

SSRI Drugs and Serotonin --- What Creates the “Need”?

Few doctors understand that the serotonin in the brain is entirely different than the serotonin in the body. Most of the serotonin in the body is actually produced in the GI tract. --- That serotonin, plus much of the serotonin produced other places, can have extremely damaging effects in terms of blood flocculation and various inflammatory responses. Anything that increases serotonin beyond the tiny amounts needed has damaging effects in many ways --- including stressing the cardiovascular system, and increasing INFLAM-AGING. ----- Serotonin must be viewed in much the same way as estrogen and essential fatty acids. A tiny, tiny amount is physiologically useful. Even the slightest amount above that physiological essential is extremely damaging.

In the brain, there is a critical balance between serotonin on one hand and the catecholamines dopamine, norepinephrine, and epinephrine on the other. When the brain catecholamine to serotonin ratio is off in either direction, mental, emotional, and physical symptoms will result. In Dysaerobic and Sympathetic patients (and perhaps some Glucogenics) there tends to be high catecholamines, and perhaps low serotonin. In Anaerobic and Parasympathetic patients there tends to be low catecholamines, and perhaps high serotonin.

The most interesting thing about brain production of catecholamines and serotonin is that both metabolic pathways use the same enzyme. So --- illustrated clinically --- if you give Tyrosine or Phenylalanine to increase dopamine and then norepinephrine, you will get a very nice response initially. But, as that enzyme is being excessively devoted to the now up-regulated catecholamine pathway, it is being pulled away from the serotonin pathway. Again, initially this is good in restoring a depressed catecholamine to serotonin ratio to normal. However, very, very quickly serotonin is depleted and you end up trading one set of symptoms for another. Most people taking Tyrosine/ Phenylalanine will at some point (although it may be in the distant future) start to deplete serotonin. The same process applies in reverse if you supplement with 5-HTP. Almost no one can take 5-HTP for any length of time without some depletion of brain catecholamines.

The main problem with the SSRI approach to depression is that almost no one has a primary serotonin deficiency. In fact, serotonin is so easy to make from tryptophan there are only three ways to run a primary deficiency of serotonin:

- a) One is in strict vegetarians who have inadequate tryptophan in the diet; the other two are hypersensitivity reactions in the immune system associated with activated macrophages that in turn catabolize tryptophan, thus diverting it from the serotonin pathway. One way to divert tryptophan metabolism is by a deficiency of vitamin D, and the other is by a Prostaglandin Imbalance. This ImmunoNeuroEndocrine Stress reaction involving macrophages characterizes virtually all your patients who are low

in serotonin --- which is to say all your depressed patients who respond favorably to an SSRI drug for the first few weeks after it is prescribed.

- b) These INE mechanisms by which there can be a serotonin deficiency require a closer look. First, consider vitamin D deficiency. Brain serotonin is synthesized from tryptophan by the enzyme tryptophan hydroxylase-2, which is transcriptionally activated by vitamin D. Inadequate vitamin D (estimated to occur in 70% of the American population) assures that serotonin synthesis is not optimal.

Refer to the Tryptophan Metabolic Pathway illustration at the bottom of this Article. You see Tryptophan in the upper left hand corner. Across the top of the flowchart you see the branch of tryptophan metabolism that goes from tryptophan to 5-HTP to 5-HT (serotonin) then on to melatonin. Note that the first step of this branch of tryptophan metabolism requires the enzyme just mentioned --- tryptophan hydroxylase. Without vitamin D, this enzyme is deficient, and this entire branch of the tryptophan pathway to produce serotonin is insufficient. Since that branch of tryptophan flow is partially blocked, tryptophan preferentially goes down the left vertical pathway. That pathway leads to kynurenine, which is actually good. --- But --- if that pathway is overloaded, the flow continues all the way down to the excess production of quinolinic acid.

- c) Next, ask yourself what activates the macrophages that divert the tryptophan pathway away from serotonin and into a branch of that pathway that involves production of pro-inflammatory quinolinic acid and the cytokine Interleukin-6? It is an excess of an enzyme, IDO. What causes the IDO excess? IDO is up-regulated by a Prostaglandin Imbalance. That Prostaglandin Imbalance involves excesses of several Prostaglandins --- PGD₂, PGE₂, thromboxane, leukotrienes, Nitric Oxide --- and then all the pro-inflammatory cytokines that feed back and feed forward into and out of the Prostaglandin pathways.

Now, look at your Tryptophan Metabolic Pathway illustration below once more, and concentrate on the vertical flow down the left hand side. You will note that the very first step of tryptophan conversion to kynurenine requires the enzyme just mentioned --- IDO. What happens in a Prostaglandin Imbalance, when IDO is up-regulated? That branch of the tryptophan pathway is potentiated and huge amounts of quinolinic acid are produced, all the while very little serotonin is produced. So you have two consequences --- depression from lack of serotonin, and devastating IMFLAM-AGING from quinolinic acid itself, plus all the macrophages that are activated as part of excess quinolinic acid production.

Here we have another one of our Vicious Cycles. The Prostaglandin Imbalance associated with virtually any/all inflammatory processes increases inflammation (INFLAM-AGING) in multiple Vicious Cycles, but also up-regulates IDO. IDO, in turn, activates macrophages, which create yet another inflammatory reaction. IDO also leads to the production of quinolinic acid --- another pro-inflammatory. All the inflammation from activated macrophages and quinolinic acid induces inflammatory reactions in a broad array of body systems --- that inflammation creating more Prostaglandins, Nitric Oxide, leukotrienes, and cytokines --- and the Vicious Cycle keeps going round and round. The deficiency of serotonin because the excess IDO diverts the metabolic pathway away from serotonin production and into excess quinolinic acid production is just one side effect of these INFLAM-AGING Vicious Cycles.

[Interesting Side Note: Excess of IDO (--- which you have just seen, results from Prostaglandin Imbalance and/or vitamin D insufficiency) is one of the key players in the latest Immuno-Therapy research to discover cancer treatments. One of the most successful and most promising Immuno-Therapy (as an alternative to chemotherapy) drugs for cancer patients is an IDO inhibitor. While excess IDO suppresses or diverts the tryptophan to serotonin metabolic pathway, it also suppresses immune cells that should attack a tumor. IDO inhibitors unleash these previously suppressed immune cells and allow the body to mount an effective counter-attack against the cancer. IDO suppression is why there is a small grain of truth in the health food industry claim that vitamin D is “good for” cancer.]

The answer to low serotonin, then, is to reduce the various sources of ImmunoNeuroEndocrine Stress that underlie the IDO-producing inflammatory reactions. That means supplementing with IMMUNO-SYNBIOTIC, ADAPTO-MAX, OXY-MAX, TAURINE, and some combination of OXY TONIC, ELECTRO TONIC and/or OXY D+.

Myint AM. Cytokine-serotonin interaction through IDO: A neurodegeneration hypothesis of depression. Med Hypotheses, 2001.

Marieke C, et al. The role of IDO in the pathophysiology of interferon-induced depression. J Psychiatry Neurosci, 2004.

These two studies implicate pro-inflammatory metabolites --- particularly Prostaglandin E2, Interferon Gamma, and Tumor Necrosis Factor Alpha --- in the over-expression of IDO, and thus diversion of the serotonin pathway into the production of other pro-inflammatory mediators such as quinolinic acid.

