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REVIEW

High-dilution effects revisited. 2. Pharmacodynamic mechanisms

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The pharmacodynamics aspects of homeopathic remedies are appraised by laboratory studies on the biological effects at various levels (cellular, molecular and systemic). The major question is how these medicines may work in the body. The possible answers concern the identification of biological targets, the means of drug–receptor interactions, the mechanisms of signal transmission and amplification, and the models of inversion of effects according to the traditional 'simile' rule. These problems are handled by two experimental and theoretical lines, according to the doses or dilutions considered (low-medium *versus* high dilutions). Homeopathic formulations in low-medium dilutions, containing molecules in the range of ultra-low doses, exploit the extreme sensitivity of biological systems to exogenous and endogenous signals. Their effects are interpreted in the framework of hormesis theories and paradoxical pharmacology. The hypotheses regarding the action mechanisms of highly diluted/dynamized solutions (beyond Avogadro–Loschmidt limit) variously invoke sensitivity to bioelectromagnetic information, participation of water chains in signalling, and regulation of bifurcation points of systemic networks. High-dilution pharmacology is emerging as a pioneering subject in the domain of nanomedicine and is providing greater plausibility to the puzzling claims of homeopathy. *Homeopathy* (2013) **103**, 22–43.

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Introduction

Homeopathy is progressively receiving scientific validation but a series of theoretical and technical questions need still to be clarified, since several problems appear to distinguish this discipline from conventional pharmacology. The physicochemical nature of the homeopathic remedies, which are produced according to a peculiar method of serial dilution followed by 'dynamization', was dealt with in a previous paper.[1] Here the recent advances concerning the possible mechanism of actions of these drugs in the body are reviewed. Pharmacokinetics is the branch of pharmacology dedicated to the determination of the fate of substances administered to a living organism up to the point at which they are completely eliminated from the body. This approach is often studied in conjunction with pharmacodynamics, the study of effects on the body. Highly diluted medications, including those produced according to the homeopathic pharmacopoeia, are hardly suitable to pharmacokinetic investigation, due to the lack of analytical methods having sufficient sensitivity. On the other hand, experimental evidence from clinical and laboratory studies is providing a remarkable contribution to pharmacodynamics of this class of remedies. The question of how these medicines may work concerns the identification of biological targets at various levels (cellular, molecular and systemic), the ways of drug–receptor interactions, the mechanisms of signal transmission and amplification, and the 'simile' rule (see Table 1). All these problems have several aspects, that can be considered according to the different doses and/or dilutions employed.

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Table 1 Aspects of homeopathic pharmacodynamics

Aspect		*Medium potencies (ultra-low doses)*	*High potencies (high dilutions)*
Nature of the medicine[a]		Very low concentrations of active molecules Nanoparticles	Nanoparticles Water clusters Coherence domains
Biological targets	Local	Molecular interactions: - Cell receptors - Enzyme activation/regulation - Gene expression	Nonlinear dynamics (bifurcation points): - Cell receptors - Enzyme activation/regulation - Gene expression
	Systemic	Neuroimmunologic networks	Neuroimmunologic networks Disease dynamics (attractors-miasms) Bioelectricity (ECG, EEG)
Amplification mechanisms		Cell responsiveness: - Receptor priming - Signal transduction - Stochastic resonance Enzyme activity: - Allosteric activation - Silica nanostructures	Neuroimmunologic networks Nonlinearity-chaos Grotthus-type water chains
Information transfer		Molecular interactions Water chains	Frequency-coded signals Water chains Water nanoparticles Bioelectromagnetics
Inversion of effects (the 'Simile')		Hormesis Dual receptors Gating by cAMP Hsps Paradoxical pharmacology	Rebound in time Systems biology theories Coherent response to stress

[a] This aspect was the subject of the preceding paper.[1]

Pharmacologic activity of mother tinctures and of low potencies (e.g., 2C–3C, containing relatively high doses of active principles) poses no problems of interpretation and requires analysis of the components and identification of their targets in the organism, in a way not dissimilar from that of herbal products, snake toxins, or mineral oligoelements. The action of medium potencies, that contain ultra-low doses of active principles (ULDs, namely from 4C–5C to approximately 12C, close to the Avogadro–Loschmidt limit) entails high sensitivity of living organisms and inversion of drug effects, in the framework of models not much distant from modern pharmacology, like hormetic mechanisms. The action of high dilutions (HDs, namely homeopathic dilutions beyond the Avogadro–Loschmidt constant) requires the identification of possible 'non-molecular' or 'meta-molecular' information transfer mechanisms. Finally, the 'holistic' approach of homeopathy as healing system goes far beyond the identification of specific information transfer mechanisms or molecular targets and should be understood in the light of systems biology.

Biological targets

The specificity of any drug effect is based on the interaction or active principles with their biological targets and the same can be conceived for homeopathic drugs. In the latter case, the identification of these interactions is complicated by several factors, including the different nature of remedies in low and high potencies, the presence of many active principles in most compounds of vegetal or animal sources, and the different sensitivities that presumably exist in healthy and sick organisms. In spite of these problems, experimental evidence gathered in laboratory studies has identified a representative number of cell and molecular targets of homeopathic drugs.

Local targets

The cornerstone of homeopathy that the whole clinical picture is considered on an individual basis is not in dispute, but laboratory models show that mechanism(s) of action of the drug can be investigated in animals, cells, tissues, and even at the molecular level. Pharmacodynamic effects of homeopathic remedies have been proven in several dozens of animal and '*in vitro*' laboratory studies. Apart from reviews on this topic,[2–5] some recent demonstrations of these effects merit to be mentioned. One of the most interesting lines of research regarded histamine and other compounds (*Lung histamine* and *Apis mellifica*), which have pro-inflammatory effects when used at high doses but trigger anti-inflammatory mechanisms when employed at ULDs and HDs. The effect of *Lung histamine* (5C and 15C) and *Apis mellifica* (9C), traditional remedies used for the treatment of allergic diseases, was assessed on *in vitro* human basophil degranulation.[6] After this early study, several independent laboratories reported a significant inhibition of basophil functions by HDs of histamine. Most studies were positive[7–14] with few exceptions.[15,16] The effect was inhibited by histamine H2 receptor antagonists cimetidine,[17] supporting the hypothesis that HDs of histamine exert their inhibitory power at the level of H2 receptors of basophilic cells. That homeopathic drugs may act through modulation of cell receptors and protein synthesis is supported also by studies from the laboratory of Khuda-Bukhsh.[18] In a model of chemically induced murine papilloma, where a known set of proteins involved in the tumor development were altered, the researchers found a significant remodulation toward normal condition after treatment with the potentized drug *Secale cornutum* 30C, driven by