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Review Article

Hormesis and homeopathy: The artificial twins

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ABSTRACT

Homeopathy claims a curative reaction from small doses of a substance, high doses of which cause symptoms similar to those the patient is suffering from. Hormesis is a concept of biphasic dose-response to different pharmacological and toxicological agents. According to this concept, a small dose of a noxious agent can exert a beneficial action. A hypothesis is defended here that hormesis as a general principle can be assumed only for the factors present in the natural environment thus having induced adaptation of living organisms. Generalizations of the hormesis phenomenon used in support of homeopathy are unfounded. Low-dose impacts may be associated with a higher risk in a state of organ sub-compensation or failure especially in the elderly patients. Practical recommendations should be based neither on the hormesis as a default approach nor on the postulates of homeopathy. All clinically relevant effects, hormetic or not, should be tested by the methods of evidence-based medicine.

KEY WORDS: Dose-response, homeopathy, hormesis, placebo

INTRODUCTION

Homeopathy claims a curative reaction from a small dose of a drug of which high doses cause symptoms similar to those from which the patient is suffering [1]. Homeopathy originated in 19th century, prior to the acceptance of the germ and gene bases of disease; it has never been based on scientific evidence [2]. Results of randomized trials do not provide acceptable evidence that homeopathic treatments are more effective than placebo [3,4]; although there are also contradicting statements [5]. It is known that the placebo-effect is used in homeopathy [6]. It is however possible that some empirical knowledge is successfully used in homeopathy unrelated to its axioms – "Like can be cured with like," "less is more" [7] or the memory of water [8].

Hormesis has been defined as a biphasic dose-response relationship in which the response at low doses is opposite to the effect at high doses [1]. According to this concept, a small dose of a noxious agent can exert a beneficial action. Some publications generalizing hormesis [9,10] can be cited in support of homeopathy. However, claims that homeopathy is based on hormesis create an illusion that it employs a scientific method. The difference between hormesis and homeopathy is that hormesis can be observed at low but measurable concentrations; while homeopathy claims effects of infinite dilutions, whereas the concept of memory of water [8] is used as an explanation. There is an opinion [2], shared by the author that the term hormesis should not be linked with homeopathy. If homeopaths have valuable empirical knowledge, it should be verified by the methods of evidence-based medicine. There must be no artisanal secrets in the health care. Potentially useful empirical knowledge gathered in homeopathy, alternative or complementary medicine, should be scientifically tested and discussed in the professional literature. The Journal of Intercultural Ethnopharmacology is an excellent forum for this purpose.

HORMESIS: GENERAL PRINCIPLE ONLY FOR ENVIRONMENTAL FACTORS

Among the known hormetic agents are pro-oxidants, heavy metals, heat, exercise, food restriction [11,12], and different kinds of stress [13]. Living organisms come in contact with all these factors in the natural environment, so that the hormetic effects can be explained from an evolutionary standpoint. The term "hormetins" has been used in the literature for hormesis-inducing compounds [14]. For antibiotics [12], hormetic effects develop secondarily along with the adaptation of microorganisms and development of antibiotic resistance. Another example: Thousands years' adaptation of certain human populations to ethanol resulted in detectable hormesis also for this toxic agent: Moderate alcohol consumption was reported to be associated with a reduced risk of coronary heart disease and other health benefits [15]. There has been no plausible explanation of hormesis as a default principle in the pharmacological theory [16]. Scientific foundations of some hormetic mechanisms were discussed within the framework of stress response pathways [17]. However, different kinds of stress are an integral part of the environmental impact on living organisms, who have been accordingly adapted to it. Hormesis as a general principle is conceivable only for the agents that have induced adjustment of living organisms, so that a deviation in either direction from an optimum would be

harmful. This is obviously the case for visible light, ultraviolet and ionizing radiation [18], atmospheric pressure, as well as for many chemical substances and microelements present in the environment. It is not surprising that potentially toxic heavy metals, which are present in the natural environment, act hermetically in plants [19]. There are no general reasons to expect hormetic responses for the factors absent in the natural environment. Among explanations for the hormetic effects, discussed in the literature, are an excess of repair mechanisms in response to mild damage [20] and a proposed existence of two receptor types (small quantity of high-affinity receptors and large numbers of low-affinity ones) [21,22]. Both hypotheses have not been sufficiently proven, in particular, as umbrella mechanisms for different types of agents. Moreover, some reported hormetic effects can be doubtful because of the difficulties of differentiation between low-level hormetic and placebo effects [23] questionable reliability of some data, poor study designs, etc. It should be stressed that a response to an agent usually increases with increasing concentration; in contrast, a placebo effect does not depend on concentrations, while homeopathic remedies can be extremely diluted so that the agent can be absent in the solution. For research purposes, placebo effects can be excluded in animal experiments without conditioning [24,25] and especially in plants [19], where hormetic effects can be studied.

Hormesis phenomenon was discussed in the context of homeopathy [1,9,16,26]; it was sometimes generalized and treated as a matter-of-course [9]. For example, the question: "Is hormesis likely to occur for all types of drugs?" was answered: "There are sufficient data to conclude that the hormetic dose response is common, reproducible, and a biological expectation in the vast majority of biological systems, end points measured, and chemical classes tested" [9]. The question "May drugs be acting hormetically even though the experimental data appear inconsistent with this interpretation?" was responded: "The hormesis concept establishes a biological context for some of the key 'rules' of pharmacology and toxicology" [9]. Such statements make an impression that the hormesis is a general principle. However, generalizations, according to which "hormetic-like biphasic dose responses may represent a general biological dose-response pattern or strategy" [9] have never been substantiated [27,28]. Moreover, hormesis, usually, relates to a single response, while toxic impacts can have different responses [23]. Some noxious stimuli can act synergistically with other factors, for example, on the cells with a limited or no capacity for cellular regeneration such as cardiomyocytes or neurons. It can be of particular importance in conditions when such cells are pre-damaged by ischemia so that even a mild additional damage would act according to a no-threshold dose-response pattern without hormesis. In conditions close to a functional decompensation of an organ, even minimal additional damage can be detrimental. In such conditions, which are not uncommon especially in elderly patients, the concept of hormesis can be dangerous if used in the clinical decision-making. For example, it would hardly be indicated to apply mild asphyxia in angina pectoris or small doses of ethanol in end-stage liver disease with a hope for a hormetic effect as a "general biological dose-response pattern" [9].

DISCUSSION

Considering the above, the statement: "The hormesis concept is a fundamental dose response, highly conserved, and set in an evolutionary framework" [9] is true a priori only for the factors that have induced evolutionary adjustment. If even hormesis was observed in studies of the substances that are absent in the environment such as antineoplastic, anxiolytic or anti-seizure drugs [22,29], or resveratrol (the latter was extensively discussed in the Volume 29 of Human and Experimental Toxicology, while relevance of the hormetic effects was questioned) [30], there is still no reason to conclude that "hormetic dose responses are broadly generalizable, being independent of biological model, endpoint measured, and stressor agent, and represent a basic feature of biological responsiveness to chemical and physical stressors" [29]. The publications containing generalizations of this kind [9] can be cited in support of homeopathy and placebo, in gerontology and other fields of medicine, also to endorse official registration of drugs without specific effects or efficacy not exceeding that of placebo. It can pave the way for homeopathy and placebos instead of evidence-based treatments, as inexpensive substitutes, especially for elderly patients. There are many examples of marketed compounds without scientifically demonstrated efficacy [31], in Russia often in the guise of evidence-based medications; while artificial theoretic concepts are created to promote them [32]. Promotion of unproven health schemes can be harmful especially for elderly people [33]. In the medical practice, deception is normally objectionable on the grounds that it limits autonomy and breaches trust; these grounds possibly do not apply to placebos when they are prescribed within appropriate ethical limits [34]; although there is an opinion that clinical placebo interventions are unethical and unnecessary [35]. If even placebo therapy with misinformation of a patient might be ethically acceptable in certain cases [36], it is still not a reason to publish biased information. Remarkably, it seems that some patients are influenced not only by medical advertizing, which is sometimes misleading in Russia, but also directly or indirectly by professional publications. In conditions when commercial considerations tend to replace medical ethics, some patients try to come clear with their ailments with the help of professional literature, which is their right. However, in Russia, public access to the medical literature is limited [37].

Moreover, persistence and development of spurious theoretic concepts can sooner or later result in the application of invasive procedures with questionable clinical indications [38]. For example, in the preceding article [32] a series of studies was commented that has become internationally known in 1986 after a publication in The Lancet with participation as coauthor of the health minister of that time [39]. There followed numerous publications in Russian and foreign journals continued until today [40-47] (more references are in [32]). Cultures of smooth muscle cells or macrophages were used for testing of blood atherogenicity, anti- or pro-atherogenic action of various substances. The agents were considered atherogenic if they enhanced cholesterol accumulation by the cultured cells. Drug dosages were

calculated on the basis of cell culture experiments [44]. In addition to the drugs, many natural substances were shown by the same researchers using the cell culture method to be effective against serum atherogenicity: Black elder berries, calendula and violet flowers [45], grape seeds and stems [46] etc. Extracts from 13 different mushrooms were shown to significantly lower serum atherogenicity [47]. However, as discussed in [32], the relationship between serum atherogenicity in a cell culture and atherogenesis *in vivo* must be inverse rather than direct. For example, in familial hypercholesterolemia, caused by abnormality of lipoprotein receptors, ineffective clearance of low density lipoprotein (LDL)-cholesterol from serum causes hypercholesterolemia and predisposes to atherosclerosis [48]. Up-regulation of LDL-receptors (and, correspondingly, of the LDL-cholesterol uptake by cells) is one of the paradigms to the atherosclerosis therapy [49]. Accordingly, if an agent reduces cholesterol uptake by cells *in-vitro*, it can be expected to cause serum cholesterol elevation *in-vivo*. Nevertheless, following their concept, the same researchers started applying extracorporeal apheresis through a column with immobilized LDL aimed at the "removal of non-lipid atherogenicity factor(s)" twice monthly for the period of 7-9 months [43]. Further experimentation in the same direction was recommended. The patients were men 46-59 years old with functional Class II-III angina pectoris, an angiographically documented stenosis of 2-3 coronary arteries and a normal cholesterol level. During this trial, the patients were reported to feel better, endure higher physical loads, and have heightened sexual activity [43], which could have been caused by a placebo effect. It is reasonable to assume that invasive procedures are associated with a placebo effect, which might be stronger than that of non-invasive procedures [50]. Blood apheresis is associated with certain risks [51], although severe side-effects such as shock or allergic reactions were reported to be very rare [52]. Efficiency of the apheresis in the study [43] cannot be excluded, although apheresis is usually aimed at removal of lipids and lipoproteins e.g., in patients with severe drug-resistant LDL-hypercholesterolemia or lipoprotein elevation and premature atherosclerosis [53,54]. Considering the above, indications to apheresis in [43] should be checked again.

CONCLUSION

Hormesis as a general principle has never been proven as an umbrella theoretic basis for factors that are absent in the environment. If an agent is present in the natural environment, existence of its optimal level can be assumed, which would correspond to the current environmental level or, considering that the natural selection is a slow process, to some average from the past. Low-dose impacts may be associated with a higher risk in a state of organ sub-compensation or failure especially in elderly patients. Accordingly, practical recommendations should be based neither on the hormesis as a default approach [55] nor on the "like cures like," "less is more" [7] or other postulates of homeopathy. All clinically relevant effects, including hormetic ones, should be tested by the methods of evidence-based medicine.

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