Hormesis: from mainstream to therapy

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Abstract This issue of the Journal of Cell Communication and Cell Signaling on hormetic mechanisms represents an important step in the evolution of the hormesis dose response concept. Since its modern resurgence in the late 1970s the widespread occurrence of hormesis has been in search of its underlying mechanisms. The present integrative set of papers builds upon significant recent advances in the elucidation of hormetic mechanisms and provides the reader with a deep and extensive view of the concept of hormesis from a broad range of researcher perspectives and in many biomedical applications.

Keywords Biphasic · Dose response · Hormesis · Hormetic · J-shaped, U-shaped

Historical foundation of hormesis

The dose-response concept has its origin in the work of the German pharmacologist/toxicologist Hugo Schulz, at the University of Greifswald with his first publications in the late 1880s concerning the effects of numerous disinfectants on the metabolism of yeast (Schulz 1887, 1888). As a young academic, Schulz was interested in selecting an emerging research area of great promise and sought to find improved disinfectants that could be used in surgery, following the striking advances of Joseph Lister in this area. Schulz's expectation as he approached this research was that each of these agents would induce a dose-dependent decrease in metabolism of the yeasts and in colony death at the highest doses. While this was the case at the higher concentrations tested,

Schulz was surprised to observe that metabolism was increased at the lower concentrations for all the agents tested. While these initial observations surprised him, he thought that the best explanation for the unexpected low dose stimulation was some type of methodological error (Crump 2003). However, upon repeated attempts at replication, the low dose stimulation response was reproducibly observed. Schulz eventually came to accept that the low dose stimulation was not an experimental artifact but part of the biological response of the yeasts to a wide range low level chemical stressors. Not knowing how to interpret his data Schulz made an initial presentation of the findings at a local medical conference in 1884.

During this same time period Schulz became aware of a report in the homeopathic literature that a low dose of veratrine was effective in the treatment of gastroenteritis (Crump 2003). Since the bacterium responsible for this condition had just been isolated and cultured in the laboratory of Robert Koch, Schulz obtained a colony and tested whether the veratrine would kill the disease causing microbe, thereby confirming a mechanism for its alleged therapeutic action. However, following extensive testing, Schulz found that the veratrine did not kill the bacteria. Despite these findings Schulz did not challenge the interpretation that the homeopathic drug was effective in the humans. The following year Schulz and Rudolph Arndt, a professor colleague at Greifswald, integrated the seemingly disparate yeast and veratrine findings into a generalized dose response hypothesis. They concluded that the veratrine most likely helped cure the patients, but not by killing the microbe directly, but rather by enhancing the adaptive response of the individual at the low dose treatment to resist infection. They then used the biphasic dose response from the yeast studies to provide the experimental support for this conceptualizing of the dose response and its generality. Schulz claimed that he had discovered the explanatory principle of homeopathy and that it was based on

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the adaptive features of the biphasic dose response. He would soon come to call this phenomenon the Arndt-Schulz Law. By linking his findings to homeopathy at a time of great dispute between homeopathy and what we now call traditional medicine, Schulz would turn his medical colleagues into professional enemies and profound sceptics of his biphasic dose response theory. It was not the best way to start a professional career nor an ideal way to promote the fair-minded testing of a potentially significant biomedical dose response hypothesis.

Resurgence of hormesis

It is now 130 years since Schulz made his first presentation on biphasic dose responses, now called hormesis from the suggestion of Southam and Ehrlich (1943). Yet, as a result of its unfortunate initial placement in the center of an historically momentous confrontation between homeopathy and traditional medicine, the biphasic dose response of Schulz became marginalized within the medical and biomedical communities for the remainder of the 19th and most of the 20th century (Calabrese 2005).

The marginalization was the result of multiple factors, including a continuing effort by leaders in the biomedical community to associate the biphasic dose response with high dilution homeopathy, the use of a threshold dose-response based hazard assessment protocol that required testing with only a few very high doses as well as a lack of appreciation that the maximum stimulation of the biphasic dose response is modest, usually being less than twice the control group value (Fig. 1) (Calabrese and Baldwin 2002).

The biphasic dose response began its resurgence in the late 1970s with convergent findings in pharmacology (Szabadi 1977), chemical toxicology (Stebbing 1981, 1998) and radiation biology (Luckey 1980). While long ignored, the history of the dose response has now been extensively reconstructed and found to have had profound effects on the evolution of

clinical medicine, toxicology, risk assessment and environmental regulations (Calabrese and Baldwin 2000a, b, c, d, e; Calabrese 2008, 2013). During this resurgence of the hormesis concept it has been necessary to better understand how to design experiments to assess biphasic dose responses, including the number of doses, dose spacing, statistical power concerns, replication and mechanistic foundations. While eventually many thousands of hormetic dose responses would be identified and documented (Calabrese and Baldwin 2003; Calabrese and Blain 2005, 2009, 2011), there was the ever pressing need to pursue the issue of mechanism.

In 2013, Calabrese published an integrative synthesis of hormetic mechanisms at the level of receptor and cell signaling pathway. This paper documents the occurrence of hormetic mechanisms for approximately 400 different hormetic dose responses for over 100 different agents. The findings indicate that there are substantial numbers of specific hormetic mechanisms which are mediated by different receptors and signaling pathways. This detailed mechanistic assessment has revealed that the low dose stimulation and high dose inhibition can be mediated by the same receptor and/or cell signaling pathway. In other cases, the receptor/pathway mediating the stimulation may not be involved with the inhibitory response. Despite their considerable biological diversity (e.g., including agent, biological model, endpoint), the quantitative features of the hormetic dose responses are independent of mechanism. In fact, it is the consistency of the quantitative features of the hormetic dose response (i.e., maximum stimulation) that is its most distinct and general feature and one with significant pharmaceutical and risk assessment implications. Despite these advances over the past several decades concerning hormesis documentation, replication, generality and mechanistic foundations, there remains little insight concerning factors and mechanisms that account for the quantitative features of this dose response. That is, while there is much research addressing the biphasic nature of the dose response it is not understood why the magnitude of the

Fig. 1 Dose-response curve depicting the quantitative features of hormesis and its application to the concept of enhanced biological performance

hormetic dose response is invariably modest (e.g., 30–60 % greater than the control at maximum) and how this is biologically sensed and mediated.

The set of papers in this issue of the *Journal of Cell Communication and Cell Signaling* provides improved mechanistic understanding of hormetic dose responses with special focus on how such developing knowledge can be translated into environmental and clinical applications. It is our hope that *Journal of Cell Communication and Cell Signaling* will encourage periodic updating of mechanistic advances in the area of low dose adaptive responses (i.e. hormesis) and their societal and therapeutic impacts.

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