The clues for new roles of vitamin D and vitamin D receptor in neurodegeneration.

Erdinç Dursun & Duygu Gezen-Ak

ISTANBUL UNIVERSITY-CERRAHPASA
CERRAHPASA FACULTY OF MEDICINE
DEPARTMENT OF MEDICAL BIOLOGY
BRAIN AND NEURODEGENERATIVE DISORDERS RESEARCH UNIT
ISTANBUL - TURKEY

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Nothing to declare
The begining...

- Last decade gave us the opportunity to investigate the role of vitamin D and its receptor in development and disorders of central nervous system.
- Yet still the debate is going on validating the action of vitamin D and vitamin D receptor in brain.
- The aim of this talk is:
  1. What we have asked?
  2. What we have proved?
  3. What we have learned?
  4. What still remains to be discovered? 😊 a lot...
- in vitamin D basis of neurodegeneration
Alzheimer’s disease

**Amyloid Plaques**

Senile plaques (Silver Staining):
Amyloid aggregations (diffuse or dense) stained dark brown.

(http://www.medlib.med.utah.edu/WebPath/CNSHTML/CNS090.html)

**Neurofibrillary Tangles**

NFT, hematoxyline eosin.
Intracytoplasmic dense fibrillary structures.

(http://www.medlib.med.utah.edu/WebPath/CNSHTML/CNS094.html)

These pathological structures cause:
- Distruption of axonal transport,
- Distruption of signal transmission between neurons,
- Distruption of neurotrophic factor synthesis
- Distruption of neuronal calcium homeostasis
- Induction of oxidative stress

(http://www-medlib.med.utah.edu/WebPath/CNSHTML/CNS090.html)
Amyloid Beta

- Generated by the cleavage of APP via the secretases
- 4kDa, 39-43 amino acid

Does vitamin D act in brain?
Vitamin D receptor gene (VDR)- Alzheimer’s disease

- 1992 Sutherland et al.: The hippocampi of the AD patients have decreased VDR mRNA expression.

- 2001 Paduslo et al.: linkage study; indicated a AD related risk locus on chromosome 12q. No significant gene reported but the locus involved VDR in addition to other genes.

- 2006-2011: the first studies indicating the relation between vitamin D deficiency and cognitive decline.

- 2007 Gezen-Ak et al.: Certain VDR polymorphisms increase the risk of developing AD 2.3 times.

- 2009 Beecham et al.: GWA study (including 550,000 SNPs) reported a AD associated novel locus at chromosome 12q13. They indicated that among other genes VDR is the most probable candidate risk gene for AD given the data of Gezen-Ak study.

- 2012 Gezen-Ak et al.: VDR “TaubF” haplotype is more frequently seen in AD patients.
Genetic background of VDR-vitamin D pathway in neurodegenerative disorders

- **Association between VDR polymorphisms and Parkinson's disease:**

- **Association between Low density lipoprotein receptor-related protein 2 (LRP2 or megalin) the transporter of vitamin D at the plasma membrane and AD:**

- **Association between LRP2 (megalin) polymorphisms and cognitive decline**

- **Association between vitamin D binding protein (GC, VDBP) polymorphisms and Parkinson’s disease:**
Serum 25OHD levels
The relation between vitamin D and neurodegeneration

- **Vitamin D deficiency and cognitive performance** (2006-2010)

- **Vitamin D levels and cognitive decline** (2009-2010)
Vitamin D deficiency and Alzheimer’s disease

- **Meta analysis**: Serum 25OHD levels of AD patients are significantly lower than that of healthy controls!

- **Vitamin D deficiency increases the risk of developing AD and vascular dementia (VaD)!**
    - A longitudinal study
    - 30 years follow up
    - 10,186 individuals

- **Vitamin D induces amyloid beta clearance of macrophages in AD patients!**

- **Annweiler and Beauchet (AD-inea)**
    - A combined treatment of both vitamin D and memantine (a well known AD drug).
    - Gave significantly better results compared with the memantine alone treated patients.
Littlejohns TJ. et al.  
Vitamin D and the risk of dementia and Alzheimer disease.  
*Neurology*. 2014

- In elderly people, increased risk of developing AD or dementia is significantly associated with vitamin D deficiency!
  - University of Exeter Medical School, UK
  - David Llywellyn
  - 1,658 elderly individuals
  - White Americans
  - Over 65 years old
  - No dementia
  - No signs of any cardiovascular diseases
  - No stroke
  - 6 years of follow up
  - 171 individuals develop dementia
  - 107 of them convert to AD

**Conclusion:**

- *Mild vitamin D deficiency* increases the risk of developing dementia by 53%!
- *Severe vitamin D deficiency* increases the risk of developing dementia by 125%

*Fig. 1. Kaplan-Meier curves for unadjusted rates of all-cause dementia and Alzheimer disease by serum 25-hydroxyvitamin D (25(OH)D) concentrations.*
Nutrient Biomarkers for Dementia

- 666 individuals with no dementia
- Plasma levels of 22 nutrient biomarkers
- 12 years follow up
- Low levels of plasma vitamin D, carotenoids and polysaturated fats are associated with significantly high risk of dementia

Table 2
Baseline plasma concentrations of the 22 candidate nutrient biomarkers according to incident dementia over 12 years in the Bordeaux sample of the Three-City study (N = 666)

<table>
<thead>
<tr>
<th>Nutrient biomarkers</th>
<th>Incident dementia (n = 110)</th>
<th>No dementia (n = 556)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D, nmol/L</td>
<td>28.4 (13.1)</td>
<td>36.3 (18.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Carotenoids, µg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-carotene</td>
<td>86.6 (64.4)</td>
<td>99.0 (78.1)</td>
<td>.06</td>
</tr>
<tr>
<td>Lycopene</td>
<td>538.6 (220.9)</td>
<td>407.2 (394.2)</td>
<td>.005</td>
</tr>
<tr>
<td>β-Cryptoxanthin</td>
<td>232.2 (150.9)</td>
<td>274.9 (170.9)</td>
<td>.75</td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>161.9 (84.3)</td>
<td>168.1 (87.9)</td>
<td>.19</td>
</tr>
<tr>
<td>Vitamin E, mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>13.9 (3.6)</td>
<td>13.4 (3.3)</td>
<td>.17</td>
</tr>
<tr>
<td>γ-Tocopherol</td>
<td>0.6 (0.4)</td>
<td>0.6 (0.3)</td>
<td>.32</td>
</tr>
<tr>
<td>Retinol, µg/L</td>
<td>-50.2 (155.8)</td>
<td>51.0 (145.3)</td>
<td>.72</td>
</tr>
</tbody>
</table>

Fatty acids, % of total fats
Saturated fatty acids
- Myristic acid (14:0) 1.3 (0.4) 1.2 (0.5) .13
- Palmitic acid (16:0) 28.4 (5.7) 27.9 (5.7) .16
- Stearic acid (18:0) 11.8 (3.8) 11.6 (3.3) .34

Monounsaturated fatty acids
- Palmitoleic acid (16:1 n-7) 2.3 (0.9) 2.3 (0.9) .85
- Oleic acid (18:1) 20.2 (3.8) 20.3 (3.7) .53

Polyunsaturated fatty acids
- Linoleic acid (18:2 n-6) 24.6 (5.5) 25.1 (5.3) .20
- α-Linolenic acid (18:3 n-6) 0.4 (0.2) 0.4 (0.2) .72
- Arachidonic acid (20:4 n-6) 6.6 (2.1) 6.9 (1.8) .17
- Eicosapentaenoic acid (20:5 n-3) 0.4 (0.3) 0.4 (0.2) .58
- Docosapentaenoic acid (22:5 n-3) 1.0 (0.6) 1.0 (0.6) .40
- Docosahexaenoic acid (22:6 n-3) 0.5 (0.1) 0.5 (0.2) .98

NOTE: Values are mean (standard deviation). P values were estimated using univariate Cox proportional hazard models with delayed entry (and age as a time scale).
The correlation of CSF vitamin D (25OHD) and CSF amyloid beta 1-42 levels in 50 patients with dementia (AD or Non-AD) (N=50; r = 0.3726, p=0.0077)

*Season adjusted 25OHD levels

Unpublished data
Growing evidence suggests a neurosteroid like properties for vitamin D.

Yet sceptics are asking the same question more than a decade:

**Is it really there?**

**In other words:**
*(Does vitamin D have an action in brain as we know it?)*
The cerebral expression of vitamin D-associated enzymes and receptors?
VITAMIN D RECEPTORS

- Vitamin D, regulates over 1,000 genes in different tissues and in different conditions via a nuclear hormone receptor which is vitamin D receptor (VDR) and via its suggested membrane receptor (1,25MARRS)
  - Vitamin D receptor
    - Location: membrane lipid rafts?, cytoplasm and nucleus
    - Genomic function - Transcription factor (cytoplasmic or nuclear VDR)
    - Fast non genomic function - Induction of various signalling pathways (membrane VDR)
  - Membrane receptor (membrane associated rapid response steroid binding protein-1,25 MARRS), ERP57, Grp58, Pdia3
    - Location: membrane lipid rafts, ER and nucleus
    - Genomic function - Transcription factor
    - Fast non genomic function - Induction of various signalling pathways
    - Protein folding

![Image of VDR and CYP24 expression levels](image.png)

**Fig. 1.** VDR expression levels in cortical and hippocampal neurons. VDR mRNA level in hippocampal neurons was higher than cortical neurons (p < 0.0012). Data are presented as a mean ± SD

**Fig. 2.** CYP24 expression levels in cortical and hippocampal neurons. CYP24 mRNA level in hippocampal neurons was higher than cortical neurons (p < 0.0038), adjusted with Welch correction. Data are presented as a mean ± SD
Long before us:

- Bidmon et al., 1991; Musiol et al., 1992; Stumpf and O’Brien, 1987
  - Initial identification of the cells that contain VDR in the brains of rats and hamsters
  - Radiolabeled 1,25(OH)2D3 and autoradiography

- The presence of the VDR was confirmed in the brains of mice, rats, chicks and humans
  - when a specific antibody against the VDR was developed
    - Eyles et al., 2005; Prüfer et al., 1999; Sutherland et al., 1992; Veenstra et al., 1998; Walbert et al., 2001; Zanello et al., 1997.

- In the adult rodent brain,
  - the VDR is located within different cell types, including
    - neurons, astrocytes (Brown et al., 2003; Cui et al., 2013; Eyles et al., 2005),
    - oligodendrocytes (Baas et al., 2000)
    - in multiple brain regions (Prüfer et al., 1999; Veenstra et al., 1998).
Landel study (2018)

- Compared the transcript expression of Cyp27a1, Cyp27b1, Cyp24a1, VDR and Pdia3 in purified cultures of astrocytes, endothelial cells, microglia, neurons and oligodendrocytes.

- Observed that endothelial cells and neurons can possibly transform the inactive cholecalciferol into 25(OH)D3.
- Neurons or microglia can metabolise 25(OH)D3 into 1,25(OH)2D3.

- Alternatively, 1,25(OH)2D3 can induce autocrine or paracrine rapid non-genomic actions via PDIA3 whose transcript is abundantly expressed in all cerebral cell types.

- Their data indicate that, within the brain, vitamin D may trigger major auto-/paracrine non genomic actions, in addition to its well documented activities as a steroid hormone.
The subcellular location of VDR

- 2014. Eyles D.W. et al. demonstrated that,
  - in all embryonic tissues
    - VDR distribution is mostly nuclear,
  - however by adulthood
    - at least in the gut and kidney,
    - VDR presence in the plasma membrane is more prominent
    - (indicating some change in VDR function with the maturation of these tissues?)
  - The subcellular distribution of VDR in the embryo
did not appear to be altered by vitamin D deficiency
  - indicating that perhaps there are other mechanisms at play in vivo to stabilize this receptor in the absence of its ligand.  
    Eyles D.W. et al. Neuroscience 268 (2014) 1-9
Subsection conclusion:

- The location of VDR and PDIA3 is well established in CNS,

- The location and action of vitamin D metabolism related enzymes including Cyp27a1, Cyp27b1, Cyp24a1 are demonstrated in major cell types of CNS

- Vitamin D has major auto-/paracrine non genomic actions, in addition to its well documented activities as a steroid hormone in CNS
Cellular and animal models of neurodegeneration
Hypothosis

Why Vitamin D in Alzheimer’s Disease?

The Hypothesis

Beppe Greco-Mk, Selma Vultur and Esteban Durán
Amyloid beta

- Induces membrane damage/apoptosis
- Increases 24OHase
- Suppresses VDR

Vitamin D

- Induces CaV1.2 and 1.3
- Suppresses calcium binding
- Induces iNOS
- Equilibrium in NGF secretion
- Down-regulating L-type calcium channels
- Protection from membrane damage/apoptosis
- Up-regulating VDR expression
- Down-regulating INOS expression
- Equilibrium in 24OHase expression

Disruption of neurotrophic support

- Induces CaV1.2 and 1.3
- Suppresses calcium binding proteins
The corrected total cell fluorescence (CTCF) was determined and calculated as

$$CTCF = \text{integrated density (area of selected cell \times mean fluorescence of background readings)}$$

<table>
<thead>
<tr>
<th>Groups in 24h</th>
<th>The percentage of induction in amyloid beta 1-42 levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDR siRNA treated neurons</td>
<td>189% induction</td>
</tr>
<tr>
<td>1,25MARRS (PDIA3) siRNA treated neurons</td>
<td>205% induction</td>
</tr>
<tr>
<td>VDR siRNA + 1,25MARRS (PDIA3) siRNA treated neurons</td>
<td>163% induction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups in 48h</th>
<th>The percentage of cells that express amyloid beta 1-42 higher than the cutoff value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDR siRNA treated neurons</td>
<td>76% of the cells</td>
</tr>
<tr>
<td>1,25MARRS (PDIA3) siRNA treated neurons</td>
<td>83% of the cells</td>
</tr>
<tr>
<td>VDR siRNA + 1,25MARRS (PDIA3) siRNA treated neurons</td>
<td>68% of the cells</td>
</tr>
</tbody>
</table>
the corrected total cell fluorescence (CTCF) was determined and calculated as
CTCF = integrated density (area of selected cell × mean fluorescence of background readings)

Groups in 24h

The percentage of reduction in amyloid beta 1-42 levels

10⁻⁷ M 1,25(OH)₂D₃ treated neurons 27% reduction

10⁻⁸ M 1,25(OH)₂D₃ treated neurons 50% reduction

Groups in 48h

The percentage of cells that express amyloid beta 1-42 lower than the cutoff value

10⁻⁷ M 1,25(OH)₂D₃ treated neurons 79% of the cells

10⁻⁸ M 1,25(OH)₂D₃ treated neurons 95% of the cells
Vitamin D induction or suppression depended on time and concentration. Pearson HA et al J Physiol 2006;575:5-10.
Subsection conclusion:

- Vitamin D and VDR definitely have functions in CNS,
- Their dysregulation in CNS has a high potential to cause or at least to be involved in
- neurodegenerative, neurological or neuroinflamatory disorders
Neurodegeneration:
Loss of function - death of a neuron

What does vitamin D do in a neuron?
How does it do that?

Future Directions:
Novel properties of vitamin D and its receptors may emerge from the relation between amyloid beta and vitamin D?

- **Hypothesis 1**
  - VDR is a transcription factor!
  - Amyloid beta 1-42 is a transcription factor?
  - Both of them regulates or at least acts on same genes or genes with similar functions?
  - A dysfunction in one of them will create an imbalance between them and may trigger pathways of neurodegeneration?

- **Hypothesis 2**
  - VDR is located on neuronal plasma membrane!
  - VDR contributes to the action of the proteins involved in amyloidogenic or non-amyloidogenic pathways located in neuronal plasma membrane!
  - Vitamin D deficiency or VDR dysfunction may contribute to dysfunction of these pathways!
Hypotesis 1

- VDR is a transcription factor
- Amyloid beta 1-42 is a transcription factor
- Both of them regulate or at least acts on same genes or genes with similar functions
- A dysfunction in one of them will create an imbalance between them and may trigger pathways of neurodegeneration

- Is amyloid beta 1-42 present in nucleus?
- Is amyloid beta 1-42 a transcription factor?
- Does amyloid beta 1-42 regulate the expression of neurodegeneration related genes?
Figure 5. Aβ 1–42 localization depends on antibiotic (PenStrep) administration. Immunofluorescent labeling of Aβ 1–42 (green), Tau46 (red) was counter-labeled as a neuronal marker, DAPI (confocal microscopy images). (A) Neurons treated with 10 IU/ml PenStrep. Aβ 1–42 is localized both in the cytoplasm and nucleus. The immunoreactivity was moderate in the nucleus compared with the 10 IU/ml PenStrep-treated neurons. (C) Unstained neurons. Aβ 1–42 is mostly localized in the cytoplasm, and weak expression was detected in the nucleus. The data indicated that the localization of Aβ 1–42 changed in 10 IU/ml PenStrep-treated neurons compared to neurons that were not treated with PenStrep, but no significant difference in the CTCF of Aβ 1–42 was found in these groups.
THE ALZHEIMER'S AMYLOID β-PEPTIDE (Aβ) BINDS A SPECIFIC DNA Aβ-INTERACTING DOMAIN (AβiD) IN THE APP, BACE1, AND APOE PROMOTERS IN A SEQUENCE-SPECIFIC MANNER: CHARACTERIZING A NEW REGULATORY MOTIF

Bryan Maloney1 and Debornoy K. Lahiri2

1Laboratory of Molecular Neurogenetics, Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN 46202, USA
2Laboratory of Molecular Neurogenetics, Department of Medical and Molecular Genetics, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN 46202, USA

Abstract

Deposition of extracellular plaques, consisting of amyloid β peptide (Aβ), in the brain is the hallmark of Alzheimer's disease (AD); however, the physiological and pathological role of Aβ is not fully understood. Herein, we demonstrate novel Aβ activity as a putative transcription factor upon AD-associated genes. We used oligomers from 5- flanking regions of the apolipoprotein E (APOE), Aβ-precursor protein (APP) and β-amylloid site cleaving enzyme-1 (BACE1) genes for electrophoretic mobility shift assay (EMSA) with different fragments of the Aβ peptide. Our results suggest that Aβ bound to an Aβ-interacting domain (AβiD) with a consensus of "KGEREITGOGG". This peptide-DNA interaction was sequence specific, and mutation of the first "G" of the decamer's terminal "GGGG" eliminated peptide-DNA interaction. Furthermore, the cytotoxic Aβ25-35 fragment had greatest DNA affinity. Such specificity of binding suggests that the AβiD is worth of further investigation as a site where the Aβ peptide may act as a transcription factor.

FIGURE 4: Microscopic demonstration of intranuclear Aβ in nuclei. A, confocal microscopy of SH-SY5Y cells treated with 50 ng/mL of unreacted Aβ1-40 or Aβ1-40 treated with 8%. B, confocal microscopy of SH-SY5Y cells with intranuclear Aβ visualized using the PI staining. C, confocal microscopy of SH-SY5Y cells with intranuclear Aβ visualized using the PI staining and 5-bromo-2′-deoxyuridine (BrdU) staining.
### Supplementary Table 1: The FpClass PPI prediction tool was used to identify partner proteins for both APP and VDR. The tool predicted 1133 partners for APP and 583 partners for VDR. An analysis of the FpClass tool data indicated that 153 of these partners interacted with both APP and VDR. A total of 153 proteins were classified according to their functions.

<table>
<thead>
<tr>
<th>Protein Translation/Modification</th>
<th>MEMBRANE/membrane related proteins</th>
<th>TRANSCRIPTION FACTORS/REGULATION</th>
<th>NF/β beta pathway</th>
<th>Nuclear receptors</th>
<th>Cell cycle/Apoptosis</th>
<th>Cytokines/Immune response</th>
<th>Intracellular Signaling pathways</th>
<th>Chaperones</th>
<th>Proteosome pathway</th>
<th>Cytoskeleton</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPL11</td>
<td>NUMB, CTNMB1, NOTCH1, CDH3, GHR (somatotropin receptor), FHL2</td>
<td><strong>JUN</strong> IRRF1, IRRF3, NEURO1, ATF2, ATF3, EID1, ET51, ET52, ET54, FOXO1, JUNB, NF2, POL2A, MYC1, NCOA2, SMRT, RUNX1, RUNX2, XRCC6, NCL, GT2B, HEH2, SMARCA4, PA60, FANCA, SPI, NFYA, CTBP2, ELK1, TSP, HDAC4, HDAC6, HDAC7, MEF2C, MEF2L2, XI18</td>
<td>RELA, TAB2, NFIB, IRS1, NR2F1, NR2F2, NCOA1</td>
<td>CDK1, CDK5, PBR, PTK2, TPS3, BAK1, TPS3BP2, CDKN2A, CDC25C, MYC, MYB, MYC, RBBP4, WWOX, BRC4, BCL2, BCL2L1, DAXX, CCND1, CCNE1, NOL3, ING1, PIK1</td>
<td>TGFBR1, TRAF5, IL1, PTMA, IKB1</td>
<td>SRC, MAPK3, MAPK3, MAPK9, MAPK11, MAPK14, STAT1, STAT3, PIAS1, GSK3B, INH1, AKT1, WW1, PAK1, PRKCA, PRKCD, CSNK1A1, CSNK1D, CSN5A, CSEK, CLIC2, SMAD2, SMAD3</td>
<td>HSP90AA1, HSP90B1, HSP70, HSP32, HSP40, HSP27, HSP90, HSPH1, HSP70, HSP27, HSP90, HSP32, HSP40, HSP27, HSP90, HSP32, HSP40</td>
<td>COP55, UBE2I, PSMD3, PSMD5, MDM2</td>
<td>WIM, ACTB</td>
<td></td>
</tr>
</tbody>
</table>
• alpha secretase (ADAM10),
• beta secretase (BACE1),
• the gamma secretase complex (PS-1, PS-2, Nicastrin),
• the substrate APP,
• APOE (the significant risk factor for sporadic form of the AD),
• TREM2 (recently indicated as a contributor to AD risk), the
• NMDR genes Grin1, Grin2a, Grin2b, Grin2c, Grin2d, Grin3
• PKCzeta as contributors of memory and learning,
• key elements of tau pathology such as tau, GSK3α, GSK3β and Cdk5,
• cholecalciferol metabolism-related enzyme 1α hydroxylase (1α OHase-encoded by CYP27b1 gene).

• Needs confirmation with ChIP
If amyloid beta 1-42 is a transcription factor then it may have important functions beyond today’s knowledge.

If that is the case then treatments targeting total elimination of amyloid beta might be reconsidered!

High amount of amyloid beta 1-42 may increase its production working as a transcription factor and change the expression of neurodegeneration promoting genes?

We know that VDR regulates most of these genes that is foretold.

If VDR and amyloid beta 1-42 effects the transcription of the same genes then the absence of one may disrupt the balance in neurons.

Vitamin D deficiency or VDR dysfunction may promote this imbalance.

The presence of amyloid beta 1-42 itself reduces VDR expression and vitamin D production and induces vitamin D catabolism.
Besides transcriptional regulation... Vitamin D and amyloid beta have a cross talk over post transcriptional regulation via miRNAs

let-7a-5p, miR-26b-5p, miR-27b-3p, miR-31-5p, miR-125b-5p, miR-192-5p,

are suggested to be related with

• vitamin D metabolism,
• neuronal differentiation,
• development
• and memory
Adequate levels of Vitamin D, well functioning VDR, 1,25MARRS/PDIA3

Healthy cell, healthy cell maintenance and aging

Adequate levels? of Amyloid 1-42

Loss of cell maintenance, neurodegeneration

Low levels of Vitamin D, dysregulated VDR, 1,25MARRS/PDIA3

High levels of Amyloid 1-42

• If VDR and amyloid beta 1-42 effects the transcription or post-transcriptional regulation of the same genes then the absence of one may disrupt the balance in neurons.

• Vitamin D deficiency or VDR dysfunction may promote this imbalance
Hypothesis 2

- **Hypothesis 2**
  - VDR is located on neuronal plasma membrane!
  - VDR contributes to the action of the proteins involved in amyloidogenic or non-amyloidogenic pathways located in neuronal plasma membrane!
  - Vitamin D deficiency or VDR dysfunction may contribute to dysfunction of these pathways!

- Is VDR present in neuronal plasma membranes?
- Is VDR colocalized with the proteins of amyloidogenic or non-amyloidogenic pathways?
x63, V3, Alexafluor 488, anti-VDR (green); TX, Alexafluor 568, anti-MAP2 (red) was used as neuronal marker.
Vitamin D receptor is present on the neocortical plasma membrane and is co-localized with amyloid precursor protein, ADAM10 or Nicastrin.
How does VDR translocates into plasma membrane?

Which proteins are interacting with VDR directly in plasma membranes?

What does VDR do in neuronal plasma membrane?

Investigations are ongoing...
Energy metabolism, vitamin D and VDR?

- The enzymes involved in vitamin D metabolism such as
  - CYP27A1 (25-hydroxylase),
  - CYP27B1 (1α-hydroxylase) and
  - CYP24A1 (24-hydroxylase),
- are located in mitochondria.
Our results indicate that:

1. vitamin D or the disruption of vitamin D pathway have effects on mitochondrial gene expression.

2. vitamin D receptor might have a role as a transcription factor in mitochondria.

3. vitamin D deficiency or the disruption of vitamin D pathway might cause mitochondrial dysfunction which is accepted as one of the major reason in the development of neurodegenerative disorders.
Conclusion

- The location of vitamin D receptors or vitamin D metabolism related enzymes is well established in CNS,

- Vitamin D and VDR definitly have functions in CNS,

- Their dysregulation in CNS has a high potential to cause or at least to be involved in neurodegenerative, neurological or neuroinflammatory disorders

- Vitamin D has major auto-/paracrine non genomic actions, in addition to its well documented activities as a steroid hormone in CNS

- Vitamin D and VDR might be a part of signal relaying complex in neuronal plasma membrane

- Vitamin D and VDR may regulate gene expression together with amyloid fragments
  - The balance in such regulation might be a key for preventing neurodegeneration

- Vitamin D and VDR regulate mitochondrial gene expression and thus energy metabolism
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