

Holistic Primary Care

Circulation:
80,000 primary care
MDs, DOs, NDs,
NMDs and DCs

VOL. 8, No. 1

• NEWS FOR HEALTH & HEALING® •

SPRING 2007

www.holisticprimarycare.net

NUTRITION & LIFESTYLE

Connexins: Optimizing Health by Improving Intercellular Communication

BY ERIK L. GOLDMAN
Editor in Chief

Look on the back of a dollar bill and you'll find a profound biological truth: *E Pluribus Unum*. Out of many, One. While the Founding Fathers meant it as a political mandate, they might just as well have been talking about physiology.

A multicellular organism, be it a simple coelenterate or a complex, keyboard-clacking higher primate, is the epitome of this concept. *Something* is holding all those myriad cells and systems together. Something allows biochemical and electrical signals to pass through tissues, guiding their differentiation, organization, and regeneration, and permitting these staggeringly complex aggregations to function as a single unitary whole.

The "something" in question, the keystone of multicellularity, is a class of proteins called *connexins*. These simple amino acid chains have a curious property in that they aggregate to form tunnel-like structures called *connexons*, which then embed in cell membranes. Connexons on one cell can then join with connexons on nearby cells to form intercellular channels called gap junctions.

Gap junctions are the primary sites for transfer of ions, metabolites and messenger molecules from one cell to its neighbor. In short, connexons are the fundamental means of direct cell-to-cell communication. Think of it as the intercellular Internet.

The relative openness of gap junctions is influenced by a host of environmental factors including pH, electrolyte bal-

ance and a variety of hormonal and biochemical signals. These factors, of course, are highly influenced by an individual's diet and lifestyle. In other words, the way we live affects biochemical communication at the cellular level, explained Darrell L. Tanelian, MD, PhD, a neurophysiologist who has spent the last 20 years studying connexin function as it applies to health and illness.

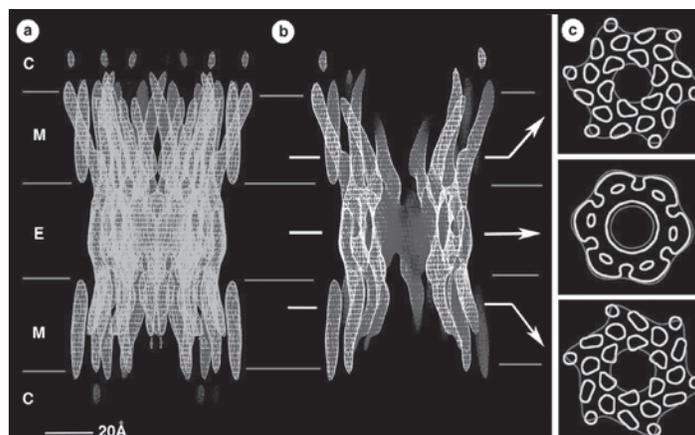
Dr. Tanelian, who formerly headed Stanford University's pain research program, and

founded the McDermott Center for Pain Management at the University of Texas Southwestern Medical Center, believes connexin research has opened up an entirely new direction in medicine, one that provides a basis for understanding the common pathways underlying seemingly unrelated disorders.

The future of medicine, he told *Holistic Primary Care*, lies in leveraging what is now known about how nutrition, stress, and exercise affect connexin function to optimize what he calls "molecular fitness."

Connexins & Chronic Disease

Connexon channels are integral to many core physiologic processes. In the myocardium, they permit rapid transfer of ions from one myocyte to the next, ensuring coordinated myocardial contraction. They allow flow of metabolites and regulatory signals through the liver. They regulate intracellular calcium and potassium concentrations throughout the brain and the nervous system. They govern the structural integrity of the vasculature and the chondral lining of the joints. They regulate wound healing and tissue repair. In



MOLECULAR ORGANIZATION OF A GAP JUNCTION, MADE OF TWO CONNEXONS ON ADJACENT CELLS, AND MEDIATING EXCHANGE OF ELECTROCHEMICAL SIGNALS BETWEEN CELLS. (A) FULL SIDE VIEW; (B) SAME VIEW WITH DENSITY CROPPED TO SHOW CHANNEL INTERIOR. MEMBRANES (M), EXTRACELLULAR GAP (E), AND CYTOPLASMIC SPACES (C) ARE INDICATED. WHITE ARROWS IDENTIFY CROSS-SECTIONS PARALLEL TO THE MEMBRANE BILAYERS. ALL CELLS PRODUCE CONNEXONS, COMPOSED OF AMINO ACID CHAINS CALLED CONNEXINS. THEIR FUNCTION, AND THEREFORE INTERCELLULAR COMMUNICATION, IS HIGHLY SENSITIVE TO NUTRITIONAL AND ENVIRONMENTAL FACTORS LIKE TISSUE PH AND MINERAL BALANCE.

Reprinted with permission from Vinzenz M. Unger, et al. *Science* 283: 1176-1180 (Feb. 1999). Copyright 1999 AAAS.

continued on p. 2

short, connexins make multicellular life possible.

Genes coding for connexins, and the degree to which existing connexon channels are open or closed, are highly sensitive to nutritional and environmental factors. Health at the organism level is a direct reflection of the functioning of connexon channels at the cellular level.

The major chronic diseases now plaguing industrialized nations—cardiovascular disease, cancer, diabetes, arthritis, osteoporosis, Alzheimer's, thyroid dysfunction, and age-related ocular problems, to name a few—are all characterized at the cellular level by dysfunction and down-regulation of specific connexins in particular tissues.

In Dr. Tanelian's view, these seemingly disparate conditions are really just different manifestations of the same core problem: a breakdown of intercellular communication and subsequent dysregulation of tissue function. Put another way, healthy cells intercommunicating optimally lead to healthy organisms; poorly functioning cells with dysfunctional communication engender illness and premature death.

A Simple System, A Host of Variants

Like many systems in nature, the connexin-connexon system is very simple in essence, but capable of myriad variations.

"There are 21 subtypes of connexins that we know of today," Dr. Tanelian explained. "They're numbered according to molecular mass or sequence homology." Functionally, connexins follow a set of rules regardless of the cell, tissue type or organism. Six connexin subunits aggregate together in a hexagonal structure with a central pore. These connexons may be comprised of 6 homogeneous connexins, 6 heterogeneous ones, or a combination of both."

Once formed, connexons migrate to the cell membrane where they embed, and ulti-

mately link up with connexons on neighboring cells, forming gap junctions.

Dr. Tanelian, who holds a PhD in neuroscience and advanced training in electrical engineering, became interested in connexins in the 1970s, while engaged in basic neurophysiological research. "We were publishing on how we sense and experience temperature, chemical and tactile stimulation. Somehow, you have to have a system that can convert very different energies into the same type of energy: electrical energy. I was studying how electrical potentials are generated in and equilibrate between cells. At that time, connexin research was really accelerating, and connexins seemed like a common factor *vis-à-vis* cell-to-cell information transfer."

Developmentally, organs form out of tissues that produce similar subsets of connexins. "Many congenital anomalies, such as congenital heart defects or congenital deafness, are due to dysfunction or absence of specific connexins," Dr. Tanelian told *Holistic Primary Care*. But these are relatively rare: far more common is the individual who produces all the right connexins, but in whom organ function is compromised because the person's diet and lifestyle impair connexin function.

Preventing Dis-Integration

Disease and death, understood at the cellular level, have a lot to do with the breakdown of intercellular communication.

"For a while, I was an attending physician at the Intensive Care Unit at Stanford Medical Center, and during that time, I saw a lot of people die," said Dr. Tanelian. It is always the same process, the same pattern of disconnection, though the "cause of death," or the starting point for the disconnection may be different. It is about dis-integration, the disconnection of organ systems from one another, and finally the functional breakdown of the organism."

He believes conventional medicine suffers from organ-

system myopia. "Specialists have real tunnel vision about their organs of choice. They all think a given disease has to do with 'their' organ, be it the heart or the kidneys or the liver. But the problems in the organs are just end-stage reflections of dysfunctions in metabolism and connexin function."

In arthritis, for example, dysfunctional connexins and gap junctions in the cartilage result in a breakdown of cartilage. Similarly, atherosclerosis is really a last step in a process that begins with deterioration of connections between endothelial cells. "In places where the vessel lining is disrupted, cholesterol will aggregate."

Cancer, of course, is the prime example of breakdown in intercellular communication. Specific connexin dysregulations have been identified in cancers of the breast, liver, prostate, bladder, ovary and kidney.

Currently, there are no clinical tools for measuring connexin function in living humans, though there are methods for monitoring this in cellular or tissue culture experiments. Dr. Tanelian noted that his future plans include research aimed at translating these bench techniques into useful clinical tools. "It is within reach, technologically."

Using the available experimental methods, however, researchers have been able to identify factors that positively or negatively affect connexins.

pH, Diet, and Connexin Function

Top on that list is pH. "Changes in pH dramatically alter flow and connectivity. You can watch this directly in tissue culture. Using bone cells as an example, at a pH of 7.4 the connexons are wide open. At a pH of 6.9, they are 80% closed." Connexons in neurons, myocytes, various types of skin cells, corneal, lens and retinal cells behave the same way. Dr. Tanelian believes optimization of connexin function is the primary physiologic "reason" why blood and tissue pH are so tightly regulated.

Extreme acidosis is lethal, plain and simple. It is interesting that pH is one of the key vital signs monitored in the ICU. "Once that starts to drop, death is imminent. But few physicians understand the physiological significance of pH, and it's function in daily life and health."

A majority of Americans walk around in a state of mild, subclinical acidosis. Blood and tissue pH are slightly lower than optimal levels—not so much so that it causes overt symptoms, but enough to disrupt intercellular communications.

Blood and tissue pH are directly related to diet. Foods can be roughly classified as acidifying or alkalinizing, not so much based on their actual acid or base content, but on the impact they have once digested and metabolized.

"The ability of something to be acidifying or alkalinizing has to do with the metabolism of its contents, and absorption of the metabolized substances," said Dr. Tanelian. "To go and measure pH of various foods you eat makes no sense. A citrus fruit has a pH of 2, but physiologically it is very alkalinizing to the body."

On the PRAL for Alkalinizing Foods

Looking at foods in terms of acid-base balance should be the cornerstone of any dietary approach to disease prevention. The objective is to increase alkalinizing foods especially fruits, vegetables, and tree nuts while minimizing acidifying foods like red meat, hard cheeses, salt, and refined grains.

The capacity of a food to be acidifying or alkalinizing is best assessed by a measure called Potential Renal Acid Load (PRAL), indicating its net acid-generating potential. This idea was first put forth by Sherman and Sinclair in the *Journal of Biological Chemistry* in 1907. The PRAL methodology, and an exhaustive listing of PRAL values for many common foods were later published by Remer and Mainz in

1995, and compiled in a user-friendly set of tables in Dr. Tanelian's recent book, *Molecular Fitness: The Connexin Connection to Optimal Health* (available at www.MolecularFitness.com; 1-800-646-1022).

PRAL provides a lot of insight into how foods function physiologically, beyond their calorie counts, glycemic index, vitamin/mineral content or other common nutritional measures. It also gives a more rational basis for common nutritional recommendations.

"For example, if you eat a lot of red meat, you end up with very high levels of cysteine, methionine, and other sulfur-containing amino acids, which are very acidifying." Red meats have a typical PRAL value around 8. Processed meats are even higher at 11. Hard cheeses can be in the range of 21, making them some of the most acidifying foods we can consume, explained Dr. Tanelian.

In contrast, vegetables like zucchini and carrots are in the range of -4 to -5. Alkalinizing heavy hitters like spinach have PRAL values of -14. Fruits are typically in the range of -2 to -5. Raisins are an alkalinizing slam-dunk, with a PRAL of -21.

"The real health problem with a high-protein, meat and cheese-rich diet is that it is very acidifying." A program like Atkins might help some people lose weight, but it's likely pushing them into a state of sub-clinical acidosis. At a cellular level, that makes for some very unhappy connexins.

Connexin-Friendly Feasting

If you consider foods from the acid-alkaline viewpoint, you'll encounter a number of surprises. Naturally occurring oils, for example, are neutral from a PRAL viewpoint. The same holds true for milk, and fermented dairy products like yogurt and buttermilk. On the other hand, some of the health food movement's sacred cows (sorry!!!) like brown rice and oats have surprisingly high PRAL values.

This is not to say that one should never eat brown rice or oatmeal; these foods have other health benefits. PRAL is only one consideration, but it does provide a handy guideline for meal-planning. People who want to minimize or avoid chronic disease should up their intake of PRAL-negative foods, and design meals that are as alkalinizing as possible, or at least neutral from an acid-base viewpoint, said Dr. Tanelian.

Your patients need not adhere to any one specific diet, nor do they have to completely give up favorite foods. They just need to learn how to balance their meals.

Say Peter Porterhouse really enjoys his steak dinners. If he eats a 7 oz lean steak, with a beer, a 7 oz side of pasta, and (to please his wife) a little broccoli, he's ended up with a total PRAL of almost 29, which is pretty darn acidifying. The same steak with a potato, spinach and red wine gives a PRAL of -18, which is nice and alkalinizing. The difference? The average potato has a PRAL of -8.0, which is a whole lot healthier than 14.6 for the pasta. Likewise, the spinach has a PRAL of -14, compared with the -1.2 for broccoli, which surely isn't bad, but not nearly as alkalinizing. The wine, with a PRAL of -4.8 is a better libation than the beer, at only -0.34.

"You can eat everything in the proper balance, and alkalinize the body," said Dr. Tanelian. "The Molecular Fitness lifestyle need not be a strictly vegetarian program unless you want it to be."

PRAL values are good guidelines, but there's nothing like self-monitoring to give patients a sense of how their diets affect their physiology. Urine pH, which you can easily teach patients to measure, fluctuates quickly in response to dietary factors, and once patients begin to see how various foods affect urine pH, they begin to make more intelligent choices.

Don't Take It With a Grain of Salt

Looking at diet from an acid-alkaline viewpoint helps explain the negative impact of things like high salt content. The problem with salt is its tendency to acidify blood and tissue fluids. The culprit here is not sodium, but the chlorine half of the sodium chloride duo. Sodium ions alone are actually alkalinizing, as are potassium ions. But chloride and sulfate ions are extremely acidifying.

"Chloride has very strong effects on connexins. Sodium chloride and potassium chloride are detrimental because of how they affect connexins." Dr. Tanelian strongly recommends eliminating chloride salts or keeping them to the barest minimum. "You make seawater out of your food when you salt it. Our ancestors figured out that drinking seawater was detrimental to health."

Interestingly, food labels only list sodium, which is meaningless except as a surrogate for chloride. "The one really meaningful thing you'd want to know—the chloride content—is one thing that they don't list."

Urine pH will certainly tell the tale, though. "If you measure it before and after eating a can of soup, which on average contains 2,500 mg of chloride, you'll see a massive change," said Dr. Tanelian. The challenge, of course, is that like high sugar levels, peoples' tastes have been conditioned to expect a lot of salt. "What most people taste as 'normal' is totally aberrant."

There is far more to the connexin story than pH alone. Glycemic load has a huge impact on connexin function in addition to its detrimental effect on insulin sensitivity. Dr. Tanelian believes disruption of connexin function secondary to chronically elevated glucose is a primary driver of the end organ damage (retinopathy, peripheral neuropathy, and renal failure) seen in diabetes. High glucose levels also have a measurable effect on connex-

in 36, an important connexin on the insulin-producing cells of the pancreas.

High arachidonic acid levels, typical with a meat and dairy-rich diet, are a big connexin closer, while essential fatty acids like eicosapentaenoic acid (EPA) from fish oils, and gamma-linolenic acid are connexin openers. Similarly, minerals, especially selenium, zinc, magnesium, potassium and calcium open connexins, thus improving intercellular communication. Dr. Tanelian said that many other nutritional sub-components, like various letter vitamins, have measurable effects on connexins.

Mind, Body, Connexins

In many ways, the gap junctions are the loci of the "mind-body" connection; they are where the signals exchange. It is no surprise then, that exercise and stress-reduction have direct effects on connexins and intercellular communication.

"Vigorous physical activity significantly increases four molecules: growth hormone, adrenocorticotrophic hormone (ACTH), cortisol and prolactin. All of these enhance connexin function," said Dr. Tanelian. When someone exercises at 100% of their maximal exertion level, ACTH and growth hormone both increase between four and twelve times their resting level. Prolactin rises more slowly, peaking at about 3 times the resting levels roughly 5 minutes after exertion. Cortisol rises within minutes and remains high for days or even weeks.

From a connexin viewpoint, vigorous exercise is key. Shoot for 80% of maximum heart rate. Brisk walking, running, cycling, swimming, rowing, squash and cross-country skiing are excellent choices. "I recommend 45-60 minutes of vigorous activity thrice weekly, complemented with strength training, stretching and relaxation training."

The latter is especially important. Chronic stress results in marked increases in

continued on p. 3

angiotensin II, endothelin I, and a host of mitogens all of which downregulate connexin function.

Connecting It All Together

For the past few years, Dr. Tanelian has focused on transmuting what is known about connexins and health into a comprehensive program that can be implemented in a busy primary care context.

The Molecular Fitness program is an integrative system that facilitates patient lifestyle and dietary changes all aimed at improving connexin function at the cellular level. Patients enroll through affiliate physicians, and they're provided with an "Empowerment Pack" that includes blood pressure, glucose, and urine pH monitoring equipment, a 30-

day supply of vitamin and mineral supplements formulated by Dr. Tanelian, a guidebook, data entry notepads, and access to the MolecularFitness.com member website.

The program provides lots of information support, including recipes and guidelines to help patients reshape their diets. But the cornerstone of the Molecular Fitness program is the self-monitoring component that fully engages patients in the quest for better health.

"It is based on conventional clinical measures like blood pressure, glucose, heart rate, and urine pH, all of which can be easily taught to patients," said Dr. Tanelian. The program's internet-based MyPHIT tools allow patients to enter their own daily data on a

secure website accessible to you, as the guiding physician. Patients can track changes so they can see the impact of their lifestyle changes. Real-time individualized data gives you as the physician a strong framework for communicating with the patient, and objective guidance for tailoring the program over time.

The idea is to integrate connexin-enhancing food choices, exercise, and patient self-education into a comprehensive system for improving health at both the cellular and the whole-person level. Ultimately it is about empowering people, something that's sorely lacking in the mainstream healthcare environment.

The "healthcare" system as it is now established rewards acute care and invasive proce-

dures, but provides little support or incentive for disease prevention and health promotion, said Dr. Tanelian, reflecting on his years administrating departments at major tertiary care centers. Clinics are focused on "billing opportunities" rather than healing opportunities. "The longer you keep someone sick, the more valuable they are to the system," he said. That perspective seemed antithetical to his core values, and his desire to leverage science in the interest of health promotion led to creation of the Molecular Fitness program.

"Each element of the program influences the performance and expression of connexin molecules," said Dr. Tanelian. "Just as with life itself, the whole is greater than the sum of the parts.")

For more Information contact:

HealthConnexin, Inc.

In the US **800-646-1022 x10**

International **617-837-9504 x10**

ConnexinCare@HealthConnexin.com

www.MolecularFitness.com