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REVIEW

Hormetic effects of extremely diluted solutions on gene expression

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This paper summarizes the results of investigations showing how molecular biological tools, such as DNA-microarrays, can provide useful suggestions about the behaviour of human organisms treated with microamounts of drugs or homeopathic medicines. The results reviewed here suggest firstly that the action of drugs is not quenched by ultra-high dilution and proceeds through modulation of gene expressions. The efficacy of drug solutions seems to be maintained in ultra-highly diluted preparations, a fact which constitutes a challenge to the dogma of quantization of matter.
The second and more important result is that the different gene expression profiles of cell systems treated with the same drugs at different dilutions suggest the existence of hormetic mechanisms. The gene expression profiles of cells treated with copper(II) sulfate, *Gelsemium sempervirens* and *Apis mellifica,* are characterized by the same common denominator of the concentration-dependent inversion of gene expression, which can justify at a molecular level the concept of *simile* adopted in homeopathy.
The main conclusion we draw from these results is that these procedures provide new kinds of information and a tool for disclosing the mechanisms involved in hormetic effects. The application of these effects to modern medicine may allow researchers to conceive unprecedented therapeutic applications or to optimize the currently used ones in the framework of a low-dose pharmacology based on a reliable experimental platform. *Homeopathy* (2015) **104**, 116–122.

Key words: Gene expression; Hormesis; Microarray; Homeopathy; Low-dose pharmacology

Introduction

The term hormesis means the phenomenon of dose–response relationships in which something (such as a heavy metal or ionizing radiation) that produces a given biological effect at moderate to high doses may produce an opposite effect at low doses. This term briefly defines the behavioral relationships between living systems and their surrounding world. In a general sense hormesis means that a living organism experiences an advantageous and favorable biological response once slightly perturbed, the perturbation being an environmental stress. Since the same stressor agent may induce harmful consequences at high doses, the theory of hormesis maintains that the reaction of a living organism to an external perturbation can qualitatively differ, according to the intensity of the perturbation.[1,2] This enantiodromic response is related to the nature of the living organism. The number of depicted examples suggests that this behavior represents a general biological law whose roots can be found in the autopoietic character of the living organism, as defined by Maturana and Varela,[3] which in turn can be described in terms of negative entropy, information theory, non-equilibrium thermodynamics, Lamarckian evolution and biological plasticity. In this sense this concept constitutes a basic pillar for defining the complex paradigm involved in the interaction of any living system with environmental

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molecular events. The enormous implications of this achievement have been reported and discussed in detail by Edward Calabrese and his co-workers in the recent past, and in this issue of Homeopathy.[4–9] This work constitutes a Keplerian revolution of toxicology and environmental sciences.

Even though hormesis should be considered a theme of the ontogeny and phylogeny of any living being, it still is not appropriately considered for its biomedical implications. This is not a novelty since it is common practice in human society for one group to try to deny access to reward to another group, if the latter invalidates the power prerequisites of the former.

Biomedicine achieved its undeniably enormous success by assuming that the complexity of phenomenology can be considered as the result of the overlap of many simple, individual events, which can be intrinsically described in terms of a linear relationship $y = kx$, the classical cause-effect quantitative relationship of Galilean philosophy. The classical approach to biomedicine presumes the existence of a direct correlation between the dose of drug and its therapeutic effect, expressed by the well known sigmoidal dose–response curve which plots the response vs. the logarithm of drug concentration. This hypothesis is valid in a limited dose range and is currently adopted in biomedical pharmacology. However, when the magnitude of the stressor (dose of drug) is diminished, a qualitatively inverted response is observed and the dose–response curve is generally better described as J-shaped. This feature, which illustrates the hormetic behavior of a perturbed biological system, can provide support to all therapeutic methodologies involving low doses of drugs or stressors and the *simile* as pharmacological philosophy.

Evidence of hormesis experimentally refutes traditional pharmacology by showing the interplay of related biological events of a living organism once perturbed by a drug.[10–13] Modern pharmacology now accepts experimental evidence by often assuming hormesis as an example of the traditional paradigm. However, it is important to emphasize that there is a big difference between the traditional view and the hormesis-based one. The difference has been outlined in the second half of the past century, starting with Warren Weaver more than 60 years ago.[14] The response of a living organism to a stressor must be considered an emergent property of a nonlinear network and cannot be interpreted with the rough approximation of a linear relationship, which is operative in a set of independent events.

Pharmacologists have difficulty with the concept of a nonlinear network because they hardly realize it in its own whole scientific perspective. In particular it is not easy to elicit an unambiguous interpretation when the observed effects are controlled by a large number of parameters and depend on the physiological state of the organism. Notwithstanding these difficulties, this interplay cannot be denied, since both useful and harmful consequences in medical care can occur.

Hormesis can support and justify some aspects of therapeutic methodologies such as homeopathy,[15–23] which are sometimes based on speculative claims. This feature has undoubtedly contributed in the past to academic pharmacology to understating hormetic phenomenology. The relevance of the hormetic concept has also been opposed by those who, like homeopaths, should have found in it the keystone of their therapeutic tenets.[24–28] As observed by Bellavite,[26] the 'holistic' approach of homeopathy as a healing system goes far beyond the identification of specific information. Using similar arguments, our proposal[20] of using hormesis to shift homeopathy into the framework of rational low-dose pharmacology has been strongly criticized.[28]

Our approach, which does not necessarily fit with any holistic consideration, is based only on experimental evidence regarding the determination of gene expression profiles by assuming that they provide a reliable experimental platform for showing the dose-dependent effects of diluted drugs in living organisms. In other words, we wish to answer the question put by Jonas and Ives "*Should we explore the clinical utility of the hormesis*?"[29,30] The present article summarizes the results of investigations showing how the use of molecular biological tools, such as DNA-microarrays, can provide useful suggestions about the behavior of human organisms once treated with different microamounts of drugs or homeopathic remedies. We are convinced that this procedure is of fundamental importance in identifying the main pathways of interaction between living organisms and perturbing drugs. We then discuss the potential impact that these studies on the future of pharmacology.

DNA-microarrays as a tool for measuring gene expression profiles

The properties of macroscopic matter are related to the properties of its microscopic units. This is in agreement with the statement that the whole is nothing but the sum of its parts. The problem is what 'the sum of parts' means. Basic research in pharmacology is carried out according to the belief that the interactions of a molecule with organism units follow simple rules, though often the application of these rules is complicated. But this in principle is relatively unimportant since it is always possible that in the future tools may be developed which could solve these complications.

Bearing this in mind, pharmacology describes its own perspective in terms of ontological or sometimes epistemological reductionism. Indeed the real problem is to conceptualize an external perturbation-response pattern in a network approach, even though the perturbation modifies the local environment of individual units according to the expectations mentioned above. In this framework the measure of gene expression profiles provides an important tool for understanding the very heart of the network system. This measurement is usually carried out by using DNA-microarray technology.

The power of this technique lies mainly in observing a change of gene expression pattern in patients with the