not because the target was incorrect or the mechanism invalid, but simply because we chose the wrong dose assuming a linear or sigmoidal concentration/dose-response relationship for safety, toxicity or efficacy. Based on what we understand of hormesis to date, we need to:

1. Define the concentration-response relationship thoroughly in vitro
   a. Do not assume a linear or sigmoidal concentration-response relationship
   b. Keep in mind J-shaped, U-shaped or bell-shaped concentration relationships

2. Identify optimal, not maximal concentrations/doses by sampling often and over broad test ranges, not only in the early stages in drug Discovery, but throughout the entire R&D process
3. Define the therapeutic index by comprehensively characterizing the safety and efficacy dose responses, and not assuming that the highest doses lead to greater toxicity or that the maximal tolerated dose is equivalent to the optimal dose having maximal efficacy.

Ultimately, drug R&D is about science, medicine and creating drugs to help people. Consequently, although this article has focused on the impact of hormesis on the pharmaceutical industry, it also applies to academic research and the elucidation of basic mechanisms of action at the molecular, cellular and systemic levels.

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REFERENCES


