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REVIEW

Cell sensitivity, non-linearity and inverse effects

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It has been claimed that the homeopathic principle of 'similarity' (or 'similia') and the use of individualized remedies in extremely low doses conflicts with scientific laws, but this opinion can be disputed on the basis of recent scientific advances. Several mechanisms to explain the responsiveness of cells to ultra-low doses and the similarity as inversion of drug effects, have again been suggested in the framework of hormesis and modern paradoxical pharmacology. Low doses or high dilutions of a drug interact only with the enhanced sensitivities of regulatory systems, functioning as minute harmful stimuli to trigger specific compensatory healing reactions. Here we review hypotheses about homeopathic drug action at cellular and molecular levels, and present a new conceptual model of the principle of similarity based on allosteric drug action. While many common drugs act through orthostatic chemical interactions aimed at blocking undesired activities of enzymes or receptors, allosteric interactions are associated with dynamic conformational changes and functional transitions in target proteins, which enhance or inhibit specific cellular actions in normal or disease states. The concept of allostery and the way it controls physiological activities can be broadened to include diluted/dynamized compounds, and may constitute a working hypothesis for the study of molecular mechanisms underlying the inversion of drug effects. *Homeopathy* (2015) **104**, 139–160.

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Introduction

According to the 'similarity' (or 'similia') principle, patients can be cured using low doses or high dilutions/dynamizations of a drug that in healthy people produces similar symptoms to the disease. However, this approach is regarded as unscientific by some circles.[1,2] One current opinion about homeopathic treatment associates this medical approach with the placebo effect, either because of some highly publicized meta-analysis[3] or because of the alleged implausibility of its theories.[4–6] While controversies concerning the clinical efficacy have been recently discussed by others,[7] here we survey the homeopathic basic principles with the aim of examining their consistency with modern scientific knowledge of biological communication at cellular and molecular levels. The low dose effects and the healing power of pathogenic substances observed in homeopathy, are linked to the high sensitivity of biological systems at various levels of organization and to the multiform ways through which the complex of mind-body homeodynamic regulations ('vital force') reacts to external stimuli. Growing evidence from several science fields suggests that hormesis and paradoxical pharmacology are included in the 'adaptation' capacity of immune, neuroendocrine and cardiovascular systems, but also in cellular defence/repair mechanisms and even in molecular dynamics and conformational changes.[8–15]

Our working hypothesis is that recognition of the function of enzymes, receptors and signal transduction and their dynamic interaction with drugs, makes it possible to look at homeopathy in a new and fully rational light. The cornerstone of homeopathy – that the whole clinical picture of the individual patient to be taken into consideration – is not in dispute, but laboratory models also allow the

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Table 1 Glossary of the terms utilized

Subject/Term	*Definition*
Abscopal effect	A phenomenon sometimes observed in the treatment of tumours: The localized treatment causes not only a shrinking of the treated tumour but also a shrinking of tumours in different compartments.
Allosteric regulation	The regulation of a protein by binding a molecule at a site other than the protein's active site. Allosteric sites allow effectors to bind to the protein, often resulting in a conformational change. The term comes from the Greek allos (ἄλλος), 'other,' and stereos (στερεός), 'solid (object).'
Clathrates	The term, from the Latin 'clathrus' (= lattice or grating), denotes hollow formations in which the guest molecule is in a cage formed by the host molecule or by a lattice of host molecules. The cage is held together by very weak forces like hydrogen bonding, ion pairing, dipole–dipole interaction and van der Waals attraction.
Desensitization	Loss of responsiveness to the continuing or increasing dose of the same factor (agonist, antagonist, drug).
DNA microarray	Also commonly known as DNA chip or biochip, is a collection of microscopic DNA spots attached to a solid surface. Scientists use microarrays to measure the expression levels of large numbers of genes simultaneously or to genotype multiple regions of a genome.
Dynamization	In homeopathic pharmacopoeia, the dilution process is followed by vigorous shaking (see 'succussion') which is believed to provide the remedy with higher pharmacological power.
Energy landscape	A mapping of all possible conformations of a molecular entity, or the spatial positions of interacting molecules in a system, and their corresponding free energy levels. While a protein can theoretically exist in a nearly infinite number of conformations along its energy landscape, in reality proteins fold (or 'relax') into secondary and tertiary structures that possess the lowest possible free energy.
Epigenetic regulation	Functionally relevant changes to the genome that do not involve a change in the nucleotide sequence. Examples of mechanisms that produce such changes are DNA methylation and histone modification, each of which alters how genes are expressed without altering the underlying DNA sequence.
G protein-coupled receptors (GPCRs)	Large family of transmembrane receptors that sense molecules outside the cell (odours, pheromones, hormones, and neurotransmitters) and activate inside signals as cyclic-AMP and phosphatidylinositol. When a ligand binds to the GPCR it causes a conformational change, which activates an associated G protein by exchanging its bound GDP for a GTP. The protein chain passes through the cell membrane seven times.
Heat shock proteins	A group of proteins induced by heat shock, toxins or other stress (UV radiation, hypoxia). The most prominent members of this group are a class of functionally related proteins involved in the folding and unfolding of other proteins.
Hormesis	A phenomenon characterized by low dose stimulation, high dose inhibition of a biological system exposed to toxins and other stressors, resulting in an inverted U-shaped dose response curve.
Metallothioneins	A family of cysteine-rich proteins that have the capacity to bind both physiological (such as zinc, copper, selenium) and xenobiotic (such as cadmium, mercury, silver, arsenic) heavy metals
Nanoparticle	A small particle composed by one or more compounds, including linked water, measuring 100 nm or less. Nanoparticulate matter has different properties from its bulk form in terms of mechanical, optical, electrical, magnetic, chemical, biological, and quantum behaviours. Nanoparticles cross membranes easily and act as highly reactive and catalytic agents.
Orthosteric site	Describing the primary, unmodulated binding site (on a protein) of a ligand. Orthosteric drugs usually block the active site of enzymes and receptors.
Paradoxical pharmacology	Term to refer to intriguing observations that chronic use of some drug types can have the opposite biological effect(s) to those seen following acute administration of the same drug.
Priming	A memory effect in which exposure to one stimulus influences a response to another stimulus. It may be homologous (same stimulus) or heterologous (two different stimuli).
State-space	In the theory of dynamical systems, is the set of values which a process can take. In physics, is an abstract space in which different 'positions' represent, not literal locations, but rather states of some physical system. When considering protein folding and free energy, this makes an energy landscape.

mechanism(s) of action of drugs to be investigated in animals, cells, tissues, and even at the molecular level. This 'reductionistic' perspective is not in contrast with the 'holistic' approach of homeopathy as a healing system, but rather represents the fundamental basis of a developing theory which would include recent advancements in complexity science and systems biology.[15–17] Given the holographic and fractal nature of all complex systems, the fundamental characteristics and rules of biological responses and related pathologies can be unravelled at any level of nature.

A glossary of the terms used is given in Table 1.

Cell sensitivity to ultra-low doses

The cell is the elementary particle of life and its sensitivity to external perturbations is the basis of both pathologic changes and therapeutic interventions. These changes at cellular level can be reduced to three dimensions: stimulation, inhibition, or differentiation. The higher the sensitivity to a regulatory factor – of a chemical, physical, or biological nature – the lower the dose or the energy capable of some 'effect'. The effects of homeopathic remedies in cellular models are well documented for a wide range of dilutions/dynamizations (Table 2).

When homeopathic drugs were tested in the same assay system at increasing dilutions, in most cases the greatest effects were observed at the lowest dilutions and also in Mother Tinctures (high molecular concentrations), but the same activity remained even at high dilutions.[20,29,30,43] In other cases, the effect was noted only in the low potencies.[31] In many instances, when the dilution exceeded the Avogadro constant, the effects appeared as pseudo-sinusoidal curves, with peaks of activity at certain dilutions/dynamizations, followed by inactive or less active dilutions.[19,29,53–56] Many of these effects have also been explained mechanistically as modifications of receptors, transduction mechanisms and gene expression changes. As there are many levels of cell regulation, there is no single mechanism explaining homeopathic effects, just as there is no single mechanism explaining the effects of conventional drugs.

High sensitivity to external regulations and nonlinear responses are frequently reported also with non-dynamized