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STRESS, NEUROTRANSMITTERS & THE "SECOND BRAIN" IN THE GUT

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Researchers have often wondered why so many of our responses to stress are manifested by gastrointestinal complaints. Numerous people get "butterflies" in the stomach before an important interview or performing before a large audience. Others complain of cramps or diarrhea when they are nervous or upset. A disgusting sight can make you nauseated or "sick to the stomach" and someone you can't stand might give you "*agita*" or a 'bellyache".

Several other GI signs and symptoms could be cited as well as disorders that are frequently stress related, such as: GERD (gastroesophageal reflux disease), peptic ulcer, irritable bowel syndrome, ileitis and ulcerative colitis. In some instances, these may be caused by stress hormones that reduce natural defenses or represent "fight or flight" responses that once were purposeful during evolution. Thus, diarrhea could have life saving value for an antelope fleeing from a tiger since lightening the load would allow it to run faster.

Walter Cannon also suggested that in such situations, blood was shunted away from the gut, where it was not immediately needed for purposes of digestion, to the large muscles of the arms and legs to provide more strength in combat or a faster exit from a scene of potential peril. Hans Selye later showed that acute and severe stress consistently caused stomach ulcers in his experimental animals.

However, few of us are subjected to this type of stress today. Nor do these observations explain other effects of stress on the gut and how stress could contribute to some of the diseases listed. Over the past few decades, research on neurotransmitters, as well as an appreciation that **the gastrointestinal tract has its own "brain" that operates independently of the central nervous system**, has provided some answers.

The nervous systems in the gut and the brain are derived very early in life from the same primitive neural crest tissue. As the fetus develops, this tissue divides and one section becomes the central nervous system and the rest migrates away to form a

ALSO INCLUDED IN THIS ISSUE

separate nervous system for the gut. Later on, the vagus nerve connects the two nervous systems. "Vagus" is derived from Latin, where it means wandering, since the vagus winds from the brain stem through the neck and chest to the abdomen and stomach. While it is the major communication pathway between the brain and the gut, neurotransmitters also seem to provide certain crucial links.

What & Where Are Neurotransmitters?

Neurotransmitters are chemicals that transmit messages from one nerve cell to another at a junction between the two called a synapse. They are particularly abundant in the brain, where neurotransmitters like serotonin, norepinephrine, dopamine and acetylcholine allow neurons to talk to each other in ways that affect how we feel, think and act. Most people are unaware that the brain is not the only place where these chemical messengers are located. As Gershon notes in *The Second Brain*, a book that views the gut as the body's second nervous system, "A hundred million neurotransmitters line the length of the gut, approximately the same number that is found in the brain. There are more nerve cells in the gastrointestinal tract than in the entire remainder of the peripheral nervous system."

Over 40 neurotransmitters have been categorized and more are likely to be discovered. **Nearly every neurotransmitter involved in communication in the brain in the head has been identified in the gut's "second brain".** That should not be too surprising since both brains originated from the same rudimentary tissue. The question is what are they doing there and why are there so many?

The first neurotransmitter was discovered in 1921 by Otto Loewi, an Austrian scientist during a dream that he described as follows:

"*In the night of Easter Saturday, 1921, I awoke, turned on the light, and jotted down a few notes on a tiny slip of paper. Then I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl. That Sunday was the most desperate day in my whole scientific life. During the next night, however, I awoke again, at three o'clock, and I remembered what it was. This time I did not take any risk; I got up immediately, went to the laboratory, made the experiment on the frog's heart, described above, and at five o'clock the chemical transmission of nervous impulse was conclusively proved.*"

The experiment used two live frog hearts. Heart #1 was still connected to the vagus nerve and was placed in a chamber filled with saline. This chamber was connected to a second chamber containing heart #2 so that fluid from chamber #1 could flow into chamber #2. Electrical stimulation of the vagus nerve attached to heart #1 caused it to slow down as expected. However, Loewi observed that after a slight delay, heart #2 also slowed down. From this experiment, he hypothesized that electrical stimulation of the vagus nerve caused the release of some chemical into the fluid of chamber #1 that flowed into chamber #2. He referred to this substance as "*Vagusstoff*".

Loewi then showed that this chemical was acetylcholine and that it was released following stimulation of the vagus and all parasympathetic nerves. He subsequently found that a substance closely related to adrenaline played a similar role in sympathetic nerve endings. Loewi and Sir Henry Dale shared a 1936 Nobel Prize "for their discoveries relating to chemical transmission of nerve impulses." The two had been close friends since 1902 when they worked in the same laboratory. Dale had identified acetylcholine in ergot extracts and his analysis of its actions confirmed and greatly extended the application of Loewi's research.

What Do Neurotransmitters Do?

We can only scratch the surface of this complicated subject since some neurotransmitters have stimulating actions, some have inhibiting effects and many, like acetylcholine can do both, depending on the nature of the receptor. The two acetylcholine receptor types are named for substances that selectively activate them. The fast acting receptor is called nicotinic because it is specifically activated by the toxin found in

tobacco. The slow acting muscarinic receptor is activated by muscarine found in poisonous mushrooms. Acetylcholine will activate it but nicotine has no effect'

Stimulation of brain nicotinic receptors by nicotine from tobacco or arecoline from betel nuts (chewed by millions of people in India and Asia) provides a feeling of satisfaction that often leads to addiction. Some studies have shown that cognitive skills may be improved by stimulation of nicotine receptors. **It has been suggested that nicotine may be able to improve Alzheimer's patients since they have reduced acetylcholine nicotinic receptors in brain sites responsible for memory and learning.** Scientists have long suspected a possible link between acetylcholine and Alzheimer's since there is a 90% loss of this neurotransmitter in the brains of patients in advanced stages.

Acetylcholine is responsible for stimulation of all skeletal muscles and some in the GI tract. Death from botulinis poisoning is due to massive paralysis because botulinus toxin blocks acetylcholine. The derivative botox used to remove wrinkles works the same way but only affects specific muscles. Acetylcholine is also present in sensory as well as motor neurons and has even been found to play a role in initiating REM (dream) sleep.

Noradrenaline was discovered in 1946 by the Swedish physician and physiologist Ulf von Euler. He demonstrated that this was the adrenaline-like chemical Loewi had identified after stimulating sympathetic nerves and showed that noradrenaline was the key neurotransmitter in the sympathetic nervous system. Like adrenaline, it is secreted by the adrenal medulla during stress and causes an increase in heart rate and blood pressure.

Noradrenaline has also been found to be essential in retrieving certain types of memories. Researchers are now studying its effects in stress related disorders like depression and PTSD, both of which are characterized by difficulties and disturbances in memory retrieval. Von Euler shared a 1970 Nobel Prize for "discoveries concerning the humoral transmittors in the nerve terminals and the mechanism for their storage, release and inactivation."

Dopamine, a neurotransmitter that is closely related chemically to noradrenaline was discovered in 1957. It was referred to as the brain's "feel good" or "reward" chemical after it was discovered that dopamine release was stimulated by nicotine, cocaine, opium, heroin, and alcohol. It was later found that a dopamine deficiency in certain parts of the brain caused Parkinson's disease. As will be explained, dopamine may also be involved in the development of schizophrenia and obesity.

Serotonin was identified in 1948 but its complex effects on mood and behavior were not recognized until the following decade. Serotonin deficiency has been shown to be associated with depression, suicide, obsessive-compulsive disorder and problems with anger control. Too little can also cause carbohydrate craving and sleeping difficulties, both of which are common complaints in depression and other emotional disorders.

Scientists had long suspected that morphine relieved pain, and heroin brought pleasure, by acting on receptors for some natural neurotransmitter. In 1975, brain chemicals with similar effects were isolated and named endorphins, for "morphine from within." In addition to reducing pain, they induced the feeling of elation seen in "runner's high" and promoted endurance by providing a "second wind." The demonstration that exercise, laughter, sex, touch, and massage can increase endorphin production helps to explain many anecdotal observations and why such activities tend to make people feel good. Twenty different endorphins have now been identified that have varied effects. Beta-endorphins activate natural killer cells that boost immune system resistance to infections and cancer.

An Odd Orchestra With No Conductor

That's just a brief sketch of five important members of the neurotransmitter orchestra. Serotonin, dopamine and norepinephrine are often referred to as "The Big Three". All these neurotransmitters are monoamines and are often converted back and forth to one another. Others that are also involved in the response to stress are composed of very different chemicals including "The Mighty Two".

This term has been used to describe glutamate and GABA (gamma amino butyric acid), which some view as illustrating the *yin* and *yang* balance of neurotransmitters. Both are present in nearly all synaptic connections between brain cells but glutamate has excitatory actions while GABA has an inhibitory role. It's not quite that simple since there are two types of glutamate receptors, one of which, NMDA, controls the flow of calcium into nerve cells. Drugs that act as NMDA antagonists have been found to decrease depression and improve memory. During stress, NMDA activity is severely impaired and increased calcium influx can cause nerve cells to atrophy.

GABA is the main inhibitory neurotransmitter in the brain and blocks the effects of excitatory agents that cause anxiety. Tranquilizers like Valium as well as barbiturates and alcohol all act by facilitating GABA activities. Depressed individuals have low levels of both GABA and serotonin in their spinal fluid. Magnetic resonance spectroscopy measurements also show low GABA in certain parts of the brain in depressed patients that may have diagnostic potential. Following improvement with electroconvulsive therapy, GABA levels doubled. Antidepressants like Prozac that are thought to act by boosting serotonin also cause a rise in GABA.

Substance P, a peptide derived from two different types of amino acids, speeds up the transmission of pain signals from peripheral receptors to the brain and increases inflammatory reactions during the response to stress. Drugs that block Substance P have been found to relieve anxiety and depression and one was recently approved for treating chemotherapy induced nausea and vomiting.

The neurotransmitter CRF (corticotropin releasing factor) also known as CRH (Corticotropin-releasing hormone) (CRH) is a much larger peptide composed of 41 amino acids. During stress, it is secreted by the hypothalamus to initiate the hypothalamic-pituitary-adrenal response that causes ACTH to stimulate the production of cortisol. In addition, it activates sympathetic and behavioral responses to stressors and causes the release of GABA in the amygdala, a portion of the brain that is often referred to as "the pleasure center."

Melatonin is another neurotransmitter hormone that is manufactured in the pineal gland at the base of the brain. It is called "The Dracula Hormone" because it is secreted at night and regulates sleep-wake cycles. Serotonin in the pineal is converted into melatonin and then the process is reversed every 24 hours. This sequence of events takes exactly 25 hours when subjects are placed in a cave at constant levels of light for a week or more. However, when exposed to the natural outdoor cycle of daylight and darkness the pineal will automatically reset the body's clock to a 24 hour day. Melatonin makes you feel sleepy at night and the surge of stress hormones in the early morning is what wakes you up. Melatonin is also a powerful antioxidant that blocks the free radical damage thought to play a role in age related diseases such as cancer, cataracts, coronary, Alzheimer's and Parkinson's disease'

There are over two dozen other neurotransmitters, including secretin, glucagon, and cholecystokinin that control digestion, hormones (vasopressin, oxytocin, prolactin, thyrotropin, and gonadotropin and growth hormone releasing chemicals) that have widespread and varied effects. Soluble gases like carbon monoxide and nitric oxide are recent additions. Nitric oxide reduces inflammation, relaxes smooth muscle in the gut to promote peristalsis and in coronaries to relieve angina, stimulates the release of adrenaline and other hormones and mediates penile erection.

All these members of the neurotransmitter orchestra are constantly interacting and do so in concert during stress. However, there are no apparent conductors or soloists.

The Dopamine Dilemma

Trying to tease out what each of these chemical messengers does from this tangled web of wide ranging neurotransmitter interrelationships is impossible, as illustrated by the very versatile dopamine. **So much has been written about the role of dopamine in sex, love, compulsive gambling, smoking, drinking, and other addictions that provide pleasure, that a movie was devoted to it.** The prize

winning *Dopamine*, which premiered at the 2003 Sundance Film Festival explores whether all of the above are merely different manifestations of dopamine activities and if romantic love is also just a chemical response.

Dopamine can have varied and even contradictory effects, including: promoting feelings of rage or falling in love, making people more talkative and irritable, depressed, schizophrenic, decreasing blood flow to the gut and coordinating muscle movements. These and other responses depend on where dopamine is located and which nervous system pathways are either stimulated or suppressed.

A 2000 Nobel Prize was awarded to three scientists who showed that dopamine improved learning and memory and that Parkinson's disease was due to a deficiency of dopamine in a certain portion of the brain. This led to the discovery of L-dopa, which is converted to dopamine in the brain as a treatment for Parkinson's. In one animal model of severe Parkinson's, rabbits that had been in a sustained stupor awakened rapidly following injections of L-dopa.

This was the basis for *Awakenings*, a 1990 movie based on a book by Oliver Sachs. A disorder similar to Parkinson's disease was seen following the Spanish flu pandemic after World War I that killed up to 40 million people and caused encephalitis that left many others in a permanent coma. In the movie, Robin Williams, a neurologist assigned to a ward of such patients, decided to try L-dopa on Robert Di Niro who had been sleeping for 30 years. The movie describes how he suddenly awakes to find that he is no longer a teen-ager and how he and other treated patients try to cope with this strange new world.

Dopamine deficiency in other parts of the brain can cause depression, which is also common in Parkinson's. While most attention has focused on correcting low serotonin levels, drugs that boost dopamine and noradrenaline are also effective. Since these three monoamines are converted to one another in the brain it is difficult to determine which is being affected. Drugs like Effexor target both serotonin and noradrenaline and Wellbutrin raises levels of all three but particularly dopamine.

In addition to its antidepressant effects, Wellbutrin has also been found effective in treating addictions. Zyban, a sustained release version, is used to aid smoking cessation. Dopamine is strongly associated with reward and learning mechanisms because you don't learn as well if you're not rewarded. Zyban works best in patients who are not motivated as opposed to primarily being anxious. Cocaine and other addictive drugs increase dopamine by binding to sites that remove it but as these effects wear off, more is craved.

Anti-Parkinson drugs that work in a similar fashion are also associated with an increased incidence of compulsive gambling, shopping, eating and sex that disappear when dosages are lowered. Some believe that **the high rate of drug use and smoking in people with eating disorders could be partly explained by their increased need for dopamine**. In one study, obese individuals had less dopamine receptors than controls of normal weight and the heavier the individual, the fewer the receptors.

Schizophrenics have increased amounts of dopamine in the frontal lobes and a shortage here is associated with poor memory. Too much dopamine in the limbic system and not enough in. the cerebral cortex can produce an overly suspicious personality given to bouts of paranoia or may inhibit social interaction. Most antipsychotic drugs are dopamine antagonists that can have strange side effects. Risperdal, one of the most popular, was recently found to induce lactating breasts in young males, in addition to the more common complaints of drowsiness, dizziness, nausea, weight gain, constipation, nervousness, fatigue and difficulty in concentrating and sleeping.

The "Second Brain" In The Gut

In addition to the myriad effects that dopamine, serotonin and other neurotransmitters have on mood, mental status and behavior, they also have important influences on the gastrointestinal tract. Antidepressant and other drugs that affect neurotransmitter levels are frequently associated with GI complaints such as nausea, diarrhea, or constipation. This is not

surprising since all these chemical messengers in the brain are also found in abundance in the nerve supply to the gut.

While this enteric nervous system communicates with the brain via the vagus, it has a mind of its own. It regulates the esophagus, stomach, small intestine, and colon by mixing food with digestive enzymes and pushing it along via peristalsis. It is structurally quite similar to the central nervous system and is composed of the same sensory and motor neurons, neurotransmitters and even glial support cells that are found in the brain. Its proximity to the structures it regulates provides "second-to-second control" and eliminates the need for cables of nerve connections to the cranial brain.

Since all these components that operate independently from the central nervous system are entirely contained in the gut, it can be disconnected from the spinal cord and brain to study various parts as they continue to function. This provides an opportunity to study the effects of different neurotransmitters. For example, serotonin plays an important role in peristalsis by promoting communication between neurons throughout the colon to insure that constriction and relaxation are cordoned up and down the line. Altering serotonin levels changes the rate of peristalsis.

Other research may help to explain why half of senior citizens in nursing homes suffer from fecal incontinence, diarrhea and constipation. Colon segments from young and old animals show a decrease in the number of certain colonic neurons that control smooth muscle cells in the bowel with aging that can be restored with serotonin. By placing an artificial pellet in the intestine, it is also possible to study the influence of different drugs on motility and which neurons they affect.

The vagus nerve sends a steady stream of messages from the brain in the head to the enteric nervous system. Thus, during stress, the brain in the gut can immediately help to prepare the organism for "fight or flight". This response can vary from slowing down normal intestinal motility, shutting it down completely or evacuating intestinal contents through excretion or vomiting. When the gut brain receives a danger signal from above, it also helps to protect the body by triggering certain immune system responses. Mast cells in the lining of the small intestine and colon release histamine, another important neuro-transmitter. This causes an inflammatory response to attract immune cells from the blood stream into the affected area to deal with animal bites, knives or other foreign objects that might allow infectious material to enter the body.

The vagus is a two way street and messages are also constantly being sent up the line. The enteric nervous system signals the brain if it senses dangerous or infected food by inducing nausea, vomiting, abdominal pain or diarrhea. **Just like the primary brain, the "second brain" in the gut is able to learn, remember, and also produce emotion-based feelings.** The sensation of fulfillment, satisfaction and sometimes sleepiness after Thanksgiving dinner may be due to the tryptophan in turkey, which is converted into serotonin or the potatoes, stuffing, pies and carbohydrates that not only increases levels of tryptophan in the brain but pulls blood away from it to help in digestion.

Our "second brain" also produces benzodiazepines that alleviate pain and are found in anti-anxiety drugs like Valium. While it is not clear whether the gut synthesizes benzodiazepines from chemicals in our foods, bacterial actions, or both, we do know that during severe stress, the gut goes into overdrive to deliver benzodiazepines to the brain to reduce pain and anxiety. Some believe that the brain in the gut provides a major source of relief from these symptoms. Like the primary brain, the "second brain" has receptors for opiates. Drugs like morphine and heroin also attach to the gut's opiate receptors and both brains can become addicted to opiates.

Emotions And Energies From The Gut?

Our brain and gut are so interconnected that both have natural 90-minute "sleep cycles." In the brain, slow-wave sleep is interrupted by periods of rapid eye movement (REM) sleep during which dreams occur. The gut has corresponding 90-minute cycles of slow-wave muscle contractions and these cycles are also

interrupted by similar short bursts of rapid muscle movement. This may explain why some people often have vivid dreams and nightmares after a late night spicy snack and others develop cramps, *agita* or diarrhea when they are very nervous or angry.

Most patients with heartburn or irritable bowel syndrome have difficulty sleeping and many have disturbed REM sleep. In some instances, antidepressants can make all these complaints disappear and in others, there may be an improvement in some and a worsening of others. We now have some clues as to why responses may be so unpredictable. Depression is associated with poor appetite, decreased salivation and constipation. On the other hand, Prozac and antidepressants that increase brain serotonin frequently cause nausea, diarrhea, or constipation. In one study, when a traceable pellet was put in the "mouth end" of isolated guinea pig colon, it traveled down to the "anal" end just as it would inside the animal. When a small amount of Prozac was added, the pellet passed through twice as fast but when the dose was increased, the pellet stopped moving.

This may explain why small doses of Prozac are often used to treat chronic constipation, larger doses cause constipation and some people get diarrhea. In addition, Prozac stimulates sensory nerves resulting in nausea or even vomiting. While these drugs benefit depression by increasing brain serotonin, less is available for the gut, where more serotonin is produced than anywhere else in the body to regulate peristalsis and secretory activities.

The cerebral and gut brain connection is so close that determining which is doing what can be difficult and confusing. This is especially true when it comes to responses to stress as well as numerous drugs that increasingly appear to affect both brains.

The Greeks and Romans believed that the heart rather than the brain was the seat of emotions but in other cultures it was the gut. Indian deities are often depicted with tremendous tummies since this is where *prana* energy to sustain life was stored. Chinese statues of *Hotei*, the obese, "Happy Buddha", have big bellies to signify generosity and good fortune that people often rub to obtain good luck. In the King James Version of the Bible's *Song of Solomon*, "bowels" are "the seat of the emotions". Greek lexicons of the New Testament also translate "bowels" as "the deep, inner seat of tender emotions in the whole personality". Expressions like "My gut reaction is", "he has a lot of guts" and "I can't stomach that fellow" still support the notion that feelings can originate in various parts of the gut.

The use of "gut" to denote spirit or force of character, usually considered as being brain attributes, is a slang word that first appeared in the 1890's. Having "guts" now often means having courage or endurance and variations of these such as backbone, chutzpah, pluck, moxie, toughness, stamina, strength of will and intestinal fortitude. In addition to feelings, the gut is also believed to be an important source of energy. As Rabelais noted over 500 years ago, ***"From the gut comes the strut, and where hunger reigns, strength abstains."*** In the martial arts, *Qi* is believed to be stored in the *dantian* to produce the "elixir of immortality." This ancient Chinese term refers to a "center of energy" located deep in the abdomen at the level of the solar plexus, a large network of nerves behind the stomach. A karate chop or boxing blow that affects the solar plexus can incapacitate an opponent by causing severe pain and "knocking the wind out" due to diaphragmatic spasm that makes it impossible to breathe.

How brain and gut activities are synchronized under normal conditions and during stress is a mystery. In addition to serotonin, there are 'brain-gut" receptors for numerous other neurotransmitters with wide ranging functions. Why these are present in both brains is not clear, but suggests that communication between the two is much more complicated than is currently appreciated.

Why We Know Relative Little About Stress And Disease Or How Drugs Work

Over the past 50 years, all the books and articles about the response to stress and how stress can cause disease invoke Cannon's "fight or flight" sympathetic nervous system and adrenomedullary

responses and Selye's "Alarm Reaction" and "General Adaptation Syndrome" featuring the role of the pituitary-adrenal-cortical axis in the production of cortisol and cortical hormones. More recent research has focused on how cortisol lowers immune system resistance to infections and possibly cancer and causes short term memory loss and cognitive disturbances, and how cortisol and other stress related hormones can contribute to depression, anxiety, PTSD and other psychiatric problems. There is rarely any reference to, much less discussion, of effects on neurotransmitters that more likely mediate depression, a variety of anxiety disorders, and addictive behaviors that are stress-related. This is quite understandable. Such research is in its infancy for several reasons. Determining the concentrations of catecholamines, cortisol or other barometers of stress in blood, cerebrospinal fluid, or saliva are now standard, and accurate, reproducible procedures that are relatively inexpensive and often reimbursable are available.

While useful, these do not necessarily reflect what is going on in the brain. Measuring levels of specific brain neurotransmitters is very costly; techniques vary and require specific sophisticated equipment and expertise. This makes it difficult for others to confirm results or to conduct double blind studies that satisfy the scientific community's requirements for proof. Most such research is sponsored by pharmaceutical companies eager to develop blockbuster drugs for stress related disorders. Few would be willing to make the substantial investment needed to prove both the efficacy and safety required to obtain FDA approval. Another stumbling block is that even if you demonstrate that a new drug provides benefits and is associated with a consistent effect on some specific neurotransmitter, there is no proof that this is the mechanism of action responsible. We are just beginning to appreciate this with respect to Prozac and other antidepressants that presumably work by boosting serotonin but have been found to affect other neurotransmitters that most likely also play a role. Similarly, it is now quite obvious that the benefits of statins are not related to lipid lowering but rather to reducing inflammation and other "pleiotropic" actions.

As indicated previously, the space constraints and the format of this and most Newsletters make it impossible to include important relevant material and references that many readers have repeatedly requested. Because of this and rising production and postage costs, we are changing over to an electronic version that will allow additional and frequently more current coverage of certain topics. This should also provide a more convenient way to save and reference issues that are of particular interest. **It will therefore be necessary for subscribers to send their preferred e-mail address to: stress125@optonline.net as soon as possible to insure uninterrupted service.**

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