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Abstract:

Though essential oils don't draw big research dollars (because those who fund medical research would not benefit monetarily from such an investment) the studies being funded for the sake of unlocking the secrets of psychoneuroimmunology (PNI) relative to drug effectiveness hold serious implications for the use of aromatherapy. Questions such as: "How do the essential oils get to the body system impacted, regardless of the method of application?" and, more specifically, "How can inhaled molecules of clary sage affect estrogen levels?" stand to be answered by the data supporting PNI's inforealm. This recently discovered web of communication connecting the endocrine system, the central nervous system, and the immune system displays insight into just how essential oil molecules can be transported throughout the body and have specific, repeatable therapeutic actions. This paper is concerned primarily with PNI research and the corresponding implications for aromatherapy in regard to the impact of stress management in the prevention of disease, as well as the impact of cognition in the management of pain.

Introduction and Background:

Years of journal-published research indicate that neurological activity impacts immune responses (Butts & Sternberg, 2008) (Schneiderman, Ironson, & Siegel, 2005) and that the immune system sends signals to the brain, altering behavior, thoughts, and mood. (Wieseler-Frank, Maier, & Watkins, 2005) These constructs have been foundational in establishing the field of PNI, but change is never easy and paradigms are difficult to shift. Not only does PNI challenge some of the previously held beliefs regarding how body systems function and communicate, but researching PNI has also been hindered by the traditional separation of medical disciplines. The territorial approach to research had been based upon the declarations of 17th century philosopher Rene Descartes that the mind and body are distinct and unrelated entities. Collaboration between the fields of endocrinology, immunology, and neurology has been and continues to be vital to unlocking the scientific secrets of how signals are sent and received between the mind and body. Twentieth and twenty-first century medical advances have continued to shift more toward a holistic view, including recognition of mental health being central to overall health and well-being, and have consequently supported an explosion of research focused on PNI.

Psychoneuroimmunology was born when the body's information biochemicals, discovered over time by multiple researchers in various labs around the world, were studied in new and different ways. The biochemicals discussed in this context include the following:

- Ligand; any of a variety of small molecules that specifically bind to a cellular receptor and in so doing convey an informational message to the cell (Pert, 1997)
- Peptide; a type of ligand and also a molecule consisting of a short chain of amino acids, smaller than a protein. More specifically, it is any of a class of compounds of low molecular weight that yield two or more amino acids on hydrolysis. (Dorland's Pocket Medical Dictionary, 28th Edition, 2009)
- Receptor; a molecule anchored in the outer cell membrane with a site accessible to the outside environment that binds with ligands, releasing the encoded information within it. (Pert, 1997)

During the 1980s and 1990s researchers began to look for and find both ligands and receptors that had previously been considered isolated to one body system actually originating from and existing in

entirely different body systems. Examples include the ground-breaking work of Candace Pert, whose 1972 finding of the opiate receptor in both brain and intestinal tissue indicated the central nervous system's link with the immune system. (Pert, 1997) Her discovery initiated many later studies that would show bi-directional communication and control channels between the immune system, the endocrine system, and the central nervous system. Only when the boundaries of medical specialty were crossed and the results considered with a more holistic view was it apparent that an entire communication and response system linking major functional systems of the body had been revealed. Individual ligands and their corresponding cell-membrane receptors were identified within the body as information chemicals stemming from various body systems and moving freely between them. Communication previously believed to occur only with the movement of neurotransmitters across the synaptic cleft was now understood to be also occurring throughout the body, with signal specificity being due to the lock and key binding of ligands to receptors.

Chemotaxis is the process by which cells recognize and move toward a specific chemical stimulus, seeking the specific ligand necessary to bind with a receptor on the cell's surface and traveling to the body location where those ligands are concentrated. It is how specific cells are called to a location in the body where they are needed, when they are needed. Once in close proximity, the ligand (often times a peptide) binds to its respective receptor and chemical information is conveyed that initiates a physiological response. One such example of this response is the analgesic effect of endorphins, an endogenous opioid peptide that is the body's own version of morphine.

About 95% of ligands are in the category known as peptides, which play a large part in regulating practically all life processes. Peptides form the constituent parts of proteins. Peptides have been found in the gastrointestinal system, the immune system, and the neurological system. Peptides found in brain tissue are often referred to as neuropeptides. At one time neuropeptides and their receptors were originally thought to be directed exclusively from centers in the brain (the frontal cortex, hypothalamus, and amygdala). It is now recognized that they actually stem from many different locations in various body systems simultaneously, thereby making the term "neuro"peptide inaccurate. The immune system, the nervous system, the endocrine system and the gastrointestinal system all send and receive chemical information that causes or changes physiological responses (Pert, 1997). This understanding is foundational in the field of PNI, as it breaks the old paradigm of a complete separation of mind and body. No longer can the brain be considered the sole source of intelligence, with one-way communication to the various body systems. Instead, we understand that the brain is one of many nodal points on a vast two-way information system of biochemicals flowing throughout the body. The limbic system of the brain has long been recognized as the emotional center of the brain. It is also here that the densest concentration of peptides and receptors are found, suggesting that a convergence of information occurs here and also leading to the conclusion that these molecules represent the biochemical substrate of emotion. (Pert, 1997)

Body:

Perhaps the most obvious application of PNI constructs is to that of stress and its impact on disease. Dr. Hans Selye defined stress as anything that seriously threatens homeostasis (Selye H. , 1956). During the 1940's Dr. Selye, a neuroendocrinologist, began to publish research revealing a causative link between the adaptation to stressors and certain immune responses. He was the first to introduce the concept of stress in medical terms in 1950. In his pioneering work regarding stress, adaptation, and disease Selye observed that severe, prolonged stress responses might lead to tissue damage and disease; particularly rheumatic and hypertensive diseases (Selye H. , 1949). Selye proposed that

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stressful stimuli induce two types of responses: 1) a general stress response, which is common to all stressors and involves the release of ACTH (adrenocorticotropic hormone) and adrenal corticosterone (similar to cortisol, but not inflammatory), and 2) individual stress responses mediated by "conditioning factors," such as genetically determined predispositions. (Selye H. , 1976) The first decades of PNI research focused on the influence of thoughts and emotions on immunity. The concept of the general stress response, as defined by Selye, was central to these early studies of the apparent link between the central nervous system and the immune system. A decade of research from the mid-1980s through the 1990s began to redefine accepted concepts regarding the endocrine-immune interface. Classic endocrine hormones, which were by definition to have a 'gland of origin' and be secreted into the circulation to their site of action, were found to be secreted by other tissues, including immune cells. (Malarkey & Mills, 2007) Several key studies solidified four key points in support of the endocrine-immune interface, that would prove to be foundational in PNI research. First, cells of the immune system can synthesize biologically active neuroendocrine peptide hormones. Second, immune cells also possess receptors for many of these peptides. Third, these same neuroendocrine hormones can influence immune function; and fourth, lymphokines can influence neuroendocrine tissues. (Weigent & Blalock, 1987) The summation of these constructs, that generalized stress causes the secretion of endocrine peptides to be bound with corresponding receptors in the immune system, may lead one to speculate about essential oil ligands existing that may bind with these receptors and, as a result, influence immune function.

A search for information regarding the effects of aromatherapy on stress yields a wealth of information regarding studies with rodent subjects and some with human subjects. Various essential oils and their individual constituents have been studied for their impact on the general stress response. Both lavender and rosemary essential oils were shown to reduce cortisol levels in a study of 22 healthy humans. (Atsumi & Tonosaki, 2007) Another study of 32 healthy adult subjects considered the effects of transdermally absorbed linalool, an active constituent of several essential oils including lavender and bergamot. The monoterpene linalool was found to decrease systolic blood pressure. (Heuberge, Redhammer, & Buchbauer, 2004) This particular study was careful to prevent inhalation of the linalool from occurring, so as to isolate the effects due to absorption and differentiate it from several other studies involving the inhalation of essential oils with linalool and the corresponding anxiolytic effects. Similar studies of *Citrus bergamia* essential oil and rodent subjects have further illustrated stress-reducing effects. (Carvalho-Freitas & Costa, 2002) (Pultrini Ade, Galindo, & Costa, 2006) A study of adolescent humans found that essential oil inhalation produced a drop in measured values for stress, anxiety, blood pressure, pulse rate, and cortisol. (Seo, 2009) Studies supporting the effects of aromatherapy on human immune function are not plentiful. One study evaluated *Citrus limonum* and *Lavendula angustifolia* for such effects. It found that lemon essential oil inhalation enhanced positive mood and boosts norepinephrine release, but other immunological data gathered did not indicate effectiveness of either essential oil.

The field of PNI holds interesting implications for the management of pain. The traditional characterization of pain focused on activation of receptors in the peripheral nervous system by disease or injury. These receptors would then transmit the pain signal to the brain. This neurotransmitter-synaptic gap model of pain experience assumes a tight correspondence between pain and pathology. Chronic pain syndromes such as fibromyalgia and osteoarthritis do not support such a relationship. More current understanding accepts that there is only a modest relationship between an identifiable physical pathology and the pain symptoms that a patient experiences. The receptor-ligand model of pain experience sheds new light on understanding and managing chronic pain. It is now more clearly understood that the pain experience as a dynamic interaction of biological, psychological, and social

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forces. (Gatchel RJ, 2007) Catastrophizing is an irrational cognitive and emotional mental state that involves feelings of helplessness when in pain, rumination about pain symptoms, and magnification of pain-related complaints. It contributes to a more intense pain experience and emotional distress. (Campbell & Edwards, 2009) In a study of 48 healthy humans the relationship between pain modulation, pain perception, and catastrophizing was analyzed. This research supports the hypothesis that catastrophizing interferes with effective functioning of our own natural pain-inhibitory systems. (Weissman-Fogel, Sprecher, & Pud, 2008) Similarly, a reduction in catastrophizing is responsible for some analgesic effect of physical treatments, such as exercise. A randomized controlled trial of 211 human subjects with chronic lower back pain illustrated this fact. Exercise, cognitive-behavioral treatment, or a combination of the two was associated with a reduction in pain catastrophizing and a resultant reduction in disability and pain intensity. (Smeets, Vlaeyen, Kester, & Knottnerus, 2006) Given that one's cognitive state impacts the pain experience, it may be derived that an essential oil with positive influence on cognition would decrease pain. Several essential oils have been found to have calming effects that may mitigate the pain experience. Ylang ylang essential oil was used in a study of 144 human subjects and found to significantly increase calmness. (Moss M, 2008) Another study with 24 participants involved the administration of *Salvia lavandulaefolia* essential oil and noted a consistent improvement in mood. (Tildesley, Kennedy, Perry, Ballard, Wesnes, & Scholey, 2005) A randomized crossover study of 26 adults evaluated the effects on pain discrimination by the inhalation lavender and rosemary essential oils. The participants reported less pain intensity and decreased pain unpleasantness after an inhalation treatment of *Lavendula angustifolia* and a trend toward less pain intensity after an inhalation treatment of *Rosmarinus officinalis*. The researchers concluded that although their study did not prove a physiological analgesic response with any statistical significance, there was a clinically relevant shift in the pain experience. They also noted that a more prolonged and/or intense aromatherapy treatment may result in an altered physiological pain response. (Gedney, Glover, & Fillingim, 2004)

Conclusions:

The efficacy of therapeutic essential oils has long been supported with anecdotal evidence, time-honored wise experience, and only a handful of statistically valid scientific studies. A potential tangential result of PNI research may be to explain in scientific terms the mechanism by which aromatherapy works in the human body and thereby gain respect within the Western medical community. At the heart of PNI is the binding mechanism of ligand molecules to receptor molecules at the cellular level, causing physiological action. When those ligands are molecules of an essential oil, the resulting physiological action is a therapeutic effect of that particular oil. One may conclude that PNI research serves to support the validity of aromatherapy as an effective complementary treatment mode, because it serves to offer scientific explanations for the function of aroma molecules within the human body. Scientific data regarding the physiological aspects of the pain experience and the ability of essential oils to influence that physiology on the molecular level is certainly adequate to allow one to extrapolate that this is an effective application for aromatherapy. Similar data exists in support of the mechanism by which molecules of essential oil may impact immune function through influencing the general stress response. With interest in the field of PNI continuing to grow and the implications for holistic human health showing great promise, complementary and natural alternative treatment modes such as aromatherapy will benefit from additional scientific support.

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