Neurochemistry of fibromyalgia and chronic fatigue syndrome

Today I'll be covering information of Fibromyalgia (FM) as there have been more studies of this disorder than pure CFS without FM. According to the American College of Rheumatology There may be a link between FM and a sleep disturbance, since most patients have disruptive sleep patterns. Psychological stress and deconditioning (lack of exercise) are often associated with FMS. Altered pain processing is thought to be a possible cause rather than contributor.

It is common knowledge that sleep disorders involve serotonin metabolic abnormalities. The primary sleep hormone is melatonin, which is derived, as does serotonin, from the metabolic processing of tryptophan. The latest theories of generalized allodynia or global pain also recognize a central sensitization phenomenon. This has been reported many times by Jon Russell MD and Robert Bennett MD.

Dr. Daniel Malone, a rheumatologist on the staff of the University of Wisconsin Hospital and Clinics, discussed chronic fatigue syndrome and fibromyalgia syndrome at Spring Seminar '98 on March 21 at the University of Wisconsin Hospital. He states, "If you invoke the problem in the control center of all these physical symptoms (of CFS and FMS) you could explain how it would all malfunction. What system contacts every other part of the body? The nervous system and the blood vessels. Which system is easier to study? The blood vessels -- you can biopsy those. Their function is to form a tube that carries a fluid. We have biopsied the blood vessels and have found no problem there. So that leaves the nervous system. And that is a problem because the nervous system's control center is not as accessible as the blood vessels are. Our nervous system's control center is the brain that is encased in a very impenetrable skull. Furthermore, it has all the functions of a three-story control center in a very small area, which means that everything is very compact. It's like trying to diagnose what's wrong with a computer chip by looking at it."

"We have an input plug and an output plug to our brain. If we do an MRI scan of that brain, what are we going to see? Nothing, most of the time. We have to go at the problem indirectly. Most researchers recognize that the problem with chronic fatigue syndrome and fibromyalgia is in the control center."

Muhammad Yunus, MD, rheumatologist and professor of medicine at the University of Illinois College of Medicine, Peoria, at the Ohio '97 fibromyalgia conference, August 8-10, 1997 described the. Dysregulation Spectrum Syndrome: A Unified Field Theory of Fibromyalgia and Related Illnesses. Yunus described the link between FM (fibromyalgia), CFS (chronic fatigue syndrome,) IBS (irritable bowel syndrome,) tension headache, migraine, and restless leg syndrome. He groups them under an

umbrella he labels "Dysregulation Spectrum Syndrome," defined as "a common biophysical syndrome characterized by endocrine dysregulation and dysfunction." Yunus sees it as related to stress, but points out that not all stress is necessarily psychological. He said he used to use the term "dysfunctional," but has dropped that because the psychiatric community takes that to mean that these illnesses, FM included, are of psychiatric origin, which Yunus thinks is incorrect.

Yunus identifies these characteristics of the DSS paradigm:

- **1. Clustering of DSS members (IBS, migraine, etc.) in a given patient group. These symptoms occur more often in this group than in the general population.**
- **2. A sharing of clinical characteristics among patients.**
- **3. A generalized hyperalgesic (heightened sensitivity to pain) state.**
- **4. Absence of the "classical disease model" (in which injury or illness can be identified by clinical signs, lab tests produce confirmation, and conventional treatment can be expected to work to effect a cure or relief.)**
- **5. Absence of the typical psychiatric model**
- **6. <u>A common neuroendocrine mechanism</u> (biophysiology, not pathophysiology)**
- **7. A common genetic linkage**
- **8. Response to neuromodulating drugs or interventions**

Statistically, IBS, headache, and dysmenorrhea (menstrual problems) occur in FM more commonly than in the general population; this occurrence is far greater than it would be by mere chance. Restless leg syndrome occurs in 31% of PWF (people with fibromyalgia), 15% of people with rheumatoid arthritis (RA), and 2% of the general population.

IBS is more common in people with FM and FM is more common in people with IBS. This is not true of inflammatory bowel disease -- Chron's, ulcerative colitis, for example.

1/3 of patients with RA have FM.

He presented arguments against FM as a depressive illness:

- *** the prevalence of depression in FM is similar to other chronic pain conditions**
- *** FMS and depression have different biochemical characteristics, as found in serotonin and hypothalamic-pituitary-adrenal axis studies**
- *** the types of sleep disturbance are different**
- *** the characteristics of cognitive dysfunction are different**
- *** FMS responds to much smaller doses of tricyclic agents (he doesn't call them antidepressants)**

A "couple of dozen" controlled studies of PWF have reported abnormalities in neurohormonal functioning.

Yunus presented arguments in favor of IBS being a centrally mediated illness rather than a gut disease:

-- No gut pathology is found -- gut motility studies show inconsistency, but motor abnormalities are present only when the patient is conscious -- the central nervous system influences gut motility

According to the Fibromyalgia and Chronic Fatigue Syndrome Channel, Research studies are looking at different aspects of fibromyalgia. At the University of Alabama in Birmingham, researchers are concentrating on how specific brain structures are involved in the painful symptoms of fibromyalgia.

One can get the predisposing factors, the contributory factors and the causes or causative factors of a disorder confused. No one is really sure of the cause of these FM, though an industry has been developed purporting to have the "answers" in the form of chemicals, nutrition, weak immune systems, chemical injury, infectious agents, Candida, coagulation problems. Are these causes or effects?

Predisposing factors for FM are gender as it is 7 times more common in females than males. Genetics as it tends to run in families and new research from the Netherlands suggests polymorphic abnormalities.

A common contributory factor is stress. Our modern culture has traded the stresses of survival found in third-world nations for a whole system of new stresses, which arise out of the technology and information-based society. These patterns of stress, when prolonged, typically lead to conditions of "running on empty" and "burn out". Poor nutrition, sedentary indoor lifestyles, lack of appropriate movement, insufficient sleep, and lack of emotional support increase the amount of "burn out" a person experiences. This condition of chronic "burn out" or "running on empty" is virtually universal in individuals who develop fibromyalgia. Several types of stress are considered in Chapter 1:

Family stress
Occupational stress
Nutritional Stress
Technological stress
Information stress
Iatrogenic stress
Financial stress

Another contributing factor in FM are connective tissue diseases such as Sjorgren's syndrome, Polymyositis, Polyarteritis nodosa, Systemic lupus erythematosis and rheumatoid arthritis. At times an elevated ANA will be

elevated over 1:80 persistently with a lack of criteria for a specific diagnosis of the family of connective tissue diseases. This disorder has been termed non - specific connective tissue disorder and the joints as well as the muscles are often affected. These disorders account for about 35% of FM cases.

Posttraumatic FM is present in about 12% of cases. This often involves a spreading effect after a whiplash, surgery, or a delivery.

Virus, such as Epstein Barr or Herpes 6, appears to be associated with some cases and secondary Candida is common. Cause or effect?

Adult Growth hormone deficiency
According to Robert Bennett MD, noted fibromyalgia researcher, writing for the Oregon fibromyalgia foundation. "Growth hormone deficiency in adults has been associated with a miscellany of symptoms that are similar to those described by fibromyalgia patients: low energy, poor general health, reduced exercise], muscle, cold intolerance, impaired cognition, dysthymia and decreased lean body mass

Consequences of adult GH Deficiency

§ Reduced skin thickness

§ Low VO2 max.

§ Reduced cardiac output

§ Reduced plasma volume

§ Cold intolerance

§Elevated lipoproteins

§Increased mortality

§ Poor general health

§ Increased fat / decreased muscle

§ Low energy

§I mpaired cognition

§ Dysthymia

§Reduced exercise capacity

§Quality of life

Furthermore GH is important in maintaining muscle homeostasis], and it was theorized that sub-optimal levels might be a factor in the impaired resolution of muscle microtrauma in FM patients . The treatment of GH deficiency in adults has been reported to improve quality of life and

energy level , reduce], improve, enhance self esteem, improve cholesterol and LDL levels, enhance cognitive psychometric performance, augment stroke volume, and improve exercise capacity and muscle strength .“

My conclusions

Some but not all Fm patients with initial GH level (IGF1) below 100 ng/ml improved with GH injections but some did dramatically. Growth hormone is one of the most abundantly produced hormones produced and secreted by the brain. A deficiency is a reflection of a disordered central nervous system with widespread hormonal imbalances not just an adult growth hormone deficiency as proposed by Bennett.

Whatever the cause or causes it is agreed that a common physiological result is a disruption in neurochemistry. Initially elevated Substance P and reduced Serotonin was identified in FM but raising the levels of serotonin did not correct the problems though these drugs may help associated depression. Drugs that raise catecholamines such as epinephrine, dopamine and norepinephrine produce better results but overall have unacceptable side effects at higher doses and inconsistency.

For thirty years I have realized the importance of the neuroendocrine system as a central theme of many disorders even before it became fashionable to do so as attested to in my early medical journal articles “the Pentamic theory” and “Stress: the civilized killer” published in Osteopathic Annals in 1979. I have also tried everyone’s theories in trying to help FM patients with variable results. Certainly we would all agree that no one has a panacea for either CFS or FM. That is why I was exited by the results of the group working with Marty Hinz MD of Duluth Minnesota (www.neuroreplete.com**).**

He has defined a non-drug method of restoring the major brain hormones to a therapeutic area several times higher than the “average” levels. By restoring the levels of serotonin, epinephrine, norepinephrine and dopamine only to average levels the treated people did not improve. That is because in part, the average or reference range is determined statistically not by examining patients. It is estimated that 28% patients in such a range have major depression and one cannot be sure of all the other problems they have. It is more appropriate to bring the levels of all of these four hormones approximately 4 times higher than the reference range and keep it there. To activate the epinephrine pathway we use L-tyrosine and sometimes dopamine in a concentrated method. To see the catecholamine pathway refer to figure 1. As you restore the neurochemistry with concentrated doses of neurotransmitter precursors (amino acids of certain types and cofactors in high dosage) using a patented method, the brain will revitalize. As commercial tryptophan is not proven yet to be totally safe even though it can be found for sale, we use concentrated amounts of 5 hydroxytryptophan. It is noted that 5HT will convert into both serotonin and

melatonin. It also metabolizes into niacin and picolinic acid. More specifically, Serotonin is synthesized through 2-step process involving a tetrahydrobiopterin-dependent hydroxylation reaction (catalyzed by *tryptophan-5-monooxygenase*) and then a decarboxylation catalyzed by *aromatic L-amino acid decarboxylase*. The hydroxylase is normally not saturated and as a result, an increased uptake of tryptophan in the diet will lead to increased brain serotonin content.

Serotonin is present at highest concentrations in platelets and in the gastrointestinal tract. Lesser amounts are found in the brain and the retina. Serotonin containing neurons have their cell bodies in the midline raphe nuclei of the brain stem and project to portions of the hypothalamus, the limbic system, the neocortex and the spinal cord.

A trickle down effect occurs once the master computer remains recharged. Signals to the lower brain and control areas also improve and the signals from the brain to the muscles normalize. Since the endocrine system receives critical messages from the lower brain that will also improve including the adrenal responsiveness. The latter has been shown to be faulty in both CFS and FM. It will also help restore growth hormone levels without costly injections in theory. No one has ever proven this yet and that is one of my projects. Coincidentally sleep improves as the abnormal circadian rhythm of melatonin reverses.

Another important technique is to realize that as you raise the brain hormones in a balanced manner, the enzymes such as S adenosyl methionine are used up faster. SAMe by itself cannot balance brain hormones but a deficiency of it promotes depression. The second part of our method is to restore methylation to the body effectively. This not only keeps SAMe levels satisfactory but also over 50 other methyl dependent enzymes including glutathione. Glutathione is a powerful antioxidant and a steady amount of it will reduce toxicity and sensitivities. Migraines and irritable bowel symptoms are significantly reduced.

Lastly, though this method has no more side effects when used correctly than placebo, it can cause various symptoms and should be monitored by urinary neurotransmitters and someone who has taken formal training in the method.

Eventually many physicians in Texas eventually will be utilizing this method but for now only a few of us are interested in working with CFS and FM patients. A modification of this method is one of the more effective ways to assist in weight loss and fight major depression. That is where most interest in the group now lies. Dr Hinz's group has treated over 250 patients with FM since 1999 with no failures. A success is defined as all symptoms gone or reduced enough so that activities of daily living are not interfered with. I am proud to be a part of this group.

I still believe that there is a role for certain supplements, treatment of food and chemical sensitivities, treatment of emotional problems with cognitive therapy, emotional freedom and thought field therapy, and body work with myofascial release and manipulative methods.

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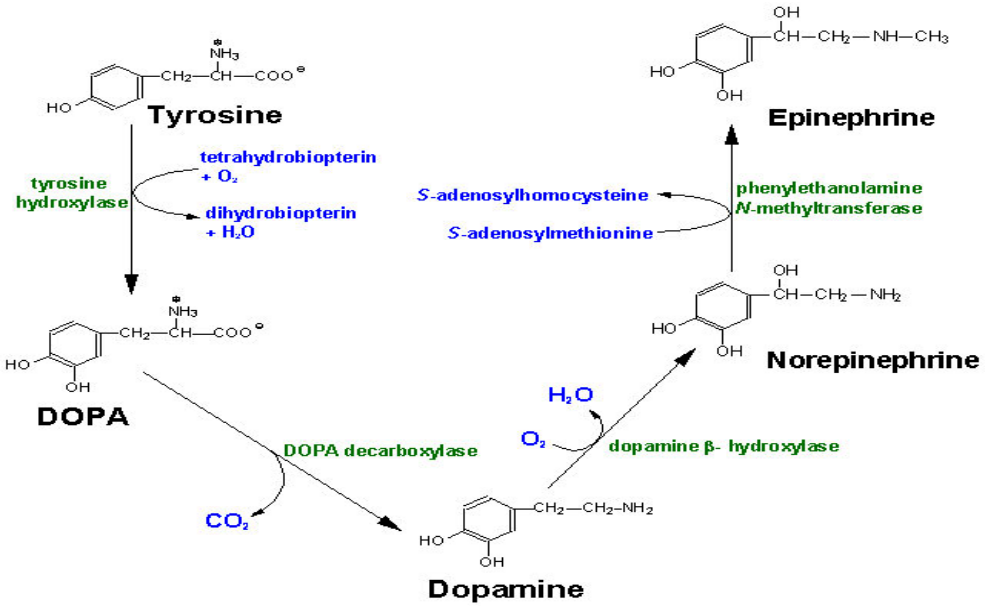

Figure 1

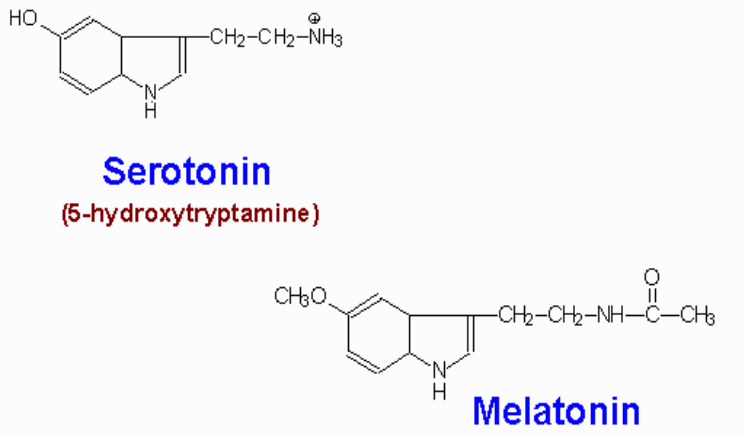

Figure 2