

Ecopharmacology: Molecular Details

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*In the last issue of **UnifiedEnergetics™** the broad strokes of the Ecological Pharmacology construct were presented. This issue we explore some of the molecular details that provide support for the ecopharmacology construct.*

The cellular membrane: signal transduction

Cellular morphology is the result of non-linear and dynamic molecular flux, especially related to the cell membrane. Although the membrane has been described as a system driven by thermodynamic equilibrium,¹ it is more accurately seen as an emergent structure consisting of highly asymmetrical structures and phase transitions.²

Typically, mammalian cellular plasma membranes consist of about eight major classes of lipids³ that include embedded proteins in its bilipid structure. Due to signal transduction and the complex behavior of chemical reactions being coupled to the dynamics of membranes, the membrane has been closely scrutinized in hopes of furthering the understanding of cellular communication and the cells' ability to receive, process and respond to information. Unfortunately, there has been (and still is) an epistemological divide between the analysis of the complex behavior involved in biochemical events and the structural aspects of the membrane involved in signaling phenomena, especially in relation to signal transduction involving exogenous molecules.²

Until very recently, signal transduction was based on a linear model based on successive steps in the decoding process and focused on high affinity and high selectivity compounds. However, the membrane, key in its interactions with the ensemble of phytochemicals that early humans were consistently

and constantly exposed to, may also respond to compounds that do not exhibit high affinity and high selectivity to a particular protein/receptor species.

Significantly, systems properties of heterogenous molecular ensembles could induce minute difference in the strength of attractive forces among molecules and increased degrees of freedom within a pharmacological system.⁴ Just as phase separations and self-assembly processes are systems properties of molecular ensembles,⁴ a phytochemical matrix interacting with another biological system requires a pharmacological systems approach.⁵ The author proposes three modes of activity based on recently elucidated behaviors of the cell membrane; two that involve the bilipid membrane and one that is based in a systems view. All three modes of activity provide molecular detail relating to the heterogeneous mixtures of phytochemicals, such as found within herbal remedies, that influence signal transduction. This stretches the current pharmacological paradigm beyond its tenets of affinity, selectivity and potency.

1. Cooperative binding by receptors: Receptor Mosaics

The discovery of direct receptor-receptor interactions rigorously challenges the historical belief that the receptor is the minimal unit for drug recognition/activity and therefore that high affinity, high specificity compounds are superior ligands.⁶ The



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existence of various types of receptor mosaics - clusters of receptors functioning as a unit that demonstrates cooperative binding suggests a plasticity of the steric conformation of receptors.⁷ In this model, each receptor is seen as a subunit of a multimeric protein.

Recall the cooperative binding of oxygen to hemoglobin. After one oxygen molecule binds to hemoglobin, the second and third (but not the fourth) molecular pockets for oxygen undergo a shift in conformation, thereby increasing their affinity for oxygen. Thus, the likelihood of subsequent binding of oxygen molecules is increased. This cooperativity is considered a mode of self-regulation by multimeric proteins⁸ and is hypothesized to also apply to particular receptor systems.⁷ In receptor mosaics the conformational change caused by the binding of the first ligand is transmitted to adjacent receptors with reciprocal contact to change the affinity for subsequent ligand binding. The change in affinity is due to the conformational change induced by the first bound ligand, which induces sequential changes of the multimeric protein's neighboring subunits. This change in protein conformation may make subsequent binding easier (positive cooperativity) or more difficult (negative cooperativity).

Since a phytochemical matrix consists of hundreds of compounds that may vary slightly in their chemical groups, but are still based on a common backbone⁹, there may be both high affinity ligands and low affinity ligands for a given species of receptor. Once the high affinity ligand binds to a species of receptor, other receptors of the same species, due to intramolecular transfer of the conformational change to the peptides of the receptors, may be able to bind the lower affinity ligands. Thus, lower

affinity compounds could potentially play a role in cellular messaging. Accordingly, the search for only high affinity compounds within an herbal remedy may miss lower affinity compounds that could bind within receptor mosaics due to cooperative binding. This suggests one possible molecular explanation of the synergy explanation so often invoked by phytotherapist to suggest that plant medicines and foods cannot be reduced to an "active" constituent. The receptor mosaic model also suggests that an expansion is needed of the traditional pharmacological methodology of searching for only high affinity agonists and antagonists within plant chemistry.

2. Shifts in membrane electronics and/or shape: Nonspecific membrane interactions by exogenous molecules

Many components of signal transduction, such as receptors, are anchored in the plasma membrane and therefore are subject to the biochemical milieu of the plasma membrane. Of the four basic receptor signaling modes - gated ion channels, metabotropic receptors, receptor enzymes and the steroid receptor - three of them are directly linked to plasma membrane processes. This lipid rich, two-dimensional environment allows for hydrophobic interactions leading to alterations in component access, orientation and effective concentration.¹⁰ Hence, modulation of the molecular organization of the membrane may have an effect on signal transduction.

Many drugs are amphiphilic or hydrophobic molecules, and a common site of action for these compounds is the plasma membrane.² Among the amphiphilic compounds, many of the central nerv-



Figure 1: The current pharmacological model searches for only high affinity & selectivity compounds and ignores lower affinity compounds for receptor (and enzyme) binding. However, given the receptor mosaic model, the low affinity compounds typically accompanying high affinity compounds in plant extracts may cooperatively bind affecting signal transduction. Additionally the concomitant compounds commonly improve pharmacokinetics (absorption, distribution, metabolism & excretion) of the low-high affinity compounds.

ous system depressants¹¹ will, due to their molecular properties, self-aggregate into micelles.² Despite significant molecular investigation into modes of activity for some of the hydrophobic drugs (e.g. the local anesthetics) no specific receptors have been elucidated.^{12,13} Rather, these compounds demonstrate activity at the plasma membrane surface.² Hydrophobic and amphiphilic compounds and their resulting micelles may induce shape changes, membrane disruption, vesiculation and solubilization to cellular membranes.¹² Consequently, these generated asymmetries induced by exogenous molecules result in changes in membrane tensions.^{14, 15} As expected of the thermodynamics of open systems far from equilibrium, the membrane perturbations due to curvature tensions and the flux of molecular movements from one monolayer to the other may shift the resting state of the membrane. As a consequence, the cellular shape is modified on membrane reorganization.² Changes in the curvature of the membrane, as well as composition, have demonstrated changes in function of the membrane when it interfaces with an exogenous molecule.¹⁶⁻¹⁸ Given that protein conformation is dependent on environment, structural change may also induce alterations in protein conformation.³ This could result in signal transduction.

Of particular interest to this discussion, many of the secondary compounds of plants are amphiphilic or hydrophobic (e.g. hyperforin from St. John's Wort and the alkylamides from Echinacea spp.) and would accordingly likely display similar behavior. Given the evolutionary history of plant ingestion by humans, membrane interactions by "non-active" compounds in plants were likely routine. Consumption of a plant led to ingestion of active constituents and phytochemicals that influenced membrane dynamics. Consequently, acknowledging the evolutionary precedent, the combination of compounds

affecting the membrane with active compounds binding to receptors was part of routine physiology. Could this be one of the reasons that many isolated plant constituents don't appear to function in the same way as when given in a whole plant extract?

3. Polyvalent Activity: Biochemical Convergence

The last two modes of activity were discussed in the realm of an isolated cell. However, physiology does not run in linear, one chemical at a time, sequential processes. Robust systems, like living organisms, are likely quite responsive to numerous signals and subtle chemical perturbations that involve networks of cells, tissues and organs.¹⁹ Recognition of such subtle perturbation would eventually create the understanding of a health modifying molecular network and further pharmacological target potential. The current number of pharmacological targets, ~ 300 – 400 are but a small number of the 10,000 estimated number of disease-modifying genes.²⁰

With this in mind molecular biology is slowly moving from studying the components of signaling, to the context in which the signal participates. Study at the molecular level alone will not progress the understanding of when and why cells interact, in their typically non-linear, non-local, multiple feedback loops.²¹ Thus, multisystem analysis will likely be found to be essential to understanding signaling networks and cellular physiology.²² Allowing for models that include multi-target and multi-pathway assaying could elucidate the informational connectivity of networks and holds great promise for therapeutics. Furthermore, monitoring targets tripped by polyvalent groups of compounds, will almost certainly lead to the recognition of more complex pharmacological models. As our range of perturbable sites improves, proteins expressed from mere "house-keeping" genes will likely be recognized as modify-

Targeting Multiple Sites

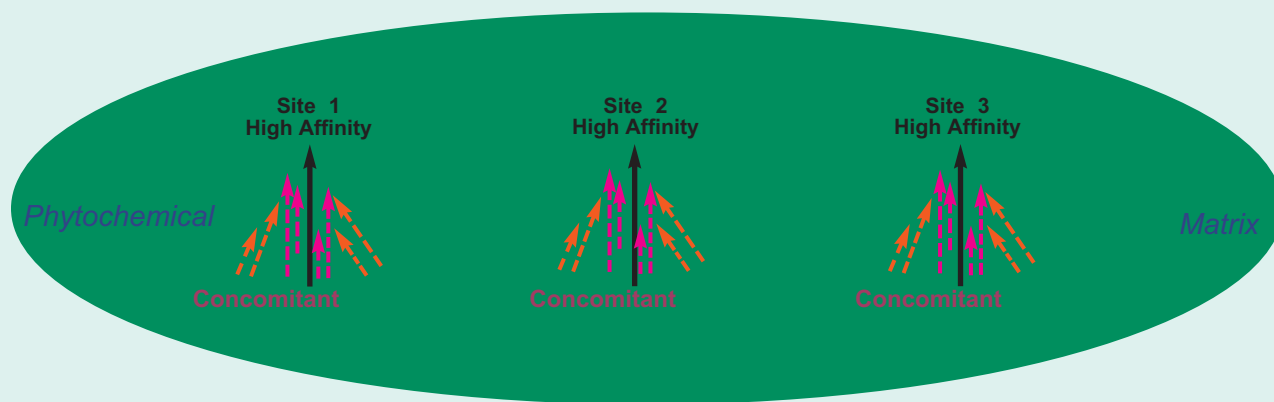


Figure 2: Physiology is a complex process that operates in symphonic manner with multiple receptor, enzymes and genes being affected in any given second. When ingesting a plant extract or food, the phytochemistry triggers many sites concurrently that can then efficiently converge on a positive outcome.

ing disease. The outcome could be an expansion of the understanding of the health modifying gene network and further perturbable sites.²⁰ Such perspective will likely lead to the acknowledgement that a multi-target perturbation, as happens with the consumption of any plant product, often offers more therapeutic activity than single-chemical, stand-alone interventions.

Using network models of pharmacology, Csermely et al.²³ have found that the partial inhibition of multiple targets offered by a mixture of chemicals are often more efficient than the complete inhibition of a single target. For example, Wald and Law²⁴ suggest that a combination of six drugs at subclinical doses - a baby aspirin, three blood pressure drugs (at half the standard dose), a statin and 800 mcg of folic acid - could extend life by eleven years.

Additionally, in a meta analysis of 56,000 patients with hypertension, Law et al.²⁵ concluded that combinations of two or three drugs at half the standard dose delivered comparable therapeutic effects to one or two full dose antihypertension medications. Yet the multiple low dose drug combination was preferable due to the reduction in side effects. Csermely et al.²³ proposes that partial, but multiple, drug inhibition could prove to be a superior pharmacological strategy over the effects of one drug action providing complete inhibition at a single target.

Keith and Zimmerman²⁰ suggest that many genes might need complementary action to modify disease processes. In other words, efficacious therapy might depend on perturbing more than one target. They comment that clinicians have historically overcome single-target insufficiency by using combination drug therapy.

When screening combinations of various pharmacological compounds, the natural outcome will almost certainly necessitate further exploration of the connectivity of physiological pathways. In other words, the focus will move from component properties of receptors and enzymes to the context in which these proteins operate; from a focus on the parts of cells to the function of cells and their parts in particular biochemical milieus.

Borisy et al.²⁶ discuss the unexpected, but beneficial interactions that a systemic screening of combinations of small molecules provide. They report, for example, that an antipsychotic agent coupled with an antiprotozoal drug, demonstrates antineoplastic activity. In addition, a fungistatic coupled with an analgesic agent, produces antifungal activity against resistant strains of *Candida albicans*. However, if broken apart and studied in isolation, these ensemble properties would have never been realized by data on component properties.

Biochemists, pharmacologists, molecular biolo-

gists and physiologists have an opportunity for an enhanced perspective: The study of phytochemical matrices interfacing with mammalian systems, with the addition of improved technology, will almost certainly elucidate biochemical pathway connectivity that has been unreachable with previous methodology. It will be necessary to embrace the understanding that the properties of a unity cannot be accounted for by accounting for the properties of its components.²⁷

Due to an evolutionary history of recurrent interactions between complex phytochemistry and mammalian physiology, plants' multi-constituent nature could form a higher order of organization while interfacing with a biological system. While some constituents are interfacing with receptors and membranes, others are influencing pharmacokinetics. For example, concomitant compounds, frequently considered excipient non-active constituents, can affect absorption, distribution, metabolism or excretion of other constituents, enhancing (or antagonizing) their bioavailability.²⁸

Nature's mixtures seem to function with broad specificity and low affinity.²⁹ This phytochemical economy, an efficient and broad spectrum ensemble of constituents, would likely act on not just one target, but on multiple targets, functionally converging on biochemical pathways.³⁰⁻³² Thus, phytochemical matrices, with their ensemble properties tripping multiple targets, may provide an enhanced pharmacological efficiency as compared to isolated compounds.^{5, 23, 29} Moreover, the use of phytomedicines, as compared to isolated chemicals, may offer a safer clinical strategy in the treatment of many diseases.^{31, 33, 34}

It is well known that the overall combination of non-nutritive phytochemicals appears to be key in plants' positive effects on health; the health-giving effects of plants are not always related to the nutrient content³⁵ and that significant consumption of secondary compounds from plants play important roles in the prevention of chronic diseases.³⁶ Additionally, the above suggested modes of activity may be one of the reasons that phytochemistry is capable of altering metabolism and changing the biological fitness of humans.³⁷

Conclusion

If the ensemble properties of a chemical matrix are necessary for physiological and pharmacological effects, then the purification process from whole plant to isolated compound is inadequate for the elucidation of pharmacological activity of many herbal remedies and plant foods.^{30, 38} While the reductionist model has provided life-saving drugs, basing pharmacology on structure and function provides little indication of the behavior of the interacting biological

networks.³⁹ Although isolation of plant constituents is methodologically convenient, it is not realistic in regard to the activity of real-time physiology.

The human genome, which is still in a Paleolithic state, is accustomed to multiple, concerted biochemical perturbations due to millions of years of recurrent interaction of mammalian genes with heterogeneous phytochemical matrices. Phytochemical intake for Paleolithic humans has been estimated to be up to eight times greater than that of modern humans.⁴⁰ Following the lead of evolutionary biology, many common plant compounds, which the human genome has come to intimately know, are often considered superfluous. Nevertheless, common phytochemical compounds likely have a role in cellular biology and, it is undeniably that a large number of phytochemicals can directly or indirectly modulate gene expression.⁴¹

Recognition of human evolutionary experience could not only guide the development of a framework for the anemic preventive medicine field, but lead to enhanced understanding of signal transduction for improved pharmacological therapeutics. Pharmacology based on the affinity, selectivity, potency and acceptable toxicity of an isolated active constituent must be revised. Phytochemicals that are “non-active” in a phytochemical matrix are probably rare.

Since biological systems are known to a) adapt to environmental context and b) reorganize in order to adapt, a logical conclusion can be reached that medicinal and food plants provide: 1) pharmacological input that presents both high and low affinity compounds binding to receptor mosaics; 2) compounds that can influence membrane dynamics and; 3) heterogeneous compounds that act in a polyvalent manner by perturbing multiple sites. Due to millions of years of repetitive interaction with plants the above molecular interactions are a routine aspect of cellular physiology and are likely part of the formation of higher levels of organization involved in the process of signal transduction through cellular networks. This should be considered as fodder for the expansion of the current pharmacological paradigm for many reasons, but primarily because it could contribute to further alleviation of human suffering. Such a paradigm is supported by an evolutionary precedent and by the logical extension of the emerging discipline of evolutionary medicine.

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