Cognitive dysfunction in women with chronic fatigue syndrome

Examining the role of the endometrium, the nuclear receptors, and the antimicrobial peptides

Amy Proal, Dept of Biology, Georgetown University

Chronic fatigue syndrome (CFS/ME) has recently been recognized by the CDC as a physiological disease that leaves patients substantially debilitated. Increasing evidence, including data from twin studies [1], points to the fact that patients with the illness also suffer from a significant degree of cognitive dysfunction - impairing their ability to process information and recall verbal and visual information [2]. We present data from a large cohort of CFS/ME patients in a study of a VDR nuclear receptor agonist, which suggest that women with CFS/ME tend to suffer from a greater decline in cognitive function than their male counterparts, and that cognitive function is at least partly restored by the agonist. The cognitive function of five women is examined in greater detail. For example, after falling ill with CFS/ME, one 45-year-old female went from being a corporate executive to reading at a 4th grade level. She became too confused to drive, lost her short-term memory, and forgot words, grammar, and basic math. Another patient was a corporate attorney who, after falling ill with CFS/ME, found that her reading skills fell to an 8th grade level. She lost the ability to solve problems and could not get beyond the first set of questions on an IQ test. In view of the recent report that the VDR nuclear receptor is over-expressed in the endometrium [3], it is possible that the severity of cognitive dysfunction among women may not be due to chance and that there is need for future research into gene expression in the endometrium.

1. Claypoole KH et al. A twin study of cognitive function in chronic fatigue syndrome: the effects of sudden illness onset. Neuropsychology. 2007 Jul; 21(4): 507-13.

2. DeLuca J et al. Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. Archives of neurology. 1993 Mar; 50(3):301-4.

3. Viganò P et al. Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. Journal of molecular endocrinology. 2006 Jun; 36(3): 415-24.

"I went from being a company executive to barely reading over the 4th grade level." --Alayne, age 45

"...and all of a sudden I couldn't understand how to find anything. I couldn't write an email, because I couldn't construct a sentence." --Natalie, age 21

"Sometimes when people are talking, it is as if some of the words are in a foreign language. I hear the words. But they don't make sense." --Claire, age 52

VDR blockage causes 1,25(OH)2D3 to rise and interfere with the feedback pathways controlled by the nuclear receptors.

"....All one can say definitively, at this point, is that the vitamin D metabolites will competitively displace cortisol and T3 from these nuclear receptors."

Marshall, Trevor G. 2008. "Vitamin D discovery outpaces FDA decision making." Bioessays 30(2).

Many nuclear receptors control the expression of families of antimicrobial peptides

"For example, the glucocorticoid receptor, RXRalpha, androgen receptor, Vitamin D Receptor, and T3R-alpha seem to be involved in control of 20, 18, 17, 16 and 15 families respectively, out of 22 analyzed."

Brahmachary M. et al. (2006). Computational promoter analysis of mouse, rat and human antimicrobial peptide-coding genes. BMC Bioinformatics, 7(Suppl 5), S8.

In women, does the fluctuation of nuclear receptor expression during menstruation and pregnancy offer pathogens an advantage?

"The expression of androgen receptor, estrogen receptors alpha and beta, progesterone receptor, and RARalpha followed cyclin A expression. There was more abundant expression in the proliferative phase endometrium than in the secretory phase endometrium."

Vlenonen A, 2004. "Expression of nuclear receptors and cofactors in human endometrium and myometrium." J Soc Gynecol Investig. 11(2):104-12.

The Vitamin D Receptor (VDR) is at the heart of innate immunity, gene transcriptions, and the expression of the beta-Defensin and cathelicidin antimicrobial peptides.

Marshall, Trevor G. 2008. "Vitamin D discovery outpaces FDA decision making." Bioessays 30(2):173-182.

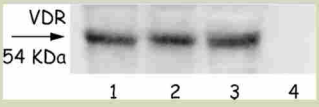
1,25(OH)2D3 and the Vitamin D Receptor are expressed in the cycling endometrium and pregnant decidua

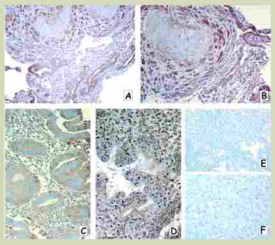
"The results of the study support the following observations: i) human cycling endometrium may be included among those sites capable of extrarenal synthesis and action of vitamin D ii) the enzyme 1-Ohase mRNA is expressed in human endometrial stromal cells independently of the phase of the menstrual cycle but its expression is up-regulated in early pregnant versus cycling endometrium."

"Taken together the results confirm the necessity to further investigate the functional role of the vitamin D system at the endometrial level."

Viganò P et al. Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. Journal of molecular endocrinology. 2006 Jun; 36(3): 415-24.

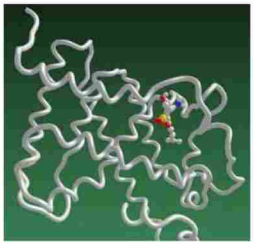
Cellular localization of 1-Ohase in human cycling endometrium and early pregnant decidua as evaluated by immunohistochemistry.





Expression of VDR in endometrial stromal cells and early pregnant decidual cells as evaluated by Western blot.

There is proof of concept that bacterial ligands can block the Vitamin D Receptor.



Bacterial capnine docked into the ligand-binding pocket of the VDR, acting as an antagonist.

Because the VDR is over-expressed in the endometrium, are women disproportionately affected by the negative effects of VDR blockage?

Could the suppression of innate immunity allow pathogens to infect the brain with greater ease?