Lenses

MOLECULAR PATHOLOGY OF MESSENGERS AND THEIR RECEPTOR SITES

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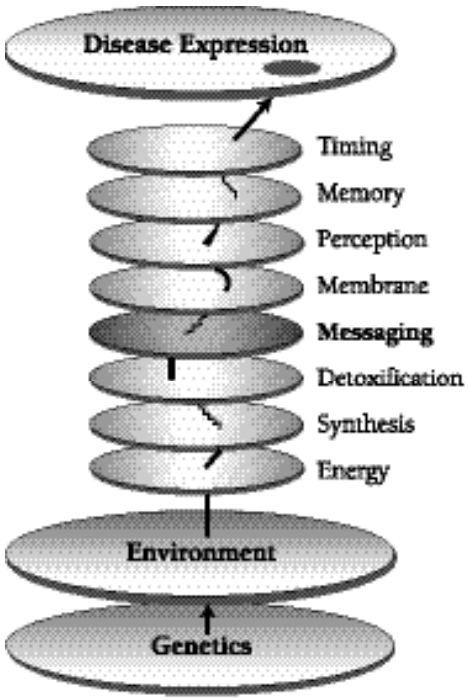
Whether I am dealing with a patient with complex chronic illness or an athlete wishing to shave a minute or two off his or her marathon time, I have a sort of checklist (as illustrated in the *Lenses* diagram) through which the impulse from my patient's genome passes toward its expression in health or disease. Efficient energy metabolism, anabolism, and detoxification, the subjects of the previous three articles in this series, are the list's big budget items in that they all have to do with the supply of the forces needed to put molecules together. The adequacy and distribution of such forces is the major factor regarding the terminal events of the main diseases in our culture: cardiovascular disease in which energy is denied to critical organs; and cancer, which steals energy from the organism until the cancer destroys its host by exceeding 5% of body mass or invites equally lethal complications of therapies aimed at defeating it.



Compared with the energy supply and making new molecules needed for growth, repair, and detoxification, the patient's need for balance in neurotransmitters, hormones, or cytokines is much more familiar day-to-day territory for allopaths (as well as the naturopath that is in the core of most integrative-medicine practitioners). We regularly test and treat problems that respond to raising or lowering levels of, or the effects of, serotonin and other neurotransmitters, thyroid and steroid hormones, or cytokines. We in integrative medicine are especially aware and skeptical of pharmacological efforts to balance neurotransmitters, endocrine hormones or cytokines, by blocking various steps in human chemistry. We would prefer to improve cell signaling by improving the function of messenger molecules without being so heavy-handed as to simply mimic or block the relevant molecules. Another feature of integrative medicine is our loyalty to the notion that when it comes to wondering whether a given patient might do better with a supplement to enhance some endocrine function, we also wonder if some stress or deficiency might obviate the need for supplementation.

Pathology has many layers, all of which may be amenable to intervention when the individual (not the disease) and balance (not suppression) are our aims. As integrative-medicine practitioners, we are also more likely than our strictly allopathic colleagues to accept the patient's word that he or she benefited from a trial of thyroid supplementation when the lab tests predicted otherwise. That very phenomenon has troubled me for the 40 years since I first observed a patient who prospered dramatically after taking a supplement of thyroid hormone, contrary to expectations based on lab tests. The same paradox is even more surprising now that lab tests have become more trustworthy. Meanwhile, endocrinology's dogmas have grown to the point of threatening a physician's license if he or she believes, as I do, that the patient is often the best lab.

The point of this essay is that paradoxes concerning the effects of messenger molecules may be explained not by difficulties with the messenger, but with mischief affecting the way the message is heard. Let's start with the milieu of the receptor site and work backwards to the messenger so that we will have an example from which to generalize a clinical sensibility for cell signaling.

The dopamine D4 receptor site sits, like all receptor sites, at the cell membrane whose health is dependent on flexibility, as determined by the status of the its constituent lipids. These lipids, mostly long-chain omega-3 fatty acids, cannot be synthesized *de novo* by animals, which depend on green plants for their supply. That supply was curtailed in the human population after about 1950 with the introduction of vegetable oils whose meager omega-3 fatty acid content was stripped during processing to extend shelf life. No matter what is wrong with a person these days, a clinician might usefully ask if the membrane surrounding a patient's receptor sites is suffering from a lack of the right materials to provide flexibility. Inflexibility is a word we readily apply to behavior. How is it that individuals who display behavioral inflexibility manifest an analogous condition in their cell membranes?

Find a patient who cannot modulate mood so that he or she is either rigid or unstable in ways that give rise to tantrums or unmodulated swings of mood between depression and mania. See if he or she has attention problems anywhere in the spectrum from attention deficit disorder (ADD) to autism. Check to see if he or she has physical evidence of stiffness of the integument as manifested by dry, flaking, brittle, crusty, or scaly skin, hair, or nails. Measure, or don't measure, his or her serum or red blood cell fatty acids, and prescribe a generous supplement of flaxseed oil with a just-in-case (Note 1) addition of gamma linolenic acid and a source of eicosapentenoic acid and docosahexanoic acid, and watch it work. It should take about three months to change oil in cell membranes when we supplement with desirable oils, but the cutaneous and central nervous response is usually more brisk, with observable clinical results within days. It is not entirely clear from the literature[1] whether the results of the many experiments that show the beneficial effects of omega-3 fatty acids are due more to membrane flexibility or to a better balance of cytokine precursors. It doesn't matter to the point of this essay because the membrane molecules are the cytokine precursors. That is, they are the basis of membrane fluidity and the source of messenger molecules for intercellular communication.

The number of molecules and receptor sites that might play a role in optimizing messaging intimidates us clinicians who might prefer to simply choose remedies based on symptoms, so that we copy the allopathic cookbook with natural remedies. Not that this is such a bad idea, but we can do better by heeding what we know of contemporary human nutritional influences on patients in industrialized cultures. Four prominent influences are a shortage of omega-3 fatty acids and magnesium, dysbiosis, and toxins such as mercury. I would like to draw an example from our experience with the epidemic of autism, in which all four influences play a part. The example concerns a chemistry (thiols) that is common to many problems, and it illustrates a clinical need to consider not only the messenger and receptor sites, but also the milieu in and pathways by which messages are sent and received.

Let's look again at the D4 dopamine receptor site, which is explained in Richard Deth's monograph on attention.[2] It is a unique receptor site, but its features still illustrate the point that messaging encounters complexities beyond the question of the adequacy of the messenger. The underlying flexibility of its membrane locale, due to its constituent fatty acids, is as important to the D4 receptor as it would be to any receptor. Methylation (addition of a CH_3 group) of the phospholipids immediately surrounding the site has a more specific contribution to the activity of the site, and constitutes one of four novel attributes of the D4 receptor. Adjacent neurotransmitter sites become modulated as a result of changes in the membrane locale provoked by methylation. Thus, in contrast to the nearly universal signaling via G proteins, the D4 receptor produces very rapid localized changes in neuronal activity by means of "solid state" modulation of nearby receptors. A second unique feature of the D4 receptor is that it can directly amplify oscillations in inter-neuronal circuits so that it participates directly in rhythmic aspects (synchronization) of information transfer. A third feature is the D4 receptor's interaction with folate-dependent aspects of cellular metabolism and energy supply. Finally, dopamine stimulation produces a trophic stimulus to the cell. Unique as the features of the D4 receptor may be, they serve to illustrate the ways that molecular messaging can go wrong or be repaired, other than by simply trying to change levels of the signaling molecule.

Another unique feature of the D4 receptor, according to Richard Deth, is that "the methyl groups that the D4 receptor uses to methylate membrane phospholipids come exclusively from 5-methyl

tetrahydrofolate (5MeTHF), not from S-adenosyl methionine (SAM) and not from methionine. There is a non-D4 receptor phospholipid methylation reaction that can use SAM or dietary methionine-derived methyl groups, but the D4 receptor can't use this because the methionine, the SAM, the s-adenosyl homocysteine, and the homocysteine are incorporated into the protein chain."[3] In other words, the familiar methionine cycle has a separate incarnation in which its component players (methionine, SAM, SAH, and homocysteine) are part of the protein molecule of the D4 receptor. As discovered by Deth, this system is specifically devoted to modulation of membrane fluidity around the receptor site itself, and not to membrane fluidity in general, which is SAM-dependent (see Figure 1).

What can go wrong? Plenty. Here is the list, starting with the items discussed above:

1. Stiff cell membranes around the D4 receptor from lack of flexible omega-3 fatty acids in the cell membrane; reduced membrane fluidity because of under-methylation of phospholipids immediately surrounding the D4 receptor site because of a shortage of 5MeTHF.
2. Failure of remethylation of the D4 receptor's methionine because of oxidative damage to methyl cobalmin in its active site.
3. Failure of remethylation of the D4 receptor's methionine side chain because of lack of methyl cobalmin to replace oxidized methyl cobalmin for its active site.

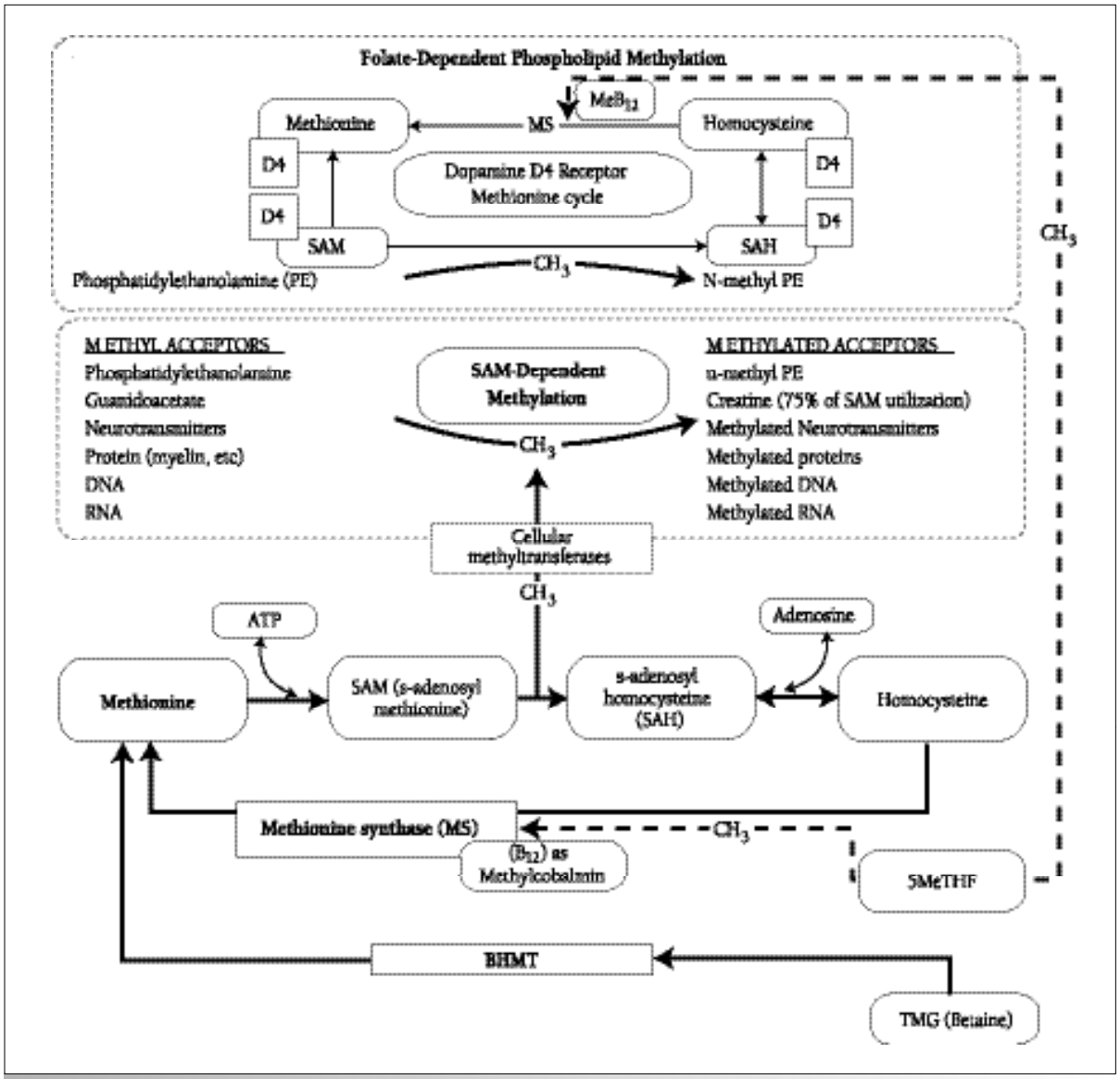


FIGURE 1
THE DOPAMINE D4 RECEPTOR PROTEIN INCORPORATES THE MOLECULAR PLAYERS OF THE METHIONINE CYCLE AND IS UNIQUELY DEPENDENT ON 5METHF.

4. Failure of remethylation because of the D4 receptor's methionine because of a lack of 5 CH3THF to remethylate cobalmin.
5. Failure of remethylation because of the D4 receptor's methionine because of an inhibition of methionine synthase.
6. Inhibition of MS due to lack of methyl cobalmin.
7. Lack of methyl cobalmin because of inhibition of hydroxycobalmin→and cyanocobalmin→gluthathionlycobalmin by Thimerosal.

Here we are, several steps away from the action, and we find a factor (#7) that has a reasonable chance to play a major causative role in the rising incidence of attention deficit disorder (ADD) and autism-spectrum disorders over the past generation. Phospholipid membrane (PLM) is inhibited by Thimerosal in lymphoblasts from autistic individuals to a far greater degree than their same-sex unaffected siblings.[4]

Proceeding with the notion that the pain of sitting on a tack is best treated by tack removal, we have to go by a more circuitous path from cause to effect, but the clinical lesson from this exploration of messenger molecules is that related mischief may yield to remedies more subtle and more remote than manipulation of the neurotransmitter, hormone, or cytokine involved. In the example I have chosen, methylation is the influence that ultimately makes the connection between cause and effect. Methylation (by SAM) is a concern in regard to neurotransmitters themselves (as apart from their methylation of membranes surrounding the receptor site in the case of the dopamine D4 receptor), methylation of proteins, phosphatidylethanolamine transformation to phosphatidylcholine, the formation of creatine from guanidoacetate, and methylation of RNA and DNA that is essential to gene expression.

DNA carries our messages from generation to generation. The chemistry I have reviewed, from cobalmin through SAM to methylation, is variably weak or strong, robust or vulnerable, in different individuals. The potential effects on intergenerational messaging provide incentives for us to understand and repair the milieu of messaging chemistry in our patients before resorting to dosing or blockading the system.

Notes

1. A weakness of the delta 6 desaturase enzyme needed for the first step in both omega 6 and omega 3 pathways would necessitate a supplement of gamma linolenic acid to prevent a bottleneck in both pathways as a result of overloading alpha linolenic acid.

References

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4. Deth R. How Genetic Risks Combine with Thimerosal to Inhibit Methionine Synthase and Cause Autism. Fall DAN! 2004 Conference, Los Angeles, CA, October 2, 2004.

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I am indebted to Richard Deth for his personal guidance, as well as his lectures and his book, which is cited in the references. This book belongs in your personal or institutional library as a masterwork of making science accessible.