COMMENTARY

Could the Olfactory System Be a Target for Homeopathic Remedies as Nanomedicines?

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Abstract

Homeopathic remedies (HRs) contain odorant molecules such as flavonoids or terpenes and can lose their efficiency in presence of some competitive odors. Such similarities, along with extreme sensitivity of the olfactory system, widespread presence of olfactory receptors over all organic tissues (where they have metabolic roles besides perception of odors), and potential direct access to the brain through olfactory nerves (ONs) and trigeminal nerves, may suggest the olfactory system as target for HRs. Recent works highlighted that HRs exist in a dual form, that is, a still molecular form at low dilution and a nanoparticulate form at high dilution, and that remnants of source remedy persist in extremely high dilutions. From the literature, both odorants and nanoparticles (NPs) can enter the body through inhalation, digestive absorption, or through the skin, especially, NPs or viruses can directly reach the brain through axons of nerves. Assuming that HRs are recognized by olfactory receptors, their information could be transmitted to numerous tissues through receptor–ligand interaction, or to the brain by either activating the axon potential of ONs and trigeminal nerves or, in their nanoparticulate form, by translocating through axons of these nerves. Moreover, the nanoparticulate form may activate the immune system at multiple levels, induce systemic various biological responses through the pituitary axis and inflammation factors, or modulate gene expression at the cellular level. As immunity, inflammation, pituitary axis, and olfactory system are closely linked together, their permanent interaction triggered by olfactory receptors may thus ensure homeostasis.

Keywords: homeopathy, olfactory system, odorants, nanoparticles

Introduction

HOMEOPATHIC REMEDIES (HRs) contain plant, animal, mineral, and metal products with specific odors such as flavonoids and terpenes in plant extracts, for example,^{1–5} and two well-recognized homeopaths, Hahnemann and Schmidt, asked their patients to smell HRs.^{6–9} Odorant molecules (OMs) and HRs share some properties: some OMs can enhance the perception of other OMs, and some odors can inhibit HRs efficiency.^{6–8,10,11} Too, OMs can exhibit different odors depending on the level of concentration in a manner analogous to how HRs can have inverse reaction depending on the level of dilution (hormesis).^{11,12} Some studies have demonstrated effects of HRs through inhalation,^{13–18} but HRs are generally too dilute for an odor to be consciously recognized.

Two hypotheses explain the differential sensitivity of individuals toward OMs, and maybe toward HRs: different levels of olfactory receptors (ORs) gene expression and anatomical differences in the nasal cavity, both resulting from genetic polymorphism.^{19,20} Notion of competitiveness, modifications of electroencephalogram (EEG) during inhalation, and modifications of genes expression, among which those of ORs by high dilutions of Gelsemium,²¹ strongly suggest that ORs can be a target for HRs.

Infinitesimal Dose Medicine

Up to now, nobody is able to explain the way homeopathy operates and this medicine acting at infinitesimal dose became a subject of distrust and sarcasm. In contrast, nanomedicine is

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expanding rapidly in both allopathic and homeopathic⁵ fields. Recently, several groups^{1,22–30} have highlighted the presence of nanoparticles (NPs) in highly diluted HRs. Bellavite and coworkers described how HRs, at different levels of dilution, can influence immunity and inflammatory factors and even modulate gene expression,^{2,21} based on a ligand–effector type interaction, whereas Bell et al.^{1,28–30} suggested a systemic reaction to HRs as stressors.^{31,32}

Demangeat³³ suggested that the two concepts would not contradict each other but rather reflect a dual character of HRs depending on their level of dilution. At low dilution, below C2–C4, HRs in a still molecular nature would act locally on cellular or intracellular receptors, whereas at high dilution, in a nanoparticulate form, they would cross cell membranes and physiological barriers as mucous membranes, lungs, blood–brain barrier⁵ (BBB), or would directly reach the brain through a neural pathway.

The Vomeronasal Organ

First, Benabdallah³⁴ and McGuigan¹⁰ suggested that the vomeronasal organ (VNO), which is very sensitive and able to induce a stereotypical behavior, could be a target for HRs. In terrestrial animals, most pheromone receptors are located in the VNO, within the nasal cavity, whereas in insects they are located in antennae.³⁵ Bombyx pheromone can be detected at exposure levels of about 200 molecules per cm,³ equivalent to a homeopathic dilution between C8 and C9.³⁵ VNO directly interacts with the pituitary axis, bypassing the olfactory cortex and generating hormone secretion that provokes behavior changes: mating, aggression, and parental behavior.^{36,37} Moreover, VNO plays a role in immunity by detecting metabolites produced by endo- or exogenous germs.^{36,38} In humans, VNO develops during fetal stage, then regresses to a vestigial organ, considered as a nonfunctional secondary olfactory organ in adulthood.^{36–38} To date, no human pheromone has been identified with certainty. However, according to some authors,^{11,39} hypothetical human pheromones are sensed by olfactory and gustatory receptors (GRs) and by the trigeminal pathway.

The Olfactory System

The olfactory system separates the brain from the outside world and keeps us informed about our environment by detecting molecules or other particles, some of which are able to directly reach the brain through the olfactory nerves (ONs) provided they are smaller than the nerve diameters,^{40,41} as some viruses do. ONs connect the nasal cavity to the olfactory bulb (OB) passing the cribriform plate of the ethmoid bone through nerve endings covered with ORs immersed in the nasal epithelium mucus.⁴² The three functions of the olfactory system are sense of smell, immune function, and ONs regeneration.⁴³ Molecules of various structure, size, and chemical properties can have an odor.^{44,45}

OMs can directly reach the olfactory epithelium by inhalation through the nostrils, or indirectly after food chewing, by the retronasal pathway. ORs activation drives a nerve impulse that reaches first the olfactory glomerulus within OB, and then, through the ON, the cortex, and the thalamus.^{46–51} OB has one of the highest capillary density in the brain.⁵² Human sense of smell can detect extremely low concentrations of odorants,^{53,54} as low as 10^{–18} g/L,⁵⁵

equivalent to a C9 homeopathic dilution. EEG can show specific changes after inhalation of odorants.⁵⁶ If an odorant is too dilute to be recognized consciously as an odor, it can nonetheless either bind ORs that possess other functions than recognition of a smell⁴³ or be unconsciously registered by EEG responses.⁵⁷ OMs can influence the sympathetic and parasympathetic nervous systems, intellectual activity,⁵⁸ neurotransmitters and neuromodulators levels, and the neuroendocrine system.

OMs can play a role in psychological behaviors as well as in various organic functions, through the endocrine system.^{37,43,46,47,58–60}

The Trigeminal Pathway

The trigeminal nerve directly connects the brain and essentially provides somatosensory feelings within its region of innervation. Detection of irritants takes place at GRs and solitary chemosensory cells located close to the nerve endings, or directly at these nerve endings.^{61,62} Keratinocytes can also participate in trigeminal nerve activation when they release adenosine triphosphate at the vicinity of nerve endings.^{27,63,64} After intranasal administration, rhodamine-labeled microspheres (20–200 nm) can translocate into the brain through uptake by the ophthalmic and maxillary branches of the trigeminal nerve that supply sensory nerve endings throughout the nasal mucosa.⁶⁵ Less than 200 nm NPs,^{41,66,67} meningitis virus,⁶⁵ and other pathogens^{65,68} can directly reach the brain through OB and brainstem^{20,66,68–70} from trigeminal pathway.

Nasal Pathway to Cure Diseases

The main interest of the nasal pathway is to be noninvasive, and thus has been investigated in numerous studies.^{20,31,68,71–78} For instance, this way is used for desmopressine and sumatriptan that are smelled to treat central diabetes insipidus and migrainous crises, respectively.⁷⁹ In the United States, a flu vaccine is administered by the nasal pathway.^{75,76} OMs can boost the immune system^{58,60,80} using direct access to the nasal-associated lymphoid tissue (NALT) and to the systemic blood circulation, notably through communication between the nasal mucosa, the subarachnoid spaces, and the lymph nodes of the neck.^{20,71} Activation of the NALT elicits a strong systemic immune response with antigen-specific IgA that is found within digestive, respiratory, and vaginal mucosae as well as in salivary glands.⁷⁵ Nasal microbiota can impact the immune system, too.^{75,81} After nasal administration, drugs encapsulated in NPs can directly follow the olfactory or the trigeminal nerve toward OB and, from there, translocate into the central nervous system (CNS).^{65,71} NPs can use either an intracellular or an extracellular pathway, that is, the ON axon or the cells that envelop the axons of the ONs.^{20,42,64–67,69,70,82}

Particularities of ORs

ORs are G protein-coupled receptors, which are among the most represented receptors in the body^{83,84}; their plasticity and ability to change conformation make them very sensitive to various ligands (photons, ions, odorants, amino acids, fatty acids, neurotransmitters, peptides, and polypeptides) as well as to 30%–40% of medicines.^{84,85} ORs are not located exclusively in the nasal cavity but widespread

over all organic tissues (ectopic ORs).^{19,41,45,47,55,83,86–99} In humans, olfactory and hormonal systems are related to each other.^{19,45,47,50,58,60,100} Ectopic ORs have a local action not linked with CNS. At the kidney level, they control blood pressure based on the level of short-chain fatty acids produced by the gut microbiota.⁸⁸ Like ORs, GRs exist on several organic tissues (digestive, respiratory, genitourinary tracts, brain, and immunity cells) where they have other functions beside perception of taste.^{37,101–105}

Homeopathy as Nanomedicine

HRs may take two forms depending on dilution levels. Low dilutions, below C2–C4, could still contain molecules in ponderable and subponderal amounts and bind specific targets as conventional remedies do, whereas high dilutions could contain the active ingredient in nanoparticulate forms that contain silica and nanobubbles, produced by shaking the remedy during the specific dynamization procedure of manufacturing. Assuming that such nanoparticulate forms of HRs possess similar properties as conventional NPs, they would exhibit much higher bioavailability, membrane permeability, and intracellular reactivity than the molecular form.^{106,107} Such properties drastically depend on NPs size, shape, charge surface, and lipophilicity.^{108,109} It has been shown by Demangeat³³ that sizes of nanostructures in HRs depend of the level of dilution/dynamization. So, the structural duality may explain various and even paradoxical actions of HRs according to their dilution levels.

Link Between OMs and NPs, and Potential Actions of HRs

Both OMs and NPs can enter the body through inhalation, digestive absorption, or across the skin.⁴¹ They can potentially directly reach all ORs located on organic tissues except those of the brain, which can be reached only through the ONs and trigeminal nerves or by crossing the BBB.^{31,59,110–114} The diameter of individual axons of the ON does not exceed 100–200 nm, meaning that this way of translocation only concerns elements with sizes <100–200 nm. As demonstrated several years ago, polio virus and other NPs can translocate from the nose to OB^{65,114} and then be found within microglia and in deeper brain regions.⁶⁹ NPs have another toxicity profile, new target organs, and a higher influx to the brain than the bulk material.^{40,51,67,111}

Inhaled NPs can penetrate into the lung interstitial tissue where they can be stored for years. The biological half-time of solid particles in the alveolar region is about 700 days in humans.⁶⁵ From there, they can slowly diffuse toward all organs including the brain through the systemic blood circulation or the lymphatic vessels.^{110,112} NPs can induce various biological responses: inflammatory response, oxidative stress, modulation of gene expression, effects on cell cycle control, and proliferation.¹⁰⁹ NPs can be recognized by the immune system, following any route of uptake into the organism.⁶⁵ Modifications of DNA and noncoding RNA have been shown for cells repeatedly exposed to NPs. Such epigenetic modifications may be very stable and sometimes pass on from one generation to another.¹¹⁵ Microglia is sensitive to disturbances in the CNS.¹¹³ For example, the nasal instillation of NPs generates pathological changes in hippocampus, striatum, and OB, such as proliferation of microglia after uptake of 20 nm Ag-NPs.^{113,116,118}

Repeated exposure to NPs causes oxidative stress, cytotoxicity, and autophagy,¹¹⁹ suppresses inflammation, and secretes proinflammatory cytokines.^{112,120} Cytokines, as IL-1, can be directly produced by microglia and act on the pituitary axis,¹²¹ which can, in turn, activate the immune system with its hormones secretion such as cortisol.¹²¹ Leucocytes also possess adrenalin, steroids, insulin, prolactin, growth hormone, and thyroxine receptors. Lymphoid organs hold sympathetic and cholinergic nerve endings and leucocytes possess catecholamine, endorphin, enkephalin, substance P, somatostatin, and vasoactive intestinal peptide receptors.¹²² The brain, organs, and cells continuously interact and communicate with each other to adapt to all kinds of stress.^{19,88,121,123–125}

When a stress stimulates the vegetative nervous system, the neuroendocrine system is activated and, if the stress persists, diseases may occur in various distant organs. Cognitive and emotional centers are also linked to the digestive tract through the gut microbiota.^{80,126,127}

Conclusion

The olfactory system is the main gateway to reach the brain and the immune system, and ORs are widespread on all organic tissues; thus, the olfactory system could constitute a suitable explanation for central, local, and immune action of HRs. Moreover, clinical effects are observed for HRs administered through inhalation, and HRs exhibit similar properties as OMs. The complex reality of homeopathy may be explained by the specific manufacturing process of dilution/dynamization, which generates different structural properties of the remedy according to the level of dilution, especially nanoparticulate forms at high dilution. The present speculations only constitute a clue that raises many questions and prompts to further investigations, such as (1) tracking homeopathic NPs through the nerves and into the brain by animal studies, (2) studying EEG responses to various dilutions of a definite HR, (3) identifying immune responses from the NALT, or (4) directly studying the action of HRs on ORs from different tissues by *in vitro* studies.

Author Disclosure Statement

No competing financial interests exist.

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