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Like Cures Like: a Neuroimmunological Model Based on Electromagnetic Resonance.

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Running Title:

Like Cures Like … .

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Abstract

Objectives: Recent investigations have pointed to production of characteristic electromagnetic waves in highly diluted sterile filtrates of different microorganisms and their associated DNA molecules. Analysis of these diluted solutions which are prepared using methods almost identical to the way that homeopathic medicines are prepared, have pointed to the existence of nanostructures capable of emitting the electromagnetic (EM) waves. Combining these results with findings which point to the interaction of EM waves with sensory nerves with subsequent activation of homeostatic efferent pathways, we propose a model to describe mechanisms underlying the effects of homeopathic remedies.

The Model: Living cells and tissues are capable of generating EM waves in their physiological conditions. When a cell deviates from its physiological state, in addition to normal EM emissions, it starts to produce EM waves with altered characteristics. According to our model, the main cause of the therapeutic effects of homeopathic remedies is the occurrence of resonance between the non-physiological EM waves of the patient and ELF (extremely low-frequency) -EM waves produced by nanostructures present in the homeopathic remedy. Resonance occurs if the frequency and amplitude characteristics of the patient's non-physiological EM waves and those produced by nanostructures of the applied homeopathic remedy are similar. Once the resonance occurs, stimulation of the patient's sensory neurons, which are sensitized due to inflammation of any origin, leads to triggering of different regulatory mechanisms, including the activation of descending antinociceptive and/or cholinergic anti-inflammatory pathways which leads to the restoration of homeostasis.

Key Words: *Homeopathy, Resonance, Nanostructures, Extremely Low Frequency Electromagnetic Waves, Cholinergic Anti-inflammatory Reflex.*

1- Introduction

The main principle of homeopathy is known as the "law of similars" or "like cures like." This principle means that a substance that is capable of inducing a series of symptoms in a healthy living system is capable of curing the illnesses which display similar symptoms (Bellavite, 2005). Since the dawn of homeopathy, two main questions have served as the source of extensive criticism against it: 1) how do homeopathic remedies work considering the high levels of dilution and 2) how is the "law of similars" practically effective? Numerous researchers have tried to address these questions. However, while a number of *in vitro* and *in vivo* studies have led to some hypotheses (Bellavite, 2007), no viable model can still explain mechanisms underlying the biological effects of homeopathic remedies. Ideally, such a model should suggest scientifically-supported, experimentally-testable mechanisms which can explain the biological effects of homeopathic remedies, and enable homeopathic practitioners to diagnose the best remedy for a patient and also discover or synthesize new remedies. The lack of such a mechanistic model is one of the main causes for homeopathy lagging behind conventional medicine.

Recent studies have pointed to the presence of a particular type of electromagnetic radiation in extremely high aqueous dilutions of pathogenic microorganisms. While the emission of electromagnetic (EM) waves by different types of biomaterial is not a new finding (Cifra, 2011a), these studies have provided strong evidence for the emission of these waves by sterile filtrates derived from microorganism-containing culture supernatants, a finding which has been attributed to the formation of nanostructures by microorganisms (Montagnier, 2009a;Montagnier, 2009b). These findings, (described in Section 1-3 below), are of direct relevance to homeopathic remedies, the way they are produced and might have important implications for the mechanisms by which homeopathic remedies work.

In a set of studies performed by our group, we had found that exposing the peripheral area of burned skin to mild hyperthermia following the burn could inhibit the progression of the burn-induced injury

(Shahabi, 2006b) and pain (unpublished data). We termed this phenomenon post-heat shock tolerance (Shahabi, 2006b). We conjectured that the effect resulting from the application of mild local hyperthermia following the burn injury resembled the homeopathic "law of similars." Indeed, a potential explanation for this finding was that the stimulation of sensitized hyperesthetic sensory neurons by mild hyperthermia could induce descending anti-nociceptive pathways, which in turn diminished the burn-induced inflammation and pain (Shahabi, 2009). Herein, we propose a model for the biological effects of homeopathic remedies that is based on the production of extremely low frequency electromagnetic (ELF-EM) waves by homeopathic remedies' nanostructures in particular settings, followed by the interaction of these waves with body's intrinsic pathogenic EM waves, and triggering of descending regulatory pathways as a result of the stimulation of sensitized sensory neurons. We suggest that the occurrence of resonance between a patient's non-physiological ELF-EM fields with the EM waves of the homeopathic remedy leads to the stimulation of sensitized sensory neurons. In addition to providing details for each aspect of the model and citing supporting experimental data, we will describe how our model can explain three main aspects of the working of homeopathic remedies, i.e. *proving*, *law of similars* and *aggravation*.

1-2 Cells and tissues generate electromagnetic fields

All objects, whether living or nonliving, continuously generate EM fields because of the thermal agitation of their charged particles. Multiple studies have repeatedly shown that living cells do produce EM fields of different frequencies. A portion of EM waves generated by living cells/tissues is located in the Extremely Low Frequency (ELF) segment of the electromagnetic spectrum (Cifra, 2011a). The so-called ELF portion of the electromagnetic spectrum consists of waves with frequencies between 3 to 300 Hertz; corresponding to extremely low energy photons. Unlike EM waves of higher frequencies, ELF-

EM waves are rarely used for purposes like radio communications, chiefly due to difficulties in detecting these waves (Anderson, 1993).

1-2-1 Cells and tissues respond to EM waves

In addition to generating EM waves, living tissues are also known to be 'affected' by EM fields, including low amplitude ELF-EM fields. In theory, if an ELF-EM field has frequency and amplitude characteristics similar to the EMs generated by the cells of a tissue, then it can affect the tissue via resonance phenomenon. This interaction leads to the amplification of the EM field in the tissue (Rosch, 2009).

While the occurrence of transient biomolecular vibrations as a result of exposure to EM fields has long been conceived by biophysicists. However, the question of whether short-term vibrations whose energy is quickly absorbed in an aqueous medium might have any considerable physiological (or pathological) effect has been subject of controversies. A critical features of any oscillator (and hence any resonator), is the so-called damping of its oscillations; i.e. the rate by which the reduction in the amplitude of oscillations takes place as a result of the oscillator's intrinsic properties or the extrinsic properties of the environment in which oscillations occur. From this perspective, oscillators could be over-damped (higher rate of energy/amplitude loss), or under-damped (lower rate of energy loss). The quality factor (Q factor) of the oscillator is a parameter describing the level of damping; with high-Q oscillators being more stable around their main frequency (i.e. underdamped) and vice versa. In the context of resonation, a high-Q recipient oscillator will be able to detect a narrower range, more specific set of frequencies. Moreover, it will accumulate energy from a low amplitude, weak driving oscillator. Biomolecular vibrations taking place in aqueous media, are generally believed to be over-damped due to the presence of water and its inhibitory/energy-absorbing effect on oscillatory molecular motion. Interestingly,

however, there is evidence suggesting that this “viscous”, dampening effect of water might be diminished under certain circumstances, giving rise to an oscillation-prone environment (Cifra, 2011b;Pokorny, 2011). The under-dampened state which results from this so-called “visco-elastic” transition of water can set the stage for a biomolecular microenvironment which is capable of receiving and accumulating energy from low amplitude oscillations at specific frequencies. . In addition to the accumulation of energy from low amplitude EM waves in high-Q microenvironments, another potential mechanism suggested for the effects of the ELF-EM fields on living tissues is stochastic resonance (Jenrow, 2004a;Jenrow, 2004b;Liboff, 2004;Oschman, 2004;Rosch, 2009). It explains the mechanism by which weak signals are detected in a noisy environment. In stochastic resonance the existence of optimal level of random noise increase the sensitivity of a system to weak periodic signals (Hänggi, 2002)(Cifra, 2011a). Indeed, findings in recent years suggest that living tissues may be more sensitive to electromagnetic fields than previously thought (Lacy-Hulbert, 1998;Simko, 2004;Vianale, 2008;Wolf, 2005), which might be subsequent to the above-mentioned mechanisms.

Following resonance, numerous intracellular activities might be stimulated or suppressed by the resulting cascade of events. It is important to note that in this paper, our purpose from "similarity between frequency and amplitude characteristics of two electromagnetic fields" is their abilities to resonate together. Two electromagnetic fields might not have identical frequencies but still they resonate with each other.

ELF-EM fields can affect different cells in a variety of tissues (Frahm, 2006;Simko, 2004;Vianale, 2008;Wolf, 2005); however, research has shown that the sensitivity of sensory neurons is greater than other cells (Anderson, 1993;Carrubba, 2007;Mesirca, 2007;Sonnier, 2001). The biological effects of ELF-EM fields may be on the cell membrane level, gene expression or signal transduction pathways. As a result, various physiological activities of the cells, such as cell proliferation, cell cycle regulation, cell

differentiation and metabolism, might be affected (Carrubba, 2007). That said, short-term exposure of cells to ELF-EM fields, even after their amplification by resonance, does not necessarily lead to an effect unless the activation threshold of the cells is lowered or that the duration of exposure becomes sufficiently long to cause accumulation of the effects. This relationship also holds for the sensory neurons that are more sensitive to ELF-EM fields than other cells (Kaune, 1987;Sonnier, 2001).

1-3- Evidence for the production of ELF-EM waves by homeopathic remedies

Considering the highly diluted nature of homeopathic remedies and the fact that these preparations are virtually devoid of any remnants of the initial starting material, numerous studies have attempted to determine whether there might be any physicochemical signals generated and/or retained in the highly diluted solutions (Bonamin, 2008;Demangeat, 2010). Recently, in a series of studies by Montagnier and colleagues, researchers discovered the existence of a particular class of electromagnetic waves in high aqueous dilutions of a variety of pathogenic microorganisms (Montagnier, 2009a;Montagnier, 2009b). Researchers' initial observations had demonstrated that filtrates of human lymphocyte culture supernatants infected with a pathogen named *Mycoplasma Pirum*, although apparently sterile due to the size of the microorganism and the filter's pores ϕ, could lead to the regeneration of the organism when incubated with *Mycoplasma*-free lymphocyte cultures. While unexpected, the findings were highly reproducible and stood rigorous scrutiny, including the use of highly sensitive nested polymerase chain reaction assays for confirmation of the sterility of the filtrates. Interestingly, researchers were then able to detect distinctive EM waves in highly diluted solutions derived from the sterile filtrates. The procedure included filtration of microorganism-containing culture supernatants by 100nm and 20nm filters, followed by multiple serial dilutions accompanied by vigorous shaking after each dilution step. When analyzed for the presence of EM signals, dilutions in the particular range of 10^{-8} to 10^{-12}

unequivocally showed the emission of EM waves at a low frequency. Of note, lower dilutions (e.g. 10^{-3}) were silent in terms of EM wave emission (at least in the range detected by the instrument).

Treatment of diluted filtrates with RNase, DNase or proteases did not affect the emission of EM waves. Conversely, heating the samples to temperatures above 70 degrees as well as freezing the samples at -80 degrees abrogated the emissions. The requirement for vigorous shaking at each dilution step, and the necessity for stimulation by low frequency background EM waves (from either natural or artificial resources) were other aspects of the process leading to the generation of ELF-EM fields. Similar results were obtained for several bacteria and viruses. Interestingly, viral suspensions could generate EM signals when filtrated through 20nm filters, whereas in the case of bacteria the filter size had to be 100nm, a finding which supported the notion that nanostructures might be involved in the generation of EM waves. Existence of these nanostructures has been supported by a number of physical studies that showed the formation of long polymers of hydrogen-bonded dipoles in water. However, these polymers tended to be short lived. Montagnier hypothesized that the emitted signals are due to a resonance phenomenon that depends upon excitation by the surrounding electromagnetic noise. The persistence of these nanostructures after the removal of the agent that forms them might be due to a coherence effect produced by the radiations themselves, as postulated by Italian physicists Emilio Del Giudice and colleagues (Giudice, 1988;Hecht, 2011) .

As mentioned above, dilution of the filtrates (and hence any associated nanostructures) up to a particular level was necessary for the detection of EM waves. Indeed, authors believed that the high concentration of the emitting structures present in lower dilutions could be responsible for the EM silence, likely due to the destructive interference caused between a huge number of slightly out-of-phase waves. The researchers then examined whether a “silent” dilution could affect the emission of signals by a “loud” dilution. Interestingly, placing a mildly diluted “silent” tube in juxtaposition to a highly diluted “loud”

tube led to the silencing of the latter. The effect was attributed to the formation of extra nanostructures in the "loud" tube, as it was reversed when the silenced tube started emitting signals again when it underwent several dilutions. Altogether, these set of findings clearly demonstrated that the process of dilutions, accompanied by vigorous shaking of a sterile filtrate which had initially been in contact with a microorganism, could lead to generation of specific ELF-EM waves in the samples. While this research was not dubbed as a "homeopathy-related" study by the authors, it bears direct relevance to homeopathic preparations of drugs and their potential mechanism of action. These findings are in corroboration with earlier controversial findings by Benveniste's group, which had shown that the highly diluted samples of anti-IgE antibodies were capable of causing degranulations in basophils (Benveniste, 1994b;Davenas, 1988). To explain the findings, Benveniste brought up the notion of "memory of water", which indicates that bioinformation exists in the solvent. His findings pointed to the possibility that the EM signals could be emitted from the solution and could be recorded and transmitted electronically to water or cells leading to specific biological effects (Aïssa, 1993;Benveniste, 1994a;Thomas, 2000). Considering the significance of his findings, other researchers tried to reproduce the results. This led to some controversies; while some groups reported that they were able to confirm Benveniste's findings (Endler, 1995;Senekowitsch, 1995), others failed to get the same results (Jonas, 2006).

1-4- Inflammation

Inflammation is an adaptive response that can be instigated by noxious stimuli and other classic inducers of inflammation (i.e., infection and tissue injury (Medzhitov, 2008)). However, tissue stress and malfunction may similarly induce a low-grade inflammation that has been described as para-inflammation in some texts (Medzhitov, 2008). This low-grade inflammation depends primarily on tissue-resident macrophages and is placed between a normal homeostatic state and a classic inflammatory response. (Medzhitov, 2008).

1-5- Neural Inflammatory and Anti-inflammatory Reflexes

1-5-1- Nervous System Perceives Inflammation:

The nervous system is composed of sensory neurons (detecting the state of the body and organs) and motor neurons (carrying signals to the body and organs) (Czura, 2005). Based on their size and speed of conduction, nerve fibers are classified into three categories: 1) highly myelinated A fibers with low activation thresholds, 2) lightly myelinated B fibers and 3) unmyelinated C fibers, with high activation thresholds (Guyton, 2006).

The sensory input from the immune system is carried to the central nervous system (CNS) through both humoral and neural routes. Different immunological mediators can gain access to the brain centers that lack a blood–brain barrier (known as circumventricular regions) or can penetrate other regions of the brain by active transport systems. Endotoxins and some inflammatory mediators (e.g., IL-1β) can activate afferent vagus nerve fibers, especially A fibers (Czura, 2007), leading to sickness behaviors, such as food aversion and fever (Czura, 2005). Both the humoral and neural routes for the communication between the immune system and nervous system are involved in the development of behavioral manifestations of an illness (Czura, 2005).

Noxious stimuli, injuries and inflammation sensitize somatic and autonomic sensory nerves, especially A fibers, and decrease their activation thresholds (Andrew, 1999;Meyer, 1981;Michaelis, 1998;Shahabi, 2009).

Peripheral inflammation may affect behavior via interactions with neural systems in the periphery and CNS that mediate pain, arousal and behavior. Multiple parallel neural pathways carry information related to sickness behavior, local inflammation and pain. For example, the stimulation of vagal sensory neurons appears to result in systemic brain-mediated responses, whereas the modulation of local inflammation and pain is undertaken by spinal viscerosensory nerves. So, the stimulation of afferent

vagal nerves may result in behavioral and mental changes that are basically controlled by higher brain structures (Bercik, 2010;Collins, 2009;Porges, 2003;Siegel, 2008).

1-5-2- Descending Regulatory Pathways:

The stimulation of somatic or autonomic sensory afferent nerves may lead to the activation of inhibitory (regulatory) reflexes that can inhibit pain and inflammation. Inflammatory mediators and noxious stimuli can decrease the activation threshold of sensory neurons, and some evidence indicates that the activation threshold of A fibers is decreased more than other sensory fibers (Andrew, 1999;Meyer, 1981;Michaelis, 1998). Furthermore, the stimulation of somatic sensory afferents, especially A fibers, by noxious stimulant or inflammatory mediators may result in the induction of descending anti-nociceptive mechanisms (Sandkühler, 1999;Sandkuhler, 1997). Some of these inhibitory mechanisms, such as alterations of sympathetic outflow and the production of endogenous opioids, can modify peripheral tissue inflammation (Levine, 1993;Levine, 1999;Millan, 1999, 2002;Raja, 1999;Shahabi, 2009). A mechanism described by Tracey and colleagues is likely the most important neural anti-inflammatory reflex. According to this mechanism, the vagus nerve stimulation leads to the activation of a cholinergic anti-inflammatory reflex, which results in an anti-inflammatory response (Oke, 2008, 2009;Pavlov, 2003;Tracey, 2002, 2007). The cholinergic anti-inflammatory reflex reinforces the concept that a neural mechanism can modulate and coordinate cytokine responses (Oke, 2008;Tracey, 2007). The reflex is comprised of an afferent (sensory) branch and an efferent (motor) branch. These branches coordinate the formation of a discrete and rapid mechanism, in which the efferent branch opposes the action that activates the afferent branch (Oke, 2008;Tracey, 2002). Inflammatory mediators activate the afferent vagus nerve signals, especially A fibers (Czura, 2007). The signals are transmitted to the CNS and ultimately lead to an increase in the adrenocorticotropin hormone (ACTH) from the anterior pituitary gland (Oke, 2008;Tracey, 2002). The increase in ACTH stimulates an increase in the systemic

glucocorticoid levels, which can inhibit proinflammatory cytokines (Oke, 2008;Sternberg, 1997;Sternberg, 1989;Watkins, 1999). Melanocyte-stimulating hormone, a potent anti-inflammatory protein, is also released as a result of afferent vagus nerve activation (Oke, 2008;Zhang, 1999). The efferent neural arc of the reflex, termed the cholinergic anti-inflammatory pathway, inhibits inflammation (Borovikova, 2000;Oke, 2008;Tracey, 2002, 2005) via release of acetylcholine. Acetylcholine binds to the α7nAChR, expressed on the surface of activated macrophages and other immune cells, and inhibits cytokine synthesis and release (Oke, 2008). The anti-inflammatory reflex triggered by vagal afferent stimulation can inhibit both systemic and local inflammation (Pavlov, 2003).

In addition to descending pain and inflammation regulatory pathways, other inhibitory pathways exist, such as for emesis (Zabara, 1972) and itching (Greaves, 2007).

An inflammatory milieu sensitizes the sensory neurons, but the sensitization is primarily targeted for the neurons that trigger the inhibitory descending pathways.

2- The Model

The homeopathic "law of similars" means that low doses of a substance that can induce a series of symptoms in a healthy living system can cure these symptoms under certain circumstances. The best homeopathic remedy for a patient is one that can most similarly produce the patient’s symptoms in a healthy person (proving phenomenon). Proving may be performed as a controlled procedure, in which low doses of the substance is consumed for a relatively long period by healthy volunteers and their signs and symptoms are monitored (Hahnemann, 2004). For some substances, the documented side effects due to abuse or toxication are added to the proving data (Hahnemann, 2004). We explain three important phenomena of homeopathy (provings, the law of similar and aggravation) with our model. We do not explain the concept of “miasms” because it is beyond the scope of this paper.

2-1- Proving

Homeopathic proving means that “the profile of a remedy can be identified by giving it to the volunteers and then recording all mental, physical and emotional symptoms experienced (Hahnemann, 2004).”

ELF-EM waves can stimulate and/or injure cells in different systems and tissues (Frahm, 2006;Simko, 2004;Vianale, 2008;Wolf, 2005). The nervous system is most sensitive to stimulation by ELF-EM waves and is the main detector of electromagnetic waves (Anderson, 1993;Carrubba, 2007;Mesirca, 2007;Sonnier, 2001). This sensitivity might be expected because the tissues and processes of the nervous system are unusually responsive to electrical signals. Chronic exposure to single stimuli that are not able to stimulate the nervous system when applied for short time can result in stimulation of the nervous system due to the accumulation of these stimuli (Anderson, 1993;Mesirca, 2007). The proving phenomenon occurs after the consumption of homeopathic remedies and may be due to the biological effects of the ELF-EM waves ~~from these~~ produced by nanostructures of these remedies via the following mechanism (figure 1).

According to our model, when a healthy person consumes a homeopathic remedy, nanostructures of the homeopathic remedy will be triggered to produce ELF-EM waves when ELF-EM waves of the cells that are adjacent to the nanostructures (as background ELF-EM field), can stimulate the nanostructures to produce ELF-EM waves. This may also be the cause that all the tissues would not be affected by a specific homeopathic remedy with equal probability.

If a homeopathic remedy is administered to a healthy person only one time, then ELF-EM waves produced by homeopathic nanostructures usually can not affect any sensory neurons or other type of cells because the energy levels of the ELF-EM waves are too low to have any significant biological effect. But, repeated administering of the remedy may lead to detectable biological effects because of chronic exposure to an electromagnetic stimulus that cannot affect a biological system in a short time period but could have biological effects due to the accumulation of the stimuli. ELF-EM waves alone

are too weak to affect biological systems, including sensory neurons. When the accumulation of stimuli of ELF-EM waves produced by nanostructures of homeopathic remedy reaches a level higher than the activation threshold of the target cells, the biological effects of the homeopathic remedy will be initiated. The sensory neurons are the first cells that are affected because they are most sensitive to EM fields. Many symptoms and signs can result. For example, the stimulation of the somatic sensory neurons may result in symptoms like pain, itching and disturbances in vision, hearing and taste. The stimulation of the autonomic sensory neurons leads to disturbances in the autonomic balances of the target tissues or the entire body. As mentioned above, the stimulation of the vagus nerve may result in emotional and mental presentations too (Bercik, 2010;Collins, 2009;Porges, 2003;Siegel, 2008).

In addition to sensory neurons, other cells may be affected by the ELF-EM waves produced by nanostructures of homeopathic remedy if the energy of the ELF-EM waves produced by nanostructures of the remedy is sufficiently high or the exposure time continues for enough time. Depending on the type of cells affected by the ELF-EM waves, the outcome will be different. The affected cells may be parenchymal cells, local inflammatory cells or endothelial cells. Different symptoms may be produced. During proving, the affected cells (tissues) initially enter the stress state. Then, malfunctions will occur. Simultaneously, the stress state or malfunctions of local inflammatory cells may result in tissue inflammation, and the inflammation may damage the tissue. If the exposure continues, then the cells may undergo apoptosis and die (Simko, 2004;Wolf, 2005). During proving, in addition to vagus nerve stimulation, the stress state or malfunctions of brain structures may result in the emotional and mental presentations. The duration of proving often continues until revealing the primary presentations, including stimulation of sensory neurons, stress states and mild malfunctions. The information about gross malfunctions and tissue injuries cited in the profile of a remedy is usually obtained from the documented side effects due to abuse or intoxication of the substance from which the remedy originated.

ELF-EM waves with different frequency and amplitude characteristics will produce different symptoms, even in the same tissue, because they affect different somatic and autonomic sensory neurons and other types of cells (Rosch, 2009). The ELF-EM waves produced by nanostructures of homeopathic remedy might be responsible for the specific quality of the generated symptoms. For example, epigastric pain might be generated during proving with two different homeopathic remedies. Differences in the frequency and amplitude characteristics of the ELF-EM waves produced by nanostructures of these remedies may result in differences in pain qualities. For example, one remedy may generate a burning pain, whereas another remedy may generate a pressing pain. Qualities that are more detailed are usually considered for this symptom, but a discussion about them is beyond the scope of this paper. Such quality differences may occur in other proving-induced physical, emotional or mental symptoms. In homeopathic prescriptions, the symptoms defined with all of the specified characteristics, i.e., location, sensation, modality and concomitants, are more important than the very general, common and undefined symptoms observed in almost every disease and present in almost every remedy (Khanaj, 2006).

The above suggested mechanism is in line with recent Mishra and Colleagues' finding that homeopathic remedies can affect physiologic parameters of the autonomic nervous system (Mishra, 2011).

In this paper, the symptoms and their qualities that are induced by a homeopathic remedy in a healthy human are named "symptoms of the homeopathic remedy".

2-2- Therapeutic Effects of Homeopathic Remedies

The main principle of homeopathy, known as the "law of similar," means that low doses of a substance that can induce a series of symptoms in a healthy living system are capable of curing these symptoms under certain circumstances (Bellavite, 2005). According to our model, this principle is explained as follows (figure 2).

When a cell deviates from the physiologic state, in addition to normal EM waves, it starts to produce EM waves with changed characteristics. (Driban, 2007;Slawinska, 1992;Slawinski, 2005;Slawinski, 1992;Van Wijk, 2008).

As the above mentioned mechanism for proving phenomenon, When a patient consumes a homeopathic remedy, it produces ELF-EM waves in a tissue if the ELF-EM field of that tissue is suitable to trigger homeopathic nanostructures to produce ELF-EM waves. Furthermore, if the characteristic of the non-physiologic EM waves are similar to those that are produced by nanostructures of an administered homeopathic remedy, then resonance will occur. On the other hand, all of the non-physiologic conditions could trigger inflammatory responses. In the cases of infections or tissue injuries, this inflammatory response is more severe, but the stress states and malfunctions in the absence of infections and tissue injuries still induce a low-grade inflammation (Medzhitov, 2008). The noxious stimulus and inflammation decrease the activation threshold of sensory neurons innervating the tissue. Decreasing the activation threshold is more significant for the sensory neurons, which triggerring the descending regulatory mechanisms(Andrew, 1999;Meyer, 1981;Michaelis, 1998;Shahabi, 2009). Therefore regardless of the type of existing disorder in the tissue, the activation thresholds of sensory neurons, especially the ones triggering the descending regulatory mechanisms, decrease because of noxious stimulus and/or inflammation. More severe tissue inflammations or the noxious stimulus cause greater reductions in the activation threshold of the tissue sensory neurons.

The patient's symptoms represent the sensory neural pathways stimulated by inflammation or noxious stimulus or, in the other words, sensitized by them. Therefore, the patient's symptoms determine which neural pathways should be stimulated to trigger descending regulatory mechanisms. Furthermore, the patient's symptoms, especially quality wise, may represent the characteristics of non-physiologic EM waves generated by the diseased cells and tissues.

If the symptoms and their qualities in a patient are similar to those of the proving of a homeopathic remedy, then it means that the patient's suffering cells and the characteristics of their EM waves and the sensitized sensory neurons are similar to those of the homeopathy remedy. For this condition, the ELF-EM waves produced by nanostructures of the consumed remedy are amplified by the non-physiologic EM waves through resonance phenomenon. On the other hand, The noxious stimuli and/or the inflammation of the suffering tissues decreases the activation threshold of sensory neurons innervating the tissues, especially those triggering descending regulatory mechanisms (Andrew, 1999;Meyer, 1981;Michaelis, 1998;Shahabi, 2009). Therefore unlike proving, a low number of doses of the correctly chosen remedy for a patient could affect the sensitized sensory neurons, especially those triggering descending regulatory mechanisms.

The sensory neurons that stimulate descending regulatory mechanisms are stimulated by ELF-EM waves with higher frequencies (De Herdt, 2009;de Tommaso, 2003;Gopalkrishnan, 2000;Proctor, 2002;Sluka, 2005). When the frequency and amplitude characteristics of the patient's non-physiologic EM waves and those of the homeopathic remedy are very similar (i.e., the patient's symptoms and those of the homeopathic remedy are very similar), a strong amplification occurs through resonance phenomenon. The amplified EM waves, which have relatively higher frequencies, will efficiently trigger descending regulatory mechanisms. A lower degree of matching between the patient's non-physiologic EM waves and the homeopathic remedy results in weaker resonance. Therefore, the amplified EM waves that have relatively lower frequencies cannot efficiently trigger descending regulatory mechanisms. This suggested mechanism for the effects of homeopathic remedies agrees with our previous findings that mild local hyperthermia immediately after an acute skin burn injury decreases both burn-induced tissue injuries and inflammation. Our findings indicate that the administration of naloxone, an opioid receptor antagonist, inhibits the protective effect of mild post-burn local hyperthermia. The post-burn local

hyperthermia should be applied to a peripheral healthy zone near the burn injury to inhibit progression of the injury (Shahabi, 2006b). This experiment can be considered as a model for the application of a similar mild sub-lethal stress after a severe lethal stress. We hypothesized that mild post-burn local hyperthermia stimulates the sensitized nociceptors in the hyperesthetic area around the injured region (Shahabi, 2009). It can be suggested that since stimulation of hyperesthetic sensory neurons sends relatively higher frequency impulses (Coderre, 1997), this results in the activation of descending regulatory mechanisms that inhibit burn injury progression (Shahabi, 2006b;Shahabi, 2009).

After amplification of the patient's non-physiologic EM waves and the ELF-EM waves produced by nanostructures of homeopathic remedy, if the stimulated sensory neurons are somatosensory, then the triggered descending inhibitory signals will be local descending antinociceptive pathways. Local descending antinoceptive pathways possess anti-inflammatory characteristics. For the activation of the somatosensory neurons, that the suffering cells and their frequency and amplitude characteristics are similar to those of the homeopathic remedy is sufficient. In contrast, the induced anti-nociceptive and anti-inflammatory effect is local and is limited to the suffering tissues. This anti-inflammatory response is able to restore the local homeostasis. If there is a systemic derangement due to a local acute condition, (e.g., systemic immunosuppression due to local severe burn injury (Schwacha, 2002)), then activated descending anti-nociceptive and anti-inflammatory pathways can restore it because the main perturbation that caused this derangement is recovered. This result agrees with our finding that post-burn local hyperthermia can decrease systemic immunosuppressive effects of a third-degree local burn injury (Shahabi, 2006a).

On the other hand, the stimulation of sensory vagus nerves by EM waves activates cholinergic anti-inflammatory reflex. The cholinergic anti-inflammatory response may be either local or systemic, depending on the severity of the afferent signals. The stimulation of afferent vagal nerves may result in

behavioral and mental changes (Bercik, 2010;Collins, 2009;Porges, 2003;Siegel, 2008). So, the proving-induced autonomic, behavioral and mental changes may mean that the vagus sensory nerves are among the targets of the homeopathic remedy administered during proving. If a patient's autonomic, behavioral and mental changes are similar to those for the proving of a homeopathic remedy, then the patient's non-physiologic EM waves and the waves produced by nanostructures of the homeopathic remedy are similar. Furthermore, the vagal sensory neurons stimulated in a patient are the same ones that are stimulated during proving of the homeopathic remedy. When the above-mentioned homeopathic remedy is administered for a patient, its nanostructures will produced ELF-EM waves that will be amplified and will stimulate the sensitized vagal sensory neurons that are able to activate humoral and neural cholinergic anti-inflammatory response. This response is both local and systemic and will restore the whole-body homeostasis. This idea agrees with homeopathic texts in that mental, emotional and general symptoms are more important than physical ones when the aim is selection of a homeopathic remedy with therapeutic effects for the whole body (Khanaj, 2006). According to our model, stimulation of the vagus nerve plays the key role in homeopathic therapeutic effects. The main regulatory mechanism that is triggered by the stimulation of the vagus nerve with amplified EM waves is a cholinergic anti-inflammatory reflex, but stimulation of the vagus nerve may induce other regulatory mechanisms. This mechanism agrees with findings that indicate that chemical or electrical vagus nerve stimulation has therapeutic effects through induction of cholinergic anti-inflammatory reflex or other mechanisms (De Ferrari, 2011a;De Ferrari, 2011b;Gross, 2007;Kirchner, 2000;Kirchner, 2006;Klein, 2010;McKenna, 2008;Miller, 2009;Pan, 2010a;Pan, 2010b;Schiepers, 2005;Xiong, 2010).

The cholinergic anti-inflammatory response has both local and systemic effects (Borovikova, 2000;Oke, 2008;Tracey, 2002, 2005). Stimulation of the systemic response appears to require more severe signals. So, the systemic anti-inflammatory response is stimulated only when "the similarity" of the patient's

symptoms and those of the homeopathic remedy, especially emotional, mental and general symptoms, is sufficient. For such a condition, the number of sensory neurons that are stimulated by amplified EM waves and the frequency of impulses sent by each sensory neuron is sufficient to trigger a cholinergic anti-inflammatory response. If “the similarity” is insufficient, then a regulatory response will not occur or it will only be a local and transient response. The more similar the patient’s symptoms are to those of the homeopathic remedy, the higher the overlap between the exited sensory neurons of the patient and those of the homeopathic remedy. This relationship increases the probability of triggering the descending regulatory mechanisms and restoring the whole body homeostasis.

The grade of inflammation and noxious stimuli is another parameter that determines the rate of the required similarity. In acute diseases, the high-grade inflammations and/or noxious stimuli, compared to that of chronic cases, dramatically reduce the activation threshold of the sensory neurons. Thus, these sensory neurons could be stimulated by the EM waves that are produced by resonance-induced amplification of partially “similar” EM waves of both the disease and the homeopathic remedy’s nanostructures. These stimulated sensory neurons would then trigger the descending regulatory responses. These events agree with the homeopathic texts: for the treatment of acute diseases, all of the symptoms of the patient and the homeopathic remedy do not need to match (Hahnemann, 2004). For chronic diseases, the grade of inflammation, compared to that of acute diseases, is low, which results in less sensitization of the sensory neurons. This low-grade sensitization of sensory neurons, in addition to the need of chronic diseases to induce a systemic regulatory response, may be the reason why the treatment of chronic diseases requires a strong match between the symptoms of the patient and the homeopathic remedy (especially for emotional, mental and general symptoms) (Hahnemann, 2004).

In acute conditions with symptoms other than pain and inflammation (e.g., emesis and itching), the sensory neurons that are responsible for transmitting the signals that produce these symptoms are

sensitized. After administration of the correct homeopathic remedy, these sensitized sensory neurons are stimulated by amplified EM waves that are produced by the resonance between the EM waves of the tissue(s) and those of the homeopathic remedy's nanostructures. Then, the descending anti-emesis or anti-itching pathways (Greaves, 2007;Zabara, 1972) will be activated by a mechanism similar to the somatosensory and vagal sensory neurons.

According to our model, the mechanism of homeopathic remedies' therapeutic effects is through the activation of sensory neurons, but this probably holds only for the therapeutic effects that follow the "law of similars." Indeed, homeopathic remedies can have beneficial effects that do not follow this principle. These clinical uses of homeopathic remedies are not based on gathering signs and symptoms during proving or documented side effects due to abuse or toxication of these remedies, instead, they are based on clinical experiences (Khanaj, 2006). Under these conditions, the affinity of the remedy to the specific tissues is through the suggested mechanism by the model. However, the mechanism by which the remedy triggers the healing process may be different. Direct stimulation of the neural or non-neural cells might be among the other possible mechanisms for the therapeutic effects of homeopathic remedies in these conditions. For example, the amplified EM waves that are produced by resonance between the EM waves of the keratinocyte(s) and the homeopathic remedy's nanostructures may promote wound healing by increasing the keratinocyte growth rate and decreasing the production of proinflammatory molecules (Vianale, 2008).

2-3- Homeopathic Aggravation

Homeopathic or therapeutic aggravation is a "temporary worsening of existing symptoms following the administration of a correctly chosen homeopathic prescription, which indicates a favorable response to treatment" (Swayne, 2000).

Such aggravations are a basic concept in homeopathy, and they are considered a sign that the correct homeopathic remedy has been applied (Grabia, 2003). The incidence of aggravations in homeopathic practice has been noted to be greater than 30% (Anelli, 2002;Grabia, 2003).

According to our model, when the non-physiologic status is continuous, the response of some of the cells (e.g. immune cells) to non-physiologic stimuli (e.g. noxious or inflammatory stimuli) decreases. This response means that for example exposure of some immune cells to noxious or inflammatory stimuli leads to the production of lesser amounts of some inflammatory mediators by these cells. Hyposensitization can be considered an adaptive response to persistent altered conditions, Hyposensitization may be due to down regulation of specific receptors, reduction of their affinity or decreased signal transduction (Bellavite, 2007). Hyposensitization is very specific on the receptor level, and this means that a cell may hyposensitized for a mediator, whereas its sensitivity to another mediator does not change or even increases (Bellavite, 2007). When a homeopathic remedy-induced regulatory mechanisms begin to restore homeostasis, hyposensitization is decreased, and the response of the cells to the remaining non-physiologic stimuli will increase, which aggravates some of the symptoms. Because homeostasis is restored by the homeopathic remedy-induced regulatory mechanisms, the aggravation of symptoms is transient. Our explanation of aggravation is similar to the one suggested by Bellavite and colleagues (Bellavite, 2007).

The induction of homeopathic aggravation following administration of a homeopathic remedy means that the regulatory mechanisms have been triggered. This triggering may be the reason that, in homeopathy, the development of homeopathic aggravation is considered to be a favorable reaction after administration of a dose of remedy (Grabia, 2003;Schepper, 2006).

Additional types of reactions are called “natural healing responses” (e.g., urticaria, diarrhea and coryza-like symptoms) (Schepper, 2006). According to our model, the development of these symptoms is due to

parasympathetic stimulation that results from the activation of cholinergic anti-inflammatory pathways. This responses agree with the findings that showed that increased parasympathetic activity may result in coryza, urticaria and diarrhea (Bellamy, 2006;Jaradeh, 2000;Jarrett, 2008;Nakamizo).

3- Discussion

According to the model in this paper, the basis for the therapeutic effects of homeopathic remedies is the resonance between the non-physiologic EM waves of the patient and produced by nanostructures of the homeopathic remedy. This resonance occurs when the frequency and amplitude characteristics of the non-physiologic EM waves of the patient and those produced by nanostructures of the applied homeopathic remedy are similar. The patient's sensory neurons that are sensitized due to inflammation or noxious stimuli play an important role in triggering the regulatory mechanisms that restore homeostasis. According to our model, the amplification of homeopathic nanostructures' ELF-EM waves by resonance phenomenon and the activation of regulatory mechanisms due to the stimulation of sensitized sensory neurons by the amplified EM waves are the two main pillars of the therapeutic effects of homeopathic remedies based on "the law of similars."

Although the descending regulatory mechanisms that are activated by homeopathic remedies possess anti-inflammatory characteristics, they do not result in local or systemic immunoparalysis, but they can strengthen the anti-microbial protective immunity. This action is expected because hyper-inflammation, which is induced during infections, not only causes tissue injuries but also disturbs the normal immune response (Fernandez-Cabezudo, 2010;Lehner, 2001;Tracey, 2007). A homeopathic remedy does not induce sustained activation of descending regulatory mechanisms because, after administration of a well-chosen homeopathic remedy, the triggered descending regulatory mechanisms remain activated until the amplified EM waves oscillate with energy greater than the activation threshold of the sensitized sensory neurons. After restoration of homeostasis by the descending regulatory mechanisms, the non-

physiologic EM waves no longer exist, so the resonance phenomenon and amplification of homeopathic nanostructures' ELF-EM waves will not occur. After resolution of the inflammation, the activation threshold of the previously sensitized sensory neurons increases, and these neurons will no longer be sensitized. In the other words, a well chosen homeopathic remedy triggers descending regulatory mechanisms only when the body needs them. In contrast to other methods that trigger descending regulatory mechanisms (Kox, 2007), a well-chosen homeopathic remedy does not lead to immunoparalysis.

Similar to other types of oscillations (Cifra, 2011a), the oscillation energy of amplified EM waves diminishes over time and ultimately stops. If homeostatic perturbation returns, then the homeopathic remedy should be re-administered to re-activate the regulatory mechanisms.

We believe that, in addition to the descending regulatory mechanisms mentioned in this paper, homeopathic remedies that follow the "law of similars" trigger additional regulatory mechanisms. We propose that these additional mechanisms are triggered according to the following model: resonance between the patient's non-physiologic EM waves and those produced by nanostructures of homeopathic remedy produces amplified EM waves that stimulate sensitized receptors, and the stimulation of these sensitized receptors may induce the regulatory mechanisms.

As the main purpose of this model is to explain "the law of similars", it could be tested in two stages:

At the first stage, it should be tested whether proving of a homeopathic remedy leads to stimulation of somatic and/or autonomic nervous systems. As an instance, it can be tested if proving of a homeopathic remedy in a group of healthy volunteers produces special and repeatable changes in "heart rate variability" (HRV) pattern which is widely considered as a marker for the balance between parasympathetic and sympathetic tone/stimulation (Huston).

At the second stage, it should be tested whether comparing and matching the proving-induced changes in the pattern of stimulation of somatic and/or autonomic nerves, as indicated by measures like HRV, with that of a patient helps to choose of an appropriate homeopathic remedy for the patient.

The main purpose of this model was to suggest a mechanism for the biological effects of homeopathic remedies but we believe that the model's biophysical/physical features have remained underdeveloped..In particular, questions remain with regard to the exact detecting resonance process on the side of the living tissues as well as the Q factor required to detect and amplify incoming ELF-EM waves. Indeed, it is hard to discuss the possibility of a resonance response in any context without any estimation of the environment's Q-factor. If a very weak signal is to be amplified by resonance, effective Q-factor of the detecting oscillator has to be very high. Thus, both theoretical and experimental studies are required to address the biophysical features of the recipient entities; i.e. sensory nerves in our model, which should include their Q factor at different subcellular locations, if they are to be receiving and transferring ELF-EM waves. Furthermore the following crucial question remains to be answered via precise empirical studies: what is the intensity, and energy of the electromagnetic signals generated by homeopathic nanostructures?

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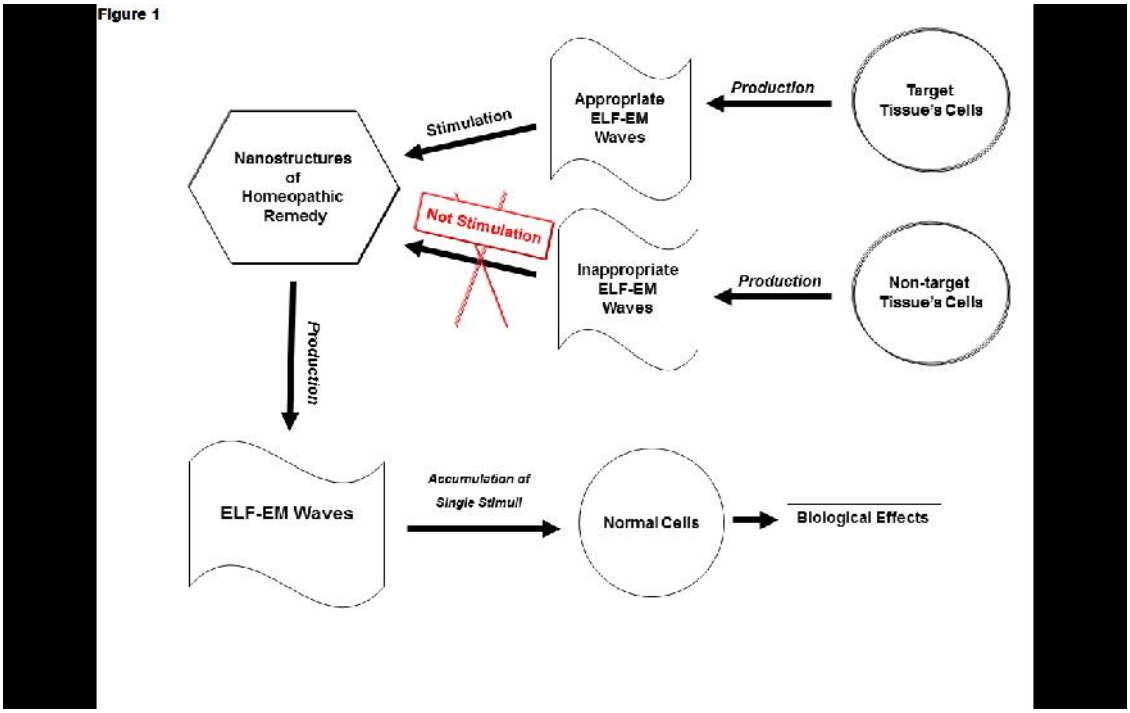
Legends:

Figure 1- The proposed mechanism for the homeopathic proving phenomenon.



*Target Cells: The cells that their EM waves have some similarity to that of the homeopathic remedy.

Figure 2- The proposed mechanism for the therapeutic effects of homeopathic remedies.