

Secretin and Autism: A Clue But Not a Cure

by Clarence E. Schutt, Ph.D.

The world of autism has been shaken by NBC's broadcast on Dateline of a film segment documenting the effect of secretin on restoring speech and sociability to autistic children. At first blush, it seems unlikely that an intestinal hormone regulating bicarbonate levels in the stomach in response to a good meal might influence the language centers of the brain so profoundly. However, recent discoveries in neurobiology suggest several ways of thinking about the secretin-autism connection that could lead to the breakthroughs we dream about.

As a parent with more than a decade of experience in considering a steady stream of claims of successful treatments, and as a scientist who believes that autism is a neurobiological disorder, I have learned to temper my hopes about specific treatments by seeing if I could construct plausible neurobiological mechanisms for the alleged successes of these treatments. At first, the secretin story seemed overinflated because secretin is not found in the brain. All that secretin does, according to most medical texts, is regulate the amount of bicarbonate in the stomach if the acid levels get too high—a built-in Alka-Selzer dispenser!

But, the more I studied, and learned from my Princeton colleagues who work in the fields of molecular biology, neurobiology, and immunology, the clearer it became that the research community has entered an entirely new phase in considering the "brain-gut" molecular communication links, of which the secretin family of hormones forms an important part.

I believe that the family of secretin receptors holds promise for developing treatments for autism. But because it is not normally found in the brain, more than likely secretin itself is not going to turn out to be the answer. Secretin is a clue, not a cure.

How Hormones Work

In the last century, physiologists believed that signalling between organs occurred solely by conduction of electrical signals along nerves, by analogy to the brain-muscle connection. The brain controls our muscles by means of meter-long neurons (or "nerve cells") that shoot down the spinal column and make contact with muscle fiber, telling it when to contract and when to relax.

But with organs like the pancreas, there were no nerve cells linking the pancreas to any other organ of the body. An outstanding riddle for these early pioneers was to explain how the pancreas could be stimulated to secrete bicarbonate and digestive enzymes into the upper intestines when the expected nerve

connections could not be found.

The answer was provided nearly one hundred years ago by Bayless and Starling, who discovered that it is not nerve signals, but rather a novel substance that stimulates secretion from the cells forming the intestinal mucosa. They called this substance "secretin." They suggested that there could be many such circulating substances, or molecules, and they named them "hormones" based on the Greek verb meaning "to excite".

A simple analogy might help. If the body is regarded as a community of mutual service providers—the heart and muscles are the primary engines of movement, the stomach breaks down foods for distribution, the liver detoxifies, and so on—then the need for a system of messages conveyed by the blood becomes clear. The hormones are like "letters" borne by the blood "postal system" to the receptor "mailboxes" on the surfaces of cell "factories".

While a telephone system—and, now, electronic mail—provides for instant delivery of information, much like the nervous system

of the body, a postal system provides reliable "hard copy" of essential, secure, and specific orders. Speed of delivery may not be as important as fidelity as the message passes through numerous check-points along the way. Studies on complex systems have shown that when a few of these orders are lost, or mailboxes cannot be found, a system can spin out of control in unexpected ways.

Today, we know of hundreds of hormones and their "receptors," including nerve growth factors, which stimulate growth of nerve cells; interleukins, which stimulate immune cell proliferation; and insulin, whose secretion from the pancreas is controlled by the hormone glucagon. The occurrence of many diseases, such as diabetes and Addison's disease, can be traced to deficiencies in these molecular signalling systems.

Once the deficiency is identified, even though the range of symptoms can be quite broad (as in autism), specific interventions, such as insulin injections for the treatment of diabetes, or new drugs, can be developed.

How an Intestinal Hormone Might Affect the Brain

How could an intestinal hormone produce the improvement in brain function we saw in the videotape of Parker Beck?

One answer may lie in the complexity of the secretin family of

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Peptides, Polypeptides, Neuropeptides, Proteins and Hormones

peptide: When researchers use the term "peptide" they are referring to a very short string of amino acids—a string far too short to be a protein. These very short strings are called peptides because whenever two amino acids combine they expel a molecule of water and form a bond called a "peptide bond."

polypeptide: The term "polypeptide" simply refers to more than two amino acids linked together.

neuropeptide: a peptide or polypeptide found in the brain.

protein: a protein is, essentially, a polypeptide that is long enough to form a 3-dimensional structure. Secretin is a polypeptide with 27 amino acids that coils up into a helix, thus becoming a (very small) protein. The researcher who developed purification schemes for secretin and sequenced its amino acids, Victor Mutt of the Karolinska Institute in Stockholm, called secretin a "mini-protein." (Ironically, Mutt died a few weeks before the DATELINE broadcast.) Glucagon, another member of the secretin family, is also a small protein with a helical structure, and is sometimes called a "minimal protein." The key to the polypeptide/protein distinction is this: once a polypeptide is long enough to develop a 3-dimensional structure it is called a protein.

hormone: The word "hormone" is simply a term for a chemical signal in the body. Some hormones are proteins (secretin and all of its relatives are proteins). Other hormones are not proteins or peptides at all, but instead are based on carbon rings. The steroid hormones, for example, such as cortisol, are not proteins. Whenever you see the term "hormone" think "signal." In other words the term "hormone" indicates a function rather than a particular structure or chemical content.

hormones. Although secretin was the first hormone to be discovered, it is no longer viewed as just a simple signal to the pancreas to release bicarbonate and water. Indeed, there remains a great deal yet to be discovered.

We know that secretin is a small protein having 27 amino acids along its backbone (see figure). Although this was known earlier from classical biochemical work, modern genetic analysis has shown that secretin is the defining member of a family of hormones having similar, but not identical, ordered sequences of amino acids along their backbones.

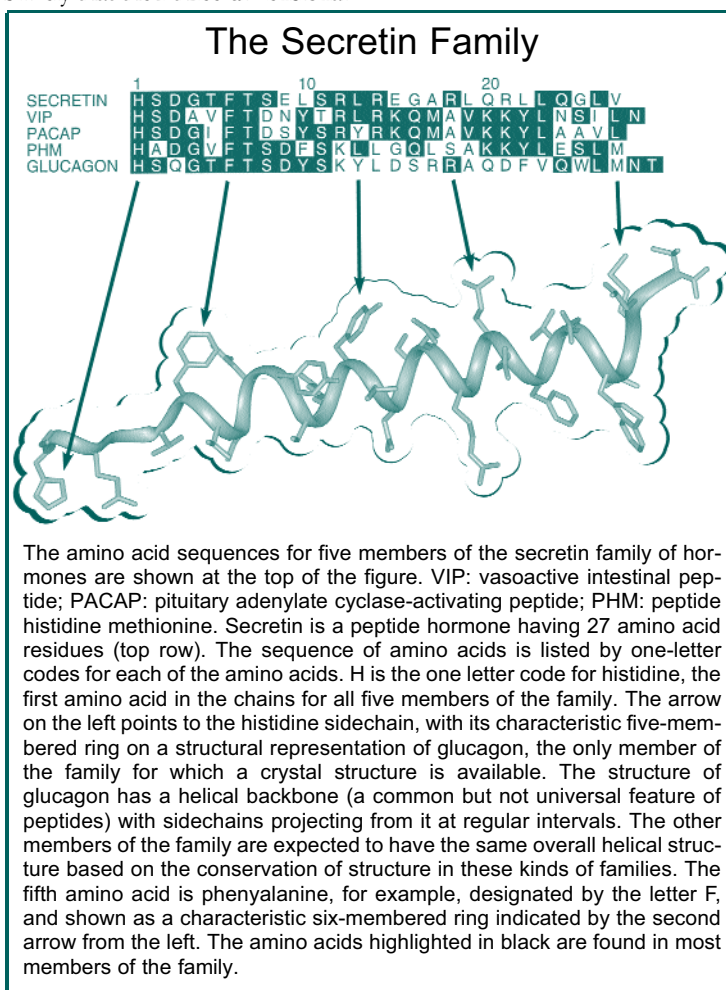
The backbone sequences of these three hormones (secretin, VIP, glucagon) are so similar that it is likely that their three-dimensional structures are alike. The differences in structure (protrusions, cavities, and charged patches on the molecular surface) will tell us what determines how these hormones are able to recognize and bind different receptors. These genomic analyses often toss up extraordinary surprises, such as the fact that the major peptide constituent of gila monster venom is a member of the secretin family!

Secretin receptors are proteins embedded in the membranes of target cells. On the outside of the cell, portions of the receptor form a pocket uniquely shaped to recognize secretin. On the inside, the secretin receptor links to so-called G-proteins whose role it is to relay to interior regions of the cell, such as the nucleus, the signal "to get going". A good example is provided by the VIP receptors on both T and B lymphocytes, which stimulate these cells to synthesize and secrete interleukin-2, and regulates their rate of migration in and out of the lymph nodes.

Because the members of the family resemble each other in structure, there is always the possibility that they can bind to each other's receptors, albeit more weakly. This "cross-talk" creates difficulties for endocrinologists (scientists who study the effects of hormones in the body) who are trying to assign specific functions to each member of the secretin family, for example.

In the autism study of Horvath et al., which reported on three autistic children who improved significantly after undergoing endoscopy with intravenous administration of secretin, the concentrations of secretin used were much higher than normally found in the bloodstream. This makes it likely that secretin was able to bind to receptors for secretin-like molecules in other regions of the body such as the hypothalamus or the hippocampus where there are no receptors for secretin itself.

Such a secretin "cross-talk" effect could have produced the startling improvements in Parker Beck because certain members of the secretin family are extremely important to brain function. Receptors for PACAP, another secretin cousin, are found on the surfaces of neurons in the hippocampus, the dentate gyrus and other areas of the brain's primary learning circuit. VIP-containing cells ("astrocytes") also appear in large numbers throughout the cerebral cortex, where their presumed role is to regulate energy levels in memory-forming neurons. The secretin-family hormones are so powerful that pharmaceutical companies are vigorously pursuing the possibility of treating ALS and stroke by administering secretin relatives intravenously to rescue "sick cells" in the brain.



The amino acid sequences for five members of the secretin family of hormones are shown at the top of the figure. VIP: vasoactive intestinal peptide; PACAP: pituitary adenylate cyclase-activating peptide; PHM: peptide histidine methionine. Secretin is a peptide hormone having 27 amino acid residues (top row). The sequence of amino acids is listed by one-letter codes for each of the amino acids. H is the one letter code for histidine, the first amino acid in the chains for all five members of the family. The arrow on the left points to the histidine sidechain, with its characteristic five-membered ring on a structural representation of glucagon, the only member of the family for which a crystal structure is available. The structure of glucagon has a helical backbone (a common but not universal feature of peptides) with sidechains projecting from it at regular intervals. The other members of the family are expected to have the same overall helical structure based on the conservation of structure in these kinds of families. The fifth amino acid is phenylalanine, for example, designated by the letter F, and shown as a characteristic six-membered ring indicated by the second arrow from the left. The amino acids highlighted in black are found in most members of the family.

It may seem surprising that the brief "pulses" of secretin infused into Parker Beck's bloodstream activated long-lasting effects; however, many hormones work via an "autocrine effect" whereby they cause their target cells to produce even more copies of themselves. It is possible that the infused secretin, by binding to the receptors for other members of the family, caused those cells to produce more of whichever "secretin cousin" actually produced the therapeutic effect.

We can only speculate about how secretin, once it began to bind with secretin-family receptors in the brain, may have restored brain function in Parker Beck. One possibility is that nerve cells that normally respond to members of the secretin family might be "shut down" in some autistic individuals. (There are many ways to imagine how cells may have gotten shut off in autistic brains; for instance during development, or due to an auto-immune response to an infection, and so on. Only further research can

find the answers.) When Parker's system was overloaded with secretin these cells may suddenly have become stimulated because of the similarity in structure between secretin and secretin-relatives that work in the brain. In other words, although secretin normally does not bind to any neurons in the brain, it may be doing so in children who respond positively to the treatment.

In mammals, the hypocretins, novel members of the secretin family, act as neurotransmitters in the hypothalamus, where they may be important in controlling overall energy balance in the body through appetite and satiety. The hypothalamus releases hypocretins not only to the pituitary via the circulatory system (or bloodstream) but also releases hypocretins directly to the central nervous system by secreting them via neural projections to different regions of the brain. It is possible that in Parker Beck secretin might have acted as a substitute hypocretin.

Animal research offers another fascinating clue to what may have happened in the case of Parker Beck. In *C. elegans*, a worm whose genetics and behavior have been extensively studied, a mutation in the receptor for neuropeptide Y, another member of the secretin family, leads to a population of worms that refuse to participate in what I call “swarming parties.” When you put food out on a plate normal worms will swarm into one spot to eat side by side. But cause a mutation in the gene for the neuropeptide Y receptor, and the worms crawl all over the plate eating; the social behavior of coming together for a meal disappears. This is a dramatic illustration of how social habits in animals, even on the lower rungs of the evolutionary ladder, are regulated by hormones of the secretin family.

What all of this means is that Parker Beck’s dramatic response to secretin may have been due to the health- or energy-promoting activity of secretin-family hormones in the brain. Thus it is possible that autism is akin to a brain-specific diabetes in that cells are not properly energized to perform the work of forming memories.

It is also intriguing that the hypothalamus also regulates the activity of the immune system, suggesting that in cases like Parker Beck’s perhaps some clearance phenomenon—like the clearance of an infection—may have been stimulated by activation of the hypocretin or VIP receptors in the brain.

Does this mean every parent should take his child to a physician for an “overdose” of secretin in hopes that the intestinal hormone will bind to receptors in the brain?

I would say no. The pancreas is one of the most delicate organs in the body, and we do not know what the effects of repeated large-dose administrations of secretin on a child’s pancreas might be. Why take a “sledgehammer” to a child’s system when, if the secretin cousins do prove effective, pharmaceutical companies will be able to develop a ball peen hammer in good time?

What Does the Future Hold?

As the genetic blueprint for human development continues to unfold, we can look at the distribution of genes for secretin-like molecules and receptors in the chromosomes and relate them to cell types and developmental pathways. Mutations and deletions should be detectable in the genes of autistic individuals if the secretin family is implicated. This approach has produced the success achieved so far in understanding Parkinson’s, Alzheimer’s and Huntington’s diseases. (The gene for Huntington’s was discovered by NAAR scientific advisory board member Jim Gusella.)

Next researchers will work with animal models, creating mice with mutations in the genes for secretin-like receptors in the brain, and then observing the changes in their behavior. Once we know which genetic mutations create autistic symptoms the groundwork will be laid for testing both hormonal treatments and new chemical compounds (drugs) that will be developed by mimicking the surface character of the secretin family of molecules.

Although it may sound easiest and safest simply to restore the missing hormone—like giving insulin to diabetics—in fact this is not necessarily the ideal solution. Drug companies are currently trying to figure out what part of the insulin protein could be mimicked by an organic molecule, i.e. a drug. For instance, it might be possible to design an oral medication that could be taken once a day, in place of the multiple insulin injections many diabetics self-administer today. A once-a-day pill might be less “natural” but still preferable.

GENES AND PROTEINS

A promise of the Human Genome Project is that we will be able to figure out how the body and brain communicate once we have before us the blueprints for all of the protein molecules that form the living substance of cells. Proteins catalyze the production of all the membranes, sugars, and nucleic acid molecules that make life possible, including of course secretin and the secretin family. A gene is a linear message that codes for the order of the amino acids that get strung together to produce a protein: we say that genes “code” for proteins. The differences among the thousands of proteins in the body lie simply in the order of the amino acid sidechains that project from the polypeptide backbone.

A note: assuming one hundred amino acids in the chain, because at any given position any one of the 20 different amino acids could appear, theoretically there are 20 to the 100th power of amino acid sequences. However, out of this astronomical sum only 10,000 or so are found to be necessary for the maintenance of life on this planet. A new field has emerged, protein engineering, to design and study proteins which have not yet appeared in any living organism.

If one or more members of the secretin family of hormones (maybe those found in the brain like hypocretin or VIP) turn out to be involved in causing the symptoms of autism, there is a clear path that a modern pharmaceutical company could take to develop a drug. Typically, in cases where a receptor is known, organic compounds (carbon-containing compounds) are developed that can bind to that receptor. For instance, if you know that serotonin, a naturally occurring neurotransmitter, is lacking in a particular disorder, you would try to create an organic molecule that could substitute for serotonin by binding to the serotonin receptor.

These chemicals, which become “drugs” once they have been fully tested and approved by the FDA, can strengthen or weaken the signal from the receptor to the interior of the cell, depending on whether the cell needs to be excited or calmed down to achieve the desired therapeutic effect. There are good precedents for thinking that treatments for autism might be found in this way. Lilly Research Laboratories developed Prozac, the

most widely prescribed antidepressant, by targeting serotonin receptors. Zyprexa, a new antipsychotic drug that is working wonders for persons who are schizophrenic, was discovered in a similar way. Active neuropeptides, such as the secretin-like hypocretins discussed above, have been known since the discovery of Substance-P by Ulf von Euler and Gaddum in 1931. Like members of the secretin family, Substance-P acts both on cells of the gastrointestinal tract and in the brain. Mostly, substance-P has been considered a vestigial message system, as if we still had Pony Express Riders available for getting packages delivered across country, since it was thought to be sluggish compared with smaller neurotransmitters like serotonin.

Recently, however, Substance-P analogues have been found that can alleviate the symptoms of major depressive disorder. This is an exciting development because it offers an entirely new paradigm for discovering psychoactive drugs, especially for diseases and conditions that have been linked to neuropeptide deficiencies or excesses.

Furthermore, many of these neuropeptides are normally present in vanishingly small amounts, rendering it more likely that molecular therapies in the form of an oral medication might work. Only small amounts of a drug would be necessary to affect the receptors these neuropeptides bind. (If very large amounts of

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these neuropeptides were required for the brain to function it would be difficult to find drugs to replace them because of delivery, solubility, and toxicity problems. As well, humans don't like to take "horse pills;" they like a nice tiny pill taken once a day.)

A second reason why a drug might be superior to simply replacing the missing hormone: most peptides, like secretin, have short half-lives in the bloodstream, meaning that they quickly disappear from the blood. This is a useful characteristic for a signal, but could pose an obstacle to a "hormone replacement therapy." In disorders where the normal response of a target cell to hormone signals may be diminished, chemical analogues or drugs might be designed to produce more sustained activity.

The secretin phenomenon, fueled by national coverage on television, has stimulated a huge uncontrolled series of experiments on our children. Taken at face value, the Dateline story may be pointing us towards considering a gastroneurological explanation for the symptoms of autism. However, there may be dangers in tinkering with the "bottle of hydrochloric acid" we all carry in our stomachs; for instance, some children could develop an immunity to the form of secretin being used (which is drawn from pigs) and begin to reject their own secretin with potentially devastating effects

There is a marvelous, though somewhat idiosyncratic, new book, *The Second Brain*, written by one of the respected pioneers of neurogastroenterology, Dr. Michael D. Gershon of Columbia University. Anyone who wants to think about other possible mechanisms and clues to understanding autism and secretin that I haven't developed in this "scenario for a future without autism"

should read Dr. Gershon's work. He tells us that there is a "second brain" in the gut with hundreds of millions of neurons articulated into an "unconscious" network of processing programs that we barely understand.

In thinking about human evolution, isn't it possible that we learned how to talk as we sat around camp fires, satiated with the day's hunt or harvest, and that communication between the gut and the brain started us all babbling? ♦

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