HYPOTHESIS

Autism: A Redox/Methylation Disorder

自闭症：氧化还原反应/甲基化作用障碍

Autismo: un trastorno de oxidorreducción/metilación

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INTRODUCTION

While autism is still a mysterious developmental disorder, expansion of research efforts over the past 10 to 15 years has yielded a number of important clues implicating both genetic and environmental factors. We can now assert with a measure of confidence that contemporary autism reflects the combined impact of multiple environmental factors on the processes that regulate development in genetically vulnerable individuals. Since epigenetic regulation of gene expression is acknowledged as the most critical factor in development and DNA methylation (the addition of a carbon atom at discrete locations) is the fundamental event for epigenetic regulation, dysfunctional methylation can be considered as a likely cause of autism. Since methylation activity is highly sensitive to oxidative stress (an abnormal redox state) and many environmental factors promote oxidative stress, we have proposed a redox/methylation hypothesis for autism causation. The narrative herein describes the evolution of this hypothesis, which is essentially a series of linked discoveries about how the brain uniquely relies on oxidation and methylation to guide its development and to carry out its cognitive functions.

D_4 DOPAMINE RECEPTOR METHYLATION ACTIVITY

Autism wasn't on my radar screen until my lab's discovery in the late 1990s that one of the dopamine receptors, specifically the D4 receptor subtype, carries out a methylation reaction involving membrane phospholipids. The key to this discovery was computer graphics–based molecular modeling, which allowed me to visualize receptor proteins and understand how the binding of neurotransmitters such as dopamine could change their shape, leading to activation. After several years of investigation, we published a study in *Molecular Psychiatry* describing dopamine-stimulated phospholipid methylation, including a rather detailed molecular explanation of how a particular methionine residue found only in the D4 receptor carried out this methylfolate-dependent reaction.[1] It turns out that the location of this methionine exhibits the largest change in position upon binding of dopamine to the receptor, exposing it for its unique methyl transfer activity. Because I am a pharmacologist, my primary initial focus was on proving that the D4 receptor was exclusively able to carry out this novel reaction. It was the first description of a protein using one of its methionine residues to carry out a methylation reaction with folate-derived methyl groups, and to my knowledge, it remains the only example. A number of graduate students—including Alok Sharma, Ren Zhao, and Martin Kramer—in particular, deserve credit for the initial research, which has since been carried forward by many others.

One doesn't get the chance to make truly novel discoveries very often. Most scientific advances are incremental, modestly advancing the field of knowledge, but I felt strongly that our discovery of D4 receptor–mediated phospholipid methylation (PLM) was important. There were a number of reasons why D4 receptor–mediated PLM seemed important. First of all, it established a direct connection among several theories about the cause of schizophrenia. Dopamine and dopamine receptor involvement comprise the central hypothesis for schizophrenia, particular the D2-like group of receptors that includes the D4. Indeed, the single most effective drug for treating schizophrenia is clozapine, which has a notable selectivity for the D4 receptor, although serious side effects limit its utility. Shortly after the D4 receptor was first identified, pharmaceutical companies rushed to identify potent and highly selective D4 receptor–blocking drugs, and Merck (Whitehouse Station, New Jersey) in particular carried out clinical trials of their lead compound (L-745870) for treatment of schizophrenia. Blocking drugs were chosen because clozapine and other neuroleptic agents are receptor blockers (antagonists). Unfortunately, L-745870 was found to be ineffective, and further interest in D4 receptor drugs was sharply curtailed.

Prior to the dopamine hypothesis of schizophrenia, impaired methylation activity was a prominent theory, known as the single carbon hypothesis of schizophrenia. It was based partly on the observation that administration of methionine to schizophrenic individuals would precipitate an acute psychotic reaction but had no effect in normal subjects. In our 1998 paper, we showed that PLM activity was depressed in white blood cells of schizophrenic subjects, suggesting that impairment of dopamine-stimulated PLM might be an important contributor.[1] However, if this is true, it wouldn't make sense to employ a highly potent D4 receptor–blocking drug to improve the situation; in fact, it would be more likely to make things worse. Notably, clozapine is a weak blocking drug, which means that when the concentration of dopamine increases, it can still activate the receptor, albeit at a slightly reduced level. Thus, the key to a better D4 is that a new theory replaces an old one. However, as elegantly described by Thomas Kuhn in his book *The Structure of Scientific Revolutions*,[2] the best hypothesis is one that encompasses the largest number of observations, and D4 receptor-mediated PLM provides an opportunity to unify both dopamine and single-carbon hypotheses.

Another reason I thought dopamine-stimulated PLM was important was because genetic variants of the D4 receptor were known to be risk factors for attention deficit hyperactivity disorder (ADHD), and ADHD rates had increased dramatically in recent years. The most common genetic variant is a seven-fold repeat in the gene receptor that is carried by about 20% of people with European ancestry but is relatively uncommon in those of Asian ancestry. The seven-repeat variant also was associated with "novelty-seeking behaviors," further adding to the D4 receptor mystique. The attention impairment in schizophrenia suggests that dopamine-stimulated PLM could play some role in the mechanism of attention. In 2002, I published *Molecular Origins of Human Attention: The Dopamine-folate Connection.*[3] The central hypothesis was that D4 receptor–mediated PLM causes attention by promoting synchronized firing of neural networks, particularly in the gamma frequency range of 30–80 Hz This was recently demonstrated in a study we conducted with Bernat Kocsis, MD, PhD, of Harvard University.[4] Even though neuropsychiatry research focuses on neuroanatomy, neurotransmitters, and synaptic function I am confident that methylation reactions and D4 receptor-mediated PLM will prove to be important. Enter autism!

METHIONINE SYNTHASE, MERCURY, AND THIMEROSAL

Not long after publishing our first D4 receptor methylation paper, my lab began to focus more on the critical supporting role of vitamin B_{12} and the methylfolate-dependent enzyme methionine synthase. We estimated that a single D4 receptor could transfer 20 to 50 methyl groups per second, an impressively rapid turnover rate. Since each one had to be provided by methionine synthase, any adverse effect on methionine synthase (MS) activity would be reflected as a loss of whatever role D4-mediated methylation played. Fortunately, MS had been thoroughly investigated by a number of eminent biochemists, including Rowena Matthews and Ruma Banerjee, so it did not take long before we appreciated that oxidative stress turns off MS by promoting oxidation of its B_{12} (cobalamin) cofactor. Thus, MS serves as a sensor of the oxidative state of cells (redox status), implying that D4 receptor responses, such as the capacity for attention, might be impaired under oxidative stress conditions. Because MS activity also controls the ratio of the methyl donor S-adenosylmethionine (SAM) to the methylation inhibitor S-adenosylhomocysteine (SAH), oxidative stress also regulates hundreds of methylation reactions affecting almost every aspect of cellular function. Clearly, MS was worthy of further investigation.

In 2002, we published another study in *Molecular Psychiatry* showing that both MS activity and PLM were strongly increased by dopamine and by neurotrophic growth factors such as insulin-like growth factor 1 (IGF-1), the most important determinant of development throughout the body, including the brain.[5] This work largely reflects the doctoral research of Mostafa Waly, who continues to be a valued collaborator in his current position as faculty member at Sultan Qaboos Uinversity in Oman. We now know that the increase is due to a decrease in oxidative stress, resulting from the ability of dopamine and growth factors to augment uptake of the sulfur amino acid cysteine, increasing synthesis of the antioxidant glutathione (GSH) and augmenting MS activity. In the same study, we showed that dopamine and IGF-1 caused a global increase in the methylation of DNA, indicating their potential for causing changes in gene expression through epigenetic mechanisms. Interestingly, alcohol (ethanol), a well-recognized neurodevelopmental toxin, potently inhibited MS activity and methylation, which we now know is a reflection of its inhibition of cysteine uptake and decreased GSH synthesis. Taken together, these observations made it clear that cellular redox and methylation status is subject to physiological regulation (eg, by growth factors) and toxic substances (eg, alcohol) can interfere with this regulation, with the potential for causing neurodevelopmental disorders.

In the same 2002 study, we showed potent inhibitory effects of lead, mercury, aluminum, and thimerosal on MS activity and PLM.[5] I think it is fair to say that these latter observations, especially for thimerosal, overshadowed the physiological findings, as they provided a potential molecular mechanism by which this vaccine preservative could contribute to neurodevelopmental disorders such as autism. These findings were made during the time a panel of the Institute of Medicine (IOM) was evaluating a possible contributory role of vaccine-derived thimerosal in causing autism, and in my naiveté, I was sure that the IOM would want to know about them as soon as possible, especially as it was becoming clear that the epigenetic consequences of impaired methylation could interfere with development. However, it was only through the efforts of a dedicated group of parents—during the brief time allotted for questions from the public—that I was able to briefly describe how thimerosal inhibits methylation reactions. As the field of epigenetics has burgeoned during the past decade, it is all the more true that mercury in any form is a potent neurodevelopmental toxin, with aluminum, lead, and other metals not far behind.

DEFEAT AUTISM NOW!

In 2003, Martha Herbert, MD, PhD, from Massachusetts General Hospital, recognized an overlap between my research and the metabolic focus of Defeat Autism Now! (DAN!), and she introduced me to Jon Pangborn, PhD, chemist at Doctor's Data and father of an autistic son, who arranged for me to speak at the think tank before the DAN! meeting in Philadelphia, Pennsylvania. Under the capable leadership of autism pioneer Bernie Rimland, PhD, astute clinician Sidney Baker, MD, nurse/meeting organizer extraordinaire Maureen McDonnell, and others, DAN! was a dynamic amalgam of clinicians and parents of autistic children searching for the causes of and cures for autism. At that meeting, a New Jersey clinician, Jim Neubrander, MD,

reported the remarkable clinical benefits he observed in a series of children, treating them with injections of methylB_{12} (MB_{12} or methylcobalamin). The ability of MB12 to reactivate MS after it has been stopped by oxidation meant that our research could indeed be important for understanding autism. During my think tank presentation at this meeting, I experienced a debilitating wave of emotion as I appreciated the deep importance of the quest for understanding the cause of autism and its potential promise for finding effective treatments. I had to stop and compose myself, which I was able to do with the support of the DAN! members. That moment was a dramatic realization that my scientific career could be more meaningful than simply publishing papers, getting grants, and building my own little area of knowledge that no one else cares about. Certainly the DAN! organization seemed to care, and that validation was enough to sustain a passionate focus on autism that still carries me and my research through today.

I have been privileged to be invited as a speaker for a series of DAN! meetings. Communicating detailed biochemical and molecular science to parents and clinicians is always a challenge, since the technical vocabulary is almost a foreign language. However, it is amazing what people can learn when the motivation is strong, which it certainly is for parents of autistic children. Very quickly, I recognized that I was learning a tremendous amount from parents, clinicians, and other researchers, who were bound together by a common purpose. It was a very special humanitarian experience, with a cast of characters whose lives intersected for a good purpose. While DAN! itself had to be retired, the Autism Research Institute (ARI) lives on, sustaining the spirit of Dr Rimland, and I have confidence that when a retrospective on the autism epidemic is written, the DAN! participants will be recognized as the ones who showed the way.

A REDOX/METHYLATION THEORY OF AUTISM

There are a multitude of theories about what causes autism, and given the broadly diverse autism spectrum, one could argue that any single theory is useless. I formulated a theory encompassing both the D4 receptor and the important role of DNA methylation in development, linking both of them to the oxidative stress that is produced by a wide range of environmental factors. What emerged is the redox/methylation hypothesis of autism.[6] While mercury and thimerosal are obvious examples of triggers, the underlying concept is applicable to an endless list of physiological and chemical substances capable of altering cellular redox status (eg, GSH levels), leading to adaptive changes in methylation status. Indeed, this is exactly the way nature (evolution) has endowed living organisms with the ability to survive and thrive in changing environmental circumstances.

The redox/methylation perspective can be applied to a wide variety of diseases. Brain disorders are perhaps the most obvious because the consequences of brain dysfunction (eg, behavior, cognitive capabilities) are externally visible and easily observed by others. In addition, development of higher brain functions is delayed until after birth, making it fully responsive to experience, especially the most recently evolved capabilities such as language and social skills. Essentially, "mind building" is held back, while more primitive brain functions develop in utero. As a result, pretty much everything that happens to us after we're born has the potential to affect brain development, including sensory and emotional experiences that we encode into memory, as well as chemical exposures that impact the redox/methylation pathways.

It is now becoming clear that epigenetic changes are the basis for memory formation; therefore it is not surprising that oxidative insults can interfere with the development of brain capabilities. As noted above, schizophrenia merits special note as a disorder for which the redox/methylation hypothesis can be applied, especially as it is associated with lower brain levels of GSH and the administration of N-acetylcysteine has salutary effects. Development of the immune system also is held back until the postnatal period, making it especially vulnerable to environmental factors.

Recently, we've investigated the effects of morphine on redox and methylation, including significant changes in DNA methylation and gene expression. Since we previously showed potent effects of alcohol and dopamine, this combination suggests that addictive drugs share the ability to exert redox/methylation effects. Moreover, since epigenetic effects are persistent across the lifespan, the redox/methylation effects of these drugs may lead directly to their addictive potential. We generally accept the idea that the heavy use of addictive drugs alters the brain, but now we can think in more specific terms that the drug-induced change involves changes in the DNA and histone methylation status.

When these abused drugs are persistently present, the brain adapts to their presence and changes gene expression accordingly in order to maintain normal redox equilibrium. During a period of abstinence, the adaptive responses induced by the drugs are inappropriate, and a period of "reverse adaptation" ensues, which we recognize as a withdrawal syndrome. However, even after the drugs have washed out, there is a residual epigenetic-based memory of the earlier exposure that lasts a lifetime, just like the memory of any important life event. Essentially, addictive drugs hijack the same molecular mechanism we rely on to form memories, but in this case, it is a chemical or pharmacological stimulus rather than a typical life experience. In addition, the events surrounding drug abuse—such as drug buying (drinking at a bar or making a connection), drug administration (a shot of vodka or intravenous injection), or activities under the influence (social contacts, altered consciousness)—are all subject to special memory outcomes because the drugs are affecting the epigenetic mechanism. Interestingly, genetic variations in the D4 receptor have been linked to the propensity for drug abuse, and N-acetylcysteine has been used for treatment of alcohol addiction.

Genetic factors are clearly important in determining the degree to which individuals are more or less sensitive to environmental factors, including the risk of autism. Single nucleotide polymorphisms (SNPs) in genes that are directly involved in methylation or in redox regulation are primary examples, but SNPs affecting other pathways (eg, synapse formation or maintenance) contribute in their own way. In many cases, SNPs result in lower activity of a specific enzyme, which can be compensated by simply increasing the amount of the enzyme by increasing transcription of its gene, resulting in a higher level of its messenger RNA (mRNA). However, methylation of DNA (ie, epigenetic regulation) exerts primary control over the level of gene transcription, so anything that disrupts methylation will tend to exaggerate the importance of SNPs, as it impairs our ability to compensate for weaker enzyme activity. The highly variable presentation of autism therefore reflects the emergence of individual genetic variations that would not be problematic if epigenetic mechanisms were functioning normally. In short, interference with methylation increases the importance of genetic variations.

EPIGENETICS AND AGING

Epigenetic regulation of gene expression was first proposed in 1942 by Conrad Hal Waddington,[7] who coined the term, but the molecular modifications to DNA and histones which exert epigenetic effects were not deciphered until the past several decades. The Human Genome Project greatly accelerated research into patterns of DNA methylation and histone modifications, and it would be fair to say that we are in the midst of the human epigenome research project, although it hasn't been formally organized as such. Epigenetic research is increasing exponentially across many fields (neurodevelopment, aging, cancer, etc). Due to its influence over the S-adenosylmethionine:S-adenosylhomocysteine (SAM:SAH) ratio, MS activity causes large changes in global DNA methylation, so it seems obvious that factors affecting MS, such as oxidative stress, would exert an important epigenetic effect.

As part of her doctoral thesis project in our lab, a former student, Christina Muratore, measured changes in the level of MS mRNA in postmortem human brain (frontal cortex) and discovered a remarkable pattern of progressive decrease across the life span, such that the level at 80 years was only 1/500th of the fetal level.[8] Despite this huge decrease, the amount of MS protein remained constant, implying that new synthesis of the protein was being cut back with increasing age while the protein turnover was decreasing. This intriguing finding is consistent with a gradually decreasing dynamic state of metabolism with age, a concept that is all too familiar for people of my age. While the pattern could be seen for MS, we proposed that it extends across all cellular pathways, as MS controls methylation and methylation is so pervasive in controlling almost every aspect of metabolism. For starters, DNA methylation controls the probability of gene transcription into mRNA, the life span of the mRNA, activity of the ribosomes that translate mRNA into protein, as well as the life span of proteins. Essentially, we proposed that MS serves as a "metabolic pacemaker," and its sensitivity to cellular redox assures us that the level of cellular metabolism is indexed to the level of antioxidant. By controlling the dynamic metabolic demand, MS helps to maintain a balance between the rate of energy-producing aerobic metabolism and the availability of antioxidants such as GSH, which protect the cell from oxidative damage. Successful aging depends upon maintaining a normal redox balance, which is akin to the concept of homeostasis.

Results from other labs also illustrate changes in methylation activity across the life span. Most striking among these are two studies from groups at the National Institutes of Health (NIH) that examined changes in brain DNA methylation and gene expression across the life span in the same frontal cortex regions where we investigated MS mRNA changes. A comparison of fetal vs infant subjects showed that the rate of change in DNA methylation was ~70-fold slower in infants, while a comparison of fetal vs adults showed that the rate was ~600-fold slower. This illustrates a progressive decrease from highly dynamic fetal development through adulthood, associated with a gradually more stable state of metabolism. Since this is the brain, it is interesting to think of this in relation to memory formation and synaptic neuroplasticity. A highly metabolic dynamic state is not conducive to retention of information (memory) as there is a constant revision of network connections, although this condition is favorable for creating new patterns of connectivity (ie, learning), as plasticity is high. In contrast, a fixed state provides for retention of information as memory but does not provide for learning. Somewhere in between these two extremes is the more ideal condition that allows a balance of learning and memory. This perspective seems to reflect changes in our brain function across the life span as we have no memory of early experiences and our adaptability and capacity for learning are greatest at a young age.

All life depends upon the adaptive ability to resist or correct oxidation, which inexorably increases from conception to death. For humans, when a selenium-rich sperm combines with a GSH-rich egg, it causes intense metabolic activity, accompanied by shifts in DNA methylation that initiate a complex epigenetic-driven program of development that continues through adulthood. Maintenance of redox equilibrium is the "golden rule" for optimum health, but in old age, oxidative stress overtakes antioxidant capacity, resulting in neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease. There is substantial evidence for impaired methylation in AD, including elevated levels of homocysteine, indicative of impaired MS activity. Oligomers of the amyloid beta (A-beta) peptide (complexes of 2-3 molecules) are thought to be the initiator of AD pathology, beginning decades before overt symptoms are evident. Nathaniel Hodgson focused his doctoral research on the redox/methylation effects of A-beta oligomers, finding that they

inhibited the ability of growth factors to increase cysteine uptake, lowered MS activity, and inhibited methylation, including DNA methylation. Based on these activities, it appears that A-beta oligomers have a physiological role to limit excessive neuronal activation, which normally helps to sustain and prolong brain function, but too much A-beta activity tilts the redox balance toward oxidative stress and neurodegeneration. Notably, several studies have demonstrated that the combination of folic acid, B_{12}, and B_6 is helpful for mild cognitive impairment and decreases the progression of AD.

GLUTEN/CASEIN-DERIVED OPIATE PEPTIDES

The abnormally low plasma levels of GSH and cysteine documented by Jill James, PhD, (Arkansas Children's Hospital, Little Rock) and others implied a whole-body deficit, which almost certainly had its origins in the gut and ultimately could lead to low levels in the brain. A gluten-free/casein-free (GF/CF) diet was one of the most effective strategies for treating autism according to parents of autistic children. Karl "Tiny" Reichelt, PhD, a physically and intellectually impressive Norwegian researcher, gave several talks about the casomorphin peptides released from digestion of the milk protein casein, which he detected in the urine of autistic but not neurotypical kids, indicating that these peptides were systemically absorbed and could potentially exert opiate effects. Notably, digestion of wheat-derived gluten releases similar peptides. At the same time, the dedicated autism and AIDS clinician Jackie McCandless, MD, showcased the benefits of low-dose naltrexone (LDN) treatments in autism and autoimmune disorders as well as in treating HIV infection in Mali.

Taken together, the above observations suggested a hypothesis that food-derived opiate peptides might be responsible for decreasing cysteine absorption from the GI tract and LDN could be counteracting their systemic effects. Fortunately, we investigated the effects of bovine (cow) and human forms of beta-casomorphin 7 (BCM7) and gliadinomorphin 7, as well as morphine, on cysteine uptake. Malav Trivedi, PhD, who recently completed his doctoral project in my lab, was the driving force behind these studies. Each of the peptides, as well as morphine, interfered with cysteine uptake by both human GI epithelial cells and neuronal cells, and their effects were indeed blocked by naltrexone. Aside from its importance for autism, this novel finding has broad implications for other GI disorders such as celiac disease and for the health benefits that are driving the gluten-free food trend.

Human breast milk is the sole source of initial nutrition for most infants; therefore, the ability of human BCM7 to modulate cysteine absorption has the potential to regulate whole-body antioxidant capacity during early development. Moreover, we found differences between human and bovine forms of BCM7, which may be important for the health benefits of breastfeeding vs formula feeding. Initial studies have shown differential changes in DNA methylation and gene expression, consistent with distinctive epigenetic effects of human and bovine forms of BCM7. These actions illustrate the ability of early infant nutrition to establish a level of metabolic activity that is in balance with the level of antioxidant provided by gut function, remembering that up until birth, the GI tract does not function and the level of metabolism during fetal development reflects maternal nutrition and placental function. Epigenetic regulation of metabolism can thus be broadly divided into prenatal epigenetic programing (PrEP) and postnatal epigenetic programing (PEP). It is now well recognized that the risk of a number of diseases occurring later in life (eg, diabetes, schizophrenia) is established during early infancy, perhaps reflecting PEP and PrEP.[9]

CURRENT AND FUTURE DIRECTIONS

Now that we have gained a rather unique redox/methylation perspective, there are many different directions in which we could extend our research. Currently, we are evaluating changes in levels of the various forms of vitamin B_{12} in the brain across the life span and in autism and schizophrenia. In collaboration with the A2 Corporation, a New Zealand-based company supplying milk and milk products that do not release BCM7, we are extending our studies of opiate peptides, including a genome-wide investigation of their effects on DNA methylation and transcription. We have a special interest in their effects on so-called repetitive elements, which comprise >40 of our DNA, as they are particularly sensitive to changes in oxidative conditions. Hopefully, we also will have the opportunity to investigate the impact of oxidative stress on D4 receptor–induced gamma oscillations, strengthening our understanding of how redox and methylation status is linked to attention and cognition. Of course, our ability to pursue each of these research directions depends upon obtaining grant support for the individual project.

During 2014, my lab will move to Florida Atlantic University (FAU) in Jupiter, which is next door to Scripps Institute and Max Planck Institute, both of which are focused on brain disorders. It is an exciting new opportunity to work with scientists at FAU, including Herb Weissbach, PhD, who discovered the adenosylcobalamin form of vitamin B_{12}. The quest to understand autism has given unexpected meaning to my professional and personal life. While autism has always been the focal point, it is clear that to understand autism you must understand the human brain in a new way and in doing so you will also illuminate other brain disorders such as schizophrenia and Alzheimer's disease. My primary role as a scientist has been to explore the expression and causation of autism at the molecular level. In addition to DAN!, I have been affiliated with the National Autism Association and Generation Rescue and have testified to the US Congress. I believe that the true value of science lies in its relevance to everyday life, and there is no better example than the ongoing controversies surrounding autism. I am optimistic that there are more discoveries to be made that will lead to better diagnosis and treatment of autism in the future.

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