Cognitive dysfunction in women with Chronic Fatigue Syndrome

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

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Numerous studies, including data from the Marshall Protocol study site, show that women are more likely to develop Chronic Fatigue Syndrome. Once they develop the disease, they tend to suffer from a greater level of cognitive dysfunction than their male counterparts.

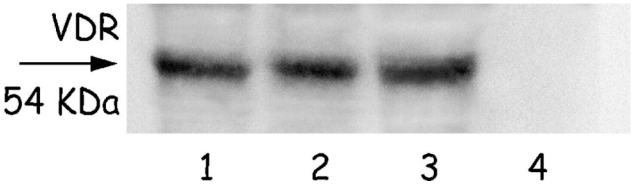
Why might this be? An obvious difference between women and men is that after puberty, the sexes express different hormones, in different quantities. Hormonal regulation is largely mediated by the nuclear receptors - the progesterone, androgen, alpha/beta thyroid receptors, etc. The Vitamin D Nuclear Receptor is also expressed in the female endometrium, marking yet another way in which nuclear receptor expression differs between the sexes.

Viganò et al recently identified that one of the hormones produced at high levels in the endometrium is the active vitamin D metabolite 1,25-D. Not surprisingly then, the research team also confirmed that both cycling and early pregnancy endometrial cells express the Vitamin D Receptor (VDR), which is activated by 1,25-D.

One of the body's most fundamental receptors, the VDR controls the activity of the innate immune system, transcribes the cathelicidin and beta-defensin antimicrobial peptides, and activates the transcription of hundreds and possibly thousands of genes.

The results of the Viganò study make one thing clear: because 1,25-D and the VDR are present at high levels in the endometrium, the substances are highly expressed in women. Why might this be?

One possible explanation is that since 1,25-D is the vitamin D metabolite that activates the VDR, it could be that early in human evolution, women acquired the ability to produce more 1,25-D and more VDRs because interactions between the hormone and the receptor would offer them an advantage during pregnancy - increased AMP production, increased gene transcription, etc.



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

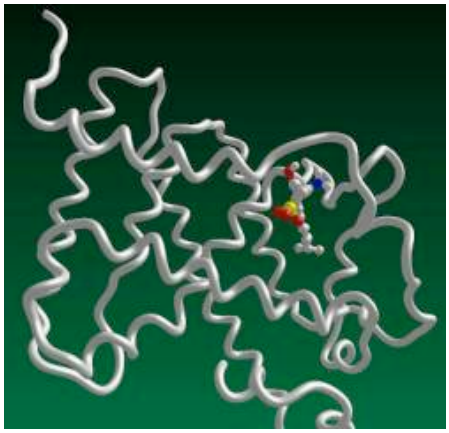
But at some point in the history of man, chronic idiopathic pathogens - L-form and biofilm bacteria, collectively referred to as the Th1 pathogens - evolved a way to take advantage of the VDR receptor by creating ligands that block its activity.

It appears that this bacterial survival mechanism turned what was intended to be a protective situation for a woman (particularly during pregnancy and menstruation) into an environment that now allows the Th1 pathogens rather than humans to gain the upper hand. Since women have more VDRs, they should, in theory, be more impacted by the negative effects of VDR blockage. This could, in turn, allow Th1 pathogens to infect the brain with greater ease, leading to symptoms of cognitive dysfunction.

Patients on the Marshall Protocol with diseases ranging from depression to ADD, OCD, anxiety, and bipolar disorder are reporting symptomatic improvement after taking bacteriostatic antibiotics aimed at killing

the Th1 pathogens. In fact, almost every patient on the Protocol is reporting mental as well as physical immunopathological reactions arising from the effects of bacterial death and the apoptosis of cells once inhabited by the bacteria. Symptoms of anxiety, depression, anger, and cognitive deficits are reported along with physical symptoms, confirming that the Th1 pathogens affect the brain as well.

As the Th1 pathogens take hold, the fact that women express more 1,25-D in the endometrium also becomes a problem. As the VDR becomes increasingly blocked, the receptor slows transcription of the gene for CYP24A1- an enzyme that metabolizes 1,25-D. With a diminishing level of CYP24A1 to keep the body's level of 1,25-D in check, the level of 1,25-D in patients with VDR blockage starts to rise. Molecular modeling, supported by clinical case reports, indicates that when 1,25-D reaches a certain threshold, it can bind other nuclear receptors, displacing the metabolites that are meant to be in them under normal conditions.



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

Furthermore, since each of these nuclear receptors transcribes various families of antimicrobial peptides, the displacement of their normal metabolites by 1,25-D potentially causes a decrease in bacterial killing, leading to immunosuppression. Brahmachary et al showed that the glucocorticoid receptor, the androgen receptor, and the Vitamin D Receptor, seem to affect the transcription of 20, 17 and 16 families respectively, out of 22 analyzed.

Since women produce more 1,25-D than men, they are disproportionately susceptible to the immunosuppression that takes place when the hormone displaces ligands from the nuclear receptors, causing a decrease in the production of so many different families of AMPs. Once again, this immunosuppression likely makes it easier for the Th1 pathogens to infect the brain, where they can cause a host of neurological symptoms.

Furthermore, since the expression of these receptors waxes and wanes during the menstrual cycle, even in healthy women, the activity of the AMPs that they transcribe may fluctuate over the course of a month. This could allow for periods when some women may be less able to kill invading pathogens. While men aren't affected by this surging and waning, it could be part of the reason why women appear to pick up the Th1 pathogens that cause CFS and the neurological symptoms associated with the disease at a greater rate than men.

Unfortunately, because 1,25-D levels rise to their highest point during pregnancy, the hormone's ability to cause immunosuppression by affecting the nuclear receptors is quite prevalent during this time. The subsequent ease with which the Th1 pathogens are able to spread, due to the drop in AMP production, may be why many women with CFS find their cognitive and other symptoms increase during pregnancy and after giving birth.

References

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