Health Condition: Cognition & Dementias

"Perhaps nowhere in medicine does a physician feel more limited in his or her abilities to effect change than in neurology. The problems we deal with are very challenging, and from a conventional medicine point of view, we are really reduced to simply the prescription pad, and the options available to us often do nothing more than provide symptomatic improvement at best…Over the past decade, we have come to understand, at least with respect to many neurodegenerative conditions, that there are many opportunities to intervene biochemically and functionally to allow an individual to begin to feel that he or she is participating in actually getting at the root of the problem and allowing functional improvement."

—David Perlmutter, MD May 1999

Who has cognitive decline and dementias?

One of the largest concerns of aging individuals is whether or not they will lose cognitive function. Since the Decade of the Brain (the 1990s), there has been an extensive scientific search to try to understand neuropathologies and to get a better mechanistic understanding of neurogenerative diseases. Tremendous strides have been made in understanding some of the molecular pathologies associated with neurocognitive disorders, like Alzheimer's disease (AD).

Even before dementia sets in, mild cognitive impairment (MCI), or the condition of causing a measurable decline in cognitive abilities, including memory and thinking skills, becomes evident. In fact, an individual with MCI has an increased risk of developing some form of dementia over time. It has been estimated that about 10 to 20 percent of people aged 65 and older may have MCI, although it is difficult to accurately assess since there are currently no tests or procedures to demonstrate conclusively that a person has MCI.

Dementia is a rather broad term to denote symptoms such as a decline in cognitive function and memory loss to the degree that a person is not functional in their daily life. Memory loss is an example. AD is the most prevalent (50 to 80 percent of cases) and well-known of all the forms of dementia (occurrence varies in different countries, but can range between 2 and 10%) while vascular dementia is the second most common form of dementia. Despite the visibility of these forms of dementia, there are other conditions such as thyroid problems and vitamin deficiencies that may result in dementia-like symptoms.

The cause of dementia is not well understood although there have been several underlying mechanisms proposed for its manifestation, including neuronal cell death, mitochondrial energy depletion and dysfunction, and inflammation, to name a few.

Diagnosis

Clinical and neuropsychological examination are the tools to diagnosis an individual with AD. While there is no established biomarker of AD for early detection, MRI and computer tomography (CT) scan are used to assess images of hippocampus shrinkage, which are useful in diagnosing advanced dementia. At present, no definitive blood test exists that is widely available to diagnose individuals with

dementia. The hallmarks of AD, plaque markers tau and amyloid beta, may eventual become biomarkers for AD.

Dr. Jay Lombard on amyloid protein and AD:

"Amyloid—especially amyloid precursor protein—is a normal molecule in our brains. What happens is it is processed abnormally. Either we have increased deposition of amyloid, or we have decreased degradation of amyloid, or we have a combination of increased production and decreased degradation of amyloid. The other important pathophysiological protein involved here is something called tau, which is associated with microtubules. Microtubules are the pillars, if you will, of cellular function, regulating things like synaptic efficiency, neurotransmission, transport of intercellular machinery, mitosis, and clearly when microtubule dysfunction occurs as a result of either aging or head injury, which is one of the major causes of microtubule dysfunction, this also produces pathophysiological changes in the brain associated with dementia. So both of these aspects, the amyloid story and the production or abnormal phosphorylation of tau protein, are implicated in dementia."

Indeed, there is a genetic marker that could identify individuals with familial forms of AD – the ApoE e4 allele – which has a positive predictive value of 94 to 98 percent in a patient who exhibits symptoms of AD. It has been proposed that it has utility for predicting pharmacogenetic-based responses in persons with AD. For example, in a study by researchers at the Johns Hopkins University School of Medicine (Alzheimers Dement. 2012 May;8(3):180-7. doi: 10.1016/j.jalz.2011.02.011. Epub 2012 Feb 1), women with dementia, particularly those with an APOE ε4 allele, were found to benefit most from cholinesterase inhibitors or memantine.

Treatment

Due to its complex, multi-factorial etiology, it is difficult to treat AD. Current management of AD consists primarily of pharmaceuticals, namely cholinesterase inhibitors: rivastigmine, donepezil, and galantamine. Memantine – a non-competitive *N*-methyl-D-aspartate antagonist – is a neuroprotective therapy that has recently come on the market and has had success. The goal of therapies is thought to be related to degradation of the amyloid protein peptide, which can be toxic for the neuronal tissue. However, there may be other mechanisms and corresponding pharmaceuticals such as anti-inflammatories (e.g., NSAIDS) to reduce the inflammation in the brain.

Through the use of various CAT scan technologies and SPEC scanning, we are beginning to see that perhaps there are indications that occur well before pathologic injury, either by the loss of nigra striatum, or the neurofibrillary tangle formation of Alzheimer's, that would help us to better understand how and when to intervene with neuroprotective therapy. For instance, the loss of smell in mid-life is one of the risk factors associated with Alzheimer's disease. The connection between neurosensory function in the nose and the brain is olfactory ability (one of the few places where the brain is directly in contact with the outside environment). Loss of the sense of smell and taste could mean zinc deficiency, but if patients don't respond to zinc and have a premature dulling of their senses of smell and taste, that may be an indication for neuroprotective therapy.

Personalized management of cognitive disorders and dementias

"One of the things that is important to understand is that predicting risk is not predicting actual disease, so if we say a patient who has a genetic test for any particular neuropsychiatric condition and they are at higher or lower risk, it does not mean that this is a fait accompli and they are actually going to develop a particular disease, which is one of the reasons that most clinicians have now adopted preclinical gene testing for Alzheimer's disease. We have not established what steps to take once the risk is identified. This is, I think, a big misguided assumption, because we do know that clearly there is strong evidence for prevention strategies. We should be taking those identifications and recommending preventative steps in patients who are identified with higher risk of Alzheimer's disease."

—Jay Lombard, DO, April 2012

The many disciplines of genomics, proteomics, pharmacogenomics, advanced laboratory analysis, and bioinformatics will greatly enhance drug development for AD. Several studies demonstrate genotype-specific responses (e.g., APO E e4) of AD patients to a particular drug or combination of drugs, although sometimes producing conflicting results. There are also studies to suggest that a certain dementia-related gene like APO E e4 may impact responses to other non-classical dementia drugs, thus alluding to the weblike interconnections of physiological systems. See abstracts below:

Drug Metabol Drug Interact. 2011;26(1):13-20. doi: 10.1515/DMDI.2011.107.

Effect of apolipoprotein E polymorphism on statin-induced decreases in plasma lipids and cardiovascular events.

Hubacek JA, Vrablik M.
SourceCentre for Cardiovascular Research, Prague, Czech Republic. jahb@ikem.cz

Abstract
Hypercholesterolemia or dyslipidemia is an independent risk factor for cardiovascular disease and statins (inhibitors of a key enzyme of cholesterol synthesis, 3-hydroxymethyl glutaryl coenzyme A reductase) are the drugs of choice for decreasing plasma cholesterol. It has been estimated that genetic factors can explain 40%-60% of final cholesterol concentrations and approximately 70% of the efficacy of statin treatment. The gene most often analyzed in the context of statin efficacy is the gene for apolipoprotein E (APOE). This review summarizes evidence of the association between variations in the APOE gene locus and the response of plasma lipids to statin therapy. Although the results are not consistent, carriers of the APOE4 allele seems to be less responsive to statins than carriers of APOE2 and APOE3 alleles. This effect is partially context-dependent (gene-gender interactions; gene-nutrition and gene-smoking interactions have not yet been studied) and the absolute differences vary between different population groups.

CNS Neurosci Ther. 2011 Oct;17(5):566-76. doi: 10.1111/j.1755-5949.2010.00189.x. Epub 2010 Aug 16.

Genomics and pharmacogenomics of dementia.

Cacabelos R, Martínez-Bouza R.
SourceEuroEspes Biomedical Research Center, Institute for CNS Disorders and Genomic Medicine, Bergondo, Coruña, Spain. rcacabelos@euroespes.com

Abstract
Dementia is a major problem of health in developed countries, and a prototypical paradigm of chronic disability, high cost, and social-family burden. Approximately, 10-20% of direct costs in this kind of neuropathology are related to pharmacological treatment, with a moderate responder rate below 30% and questionable cost-effectiveness. Over 200 different genes have been associated with the pathogenesis of dementia. Studies on structural and functional genomics, transcriptomics, proteomics and metabolomics have revealed the paramount importance of these novel technologies for the understanding of pathogenic cascades and the prediction of therapeutic outcomes in dementia. About 10-30% of Western populations are defective in genes of the CYP superfamily. The most frequent CYP2D6 variants in the Iberian peninsula are the *1/*1 (57.84%), *1/*4 (22.78%), *1×N/*1 (6.10%), *4/*4 (2.56%), and *1/*3 (2.01%) genotypes, accounting for more than 80% of the population. The frequency of extensive (EMs), intermediate (IMs), poor (PMs), and ultra-rapid metabolizers (UMs) is about 59.51%, 29,78%, 4.46%, and 6.23%, respectively, in the general population, and 57.76, 31.05%, 5.27%, and 5.90%, respectively, in AD cases. The construction of a genetic map integrating the most prevalent CYP2D6+CYP2C19+CYP2C9 polymorphic variants in a trigenic cluster yields 82 different haplotype-like profiles, with *1*1-*1*1-*1*1 (25.70%), *1*1-*1*2-*1*2 (10.66%), *1*1-*1*1-*1*1 (10.45%), *1*4-*1*1-*1*1 (8.09%), *1*4-*1*2-*1*1 (4.91%), *1*4-*1*1-*1*2 (4.65%), and *1*1-*1*3-*1*3 (4.33%), as the most frequent genotypes. Only 26.51% of AD patients show a pure 3EM phenotype, 15.29% are 2EM1IM, 2.04% are pure 3IM, 0% are pure 3PM, and 0% are 1UM2PM. EMs and IMs are the best responders, and PMs and UMs are the worst responders to a combination therapy with cholinesterase inhibitors, neuroprotectants, and vasoactive substances. The pharmacogenetic response in AD appears to be dependent upon the networking activity of genes involved in drug metabolism and genes involved in AD pathogenesis (e.g., APOE). AD patients harboring the APOE-4/4 genotypes are the worst responders to conventional antidementia drugs. To achieve a mature discipline of pharmacogenomics in CNS disorders and dementia it would be convenient to accelerate the following processes: (i) to educate physicians and the public on the use of genetic/genomic screening in daily clinical practice; (ii) to standardize genetic testing for major categories of drugs; (iii) to validate pharmacogenomic information according to drug category and pathology; (iv) to regulate ethical, social, and economic issues; and (v) to incorporate pharmacogenomic procedures both to drugs in development and drugs on the market in order to optimize therapeutics.

Pharmacogenomics J. 2007 Feb;7(1):10-28. Epub 2006 Jun 13.

Complex disease-associated pharmacogenetics: drug efficacy, drug safety, and confirmation of a pathogenetic hypothesis (Alzheimer's disease).

Roses AD, Saunders AM, Huang Y, Strum J, Weisgraber KH, Mahley RW.

Source

Genetics Research, GlaxoSmithKline Research and Development, NC 27709, USA. allen.d.roses@gsk.com

Abstract

Safety and efficacy pharmacogenetics can be applied successfully to the drug discovery and development pipeline at multiple phases. We review drug-target screening using high throughput SNP associations with complex diseases testing more than 1,800 candidate targets with approximately 7,000 SNPs. Alzheimer's disease data are provided as an example. The supplementation of target-selected screening with genome-wide SNP association, to also define susceptibility genes and relevant disease pathways for human diseases, is discussed. Applications for determining predictive genetic or genomic profiles, or derived biomarkers, for drug efficacy and safety during clinical development are exemplified by several successful experiments at different phases of development. A Phase I-IIA study of side effects using an oral drug for the treatment of breast cancer is used as an example of early pipeline pharmacogenetics to predict side effects and allow optimization of dosing. References are provided for several other recently published genetic association studies of adverse events during drug development. We illustrate the early identification of gene variant candidates related to efficacy in a Phase IIA obesity drug trial to generate hypotheses for testing in subsequent development. How these genetic data generated in Phase IIA are subsequently incorporated as hypotheses into later Phase clinical protocols is discussed. A Phase IIB clinical trial for Alzheimer's disease is described that exemplifies the major pipeline decision between program attrition and further clinical development. In this case, there was no significant improvement in 511 intention-to-treat patients but, applying a confirmed prognostic biomarker (APOE4) to segment the clinical trial population, all three doses of rosiglitazone demonstrated improvement in patients who did not carry the APOE4 allele. The data for the APOE4 carriers demonstrated no significant improvement but suggested that there may be a need for higher doses. Thus, a development program that would have been terminated progressed to Phase III registration trials based on the results of prospective efficacy pharmacogenetic analyses. The implications of using APOE genotype as a biomarker to predict efficacy and possibly dose, as well as supporting the basic neurobiology and pharmacology that provided the original target validation, is discussed. Citations are provided that support a slow neurotoxic effect over many years of a specific fragment of apoE protein (over-produced by apoE4 substrate compared to apoE3) on mitochondria and the use of rosiglitazone to increase mitochondrial biogenesis and improve glucose utilization. Pharmacogenetics is currently being used across the pipeline to prevent attrition and to create safer and more effective medicines.

Hence, the pharmacogenomics research and continued application may be conducive to optimizing drug development and therapy for AD patients by increasing efficacy and safety while reducing side effects.

Is AD all about the genes?

Is AD strictly a genetic disorder that is hard-wired in our genes? That is the question of our age. Using techniques such as micro-array analysis and monoclonal antibody analysis, tests were developed in the 1990s that help define genetic uniqueness. One example of this is genotyping the apolipoprotein E (apoE) type. In January 2012, Dr. Bland interviewed, Suzanne Craft, PhD, who is a professor in the Department of Psychiatry and Behavioral Sciences at the University of Washington and also Associate Director of the Geriatric Research, Education, and Clinical Center for the VA Puget Sound Health Care System. Dr. Craft explained apoE genotyping in this way:

"I think the best way to describe it is that there is the apolipoprotein E, which is a lipoprotein that is very important for lipid distribution and has been associated with cardiovascular disease for a long time, and it comes in three "flavors" (three alleles) that are designated apolipoprotein E2, 3,and 4. The apo E4 isoform produces a large increase in risk for Alzheimer's disease, so the E4 allele is associated with between something like a two-to-five-fold increase in one's risk for developing Alzheimer's disease across the lifetime."

But having the apoE4 allele does not solely determine the risk of developing Alzheimer's disease. Dr. Craft, who specializes in the study of insulin resistance and the development of cognitive impairment and dementia, explains:

"What we have observed is that when you have a group of patients with Alzheimer's disease, about 50% of them will have this E4 allele. That's a much higher percentage than in the general population. But for the other 50% who do not have the E4 allele, they have Alzheimer's disease, but they do not have a genetic risk factor that, as of yet, has been identified. But interestingly, these patients are much more likely to have insulin resistance. The patients with Alzheimer's disease with the E4 allele do not typically have insulin resistance or, really, a potentially greater level of insulin resistance than the normal population. The way we think about this is that there are potentially two paths to Alzheimer's disease, and probably more than that, but two main paths that we consider, one of which is driven by the physiological processes that are associated with the E4 allele, and then the second major pathway would be driven by factors that are related to insulin resistance."

In the past, we have been quick to make a gene connection to a condition, assuming flawed genes or genetic polymorphism cause the condition. But we should not jump to conclusions of that type, even in the case of neurodegenerative disease. We can modify the influence of many genetic characteristics—our sensitivities—on the basis of how we treat those genes. We really should be asking, therefore, if we can modify the environment so the apoE4 genotype does not exhibit undue influence on the physiological state that results in early neuronal death in the hippocampus and cortex. This is a very different hypothesis, and a different approach toward medical evaluation and intervention, from any we have previously asked when our focus has been on diagnosis and treatment.

Neuronal Plasticity

Let us talk about protection of the brain. It was only about 10 to 15 years ago that the brain, once injured in the adult, was considered irreparable. Lost neuronal reserve from neuronal injury caused premature cell death (called “apoptosis”), and that was that. The emerging model is that the brain can repair itself; the broken brain can be partially fixed. For almost 100 years, neuroscience embraced the dogma that a mature adult’s brain remained a stable, unchanging, computer-like machine with fixed memory and processing power. If brain cells were lost, new ones could not be gained. That was the deterministic model.

In September 2003, several papers appeared in *Scientific American* about the ability of the brain to repair itself. The brain is plastic; it is changing; it can learn as we grow older; and it can defend itself against certain agents. There may be significant ways that brain function can be improved by protection and stimulation.[3] There may be natural agents to be discovered which block the brain’s destructive process—the apoptotic process, the neuronal suicide process. These substances, as they are discovered, will allow for better delivery of neuroprotective therapy.

It is beginning to be understood that there are stem cells present in the brain that can engage in regeneration, admittedly slowly and not with the same reparative ability as the liver or the skin, but enough to have a positive effect. Neurologists are now moving toward interventions that would help to protect against the loss of neuronal function and to support repair of the brain. In the past 5 to 10 years, neuroscientists have discovered that the brain does, indeed, change throughout life and that such revision is a good thing. New cells and connections that have been documented through studies done at cognitive and neuroscience levels, provide the capacity for the brain to manage the challenges that increase as we grow older. There are many experiences in life we want to hold onto, plus many new things to learn. The environment is continually changing.

Metabolic Disturbance

Elevated homocysteine has also been statistically associated with both increased incidence of Alzheimer’s dementia and of coronary heart disease.[8] It has been suggested the reason for this is that homocysteine is either a cause or an effect of inflammatory processes in specific tissues. In actual fact, when we start looking at homocysteine, it often comes as a biomarker in conjunction with a couple of other biomarkers that are elevated, and those are high sensitivity C-reactive protein (CRP) and also uric acid, which we often associate with gout, but also is another marker that is associated with increased upregulation of oxidative inflammatory stress.[9] So the combination of elevated homocysteine in conjunction with elevation of high sensitivity CRP and uric acid reflects a certain kind of metabolic disturbance that has a statistical association with Alzheimer’s disease, with type 2 diabetes, and with coronary heart disease.

Mitochondrial Dysfunction

"Up until as late as 2000 in our literature, you'll see statements such as 'Alzheimer's disease is a neurodegenerative disease, but the underlying pathophysiology is not really understood.' That's in our textbooks; it's in our literature; it's in our current articles. That has all made a transition. Paramount is understanding some of the unique features of the nervous system. Among those is being highly dependent upon the availability of glucose, and upon the productive ability of the mitochondria to maintain an energy gradient. That's because the nervous system is an electrochemical system in and of itself. It is highly energy-dependent. Disorders associated with mitochondrial dysfunction gave us great insight as to how the mitochondria, in several ways, may impact neurodegenerative processes. That has been the beginning of so many attempts at research arms of treatment—trying to ascertain if improvement of mitochondrial function could be achieved, and whether or not the cell can be protected from a course of death in terms of any of the neurodegenerative diseases. We used to say these disorders were very different. It is now clear that they share certain things related to the pathophysiology of a post-mitotic tissue…There's an entire cascade now being discussed in terms of genetic risk for disability to dedifferentiate and then incur apoptosis, as to whether or not healthy mitochondrial function can protect the cells from that particular demise. That's where a lot of basic research is being directed—trying to identify genetic risks for that outcome, including mitochondrial dysfunction, but also other inborn errors that may put a cell at risk. Over a lifetime, a cell may not die right away, but it sets itself up for apoptosis because of those risks. There are several good discussions in an article by Zhu et al. in the April 2004 issue of Lancet Neurology.1 They talk about the "two hit hypothesis" of neurodegenerative diseases. Among those intricate to that discussion is the role of the mitochondria and oxidative stress that may arise out of dysfunction." – From Catherine Willner, MD

Inflammation

In one of the Scientific American articles titled "The Quest for a Smart Pill," the author discusses how we can improve memory and cognitive performance in impaired individuals, and asks if there is a general theme that connects to other diseases of aging.[4] The theme that seems to be emerging is one of inflammation. We know from epidemiological studies that people on non-steroidal antiinflammatory drugs (NSAIDS) for osteoarthritis, or low-dose aspirin for the prevention of heart disease, have a 50 percent statistically lower incidence of Alzheimer's disease (in an age-adjusted study). Such research has been published in a number of journals, including a prominent study that appeared in the journal *Neurology* in 1997,in which it was suggested that antiinflammation has a positive impact on the prevention of brain injury.[5]

What goes on in the brain that creates inflammation? A great portion of the brain's mass is its immune system, the microglia. The microglia, just like the immune system in our body, the Kupffer cells in our liver, or the immune system in our gut (gut-associated lymphoid tissue, or GALT), all receive messages from the environment that potentially upregulate inflammation. When inflammation is upregulated in the brain, it is the same process that goes on in the liver, intestines, or blood. There is increased oxidative stress; there is an adverse impact on mitochondrial function that triggers cell signaling to

create more likelihood for apoptotic cell death; and nitric oxide (NO) output is increased, producing peroxynitrite. Increased risk to loss of organ reserve (the brain cannot repair itself as quickly as, say, the liver), may lead to compromised neuronal reserve and, ultimately, to dementia.

This is a complex, multifactorial process. All the good neuroprotective therapy in the absence of any neurologic stimulation will still lead to degeneration. That is the "use it or lose it" concept. If a person has no reason for living, no raison d'être, no biology of hope, feels despair, feels lonely, feels disconnected, and feels no affirmation as an individual, what are those feelings going to do to the ability of their molecules of emotion to produce repair? They are going to lower it. That is well recognized from the results of many neurological studies in animals and humans. It is important to feel that one's life has some sense of value, that there is something exciting to do, worthy of attention and intellectually stimulating. People need to keep moving. This concept is described in an article written by Dr. Mark George in Scientific American, titled "Stimulating the Brain."6 Activating the brain's circuitry with pulsed magnetic fields may help ease depression, enhance cognition, and even fight fatigue."

The Gut as the Second Brain

In March 2002, Dr. Bland interviewed Michael Gershon, MD, author of a book titled *The Second Brain*. In his book and in his interview with Dr. Bland, Dr. Gershon elaborated on the interrelationship between the brain and the gut:

"Like the brain, the gut also has dopaminergic neurons, whose function is yet to be determined. Right now every single class of transmitter that has ever been found in the CNS has also turned up in the gut. So you can think of the enteric nervous system as 'the second brain,' but another way of thinking about it is just simply as 'the brain gone south.' …When I was a student, ulcerative colitis was thought to be a psychosomatic disease. We now know ulcerative colitis and Crohn's disease are autoimmune diseases. There was something called the ulcerative colitis personality, which I think was real enough, but it wasn't that thinking bad thoughts put holes in your colon so much as having holes in your colon caused you to think bad thoughts. The gut has a real ability to cause mental disease. When you look at studies that show one form of anxiety or another, depression, or other psychoneurotic conditions in patients with IBS, you really wonder about the relationship. Is it primarily in the head or is it primarily in the bowel? It could be either. If your entire life is devoted to pain from your gut and intestinal agony, you can become crazy from it."

Some researchers, in fact, are examining potential linkages between the etiology of Alzheimer's disease and the digestive tract, with a specific focus on the oral cavity. Dr. Jay Lombard described this stilltheoretical work in April 2012:

"This is work that really comes from Rudy Tanzi's lab at Mass General. His lab identified that antimicrobial peptides, which are endogenous peptides involved in scavenging any kind of immune challenges, whether it is bacterial, viral, or even head injury, there's activation of these antimicrobial peptides.[11] What is so interesting about antimicrobial peptide, which abbreviated as AMP, is that the conformational structure, the molecular makeup of antimicrobial peptide, very closely resembles amyloid. So the theory is—and, again, this is still a theory but there are lots of leading witnesses that point to this being a significant culprit in Alzheimer's disease—is

that low grade infectious processes, in particular bacterium in the oral cavity, lead to increased expression of antimicrobial peptides. These antimicrobial peptides induce amyloid-like properties in the brain, and this is what's causing us to have an increased amyloid burden: an immune driven response to low grade infectious processes. This is also supported by the fact that there are higher rates of *Porphyromonas gingivalis* (*P. gingivalis*) in dementia patients, and other antibodies indicating an immune response.[12] The implications of this, of course, are quite profound. Because if we truly can establish a link between high levels of persistent 'benign' bacteria (chronic low grade inflammatory processes like gingivitis or periodontal disease), this may be a call to action to give people: A) much better vigorous oral hygiene; but B) consider a low dose of antimicrobial agents to reduce the infectious process in people who are at risk of developing dementia as a result of that process.

Personalized Lifestyle Medicine Therapies

When we start looking at various types of environmental exposures or environmental features that might associate themselves with Alzheimer's disease, we are obviously led to questions surrounding the diet. Food has classically been perceived as a means to provide energy and building material to the body. We have learned from Casimir Funk, the Goldbergers, Albert Szent-Gyorgyi, and others, that there are these small molecules that we call "vitamins," or vitamins. These are life-giving amines that are necessary to prevent deficiency of diseases like scurvy, beriberi, pellagra, xerophthalmia, and rickets; protein for kwashiorkor and marasmus. Food is relegated to energy and material construction of our connective tissues and bones, and these small regulatory micronutrients are there along with trace minerals to activate enzymes and produce our function. But research over the past years has provided exciting evidence that there are other mechanisms by which nutrients and the array of phytochemicals (thousands of them) can influence molecular systems and mechanisms that maintain things like mental function.

Historically, we have been eating foods that influence the function of our nervous system as a consequence of this interaction of the structure of molecules in the food with the function of our nervous system through a whole series of cell signaling modulations. Cell signaling refers to the fact that the structure of these molecules in the food interact with certain receptors that then signal through the cellular functions of the nervous system to induce (or produce) states of functional change. These would be things like enhanced alertness, or alterations of cognition or memory. These discoveries are leading to new food concentrate derivatives to try to improve central nervous system function, or normalize nervous system function, or to develop neuroprotective effects .

Let's look at the influence of plant-derived phytochemicals (food-derived materials) on neurological function. There is a rich history of the use of plant substances to alter perception and cognition and produce states of altered consciousness. But we recognize that virtually thousands and thousands of phytochemicals and plants may have direct or indirect influences on cell signaling processes that could be either directly, or by feedback processes, influencing nervous system function.

Dr. Mark Mattson, of the National Institutes of Health (NIH) has written several papers on neurohormetic chemicals found in our diet. Neurohormetic chemicals are actually phytochemicals, which he postulated (from animal studies) might have a positive impact on the prevention of

Alzheimer's-like etiology through the emerging mechanism of production of neurofibrillary tangles (another hallmark associated with Alzheimer's disease).[10] These phytochemicals—these neuroprotective phytochemicals—include things like sulfurahane from cruciferous vegetables, and epigallocatechin gallate (EGCG) found in green tea, things that are related to red wine and peanut skins, like resveratrol polyphenols, and alpha-acids that come from various foods that relate to the root vegetable family. These, Dr. Mattson's research suggests, are chemicals that in animal models are found to actually slow the rate of what might be considered the animal model of dementia.

How is it that food—entering the body through the mouth and traveling through the digestive system—can have impact the central nervous system (CNS) and cognitive function? The neuroendocrine immune system is an oxidative stress and inflammatory-related pathway. Gut-immune activating substances, which for many people may be things like food sensitizing proteins (i.e. gluten-containing proteins) that increase gut mucosal permeability, encourage the release across the gut mucosa of potential larger molecules, and can induce, then, inflammatory response.

Summary

What is the takeaway message for both consumers who are interested in maintaining optimal neurological health and for the practitioners who care for them? The message that genetic and physiological information combined with lifestyle strategies can influence outcome, even decades in the future. In December 2012, Dr. Bland interviewed Dale Bredesen, MD, founding president of the nonprofit Buck Institute for Research on Aging and a noted neuroscientist specializing in Alzheimer's disease research. Dr. Bredesen said this:

"We're arguing that Alzheimer's disease is no different than other chronic illnesses, such as cancer, osteoarthritis, and atherosclerosis. These all have to do with chronic imbalances that are because of the physiological set up…All of us should be practicing prevention from day one, and we should be looking early on for the earliest indicators. Don't wait until you have symptomatic Alzheimer's disease. We should all know what our CRP is. We should all know what our homocysteine level is. We should all know what our insulin level is. You can go on and on, and that includes genetic markers as well, so we know where we stand in this process. The Achilles' heel of these chronic illnesses is that you can see them coming in a way that you can't for acute illnesses, so you have a long-term warning system—if you choose to look at it—to warn you far ahead, and potentially avoid these illnesses."

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