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DEBATE

Hypothesis: do homeopathic medicines exert their action in humans and animals via the vomeronasal system?

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There is significant debate on the nature of the active therapeutic ingredient in homeopathic medicines and whether the effect of homeopathic medicines is exerted locally. This paper accepts that there is an active therapeutic ingredient in homeopathic medicines that acts pharmacologically in the body and proposes a possible receptor site.

The vomeronasal organ (Jacobson's organ) is the receptor site for the detection of non-odorant molecules, eg pheromones, in reptiles, amphibians and mammals. The organ forms the main part of a chemoreceptor system known as the vomeronasal system. This paper proposes that it is this system that constitutes the receptor for homeopathic medicines in both animal and human subjects. *Homeopathy* (2007) **96,** 113–119.

Keywords: vomeronasal system; Jacobson's organ; solitons; homeopathic receptor site; inactivation by strong odours; homeopathic provings; placebo-controlled trials

Introduction

There has been much debate on the nature of the active therapeutic ingredient in homeopathic medicines and whether the homeopathic effect is exerted locally (ie pharmacologically or quasi-pharmacologically)[1] or non-locally (eg via quantum entanglement).[2]

This paper accepts the premise that there is an 'active therapeutic ingredient' in homeopathic medicines that acts pharmacologically in the body and proposes a possible receptor site for homeopathic medicines. The vomeronasal organ (VNO), also known as Jacobson's organ, is the receptor site in reptiles, amphibians and mammals that can detect non-odorant molecules (NOMs) in extreme dilution. This paper proposes that this organ and the vomeronasal system (VNS) is also the receptor system for homeopathic medicines.

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When I worked in the Anatomy Department of Glasgow University I became interested in a structure within the nose called Jacobson's organ.[3] This structure was thought to be part of an alternative olfactory system specifically for the sensing of pheromones. These NOMs are important in animals for reproductive, maternal and social behaviour. We debated whether the VNO in humans was merely a vestigial organ. Later, during homeopathic training, I speculated that if animals could detect very low concentrations of NOMs this could also be the way that the extreme dilutions of homeopathic medicines (remedies) are detected by the body.

Samuel Hahnemann (1755–1843), investigated many substances as possible homeopathic medicines and found that dilution reduced their toxic effects. He also noted that a succussed dilution was more powerful than the dilution without succussion. It has been proposed that solitons produced during succussion may carry on the unique signature of the original substance in the form of phonons within the diluent even beyond the point where no molecule of the active remedy substance is present.[1]

Hahnemann stated that remedies could be administered by ingestion, olfaction, inhalation and dermal

routes.[4] However, in the fifth edition of *The Organon* (1849) he states, 'Homeopathic remedies operate with the most certainty and energy by smelling or inhaling the medicinal aura constantly emanating from a saccharine globule that has been impregnated with the higher dilution of the medicine'.[5]

Many homeopathic provings have been carried out since Hahnemann's death although they vary greatly in methodology and quality.[6] Sherr (1994) has stated, "It has been my repeated experience with provings that symptoms highly consistent with the proving symptomatology have occurred in people who were not participating in the proving directly but who were in close proximity to the provers".[7] This phenomenon is sometimes called the 'herd effect'. It is also recognised that exposure to strong-smelling chemicals can inactivate a homeopathic medicine in storage.[8]

Strong smells can also have an effect on a patient's response to a homeopathic medicine. Hahnemann advised that in chronic diseases 'medicinal aromatics, all kinds of punch, spiced chocolate, sweet waters and perfumery of all kinds, odorous flowers in the room, preparations for the teeth either in powder or liquid wherein medicinal substances are included, perfumed bags, strongly seasoned viands and sauces' should be avoided by the patient.[9]

I have had patients who were progressing well on a homeopathic remedy until exposed to a strong novel smell or a pungent smell, eg paint or ammonia, whereupon their symptoms came back within hours. One patient said that it was like 'turning off a switch'. Repeating the dose and avoiding the odour re-establishes the homeopathic response.

I formed the hypothesis that homeopathic medicines exerted their effects on the body primarily by olfaction via Jacobson's organ and the VNS.

The main olfactory system

Over the past 15 years there has been an explosion in research into the processing of the main olfactory system (MOS).[10] Odorant molecules (OMs) are volatile, hydrophobic and of molecular mass < 300 Daltons (larger molecules are non-odorant). The olfactory receptor cells (ORCs) are ciliated, bathed in mucus and line the walls of the olfactory epithelium. OMs are sensed by receptor binding proteins (RBPs) produced by the olfactory cells. Each cell can only produce a few types of RBPs that bind related OMs.

The receptor cell axons then synapse with the mitral cell in the olfactory bulb. The axons from these second-order neurones travel in the olfactory tract to terminate in the olfactory cortex and other parts of the brain where smell is sensed and memorised. In 2004 Richard Axel and Linda Buck jointly received the Nobel Prize in Physiology and Medicine for their discovery of main types of odorant receptors[11,12] and the organisation of the olfactory system.

The sense of taste is also closely associated with smell. We can only detect the true flavour of food by combining our basic taste senses of sweet, salt, bitter and sour with the smell of the volatile compounds in food that are sensed in the olfactory mucosa.

The Vomeronasal system

The vomeronasal system (VNS) is responsive to much larger non-volatile (non-odorant) molecules. It is also sensitive to some less volatile or less water-soluble OM.[13] Research has indicated that the VNS responds not only to pheromones but to a wide range of chemosignals.[14-16] The term vomeropherins has been suggested for any chemicals that stimulate the VNS of any species.[17]

In the 19th century the VNO was identified in many animals by Jacobson.[3] Later in the century it was found in human adults by Potiquet.[18] In animals it is two blind-ended tubules or pits in the nose surrounded by large vascular structures. These vessels can constrict, widening the tubule and creating a suction effect in the chamber, drawing air into the duct. This constriction seems to occur in response to *novel* stimuli.[19] Non-volatile pheromones can be detected by the mammalian VNO at detection thresholds as low as 10^{-11} M placing these neurons among the most sensitive chemodetectors in mammals.[20]

Recently researchers have found a new vomeronosal receptor site in the anterior part of the nasal epithelium in rodents. Known as the septal organ or ganglion of Grueneberg, the neurones appear to be fibres of the nervus terminalis (cranial nerve zero). The axons of these cells run with main olfactory neuronal axons to synapse in specific glomeruli of the anterior part of the olfactory bulb.[21] It is thought to have a pheromone sensing function; other axons of the nervus terminalis containing gonadotrophin releasing hormone and acetyl choline may modulate the sensitivity of the olfactory and vomeronosal systems at reproductively important times for the organism.[22] Nervus terminalis fibres also run under the epithelium of the VNO. There may be other vomeronasal receptor sites yet to be discovered in the body.

The evidence for a functioning VNS in humans

In Old World (OW) primates and man, the morphology and functionality of the VNO appears to be in decline.[23] This coincided with the evolutionary acquisition of full trichromatic colour vision.[24] Chimpanzees and humans have VNOs different in site and morphology from those of other primates. The epithelium has a homogeneous pseudostratified columnar morphology with mucus producing structures interspersed through the epithelium.[25]

The VNO and accessory olfactory bulbs are present in the human embryo.[26] However, during intra uterine development, the structure of the VNO becomes

simplified, although it is present in the fetus up to 30 weeks.[27] In over 90% of adult humans a recognisable VNO has been found.[28] It appears as a pit in the septal wall of the nostril 2–3 cm from the nares. These pits lead into blind ended tubules of variable length and complexity[29] lined with pseudo stratified epithelium with some submucosal glands. There do not appear to be vascular chambers running alongside the tubules as found in other species. There are no recognisable vomeronasal sensory neurons (VSNs) in humans but there are unusual cells in the human VNO epithelium called microvillar cells with surface microvilli and a basal area that narrows into an axon-like projection that only reaches the basement membrane.[30] They may be neurosensory cells. These 'microvillar' cells do not appear to have connections to neurons running out of the VNO to synapse on central cortical structures,[31] nor direct links with the bundles of non-myelinated axons found in the submucosa of the human VNO.[32] However, in the MOS unmyelinated presynaptic axons from receptor cells expressing the same receptor gene run parallel to each other in fascicles to form the olfactory nerve. They are thought to be able to synchronise their action potentials within the same fascicle as a method of signal amplification although there are no synapses between them. They communicate by ephaptic coupling (current flow through the extracellular space),[33] potassium ion extrusion[34] or gaseous messengers.[35] A similar method of communication could exist between human VNO microvillar cells and the unmyelinated axons running in the lamina propria of the human VNO.

There is also evidence that humans do react to pheromones.[36,37] Monti-Bloch *et al*[38,39] found evidence of electrical depolarisation within the human VNO mucosa (electrovomeronasogram or EVG) to puffs of gas containing putative pheromones. Much smaller depolarisations occurred with diluent alone or with olfactory test stimuli eg clove oil. These depolarisations occurred in readings taken around the VNO pit and diminished as the distance from the pit increased. This appears to be the best evidence for a selective chemosensory process in the VNO region.[40] Sobel *et al*[41] using olfactometry and fMRI scanning also found consistent activation of the thalamus, the inferior frontal gyrus, the amygdala and the cingulate gyrus during stimulation with non-odorant putative human pheromones that had been shown to stimulate the human VNO. Although they could not be certain that other olfactory pathways were not stimulated it does show that humans have brain activation in response to unconscious sensing of NOMs. The areas of brain activation were similar to those associated with the VNS in mammals.[42] In the late nineties two main groups of mammalian genes were found that code for VNO chemoreceptor molecules.[43] Similar genes have been found in the human genome.

What factors could have caused the changes in the VNS in man?

In mammals pheromones are usually sensed by close contact of the nose to a scent trail so do not need to be volatile. However, the VNO in OW primates and man has a position high up in the nose, useful for the sensing of airborne volatile compounds in the inspired air. This change of position may be related to the evolution of these species to become bipedal. Full trichromatic vision appeared in OW primates 23 million years ago, after they diverged from New World (NW) primates but before their separation from hominoids. OW primates lived in small social groups in the forest and regularly came in contact with other groups. Because of this and with the development of trichromatic vision (due to a duplication of the x-linked red/green opsin gene) there was less need for pheromone signals and the VNO went into decline. However after divergence of the hominoids from OW primates the huge forests in Africa receded and both primates and hominoids left the trees for the savannah, becoming bipedal to see over the tall grass. Groups became isolated and scattered over wide areas. It became harder for small family groups to meet for reproduction. It is possible that family groups who still had some VNO function had an advantage as they could find genetically different groups some distance away. Family groups without a functioning organ relied on chance to find genetically different mates and inbreeding eventually led to these groups dying off. So at a time when the VNO of primates was declining, habitat changes gave a stimulus to develop its function again.

It was hypothesised that a functioning VNO could not be found in the presence of full trichromatic vision. NW primates diverged from OW primates 35 million years ago and did not develop full trichromatic vision. However recent research has discovered that NW howler monkeys also developed full trichromatic vision through an independent duplication of the same red/green opsin gene and they have a fully-functioning VNO.[44] In OW primates and man a new system developed from an old VNO apparatus that was in decline (with parts vestigial or absent) and so is morphologically different from the old VNO but is still a functioning organ. It is possible that the newly evolved parts use a different transduction system from that in the old VNO.

Some features of homeopathy that may be explained if the VNS is the receptor site for homeopathic medicines

Remedies seem to cause a response in the patient at extremely high dilutions

The MOS and VNS are classic systems to pick up highly diluted smell 'signals' of any type. Research

over the last 15 years has shown just how sensitive olfactory systems can be. Moths are sensitive to pheromones at a dilution of 6×10^{-9} g[45] other insects can sense pheromones at dilutions as low as 10^{-16} M.[46]

During homeopathic provings symptoms have been observed in people who have not taken the homeopathic medicine but who were in close proximity to the provers

The hypothesis could give a possible explanation for this phenomenon. The VNS can sense vomeropherins in the air and is the most likely sensor for homeopathic medicines that have no odour and are in extreme dilution. There is no conscious awareness that a NOM is being smelled. It is possible that the phenomenon of 'herd effect' in those people who are in close proximity to provers is due to them sensing the homeopathic remedy in dilution in expelled air from the nose and respiratory tract of the prover at the time of administration or in the air of the room in which the remedies are being administered. The sensitivity of the VNS varies between individuals and some people are more likely to experience this effect than others.

In an asthma trial at Glasgow Homeopathic Hospital some patients in the placebo group 'produced aggravations and ameliorations from placebo along with the homeopathic phenomena of direction of cure and the return of old symptoms'.[47,48] This has been noted in other provings and in clinical trials. Inadvertent airborne contamination of placebo groups by active remedy should be considered a possible explanation for these effects.

Some people seem to be more sensitive to homeopathic medicines than others

The VNO is present in >90% of humans, but its morphology varies markedly between subjects and the appearance of the VNO pits can change in the same subject on repeated observations. This may indicate differing sensitivity across populations and in the same individual at different times.

There is evidence of different sensitivities to a putative human pheromone 4, 16-androstadien-3-one between men and women and a bimodal distribution of sensitivity across the general population. A small subgroup was found to have high sensitivity.[49]

There has also been research to show that anosmic subjects can detect pheromones.[50] Hahnemann also noted that homeopathic medicines acted in patients who were anosmic; "even those organs that have lost their peculiar sense eg a tongue and palate that have lost the faculty of tasting, or a nose that has lost the faculty of smelling, communicate the power of the medicine that acts first on them alone not less perfectly to all the other organs of the body".[51]

The homeopathic response in a patient can be inactivated by strong smells

If the VNS is the receptor site for homeopathic remedies this could explain the phenomenon of inactivation by strong smells. Research in animals has indicated that OMs can either activate or inhibit specific odorant receptor cells and that excitatory or inhibitory currents were not strictly associated with a particular odorant mixture.[52] The VNS uses similar RBP and there is some crossover of function between the MOS and the VNS.[53] Some VNS axons run alongside main olfactory axons in the olfactory nerve[21] and so it is possible that strong odorant chemicals may interfere with homeopathic responses.

Another olfactory system, the Trigeminal system, seems to be the receptor for very pungent, intense (and toxic) odours and seems to be linked to pain sensation. The body's response to such odours is an instinctive backing away from the smell and its source. It is a survival response and probably takes precedence over other olfactory systems. Recent research in humans has indicated that, in the MOS, the neural representation of odour is modulated by trigeminal stimulus during odour encoding.[54]

I believe that high concentrations of *novel* OMs can also directly interfere with the action of a homeopathic remedy. In my experience patients seem to be unaffected by strong smells that are part of their everyday environment but may be affected by intense novel odours. The VNS is geared to respond to novel olfactory signals in the environment (another primitive survival strategy) and this would explain why homeopaths sometimes have difficulty deciding if a substance eg coffee interferes with homeopathic medicines. If a person drinks coffee regularly or coffee smells are part of the normal environment it is unlikely to interfere with a medicine. However even in the latter circumstance drinking excessive amounts of coffee may reach a level where the VNS treats it as 'toxic' and so, like a trigeminal stimulus, it would take precedence.

Homeopathic remedies can be rendered inactive by odorant chemicals in high concentration

If a specific chemical 'signature' is the 'active therapeutic agent' of homeopathic medicines acting through olfaction, then contamination of stored remedies by highly odorant chemicals could interfere with the chemical signal.

Return of old symptoms

When a homeopathic medicine is having a curative effect on the body old symptoms may recur.[55] There may be a series of old symptoms going progressively back in time. What does this phenomenon have to do with olfaction?

Memory and smell are closely linked. The most primitive creatures need to remember smells for survival and procreation. It was this need for memory

that probably stimulated the formation of the earliest part of the brain, the rhinencephalon. The brain seems to 'remember' the virtual map of neuronal activation in the olfactory bulb. Various parts of the brain feed into the olfactory cortex where smells are consciously remembered. It appears that various areas of the brain are intimately involved in both the memory of smells and cognitive memory. Alzheimer's disease, Lewy body disease, Parkinson's disease and alcohol abuse have all been shown to cause a reduction in olfactory sensitivity and the smell memory.[56] If smell was the first memory system evolved in the brain then higher complex memory is probably closely linked to the memory of smell. Everyone has experienced a smell that suddenly triggers very intense and emotional memories of a past experience. The VNS is not connected to the cortex in mammals and so is an unconscious sense. However, it too must have some link to a subcortical memory system for future recognition of vomeropherin signatures.

The phenomenon of 'return of old symptoms' as seen in the homeopathic response seems to be a memory of the body's physical response (symptoms) to an earlier illness or trauma. The appearance of this phenomenon usually indicates a good response. If the VNS is the receptor for homeopathic remedies then is it possible that just as a smell can trigger memories of past events, stimulation of the VNS can produce 'symptom memories' of past pathophysiological states?

Why should homeopathic remedies activate the VNS?

In mammals the VNS is particularly activated by 'novel' smells eg a stranger in your territory who could be a threat.[20] A homeopathic medicine is 'novel' in that it is a man-made, succussed, substance and because of its extreme dilution, non-odorant.

Experimental testing of the hypothesis

The VNO is reasonably accessible for research purposes:

1. *Electrovomeronasogram research*: The experiment of Monti-Bloch and Grosser,[57] where electrical depolarisations within the human VNO pit (electrovomeronasogram or EVG) in response to a putative human pheromone or a standard olfactory test stimulant could be repeated. In a new experiment a homeopathic medicine could be compared to a standard olfactory test stimulus to see if the VNO is sensitive to homeopathic remedies. If positive the experiment could be repeated using active homeopathic medicine against control and homeopathic placebo against control.

2. *Endoscopic assessment and CT scanning*: (a) Subjects who have had a good effect from a homeopathic medicine in the past or who have been noted to be particularly sensitive to homeopathic medicine could be assessed by nasal endoscopy and CT scans to see if there is a relationship between the size and morphology of the VNO and its sensitivity.

3. *Functional magnetic resonance imaging (fMRI) scanning*: (a) fMRI scanning could be used to see what parts of the brain become active in response to a homeopathic medicine. Are the brain regions that responds to homeopathic medicines the same areas that are involved with the processing of other vomeronasal stimuli eg pheromones?

(b) Are there differences between scans when an active homeopathic medicine is administered in contrast to placebo?

(c) Do different homeopathic medicines activate different brain areas?

(d) If an fMRI scan shows areas of the brain that are activated in response to a homeopathic medicine what happens when a strong or pungent smell is administered?

Discussion

We still do not know the full extent of the structure and function of the VNS in animals and man. NOMs and pheromones in particular are sensed by both the VNO and certain areas within the main olfactory epithelium. These inputs and their central connections form the VNS. There may be other receptor sites that also connect to the system. The VNS appears to be a candidate as a receptor for homeopathic remedies as the remedies are in high dilution and so non-odorant.

There is now a wealth of evidence that humans have a functioning VNS although the VNO in OW primates and man is different from that of other mammals. The newly developed morphology of the VNO in these species may have led to a new system of signal transduction within the VNO.

Homeopathic medicines appear to trigger a healing response in the patient. The length of this response depends on various factors, which may include having a functioning VNS.

The hypothesis that the VNS is the receptor site for homeopathic remedies may explain some clinical phenomena seen in the homeopathic response including the 'switch off' of the homeopathic response in the presence of novel or noxious odorant stimuli and the observation that some placebo subjects can experience the same symptoms as those of the verum group in homeopathic trials and provings.

In my experience strong odorant stimuli do not invariably 'switch off' the homeopathic response. Only odours that are dangerous, novel or unusual in the patient's environment, if strong or prolonged, seem to cause this phenomenon. The homeopathic response can be re-established by repeating the remedy once the odour has been eliminated or avoided or after the patient has become acclimatised to the new odour in his environment. The VNS theory of homeopathy has ramifications for the design of future trials of

homeopathic medicines. Active and control subjects should be kept separate and have no close contact when the medicines are being administered. Provings where the subjects receive their remedies by post and never meet together during the proving period may eliminate most contamination.

There are many possibilities for future research to prove or disprove my hypothesis. If proven it would change the profile of homeopathic medicine and have wider ramifications.

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