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Inverse effect and receptor dynamics – Coffee, Opium and Wine's secondary pharmacology

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A homeopathic widespread belief is that the inversion of effect of the drugs in homeopathic medical practice is due to dilution or very low doses, but there are many practical homeopathic incoherencies. First of all the historical conception of the similia principle was due to experiments with *ponderal/pharmacological doses* in healthy and diseased subjects[1]. Furthermore the classical foundations of the similia principle in Organon[2], primary and secondary actions, were thought to be connected with opposite time-dependent reactions of the body to high doses and the inversion of effect was seen in temporal sequence after a strong dose and not after changes of doses. so the idea that dilutions are responsible for inversion of effects is not suitable to the classical theory. And lastly homeopathic provings or pathogenetic trials have frequently mixed, unregarded to the doses, occasional toxicological symptoms and symptoms obtained through diluted substances[3], reinforcing the idea that, on healthy subjects, in several cases many substances produce the same symptoms in pharmacological or infinitesimal doses. So at least the dose-dependent inversion of effect is not generalized in a great part of the collected symptoms. Biological foundations to similia principle have to be searched in other directions[4], as in different sensitivity to drugs between health and disease, or in different time-dependent effect of drugs on specific cell sensitivity. In the vision described here both these conditions represent the same phenomenon of altered cell sensitivity. It is aim of this article to show that the original hahnemannian idea to explain homeopathic similia principle starting from a pharmacological and biological point of view with ponderal doses, seems correct, rationally comprehensible and based on modern knowledges. The three pharmacologic examples that best illustrate this reasoning, coffee, opium and wine, will be discussed.

In origin, following Hahnemann's steps, secondary action of drugs was described as a property of the living beings, a response of the organism to different pharmacological stimuli, exciting or depressing. And the characteristic of the phenomena described by him is that this response has opposite symptoms respect to the rewarding drug effect. This phenomenon is really consistent with the *withdrawal syndrome*, but related also with others as drug tolerance, rebound effect, and dependence. These four phenomena are strictly interdependent, but are not the same. The term *tolerance* is described by pharmacologists as “a more gradual decrease in responsiveness to a drug, taking days or weeks to develop”[5]. It may be due to different mechanisms, but here are considered only receptor changes and traslocations, because of the connection with the hahnemannian examples. *Rebound* and *withdrawal* effects are similar phenomena and as reported in Texeira's review[4], in the literature different authors consider them as synonyms. They represent an increase of symptoms more severe than the baseline after the discontinuation of a drug. It is recognized that withdrawal or rebound symptoms “are typically opposite to the acute and rewarding drug effects”[6]. *Dependence* develops when continued drug exposure is required to avoid negative symptoms during withdrawal. An example of tolerance, withdrawal symptoms and dependence is found in benzodiazepines (BDZ) administration and is due to receptor subsentivity[6,7], then chronic exposure to BDZ “alters specific neurotrasmitter receptor pathways and can produce agonist-induced down-regulation of the receptors they affect”. Consequences are loss of drug actions, and rebound anxiety or insomnia after withdrawal.

In recent years the knowledges in receptor dynamics have greatly improved and have changed both the classical 'key-lock' receptor model and the clinical practice in some cases, until to conceive paradoxical cure in some established or proposed therapies, like prescribing beta-blockers instead of beta-agonists when the receptors are down-regulated or impaired, as happens respectively in heart failure or asthma[8], that may resemble the homeopathic paradoxical cure of 'the like cures the like'. In synthesis these studies recognizes that receptors: 1. are considered the main target of drug action in the modern pharmacology, 2. are inhibited and not only blocked by most antagonists, which are termed now *inverse agonists*[9], 4. are not passive structures, but they have a low *constitutive activity* in absence of agonist[5], 5. react in an opposite, secondary direction to the main pharmacological action [6,8,10]. This means that during conventional therapies high doses of *agonist* frequently lead to **l**oss of receptor sensitivity to drugs and that high doses of *inverse agonist*, are generally able to increase receptor sensitivity (in number of receptors)[10], as a secondary reaction of the body that sometimes has been called Secondary Pharmacology [5,11]. They are due to traslocation and internalization of receptors or to recycling of receptors to the membrane.

These changes of receptor sensitivity to drugs are the base to explain the onset of opposite withdrawal symptoms after drug discontinuation, like rebound sleeplessness after benzodiazepine withdrawal or rebound tachycardia after beta-blockers withdrawal[12], or to explain drug tolerance, as in insuline tolerance. A lot of withdrawal syndromes are due to homologous (or sometimes heterologous) receptor increases or decreases of membrane receptors density like an **inverse defence reaction** to the main drug action. These cell reactions occur in normal conditions and have the functional properties to maintain homeostatic cell activity, avoiding excessive cell activation or inhibition. Furthermore these receptor dynamics and their corresponding withdrawal syndromes are accompanied by symptoms opposite to the main action of the drug used.

The property to invert the cell sensitivity, depending by the first action of the drug (agonist/inverse agonist), resembles the homeopathic notion about the contrary or secondary action of the body to the drugs and indeed, if there is a structure in the body that perform an impressively similar behaviour to this counteraction described in Organon[13], this structure may be the receptors. I studied the pharmacological examples, made by Hahnemann in his main work to rationally found the homeopathic therapeutic method of the similia principle, coffee, opium and wine, to verify the possibility they could be based on these receptorial dynamics and I met a great consistency between the symptoms described, the rebound withdrawal effects and the recently discovered receptors adaptations. In these examples Hahnemann considers the effect of high doses, like 'strong coffee' or 'excessive wine', which for him, even in a single dose, could give opposite symptoms in a second time; this fits well with the recent receptor investigations, which show that even a single pharmacological dose may induce receptor 'set point shift', as in the case of benzodiazepine[6] and morphine[14].

Coffee contains caffeine, which is an inverse agonist of adenosine receptor and its use leads to receptors up-regulation which explains the secondary symptoms described by Hahnemann as a withdrawal/rebound effect[15-17], -*drowsiness after excessive vivacity***.** Adenosine receptor promotes sleepiness, when stimulated by its natural agonist, adenosine. Inversely caffeine antagonises adenosine receptor activity and promotes vigilance and excitation. After chronic intake of coffee/caffeine, receptor expression on the membrane is increased in nervous system and in platelets, giving rise to withdrawal syndrome after discontinuation of the intake with sleepiness and low attention, untill the next intake of coffee. It is well established, in receptors researches, that the majority of inverse agonist (called antagonist in the past) give rise frequently to homologous receptor up-regulation. In the other side *opium* and its main constituent morphine is a receptor agonist leading to receptor down-regulation which explains the secondary symptoms described by Hahnemann as another withdrawal/rebound effect[14,18], -*sleeplessness after profound stupefied sleep*. Like for inverse agonists also for most agonists the same counter-action occurs, after prolonged activation and their receptors decrease in number on the surface of the membrane as a naturally occurring phenomenon[5,9]. The

same for *alcohol*, the change in different receptors pathways in nervous and autonomic system [19,24] are the cause of the symptoms described by Hahnemann as a third withdrawal/rebound effect -**c***hilliness after having become heated*. The receptor changes after alcohol exposure are complex, but very well studied in more than one receptor class, like for example in Gprotein receptors as adrenoceptors and in ionic channels as NMDAR. Both these receptors are inhibited by ethanol exposure, which is consistent with vasodilation, but chronical exposure induce increased receptors and increased sympathetic activity, which exert an opposite action on vasculature.

If the observations of this paper are correct, Hahnemann based the homeopathic method on the biologic capacity of living cell to change its sensitivity in an opposite way to the stimuli, as a defense reaction of living beings. It appears completely rational that today these defense reactions have been shown to be dependent by receptor modulations in activity and number tending to counteract excessive activation or inhibition. In this vision the selection of individualized symptoms made by homeopatic practicians to choose the correct prescription could be correspondent to the choose of individual, single or multiple, receptor disrutpions, whose alterations in a specific subject could have produced individual disease symptoms. Giving the activating remedies to activated receptors or inhibiting remedies to inhibited receptors, in low doses to avoid aggravations, should be the best way to modulate receptor disturbance in the opposite direction to cellular alterations of the natural disease, for the innate demonstrated capacity of the living cell to counteract drug action. Otherwise the prescription of palliative drugs, activating inhibited receptors or inhibiting activated receptors, maintain the same pathological receptor adaptations, and contribute to worsen them and to chronicity of the diseases. The processes here considered are more and more complex in the whole organism than it could be thought studying these few examples, so we need more researches to study and verify these hypothesis.

If the hypothesis here presented will be proven, a new paradygm could open, rationally and biologically based, in therapeuthics, the same of Hahnemann's, to use drugs similar to diseases. The rational base is that the body normally reacts to drugs modifying its sensitivity to them[5], dampening sensitivity when a contrary treatment is used but increasing it when paradoxical similar treatment is given. This phenomenon has just been seen in heart failure, and is now proposed in asthma[8], but a lot of other examples are present, not discussed here. In every physical or psychological disease, occur important changes in regulation of normal signaling processes and in these processes the receptors have one of the main role. If these observations could be confirmed, the dilution/dynamization enygma would be correctly regarded and addressed as a simple amplification of the property of chemical compounds. Chemical and diluted compounds act in biological tissues and living cells in the same direction, in most cases, as recently some investigators have confirmed[25].

Hopefully, these modern researches could open a new frontier about the rational use of the simile and could suggest the option to use it in new ways and possibilities, that where unrecognized till now by homeopathic and mainly by conventional medicine. On the other size they may give rational support to conventional medical practicians to be careful in administration of palliative and allopathic therapy without consider the risk to worsen biological and complex cell machinery which governs health and disease states.

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