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Vitamin D Affects Neuronal Peptides in Neurodegenerative Disease: Differences of V-D₂ and V-D₃ for Affinity to Amyloid- β and Scrapie Prion Protein In Vitro

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Additional information is available at the end of the chapter

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Abstract

The misfolding of neuronal peptides such as A β _{40/42} in Alzheimer's disease and cellular prion protein in scrapie induce abnormal aggregation of the peptides in the brain. The seeding of peptides' oligomers from monomers is the initial step to form molten-globule states before abnormal aggregation. Therefore, compounds targeting the step are useful to clarify the mechanisms underlying aggregation of the proteins and Vitamin D derivatives, which can interact with both A β ₄₀ and cellular prion protein; however they show different effects in the oligomerization step of the proteins. We discuss the different effects of Vitamin D₂ and Vitamin D₃ in the interaction with these peptides in brain.

Keywords: Alzheimer's disease, prion disease, amyloid- β , human PrP^c, Vitamin D derivatives, oligomerization

1. Introduction

Recently, involvement of Vitamin D (V-D) in cognitive impairment is reported.

V-D is a secosteroid and occurs in two distinctive major forms: Vitamin D₂ (V-D₂) and Vitamin D₃ (V-D₃). V-D₃ is a 27-carbon derivative of cholesterol, and V-D₂ is a 28-carbon derivative from plant ergosterol. The structure of V-D₂ differs from V-D₃ by containing an extra methyl group and a double bond between carbon 22 and 23 (**Figure 1**). Both V-D derivatives appear to have

similar biological effects in humans [1, 2]. V-D₃ is about four times as potent as V-D₂ [3]. Interestingly, V-D₂ is a naturally occurring V-D form derived from a fat extract of yeast by the exposure to UV light, and the metabolites were not detectable in the blood of vertebrates such as humans, unless administered from an external source [3, 4]. Thus, V-D₂ is not synthesized in vivo and is regarded as a supplement. The metabolites derived from V-D₂ are not equivalent to those for V-D₃ [5]. In contrast to V-D₂, V-D₃ is the naturally synthesized within the skin and oils of fur. Although both microsomal and mitochondrial 25-hydroxylases act on V-D₃, they do not act on V-D₂ [4, 6, 7], and furthermore the V-D binding protein shows lower affinity for V-D₂ than V-D₃ and its metabolites [8]. Currently, clinical applications of V-D for immunosuppression and reduction of pro-inflammatory immune pathways demonstrate that V-D is a prosteroid hormone rather than a vitamin [9, 10]. V-D cross blood-brain barrier by passive diffusion and enter the cerebrospinal fluid and brain. The beneficial effects in reducing the relapse risk in multiple sclerosis through its immune-regulatory effects were reported [11].

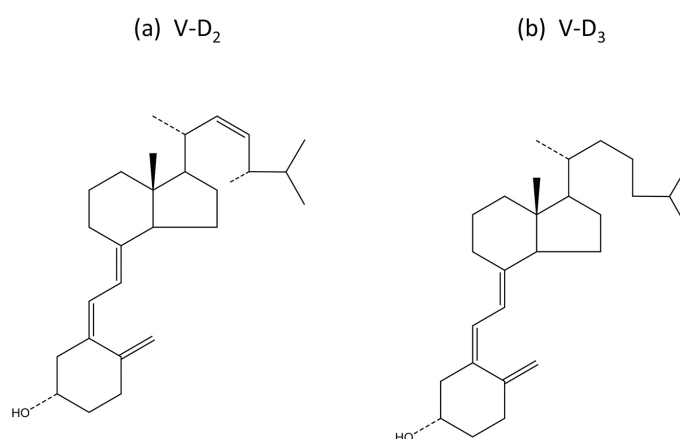


Figure 1. Structural differences between Vitamin D₂ and Vitamin D₃.

Recent epidemiologic studies report V-D₃ deficiency as a risk factor of cardiovascular disease including cardiac hypertrophy, myocardial remodeling developed to heart failure (HF) [12, 13] and some prospective studies report the relationship between hypovitaminosis-D and an increased risk of cognitive decline in elderly population [14] and suggested that supplementation of V-D could prevent the cognitive disorders [15–17], and its effects for the clearance of aggregated amyloid- β (A β) in AD brain [18].

In this chapter, we present the different binding affinity of V-D₂ and V-D₃ to amyloidogenic protein in brain: A β and prion protein.

2. Amyloid- β protein in Alzheimer's disease and scrapie prion protein in prion disease

AD and prion diseases are neurodegenerative diseases in brain and cause dementia. AD is the most common case of senile dementia and the number of AD patients is increasing and recent

study shows that 46.8 million of AD patients live in the world and it is estimated to reach 131.5 million by 2050 [19]. It is featured by memory loss, deterioration of cognitive and behavioral process, and diminished social life. These symptoms do not improve and progress with life time.

The main pathological hallmark with AD patients is the senile plaque in the brain [20]. Extracellular accumulation of insoluble A β protein is the main component of the plaque that induces synaptic dysfunction and neuronal loss resulting in progressive dementia [21]. The A β is composed of 39–43 amino acids, naturally produced by proteolytic cleavage of integral membrane protein, 100–135 kDa amyloid precursor protein [22]. The majority of the secreted A β alloform includes the C-terminal A β 40 and A β 42. Quantitative analyses have shown that, on average, 60% of all plaques contain A β 42 and 31% contain A β 40 [23]. The misfolding and aggregation of A β and tau proteins are two principal aggregating proteins in AD brain [24, 25]. Growth of the fibrils occurs by assembly of the A β seeds into intermediate protofibrils, and self-associates to form mature fibers [26]. This multistep process may be influenced at various stages by factors that promote A β fiber formation and aggregation, and the seeding of A β 40 oligomers is the initial step of the process [27, 28].

The emergence of a prion disease in cattle is known as bovine spongiform encephalopathy (BSE) and a possible transmission to humans by the exposure to BSE has been suggested [29, 30]. Gerstmann-Straussler-Scheinker disease and Creutzfeldt-Jacob are well-known naturally occurring prion diseases in human and they are transmissible and fatal. The main event contributing to the pathogenesis of prion disease is the conversion of the cellular prion protein (PrP^c) into scrapie prion protein (PrP^{sc}), which is a protease-resistant, insoluble protein [31, 32]. PrP^c is predominantly expressed in neurons, and attached to extracellular space of plasma membrane through a glycoposphatidylinositol. It is a sialoglycoprotein with a molecular weight of approximately 33–35 kDa [33, 34]. Studies have shown that PrP^c(90–231), which is N-terminal truncated fragments of PrP^c and corresponds to the core of the protease K (PK) resistant prion protein, preserve the pathogenic features of PrP^{sc} [35, 36]. Gerstmann-Straussler-Scheinker disease and Creutzfeldt-Jacob disease are caused by mutations in the PrP gene [37] and the mutations directly link to conformational conversion from PrP^c to PrP^{sc} and amplification of PrP^{sc} without exogenous PrP^{sc} [38, 39], and the infectivity can be explained by the direct PrP^{sc}-PrP^c interaction [40]. In vitro generation of infectious PrP^{sc} has demonstrated the protein-only hypothesis of prion propagation [41, 42]. Many reports have suggested that the multistep process of conversion from PrP^c into PrP^{sc} includes an oligomerization/polymerization step [43, 44]. The oligomerization or molten-globule state is a preliminary step required for the formation of insoluble protein in the brain like that of A β aggregates in AD brain, and soluble oligomers appear to be more cytotoxic than mature aggregates [45].

2.1. V-D-induced A β 40 oligomerization

Quartz-crystal microbalance (QCM) measurement is a highly sensitive mass-measuring system [46, 47]. The instrument is equipped with a 27 MHz QCM plate at the bottom with a stirring bar. Changes of frequency are calculated by Sauerbrey's equation [48] as below.

We applied Sauerbrey's equation for the QCM in the air phase:

$$\Delta F = -2F_0^2 \Delta m / A \sqrt{\rho_q \cdot \mu_q}$$

where ΔF is measured frequency change (Hz), Δm is mass change, F_0 is fundamental frequency of the quartz-crystal, A is an electrode area, ρ_q is density of quartz-crystal, and μ_q is the shear modulus of quartz-crystal.

The equation indicates that a 0.61 ng/cm² increase in mass means a -1 Hz decrease in frequency. The change of frequency is proportional to that of mass.

The change of mass in A β 40 with V-D₂ or V-D₃ was determined [49]. A significant decrease in frequency started after 15 min upon addition of A β 40 to the V-D₂ solution, and found that the frequency decrease depends on both V-D₂ concentration and incubation time. A β 40-V-D₂ complex formation occurs in solution and accelerated after 15–60 min later (**Figure 2a**). After 60 min, the calculated A β 40 molecules aggregated by an A β 40 was 4.21394 e¹⁹ at 0.1 M of V-D₂, 6.74725 e¹⁹ at 0.5 μ M of V-D₂, and 8.85697 e¹⁹ at 1.0 μ M of V-D₂ (**Table 1**). In case of V-D₃, however, no considerable decrease in frequency upon A β 40 addition was observed (**Figure 2b**). These results show a different potential of V-D₂ and V-D₃ for A β 40 oligomerization in vitro.

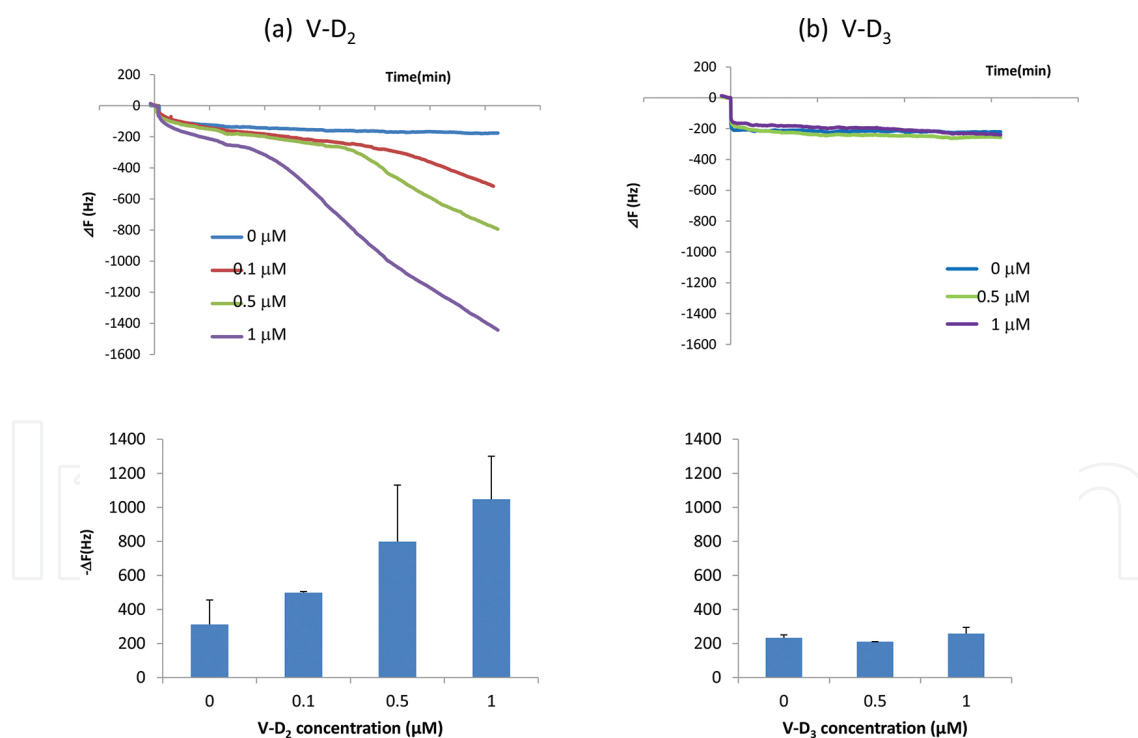


Figure 2. Quartz-crystal microbalance pattern for A β 40 aggregation with V-D derivatives. Typical real-time monitoring of A β 40 (12 μ M) aggregation with V-D₂ at the concentrations of 0, 0.1, 0.5, and 1 μ M (a) or with V-D₃ at the concentrations of 0, 0.5, and 1 μ M (b) in quartz-crystal microbalance measurements. The changes of frequency of A β 40 with V-D₂ or V-D₃ for 60 min are shown. The data are representative of three experiments. Total amount of A β 40 aggregates with V-D₂ (a). V-D₂ induced potential dose-dependent A β 40 aggregates. Total amount of A β 40 aggregates with V-D₃ (b). V-D₃ did not induce A β 40 aggregation after 60 min.

V-D ₂ (μM)	-ΔF (Hz)	Δm (ng/cm ²) ^a	Δn (atoms/cm ²) ^b
Control*	3111 ± 44	190	2.63507 × 10 ¹⁹
0.1	498 ± 6	304	4.21394 × 10 ¹⁹
0.5	798 ± 332	487	6.74725 × 10 ¹⁹
1	1048 ± 252	639	8.85697 × 10 ¹⁹

* Direct binding of Aβ₄₀ peptide to the Au electrode without V-D₂.
^a A 1 Hz decrease in frequency results in a 0.61 ng/cm² increase in mass.
^b Calculation using a molecular weight of 4331 for Aβ₄₀.
 Data are presented as mean ± SD values for three independent experiments.

Table 1. Measurement of frequency decrease in Aβ₄₀ aggregation by V-D₂ on performing QCM 60 min later.

2.2. Electron microscopic observation exhibited V-D₂-induced Aβ₄₀ oligomerization

Aβ₄₀ in artificial cerebrospinal fluid without V-D as a control induced weak self-oligomerization and V-D₃ induced no enhancement to the control, however V-D₂ enhanced potent oligomerization for Aβ₄₀ as **Figure 3(a–c)** [49].

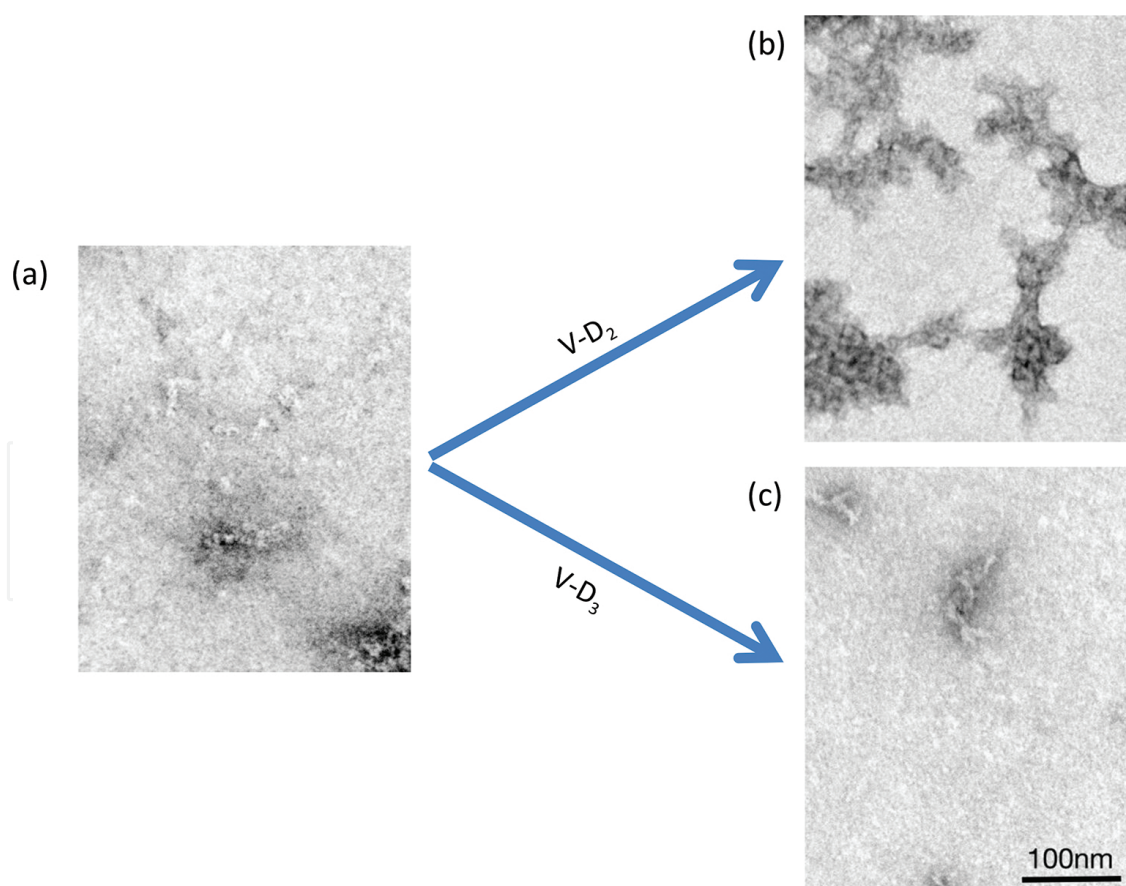


Figure 3. Electron microscopic observation for Aβ₄₀ without or with V-D₂ or V-D₃. Aβ₄₀ without V-D as a control (a), Aβ₄₀ with V-D₂ (b), and Aβ₄₀ with V-D₃ (c). Aβ₄₀ in the photo indicates 100 nm for (a), (b), and (c).

2.3. Thioflavin-T assay revealed β -sheet formation of A β 40 with V-D₂

Amyloid fibers are ordered β -sheet-rich proteins. Benzothiazole dye, Thioflavin-T (Th-T) is used to probe amyloid fibril formation due to specific noncovalent interactions that yield strong fluorescence upon binding [50]. A β 40 showed a peak at 490 nm, indicating β -sheet formation [51]. V-D₂ increased peak intensity at 490 nm dose-dependently, indicating that V-D₂ facilitates β -sheet formation in A β 40. The V-D₃ do not increase peak fluorescent intensity at 490 nm, indicating that V-D₃ facilitate no β -sheet formation in A β 40 peptide (**Figure 4**) [49].

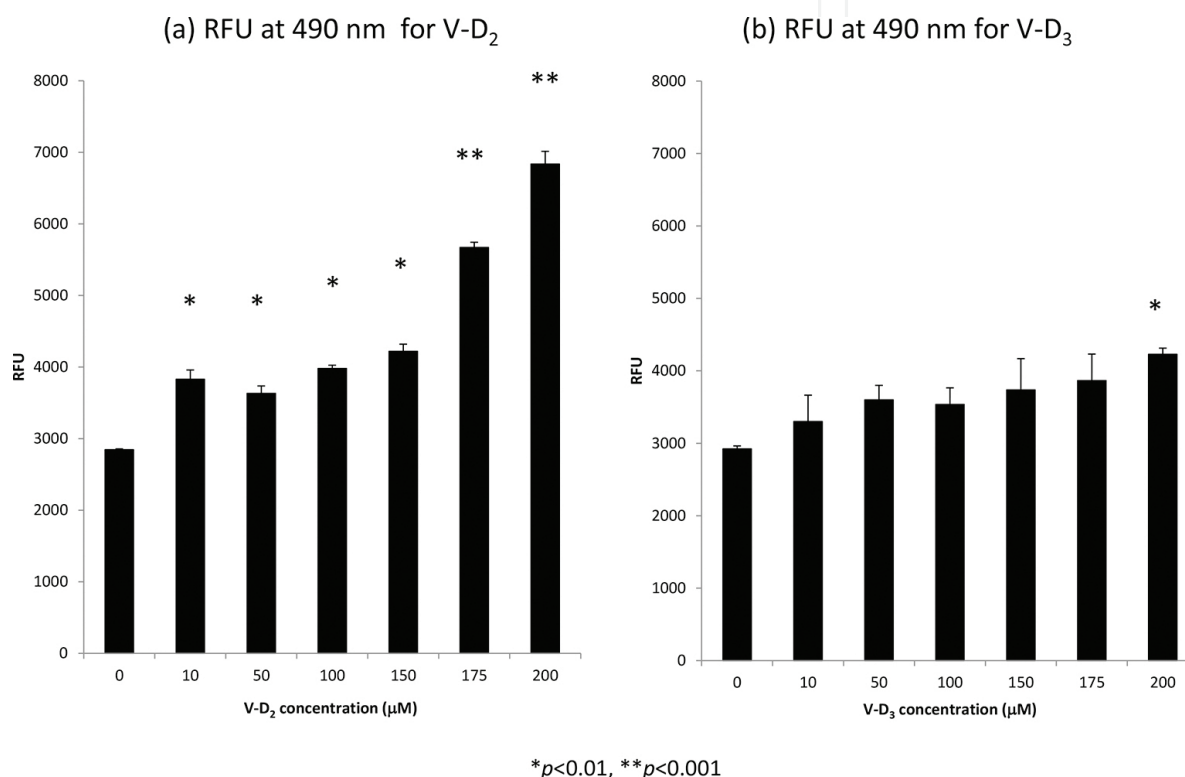


Figure 4. Th-T fluorescence monitored β -sheet formation of A β 40 in the presence of V-D₂, V-D₃. (a) V-D₂ facilitates strong β -sheet formation in A β 40 and (b) V-D₃ induced weak β -sheet formation in A β 40. Y-axis indicates relative fluorescence units (RFUs). Data represent the mean \pm SD values (bar) for three independent experiments. * $p < 0.01$, ** $p < 0.001$ vs. without V-D derivatives.

2.4. Docking simulation between A β 40 and V-D₂ or V-D₃

In silico docking analysis at the tertiary structure level by Molecular Operating Environment (MOE) software indicates the different interactions between V-D₂ or V-D₃ and A β 40 peptide. The calculated minimum energy for V-D₂ was -40.36 kcal/mol and for V-D₃, -12.46 kcal/mol; for cholesterol, the calculated minimum energy was -25.89 kcal/mol. The result showed that both V-D₂ and V-D₃ bind common amino acid residues 7–8, 11–12, and 15–16 of A β 40, and the C22–C23 double bond in V-D₂ stacks with the benzene ring of Phe19 in A β 40, whereas V-D₃ has no double bonds and showed no stacking (**Figure 5**) [49].

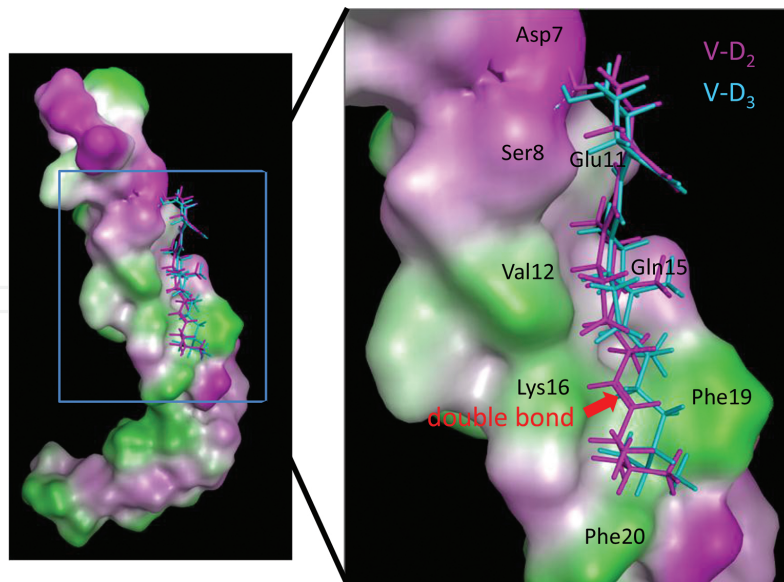


Figure 5. Docking simulation between A β 40 and V-D₂ or V-D₃. Purple indicates hydrophilic residues and green indicates hydrophobic residues in A β 40 (backbone). The double bonds (red arrow) of V-D₂ stack on the benzene ring of Phe19 in A β 40. The minimum energy between A β 40 and V-D₂ was -40.36 kcal/mol, that between A β 40 and V-D₃ was -12.46 kcal/mol.

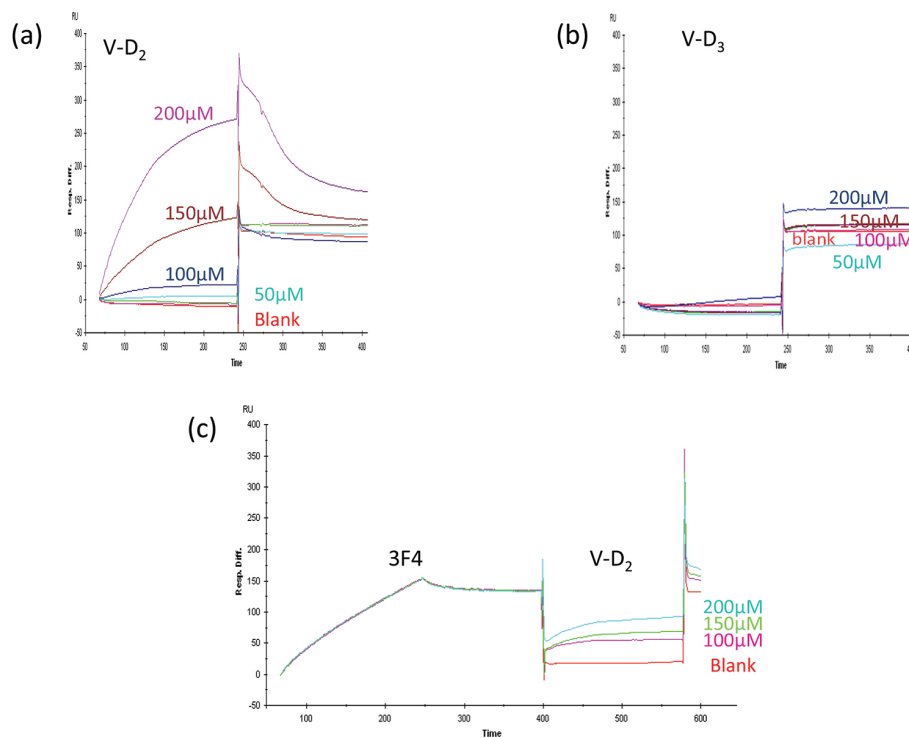


Figure 6. Affinity of V-D to PrP, as measured using the Biacore system. (a) The interaction between PrP^c(90–231) and V-D₂ showed high binding affinity, with a K_a of 6.17×10^8 and a K_d of 1.62×10^{-9} . (b) The interaction between PrP^c(90–231) and V-D₃ showed no binding affinity. (c) The interaction between PrP^c(90–231) and V-D₂, after saturating with the anti-3F4 mAb.

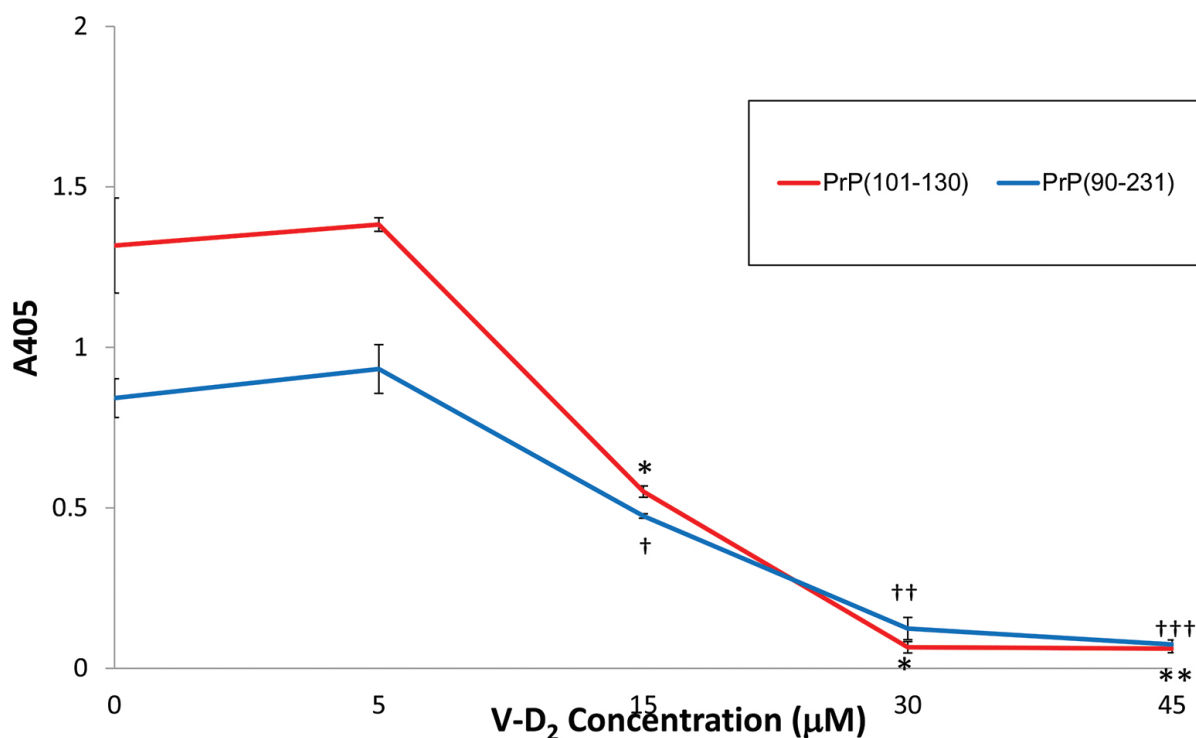
2.5. Affinity of V-D₂ to PrP^c(90–231), as a Biacore assay

A Biacore assay indicates a high affinity of V-D₂ for human recombinant cellular prion protein (Hu-rPrP^c)(90–231), and after saturating PrP^c(90–231) with the anti-3F4 antibody, specific for amino acid fragment 109–112 of PrP^c, V-D₂ binding to PrP^c(90–231) was decreased (**Figure 6a and c**), indicating that within the 3F4 epitope, PrP^c(90–231) was responsible for the interaction with V-D₂. However, V-D₃ showed no affinity for PrP^c(90–231) (**Figure 6b**), The binding kinetics of V-D₂ to Hu-rPrP^c(90–231) was shown in **Table 2** [52].

Ligand	Analyte	K_a (1/M)	K_d (M)
PrP ^c (90–231)	V-D ₂	6.17 e ⁸	1.62 e ⁻⁹
	V-D ₃	ND*	ND*
	3F4 + V-D ₂	1.12 e ⁸	8.95 e ⁻⁹

* ND, not detected.

Table 2. Binding kinetics of V-D₂ and V-D₃ to Hu-rPrP^c(90–231).



* $p < 0.006$, ** $p < 0.003$ vs. PrP^c(101-130) without V-D₂,
† $p < 0.005$, †† $p < 0.01$, ††† $p < 0.05$ vs. Hu-rPrP^c(90-231) without V-D₂.

Figure 7. Reactivity of mAbs against PrP^c with V-D₂ by ELISA. The 3F4 epitope on PrP^c was affected by V-D₂ in a dose-dependent manner. The blue line indicates signals for PrP^c(90–231) and the red line for PrP^c(101–130).

2.6. Reactivity of 3F4 antibody with Hu-rPrP^c(90–231) bound to V-D₂, as monitored by ELISA

The responsible fragment within Hu-rPrP^c(90–231) that was affected by V-D₂ was determined by ELISA. The reactivity of the 3F4 antibody to PrP^c(90–231) that was incubated with V-D₂ showed decreasing signals toward PrP^c(90–231) bound with V-D₂ in a dose-dependent manner (Figure 7) [52]. These results confirm the observation by Biacore assay (Figure 6).

2.7. Specific sequences of Aβ₄₀ and PrP^c(90–231) responsible to conformational transition

The Aβ hydrophobic core 16–20 (KLVFF) was the minimum sequence required in a binding screen of full-length and trimeric to decameric peptides spanning the entire Aβ₄₀ sequence. Alanine substitution demonstrated that Lys16, Leu17, and Phe20 are critical for this interaction [53]. The stereospecific binding of KLVFF to the homologous Aβ sequence was later confirmed as the product of specific hydrophobic and electrostatic interactions. Controlling amyloid β-peptide fibril formation with protease-stable ligands was reported [53]. The sequences of Aβ (9–14): GYEVHH and Aβ (17–21): LVFFA, are responsible to pH-shifts [54] and thermal-induced structural transformation from α-helix/random coil to β-sheet in Aβs were Aβ (16–23) and Aβ (17–24) [55]. The conformational transition from Aβ₄₀ monomer to oligomers may occur in response to small chemical compounds and may be dependent on specific Aβ₄₀ sequences. The key amino acid of Aβ₄₀ for interaction with V-D₂ is the Phe at a position 19, and it is around the sequences responsible to pH shifts and thermal stress [54, 55].

In case of PrP^c(90–231), the sequence of PrP^c(107–112): TNMKHM is pH dependent [56], and it contains PrP^c(109–112), the responsible sequence for the interaction with V-D₂.

2.8. Structural difference of V-D₂ and V-D₃ could explain different potential for the affinity to Aβ₄₀ and PrP^c(90–231)

The C22–C23 double bond contained in V-D₂ structure may influence the conformational flexibility of the molecule through allylic strain and rigidity of the double bond against rotation [57, 58]. Therefore, we hypothesize that conformational restriction by the double bond in the V-D₂ side chain facilitated binding of V-D₂ to the recognition site of Aβ₄₀ and PrP^c(90–231).

3. Conclusion

We detected V-D₂-induced Aβ₄₀ oligomerization by QCM, and electron microscopic observation demonstrated the potential of V-D₂ for Aβ₄₀ oligomerization through β-sheet formation as revealed by Th-T study. V-D₂-mediated Aβ₄₀ oligomerization occurs through interaction between the Phe19 benzene ring of Aβ₄₀ and the C22–C23 double bond of V-D₂. In case of prion, the fragment of V-D₂ binding to PrP^c(90–231) is around 3F4 epitope, 109–112 amino acid in PrP^c(90–231). These fragments are involved in the sensitive fragments to pH shifts and thermal stress. The binding of V-D₂ to amyloidogenic peptides in brain might give some insights to oligomerization of these peptides in the brain.

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