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Molecular Mechanism of Action of Homeopathic Potencies with Reference to Holism

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Abstract

Potencies of homeopathic medicine above 12 cross the Avogadro number and are, therefore, too dilute to contain any drug molecules. However, spectroscopic studies with respect to NMR, FTIR and UV, and thermoluminescence of potencies show that they differ from each other and also from their diluent medium, aqueous ethanol. This difference has been attributed to the difference in the pattern of hydrogen bonding network of water molecules preserved by ethanol in different potencies. Each potentized drug bears two components, a constant identity component and a variable dilution component. While the former is borne by the specific H-bonded network pattern of aqueous ethanol, the latter is carried by strength of the hydrogen bond, homogeneity of solution structure and increased thermal motion of water molecules. All these characticestics are facilitated by succussion or sonication which are applied during the process of potentization of drugs. Potencies are effective on man, animals, plants, isolated organs and cells, and the common feature in all these cases in cell membrane. Plasma membrane is made up of lipid bilayers embedded with proteins. Water occurs as a continuous medium bathing all the cells and biomolecules of an organism. A homeopathic potency first makes contact with the existing water structure over the plasma membrane and tends to reorganize the water structure over the membrane leading to alteration of the conformation of integral membrane proteins. As a result the activity of the proteins undergoes a change triggering a change in cell physiology. Homeopathic potencies can bring about a change in the conformation and activity of proteins *in vitro*. There exists a three-dimensional molecular network, made up of proteins and carbohydrates, which interact with each other at plasma membranes to form a global molecular network (GMN). Diseases and drugs can bring about a change in the organization and function of the GMN. Cells with their GMN respond to the injury / disease in a coordinated fashion. An appropriate homeopathic potency is actually a complementary water structure which interacts with the opposite morbid water structure over cell membranes thereby changing the conformation of proteins. This local change in the conformation of a protein domain induces conformational change in the domains of associated proteins resulting in a chain reaction affecting the entire protein network. This is the scientific basis of holism in homeopathy.

Key words : Protein network, Plasma membrane, Conformational change, Molecular mechanism, Homeopathic potencies.

Homeopathic medicines have been used for a couple of centuries for the treatment of patients. Samuel Hahnemann formally introduced homeopathy in 1810 with the publication of his book 'Organon of the rational system of medicine.' Homeopathic remedies are selected on the basis of the totality of symptoms of individual patients, and the medicines act in a holistic manner. In spite of its growing popularity, the system suffers a major drawback because it uses potentized drugs, which are too dilute to contain drug molecules. According to Avogadro's hypothesis (1812), one mole of a drug contains 6.022×10^{23} molecules. In 1909 Jean Baptiste Perrin determined the Avogadro number which was confirmed later by other physists (1, 2). Thus all homeopathic potencies above 12 (dilution 10^{-24}) do not contain any drug molecules. One of the fundamental principles of pharmacology is dose response. The higher is the dose the stronger is the response from the organism. Higher dose means greater number of molecules of the drug used. So, the effect of a drug should disappear totally at a dilution of 10^{-24}. But in homeopathy, the higher is the dilution, the stronger is the effect. Homeopathic potencies used for treatment are 6, 12, 30, 200, 1000, 10000, 50000, 100000 or even higher. They not only produce therapeutic effect but retain specific identity of concerned

drugs at infinitesimal dilutions. The question is whether those potencies really produce any biological effect at all? If they do, how do they interact with the biological system without any drug molecules ? If no drug molecules exist in a potency, what is the other physical basis that interacts with an organism ? This paper makes an attempt to address these fundamental questions and develop a hypothesis explaining the mechanism of action of potencies.

Results from Studies on Man, Animals and Plants

Clinical studies on a large number patients treated with homeopathic potencies showed positive effects (3—6). However, negative effect was also reported by Shang et al. (7) who compared 110 homeopathic and 110 matched orthodox trials by statistics. This study did not measure individualized classical homeopathy Further, almost three quarter of the examined 110 homeopathic studies showed positive results (8). High dilution of drugs prepared homeopathically produced significant effects on animals (9—13) and plants (14—18). Potencies are administrated orally for man and animals, and sprayed on leaves on plants. So, the first contact between an organism and potencies occurs at tissue surfaces.

Evidences from Ex Vivo Experiments

Potencies of *Belladonna* (1C—200C) produced significant effect on the ACh-induced spasm of the isolated rat duodenum mounted in the organ bath (19). *Agaricus* 30, 200, 1000, and *Nux Vom* 1000 producd excitatory effect on the isolated rat ileum immersed in ringer solution in an organ bath (20). Here the drug was dropped into the bath solution. *Merc cor* 30 and *Nux Vom* 30 facilitated water permeability in erythrocytes of catfish. Here the potencies were dropped into distilled water in a test tube containing red blood cells (21). Cultured cells incubated with high dilutions of *Cadmium* showed protective effect against the toxic doses of the same metal (22).

Deduction I. Since homeopathic potencies are effective on man, animals, plants isolated organs and individual cells, they would initiate their action on the plasma membrane which is common to all these cases, and receives the drugs first.

In Vitro Effect of Potencies on Proteins. In a classical experiment Boyd (23) first observed that *Merc cor* 30 enhanced the activity of diastase, a mixture of starch-digesting enzymes. In a later study it was shown that *Merc cor* 30 and *Merc iodide* 30 enhanced the activity of a single enzyme, α-amylase (24). Here the potencies were mixed with α-amylase solution to which the starch solution was added. Using fluorescence emission and electronic circular dichroism spectra it was demonstrated that *Chelidonium* 30, *Sulfur 30, Nux Vom* 30, *Santonin* 30 and *Ethanol* 30 produced different conformations of a protein, bovine serum albumin (25).

Deduction II. Homeopathic potencies can alter the conformation and activity of proteins.

Physical Basis of Potencies

There exist several hypotheses concerning the nature of the physical basis of potentized drugs. All these hypotheses are based on the molecules of the diluent medium, aqueous ethanol details of which are available in reviews (26—28). Intermolecular hydrogen bond cooperativity is closely associated with changes in the water structure surrounding a solute like aldohexopyranose sugars (29). During dynamization water structures around drug particles assume specific H-bonding network depending on the intramolecular H-bond cooperativity of the drug particles. There is evidence that hydrogen bonding is strengthened by chemical compounds in alcoholic beverages (30). Obviously, the same effects would occur in mother tinctures of homeopathic drugs prepared in aqueous ethanol. In one hypothesis it has been postulated that drug molecules do not totally disappear during the process of successive dilution 1 : 100 followed by succussion. This is thought to be due to an increase in the dielectric constant of the medium during the process of dynamization (31). But a few homeopathic potencies are produced without taking any substance in the diluent medium initially. These are Alcohol, X-ray, Magnetis polis arcticus and Magnetis polis Australis.

Homeopathic potencies and their diluent medium show marked differences among them with respect to their electronic, NMR and FTIR spectra (28, 32—34). In one study using a high sensitivity proton NMR spectroscopy no difference was observed between

homeopathic potencies and their diluent medium, all prepared in water (35). Efficacy of homeopathic potencies, prepared in pure water, deteriorates rapidly (23, 24). Ethanol having a large non-polar tail actually promotes water structures (28). Using the technique of thermoluminescence Rey (36) demonstrated that *Lithium chloride* 15c and *Sodium chloride* 15c produced thermoluminescence characteristic of the original solution of the two salts (36).

Homeopathic potencies, derived from a single element, single compound or a mixture of several compounds, assume an integrated hydrogen bonded network of water structures having a geometric configuration specific to the starting substance (28). Hydrogen bonds break and reform continuously. In alcohol in solution the sequential hydrogen bond dissociation and reassociation occur between the same O-H groups (37). Thus in a homeopathic potency H-bonded water structures are in a dynamic equilibrium (28). In a mixture of water and alcohol, the components tend to preserve to some extent the pattern of H-bonds they had prior to mixing (38). The pattern of H-bonds undergoes a change not only by a starting substance but also by radiation as in X-ray where aqueous ethanol is simply exposed to X-radiation initially. Cohly et al. (39) observed that a 40-day exposure of water to solar radiation changes chemical and physical properties and influences on biological activity. This further confirms that water structures can undergo a change due to radiation and this remodelled water structures are capable of producing biological effects.

Deduction III. A homeopathic potency is essentially a specific water structure maintained by H-bonded network and preserved by ethanol. Now the question is whether succussion could induce any change in the H-bonded network of aqueous ethanol and whether that change could produce any biological effect. Manual succussion, used for preparing homeopathic potencies, is a kind of mechanical agitation, which can also be produced in a more precise and measurable way by sonication. In fact, potencies produced by sonication show stronger biological effects than those produced by succussion (28, 40). Aqueous ethanol subjected to weak ultrasonication (40 KHz, 12 mw, I weak) accelerates the thermal motion of water molecules to some extent and this disperses the ethanol molecules among the water molecules to create more homogeneous and compact solution structure. This structural change alone produces significant biological effects (41). Since hydrogen bonding results from electrostatic force, succussion or sonication could add to the strength of the H-bonds in a potency. The higher is the potency, the stronger is the H-bond, and the more homogeneous is the aqueous ethanol solution.

Deduction IV. Succussion increases the strength of H-bonding in the H-bonded network of a potency, accelerates the thermal motion of water molecules and makes the aqueous ethanol solution more homogeneous and compact. All these changes are capable of producing biological effects.

It is evident from deductions III and IV that a potentized homeopathic drug carries two physical components, an identity component and a dilution component. The former is constant and bears the specific H-bonded network of water molecules preserved by ethanol. It carries the H-honded signature of a drug like *Nux Vomica, Sulfur, Bryonia alba.* The dilution component is variable and bears the mark of a particular potency of a drug, say Sulfur 30, Sulfur 200, Sulfur 1000 (28).

Action on the Primary Target of a Potency

As mentioned earlier, the primary target of a potency is the plasma membrane which is made up of amphipathic lipids with many kinds of globular proteins embedded in it. The lipid bilayers have hydrophilic (polar) heads exposed to the outer aqueous environment and to the inner aqueous cytoplasm. Some of the proteins are embedded on the outer surface of the cell membrane; some on the inner surface and others remain as transmembrane units. The lipid and protein molecules move in the plane of the membrane, a process known as lateral diffusion.

In a living organism water occurs as a continuous medium bathing all the cells and the biomolecules. Different non-covalent forces, which locally alter the structure of water are Lifshitz-van der Waals (LW) forces and electrostatic (EL) forces. Since the heads of lipid bilayers are hydrophilic, they have two layers of water of hydration which are attached via AB and LW forces. Of these AB forces are dominant (42). A homeopathic potency, which is specifically structured water, first interacts with the integral membrane pro-

teins, which are ubiquitous in all the living organisms (28).

Proteins are capable of steric fitting with other proteins to form a high molecular complex with emergent function called the lego property. There exists a three dimensional molecular network, mainly made up of proteins and carbohydrates, which might interact with each other at boundaries of compartments such as plasma membranes to form a global molecular network (GMN). Alteration in protein conformation could alter the GMN organization resulting in a functional change (43). A small change in one domain of a protein can be propagated through the entire protein. It can induce conformational change in the domains of all associated proteins. A minute alteration in the building block network of proteins helps in the formation of different supermolecular complexes. This leads to assembly/ disassembly of the same set of proteins into assemblages with different functional properties (44). A global comparison of four basic networks of protein molecules such as regulatory, co-expression, interaction and metabolic has been reported. The authors' analysis shows that interaction and co-expression networks have short-range relationship, with directly interacting and co-expressed proteins sharing regulatory networks. The metabolic network contains many long-distance relationships. Far-away enzymes have time delayed expression relationships, which are coordinated by bridges connecting their regulators (45). Thus we see that a global macromolecular interaction in the whole body maintains the homeostasis in the living organism under the normal state of health. We now see that a disease also manifests itself globally affecting the entire network of proteins. Heat shock usually induces expression of specific genes to prevent protein misfolding and aggregation and to promote degradation of the irreversibly denatured proteins. In a plant-pathogenic bacterium it has been shown that a compex network of genes works together in response to a heat shock (46). Thus we see that a physical injury to a bacterium results in a global expression of genes vis-à-vis proteins. Using human protein-protein interaction network constructed by computational methods it has been shown that human proteins translated from known cancer genes exhibit a network topology that is different from that of proteins not documented as mutated in cancer. Cancer proteins show an increase in the number of proteins they interact with (47). In a global network investigation of the genotype-phenotype data set concerning the recovery of the yeast *Saccharomyces cerevisiae* from DNA-damaging agents, it has been shown that toxicity modulating proteins has similar topological properties as essential proteins. This suggests that cells initiate highly coordinated responses to damage similar to those needed for vital cellular functions (48).

A global network of constitutively expressed natural auto antibodies interacting specifically with different extra cellular, membrane, cytoplasmic and nuclear antigens maintains homeostasis in a healthy individual. But under a diseased state this network undergoes a significant change, rather qualitative than quantitative (49).

Deduction V. A global network of proteins interacting with earch other maintains vital function in an organism, and responds to injury and disease in a coordinated fashion. The protein network topology undergoes a change during injury and disease.

The whole network is covered with water. It is thought that a homeopathic potency first alters the water structure over a cell membrane, and this effect spreads fast from cell to cell and influences the global network of proteins. At first it alters the conformation of proteins, which results in a change in their function. We have already evidences that homeopathic potencies could alter the conformation and function of proteins (24, 25). We have also provided experimental evidences that homeopathic potencies could affect the function of an integral membrane protein like aquaporin (21).

Homeopathic potencies are sometimes mixed with drinking water and then administered on patients. Drinking water contains ions in solution. Do these ions interfere significantly with the specific H-bonded network of a homeopathic potency ? In a recent study using solution neutron and X-ray diffraction analysis it has been demonstrated that even di and tri valent ions do not significantly alter the density and orientation of water more than two water molecules (5A) away (50). Thus homeopathic potencies could retain their specific structure even after dilution with drinking water. This is also true when a potency is dropped into oral mucosa which is covered with a film of water containing ions.

We now provide further evidence, direct or indi-

rect, in support of the effect of potencies or alcohol solution on integral membrane proteins. Alcohols can modulates the oligomerization of membrane proteins in lipid bilayers. In addition to their direct effect on the membrane, alcohol-water mixture perturb membrane proteins directly by solvating the hydrophobic regions of the protein. Alcohols provide access to a diversity of conformations for membrane proteins (51). Influence of a homeopathic preparation, stimulated phosphoric acid at low dilutions of 10^{-14} and 10^{-42}, and non-stimulated phosphoric acid at high dilutions of 10^{-200} and 10^{-400} on transmembrane transport of Na+, K+, Ca^{2}+ K-ATPase, Na-ATPase and Ca-ATPase was investigated by means of ino-selective electrodes. While low dilutions stimulated the transport phenomena, high dilutions suppressed them (52). It has been shown that the formation of a spanning two-dimensional hydrogen-bonded water network at the surface of proteins via a percolation transition enables their activity (53). It is possible that homeopathic potencies interact with the water network at the surface of proteins and modulate their activity. Using molecular dynamic simulation it has been shown that rearrangement of water molecules contributes favorably to the binding affinity between a protein and a ligand (54).

Deduction VI. A homeopathic potency acts on the global water structure vis-à-vis protein network of an organism helping the latter respond to the disease/injury in a coordinated fashion. The effect involves transport of inos, water, enzymes through membrane channels and expression and repression of proper genes.

The hypothesis

Based on the evidences and deductions mentioned we propose the following hypothesis concerning the mechanism of action of homeopathic potencies.

1. A homeopathic potency initially interacts with and modulates the water structure over the plasma membrane thereby bringing about a conformational change of protein domains in contact on the membrane. This induces a conformational change in the domains of associated proteins. The effect is propagated throughout the global protein network of the organism.

2. Under a diseased state the global protein network undergoes a change with a concomitant change in water structure over the surface. An appropriate homeopathic potency would modulate the perturbed water structure vis-à-vis the protein network thereby helping the latter restore homeostasis. Restoration of health may involve ion, enzyme and water transport and expression and repression of genes.

3. Thus a homeopathic potency acts truly in a holistic manner through the global water structure and protein network of an organism.

Verification

The hypothesis can be verified, at least partly, in a bacterium, say *Xylella fastidiosa*, by global gene expression analysis. The bacteria may be transferred from a low temperature (28—30 C) to a high temperature (40—42 C). A global transcript levels in the bacteria may be investigated DNA microarrays (46) in the following groups : 1. Unexposed to higher temperature and untreated. 2. Exposed from low to high temperature and untreated. 3. Treated with *Cantheris* 200 but not exposed to higher temperature. 4. Pre-treated with *Cantheris* 200 and then exposed to higher temperature.

The relative proportion of induced and repressed genes may be compared among the four groups. Anticipated results : group 3 would behave globally as if it was given heat shock. Group 4 would show the protective effect against heat shock in a global way. *Cantheris* is a homeopathic remedy for acute heat induced ailments. *Cantheris* 200 can be prepared in distilled water and should be used within 24 hours. Treatment should be repeated 4/5 times at an interval of 5 min.

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