Vitamin D: A Health/Disease Switch in MS

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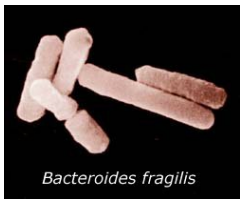
Introduction

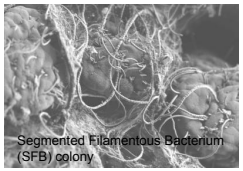
There is mounting evidence that alterations in the gastro-intestinal microbiota (due to lifestyle changes) have disrupted microbial-mediated mechanisms of immunological tolerance within and outside the gut and can affect various immunologic diseases in humans[1].

MICROBIOTA in the gut prevent or induce experimental autoimmune encephalomyelitis (EAE), a mouse model of Multiple Sclerosis.



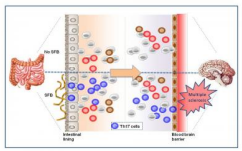
Bacteroides fragilis

Bacteroides fragilis' immunomodulatory molecule, polysaccharide A (PSA), mediates the conversion of $CD4^+$ cells into $Fox3^+$ Treg cells that produce IL-10. PSA does not just prevent EAE but also cures it[1,2].



Segmented Filamentous Bacterium (SFB) colony

Segmented Filamentous Bacteria (SFB) uniquely coordinate the intestinal T cell profile. SFB promote IL-17 production in the gut, and IL-17A-producing $CD4^+$ Tcell (Th17) in the CNS, and induce EAE[3,4]. This demonstrates that gut bacteria can affect neurologic inflammation in mice.



The hypothesis has been proposed that dysbiosis, imbalance, of the intestinal microbiota is an important factor in the development or severity of MS[4].

MUCUS in a healthy gastrointestinal tract (GIT) separates its content from its epithelial cell wall. The mucus layer coating the GIT is the front line of innate host defense[5]. It is transparent, and consists of 2 layers[6,7]. The outer layer (MUC2) is viscous and contains the microbiota[7]. The inner layer (MUC1) is anti-bacterial and is attached to the epithelial cells[7]. MUC2 deficiency in mice leads to inflammation of the colon[7]. Intestinal goblet cells synthesize MUC2 and bioactive molecules[5].

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CATHELICIDIN (hCap18/LL37) is an antimicrobial peptide (AMP). It increases mucus thickness and prevents inflammation in the colon[8]. Thus it enhances the intestinal epithelial barrier function. LL37 can directly stimulate mucus synthesis through a more than 50% increase in MUC1 and MUC2 mRNA levels[8].

VITAMIN D levels strongly upregulate the cathelicidin gene expression and production of cathelicidin/LL37 [9,10]. Interestingly, vitamin D deficient animals showed elevated levels (50-fold) of bacteria in colonic tissue[11].

Results

Serum vitamin D (25OHD) level of MS and controls.
(Summer and winter, Amsterdam, latitude 52°)

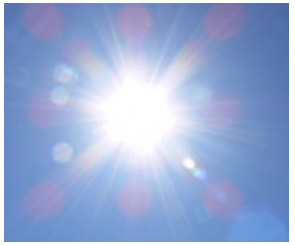
	MS patients (n=107)	Controls (n=101)	*P* values*
Summer nmol/L	97.4 (34.3)	102.5 (31.6)	0.269
Winter nmol/L	59.9 (24.9)	65.7 (27.1)	0.119
Summer-Winter nmol/L	**37.5**	**36.8**	

Values are shown as means with standard deviations in parentheses.
**P* values of Student's *t*-test.
Kragt et al., 2009[12]

- No statistically significant differences in serum 25OHD levels in summer and winter could be detected between MS patients and controls[12].
- The difference between summer and winter serum 25OHD levels is ~37 nmol/L[12].
- The lower serum 25OHD levels in winter are associated with higher incidence of MS and with higher MS-related disability (EDSS) in woman[12].

Discussion

It can be argued that the causative difference between the serum 25OHD levels of MS patients and controls may only have been present at disease onset[13].



In recent years, our view of what constitutes a sufficient vitamin D level has changed dramatically.

Studies to date argue that it is important for individuals to have sufficient serum 25OHD levels to allow cells in the body to synthesize cathelicidin when microbiota need to be killed[9,10,11,14]. Catelicidin in turn stimulates mucus production[8].

A serum vitamin D level of at least 75 nmol/L is considered a physiologic cutoff for vitamin D deficiency[15].

Vitamin D levels of 125 nmol/L, as found in summer, are considered a possible therapeutic target for MS[16].

The most recent lifestyle change is living a sun-deprived life, which causes vitamin D deficiency[17].

The other 'major' lifestyle change is diet: Switching from a low-fat, plant polysaccharide–rich diet to a high-fat, high-sugar "Western" diet shifted the structure of the gut microbiota within a single day[18].

A final intriguing question: ***Could one or all of these - Vitamin D, diet or a transplant with gut bacteria from a 'healthy' human - cure MS?***

Literature

Kragt J, van Amerongen B, Killestein J, Dijkstra C, Uitdehaag B, Polman Ch, Lips P. Higher levels of 25-hydroxyvitamin D are associated with a lower incidence of multiple sclerosis only in women. Mult Scler. 2009 Jan;15(1):9-15.

Literature is available on a separate handout.

MS Center Amsterdam