Potentised homoeopathic drugs act through regulation of gene-expression: a hypothesis to explain their mechanism and pathways of action in vivo

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SUMMARY. A working hypothesis to explain the mechanism of action of potentized homoeopathic drugs in viv has been proposed. The model is partly substantiated from our own research data on repair of chromosomal damages in X-irradiated or toxic chemical-treated mice by the oral administration of some potentized homoeopathic drugs, and partly from some of the unpublished and published work of other researchers in the field of homoeopathy. In this model, strong scientific arguments have been made to form the hypothesis that the potentized homoeopathic drugs act through regulation of gene-expression, presumably through hormone-hormone-protein complexes - the sensorgene-integrator gene receptor gene-producer gene-pathway of Britten and Davidson's model, or else through the regulator/mutator gene-operator gene-structural gene pathway of Jacob and Monod's model among some other independent mechanisms. Scientific details of some possible pathways, admittedly speculative for some steps, have also been provided to stimulate research in this direction to verify the correctness of the hypothesis.

INTRODUCTION

Although the methodological weakness of some homoeopathic research carried out in the past, e.g. lack of independent replication, have made the claim of efficacy of the potentized form of homoeopathic drugs rather inconclusive and subject to further scientific research results of numerous clinical trials published in some peer-reviewed journal seem to prove the efficacy of homoeopathic drugs in removing disease symptoms[1]. The paradoxical problem of how the medicinal property could be conveyed to the solvent in potencies diluted far beyond the Avagadro's number in the absence of even one original

drug-molecule has been addressed by many eminent researchers by using various studies including UV spectra, conductivity measurement and infrared analysis, surface tension measurement, nuclear magnetic resonance spectroscopy and other methods[2-9]. which have revealed that there are physical differences between the potentized dilutions and the solvent itself.

Several theoretical attempts have also been made to explain the unusual behaviour of microdilutions in respect of a certain organization, e.g. polymerization, of water molecules[10]. Excellent working hypotheses have also been advocated to explain how the specific organization of solvents is able to retain and maintain some properties of the initial substance[13-14]. But there seems to be little explanation as to how homoeopathic remedies, in much higher dilutions in vivo, can bring forth spectacular metabolic changes in living systems after they are administered in microdoses on the tongue.

Sukul and his collaborators[15-20] tried to explain, through their experimental studies, mostly carried out in rats and mice, that the homoeopathic medicines acted through the autonomic nervous system (ANS), which is centrally regulated in hypothalamus. These researchers demonstrated a change in firing rates (recorded with oscilloscopes) in the hypothalamic neurones after the administration of potentized homoeopathic drugs in anaesthetized rats and mice. They also reported subtle change in neurosecretion after the administration of homoeopathic drugs. However, as the experiments were conducted on anaesthetized animals, while the central nervous system (CNS) was silenced, it could not be known whether the CNS also has any role or not. However the question of what happens after the emission of neurosecretory signals remains largely unknown, although the involvement of the immune system and the cell's own defence mechanism has been implicated[21-24]. In the following, therefore, an attempt has been made to throw some light on this aspect with supporting evidence and scientific logic (Fig.).

THE WORKING HYPOTHESIS

The homoeopathic drug, being administered on the tongue, excites nerve-endings and the signal finally reaches the hypothalamus, either through ANS or CNS (we would not exclude the involvement of CNS unless excluded by specific experimentation, as the taste-buds are beset with numerous nerve-endings from the 7th and 9th cranial nerves). As a response, suitable hypothalamic neurones would be stimulated to release signals by suitable neurosecretion. The neurotransmitter signals may proceed through nerve-impulse propagation to act directly on the target organs, or else may excite certain endocrine glands to release specific hormone(s) from suitable endocrine gland(s). Hormones nay be either of steroid or protein nature. Some of these hormones either stimulate other glands to synthesize/release their product(s) to act on target organs.

However, on the other hand, some of the hormone(s) may form specific hormone-protein complexes which can act as 'gene regulatory' signals to activate some 'sensor' genes as contemplated by Britten and Davidson[25]. According to this popular and most widely accepted model, specific 'sensor' genes represent sequence-specific binding sites (almost analogous to CAP-cAMP binding site in the *Escherichia coli* promoter in prokaryotes) that responds to specific signals (such as hormone-protein complexes). When 'sensor' genes receive the appropriate signals, they activate the transcription of the adjacent 'integrator' genes. The products of 'integrator' genes then interact in a sequence-specific manner with 'receptor' genes. The model also indicated that the products of 'integrator genes could be activator ribonucleic acids (RNAs) that interacted directly with the 'receptor' genes to trigger transcription of the contagious 'producer' genes (analogous to 'structural' genes in the operons of prokaryotes).

In this model, it is further stated that, by making either the 'receptor' genes or the 'integrator' genes redundant, various combinations of the 'producer' genes can be turned on in response to different signals. Alternatively, the

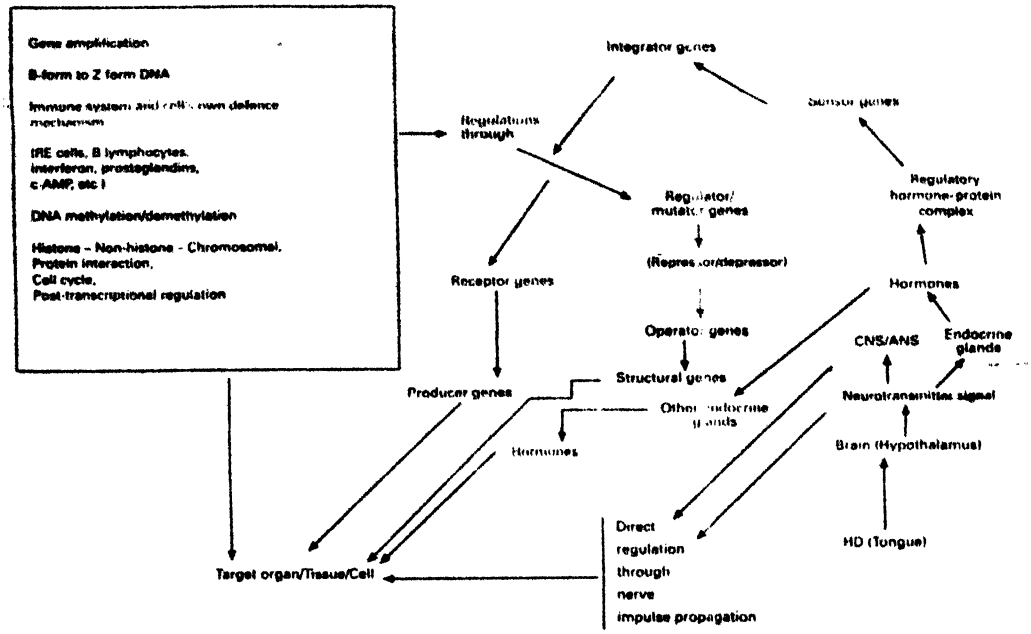

Figure Showing possible mechanism and pathways of action of homoeopathic drugs (HD)

Jacob-Monod pathway of regulator/mutator gene-operator gene-structural gene-pathway may also be considered in which an unknown protein acts as 'repressor' or 'derepressor' to switch on or off the transcriptional activity. In our preliminary experiments (results unpublished), administration of homoeopathic drugs was found to effectively alter some hormone and enzyme levels as claimed also by some other researchers[26-29] earlier in experimental animals. It seems quite possible that some regulatory hormone-protein complexes might also be formed which would regulate the gene expression in the desired way.

Data from our extensive studies with some cytogenetical and haematological parameters, some of which have been published[30-38] or presented at scientific seminars, demonstrate positively that certain potentized homoeopathic drugs are capable of repairing chromosomal or sperm-head damage. If we take only the repair of chromosomal damages into consideration, the hypothesis of regulation through gene-expression would seem to be the most attractive and plausible scientific explanation for the events that could make repair of chromosomes possible. The chromosomes consist of both DNA and protein; a repair of chromosome/chromatid break will therefore involve the repair of both DNA and protein. As a matter of fact, repair of radiation-induced damage has been the subject of extensive study and elaborate mechanisms (many of which are now scientifically established) have been suggested.

Of these, three mechanisms, widely accepted and believed to be universal for all kinds of radiation-induced DNA damage[39], are: (1) photoreactivation; (2) excision; and (3) post-transcriptional repair. While the photoreactivation process involves an enzyme that splits thymine dimers directly without removal of any nucleotides, excision repair involves a sequence of enzyme-catalyzed steps in which the thymine dimers are removed from the DNA molecule and a new segment of DNA is synthesized.

The third mechanism, the post-transcription type, involves both replication and recombina-

tion, but the exact details of this repair mechanism need further scientific examination. It would therefore imply that the administration of the potentized homoeopathic drugs in X-irradiated mice precisely brought forth one or all of these mechanisms into operation which are exclusively gene-controlled. Further, the synthesis of chromosomal proteins would also necessarily be under genetic control. Thus, when we propose that the homoeopathic drugs act through the regulation of gene-expression, it would be customary to focus on the different mechanisms through which gene action may be accomplished or mediated.

If we look into the scientifically established facts, this can either be mediated or accomplished through: (1) gene amplification; (2) converting B-form to Z-form DNA; (3) DNA methylation-demethylation process; (4) influencing histone-non-histone-chromosomal protein interaction; (5) post-transcriptional regulations; (6) altering or affecting cell cycle; and (7) triggering the proper immune system and cell's own defence mechanisms (e.g. reticuloendothelial cells, B lymphocytes, interferons, prostaglandins, cyclic AMP, anti-sense RNA, etc.) (see[39] for further information). These are, the areas to search for a positive change due to the administration of homoeopathic drugs.

Incidentally, the mitotic division of bone-marrow cells, which is stated to be under genetic control, has already been demonstrated by us to alter by the administration of certain potentized homoeopathic drugs, which would lend additional support to our hypothesis. Further, our preliminary results in combatting cancer in a mouse model were encouraging and our preliminary data (to be extended further and verified) indicated that some homoeopathic medicines could extend the life-expectancy in cancer mice, as compared to controls, which would again lead to the same conclusion, since the role of genes (activation of proto-oncogenes into oncogenes and that of anti-cancer genes) in cancer has now been firmly established, and cancer has been suggested as a manifestation of the loss of regulatory mechanism of cell division, which, is again under genetic control[40].

On the basis of the facts known about regulation of transcription, the various regulatory mechanisms fit into two general categories[39,40]. The first category includes mechanisms involved in the rapid turn-on and turn-off of gene expression in response to environmental changes, mostly found in lower organisms (prokaryotes), the second major category of regulatory mechanism includes what is known as 'pre-programmed circuits of gene-expression'. In the latter case, some events (such as infection by a virus, release of a hormone into the blood stream, etc.) have been shown to trigger the expression of one set of genes. The product(s) of one (or more) of these genes function(s) by turning off the transcription of the first set of genes and/or turning on the transcription of a second set of genes, and so on. Therefore, even the infection of virus may cause certain genetical changes in the host.

The antiviral efficacy of certain homoeopathic drugs against animal viruses[41] would, therefore, suggest that the drugs actually corrected transcription of a set of genes that were possibly temporarily deranged in their activity, due to virus infection. The contention of the action of homoeopathic drugs through gene-expression also finds support from their action on some plants against various microbe-mediated diseases[42] and on plant growth[43,44]. Further, the repair of chromosomal and other genotoxic damage induced by injection of arsenic (poison) in mice following oral administration of the potentized homoeopathic drug *Arsenic alb* (unpublished data) would further testify our contention that regulation of gene-expression is one of the major mechanisms by which homoeopathic drugs work. Thus, pending further experimental verification, the idea that the potentized forms of homoeopathic medicines could act through regulation of gene-expression and also through hormonal regulations seem to us to be a very good working hypothesis which should attract the attention of open-minded researchers who will seek either confirm or refute it through well-designed experimentation.

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