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Original Article

Unveiling Potential Therapies: Molecular Docking Analysis of CAMKK2 and Its Mutant Variants with CAMKK2 Inhibitors in Indonesian Patients with HIV-Sensory Neuropathy

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ABSTRACT

HIV sensory neuropathy (HIV-SN) is one among many complications that impair patients' quality of life. Studies in Asian and African populations found that single nucleotide polymorphisms (SNPs) of calcium/calmodulin-dependent protein kinase 2 (CAMKK2) influence the risk of HIV-SN. This study attempts to explain the influence of CAMKK2 mutations on HIV SN by studying bioinformatics interactions between CAMKK2, its mutants, and their inhibitors by molecular docking with AutoDock in order to observe their interactions with CAMKK2 inhibitors. Results showed that CAMKK2's binding energy with its native ligand (ATP) is stronger than the mutant variant of CAMKK2MT85 and CAMKK2MT363. Conversely, interaction between CAMKK2 and its inhibitors (KN-93, STO-609, and trifluoperazine) have the lowest mean binding energy compared to CAMKK2MT85 and CAMKK2MT363. This indicates that the mutant variants have weaker interactions with the native ligand and the inhibitors, therefore disrupting the normal function of CAMKK2, its interactions with the inhibitors, while increasing the likelihood of HIV-SN.

Keywords: HIV-SN, CAMKK2 inhibitors, SNP, molecular docking, mutation.

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INTRODUCTION

According to the Global HIV & AIDS statistics from UNAIDS, 38.4 million people were living with HIV in 2021 and 650,000 people died from HIV-related illnesses.[1] By March 2022, approximately 543,100 new cases of HIV were reported in Indonesia.[2] With its increasing trend, HIV continues to debilitate due to its various complications, including HIV sensory neuropathy (HIV-SN). One of the strongest culprits is the consumption of certain antiretroviral drugs. HIV-SN has a high prevalence of 35-50% in patients treated with Nucleotide Reverse Transcript Inhibitors (NRTI) such as stavudine.[3] Yet, Octaviana et. al. revealed that the cessation of stavudine decreased HIV-SN's incidence but does not completely eliminate it; suggesting how sensory neuropathy occurred before antiretroviral combination therapy was administered.[4]

An animal research study by Hao et al. and Mountford et al. revealed how inflammation and immunity accounts on HIV-SN's pathogenesis. GP120, one of the HIV virus' proteins, is proven to induce the expression of Tumor Necrosis Factor α (TNFα), interleukin 1 (IL1), and other cytokines, which leads to axonal degeneration.[5–10] Another molecular factor that affects HIV-SN is calcium/calmodulin-dependent protein kinase 2 (CAMKK2) on chromosome 12. This protein plays an important role in peripheral nerve inflammation as well as repair mechanisms. Goullee et al. found that there were six SNPs in CAMKK2 correlated with HIV-SN. Among the African population studied, three SNPs increased the risk whilst the remaining three decreased the risk.[11] The lack of similar study on the Asian population necessitates the research even further.

Although not fatal, neuropathic pain decreases an individual's social and economic function, impairing the quality of life.[11] Therefore, risk factors of HIV-SN other than age, height, CD4+ and viral count[12,13] should be further studied, thereby requiring genetic research backed by bioinformatics processing to further understand its pathogenesis and incidence.

MATERIALS AND METHODS

Data Collection

A retrospective study of 123 HIV patients was conducted at the Integrated POKDISUS HIV Care Clinic and the Neurology Outpatient Unit, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from August 2015 to February 2017. Patients who met the inclusion criteria: >18 years old, used non-stavudine antiretrovirals (ARVs) for more than 12 months, and agreed to participate through written consent were included in the study. Demographic, clinical, and laboratory data were collected based on medical record data. DN4 questionnaire, electroneurographic examination, Stimulated Skin Wrinkling (SSW) test and genetic examination were also conducted. The result of the demographic and the clinical data of this study has been published by Safri et al. in 2020.[14]

Genetic Examination of sample

DNA extraction was performed using the FavorPrep Blood Genomic DNA Extraction Mini Kit from the patient's blood samples. DNA quantification was then carried out with the Qubit 3.0 *NanoDrop Microvolume Spectrophotometer and fluorometer* and

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was normalized to 1-20 ng/µL. 64 SNPs were selected for the Open Array examination. The SNPs were selected based on their significance, and HIV-SN-related haplotypes were based on the study by Chew (2010) on the TNF block gene and Goullee et al.'s 2016 study on the P2x4R, P2X7R, and CAMKK genes. There were 12 SNPs derived from the Major histocompatibility region of 6 chromosomes. These SNPs were then further filtered to identify the minor alleles with more than 5% frequency in global, African, and South Asian races in 1000 genomes, WXAC and HapMap. The SNPs were then selected based on publications regarding the distance between the related SNPs.

Homology Modeling and Validation

Unavailable files in the RCS PDB or PubChem database, e.g. mutations in the CAMKK2 protein (CAMKK2 mutation 85, CAMKK2 mutation 363), were modeled using SwissModel (https://swissmodel.expasy.org/). The FASTA sequence for each mutated CAMKK2 protein was uploaded to SwissModel for cDNA translation to 3D models and saved in .pdb format. **Validation of Homology Modeling.** After homology modeling of CAMKK2MT85 (CAMKK2 mutation 85) and CAMKK2MT363 (CAMKK2 mutation 363) were obtained, its molecular assessment was validated with the Ramachandran Plot. Sequence identity similarities were also obtained.

Ligand and Protein Preparation

The CAMMK2 protein [Protein Data Bank (PDB) ID: 10.2210/pdb5YV8/pdb] was downloaded from www.rcsb.org in the pdb format. The protein we used has unmodeled position 151-159 and position 171-179 as its binding site. **Converting Conformer File to PDB.** Several compounds which were not available in the RCS PDB database, e.g. Trifluoperazine, were obtained from PubChem (https://pubchem.ncb.nlm.nih.gov) as an alternative database. The files of the 3D conformer were downloaded in .sdf format before being converted to .pdb format using MarvinSketch.

Molecular docking and interaction

The two and 3D structures of target ligands were created using MarvinSketch. Molecular docking and 3D visualizations were studied using AutoDock version 1.5.6. The ligand-receptor complex residues were processed using the Protein Ligand Interaction Profiler. These tools require at least a minimum of 256 MB RAM and 200 MB of hard disk space. ***Molecular Docking was docked between*** Both .gpf and .dpf files with AutoDock to generate binding energy results of CAMMK2 and ATP. Repeated steps were done for each CAMKK2, CAMMK2Mt85, CAMKK2Mt363 with CAMKK2 inhibitors, KN-93, STO-609 and Trifluoperazine.

RESULTS

Selection of CAMKK2 SNP Candidates

The result of the genetic analysis with clinical correlation has been published by Safri et al. in 2020.[14] From this publication we propose five SNPs to be analyzed bioinformatically (Table 1).

According to Table 1, there are three CAMKK2 SNPs that affect the incidence of neuropathy based on BNPST, i.e. rs7975295, rs1560568, and rs1132780. SNP rs7975295 and rs1560568 are found in the intron, hence sparing the amino acid arrangement of CAMKK2 protein. Only one SNP affects the incidence of neuropathy based on BPNST and is found in the DNA exon, i.e. rs1132780. This minor allele (T) converts the amino acid arginine into cysteine (A363S) on amino acid sequence 363 in the protein domain kinase of CAMKK2. Another SNP located in the CAMKK2 gene exon, rs3817190, is known to affect the incidence of neuropathy according to SSW. This SNP converts the 85th amino acid sequence from threonine to serine (T85S). The bioinformatics analysis on the CAMKK2 protein variants (A363S and T85S) is needed in order to look at the changes in the structure and function of proteins in these variants. Until now, there has been no variation that associates the mutation of the CAMKK2 (A363S) protein with a specific disease. On another hand, rs3817190 has been known to be associated with severity of panic and agoraphobia symptoms.[15]

3D modelling of CAMKK2 SNP Candidates

Based on the cDNA protein sequence CAMKK2 and its variants, a projection of the three-dimensional structure of the protein was made using the *swissModel* application with the following results:

Validation

The validation of the CAMKK2 3D protein structure was carried out using Ramachandran Plot. The results of CAMKK2 (T85S) homology modeling showed a sequencing identity of 99.34% and Ramachandran Favoured of 96.35%. It is known that the similarity of >90% ensures the validity and recognizability of the model. Bioinformatics analysis for validation on the CAMKK2 protein model (A363S) showed that the model has a sequencing identity of 99.00%.

Through bioinformatics analysis, validation of the 3D structure of the CAMKK2 protein with its variants using the Ramachandran Plot was carried out. The results of homology modeling CAMKK2 (T85S) showed that the model had an identity sequencing of 99.34% and Ramachandran Favoured of 96.35%. It is known that models with above 90% similarity, can still be recognized and validated. As per Figure 2A, the secondary structure in the CAMKK2MT85 model found is a right-handed alpha helix, collagen triple helix, and also beta sheets.

Bioinformatics analysis for validation on the CAMKK2 protein model (A363S) was also carried out using the Ramachandran Plot. The results of homology modeling CAMKK2 (A363S) showed that the model had a sequencing identity of 99.00% According to Figure 2B, the secondary structure in the CAMKK2 model (A363S) which was found to be right-handed alpha helix, collagen triple helix, and also beta sheets.

Molecular Docking interaction

Molecular docking parameters have been optimized by redocking with native ligands, in this case ATP, using four different grid boxes, i.e. 40x40x40, 50x50x50, 60x60x60 and 70x70x70. The binding energy is shown in Table 2.

The basic criterion of a good docking result is a low binding energy. According to Table 2, the 60x60x60 grid box has the lowest binding energy of -5.27 kcal/mol, hence enabling it for molecular docking. The interactions between CAMKK2, CAMKK2 mutation variants and each inhibitor with a 60x60x60 grid box are shown in Table 2.

Based on Table 3, CAMKK2+ATP has the lowest binding energy with only -5.27 kcal/mol. As comparisons, the binding energy of CAMKK2MT85 + ATP and CAMKK2MT363 + ATP are -3.26 kcal/mol and -4.28 kcal/mol, respectively.

As shown in Table 3, the mean binding energy between CAMKK2 and its inhibitor, KN-93, is -6.99 kcal/mol. CAMKK2MT85+KN93 has a mean binding energy of -6.93 kcal/mol. In contrast, the mean binding energy of CAMKK2MT363+KN-93 is -7.32 kcal/mol, which is the lowest among the others.

From Table 3, it was found that precisely the normal variant of CAMKK2 with STO-609 has the lowest binding energy of -9.51 kcal/mol. The CAMKK2 mutant variants of mutations 85 and 363 have binding energies of -6.61 kcal/mol and -6.59 kcal/mol, respectively.

According to Table 3, the normal variant of CAMKK2 with Trifluoperazine has the lowest binding energy of -8.64 kcal/mol. The

Table 1: CAMKK2 SNP Candidate Selection Table for BPNST, NCS, and SSW Multivariate Analysis.

No	SNP	Functional Consequence	BPNST (+) P value	OR	NCS (+) P Value	OR	SSW (+) P value	OR
2	rs11065504	Intron	0.25	0.61	0.68	1.19	*0.05*	1.95
4	rs7975295	Intron	0.04	0.43	0.32	1.53	0.71	1.13
6	rs1560568	Intron	0.04	0.42	0.34	1.5	0.6	1.2
7	rs1132780	*Missense Mutation*	0.04	0.42	0.34	1.5	0.6	1.2
3	rs3817190	*Missense Mutation*	0.52	0.74	0.34	1.5	0.05	1.99

MAF: Minor Allele Frequency, SAS: South Asian Population, AFR: African Population

Table 2: Optimization docking parameters.

	Mean binding energy (kcal/mol)			
	40x40x40	**50x50x50**	**60x60x60**	**70x70x70**
CAMKK2 + ATP	-3.44	- 4.97	- **5.27**	- 2.30

Table 3: Mean binding energy complexs of CAMKK2 with native ligand and inhibitors.

	Mean binding energy (kcal/mol)			
	ATP	**KN-93**	**STO-609**	**TFP**
CAMKK2	- **5.27**	- 6.99	- **9.51**	- **8.64**
CAMKK2MT85	- 3.26	- 6.93	- 6.61	- 6.00
CAMKK2MT363	- 4.28	- **7.32**	- 6.59	- 5.90

ATP: adenosine triphosphate, KN-93: N-[2-[[[3-(4-Chlorophenyl)-2-propenyl]methylamino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxybenzenesulfonamide, STO-609: STO-609 stands for 7-oxo-7H-benzimidazo[2,1-a]benz[de]isoquinoline-3-carboxylic acid acetate, TFP: Trifluoperazine

Table 4: Docking parameters optimization of CAMKK2 and its natural ligand, ATP, according to Figure 3.

Hydrogen bonds —									
Index	**Residue**	**AA**	**Distance H-A**	**Distance D-A**	**Donor Angle**	**Protein donor?**	**Side chain**	**Donor Atom**	**Acceptor Atom**
1	173A	LYS	2.36	3.08	126.38	√	x	164 [Nam]	28 [O3]
2	174A	GLY	1.94	2.87	150.41	√	x	177 [Nam]	26 [O3]
3	175A	SER	3.17	3.58	105.22	√	x	182 [Nam]	18 [O2]
4	176A	TYR	2.03	2.80	134.29	x	x	26 [O3]	193 [O2]
5	176A	TYR	3.10	4.08	161.58	√	x	190 [Nam]	18 [O2]
6	314A	LYS	2.67	3.48	136.18	√	√	1574 [N3+]	5 [Npl]
7	316A	SER	2.83	3.74	160.88	√	√	1591 [O3]	5 [Npl]
8	330A	ASP	2.86	3.62	131.39	√	x	1710 [Nam]	22 [O2]
Salt bridges									
Index	Residue	AA	Distance	Protein positive?		Ligand group		Ligand atoms	
1	194A	LYS	4.35	√		Phosphate		29, 29, 17, 18, 19, 26	
2	194A	LYS	4.38	√		Phosphate		30, 30, 19, 20, 21, 25	

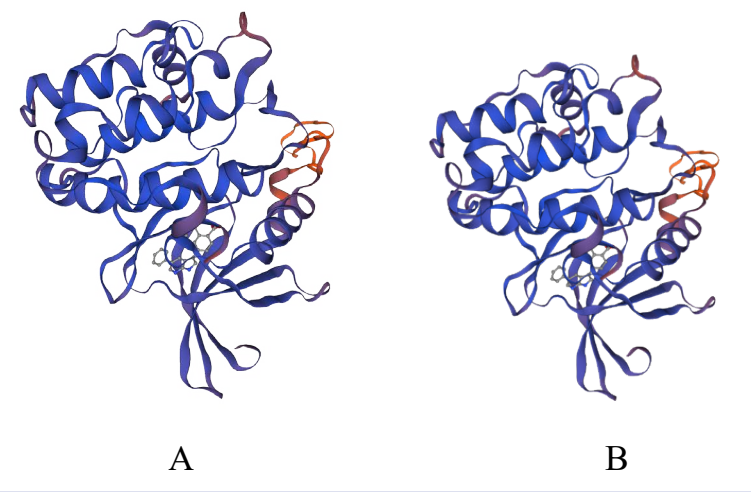

Figure 1: 3D Structure of CAMKK2 A. mutation T85S and B. mutation A363S.

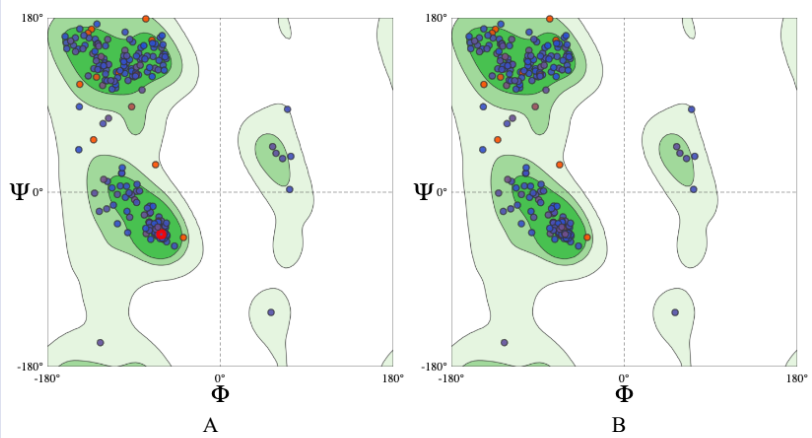

Figure 2: Validation CAMKK2 using Ramachandran A. Model T85S, B. Model A363S.

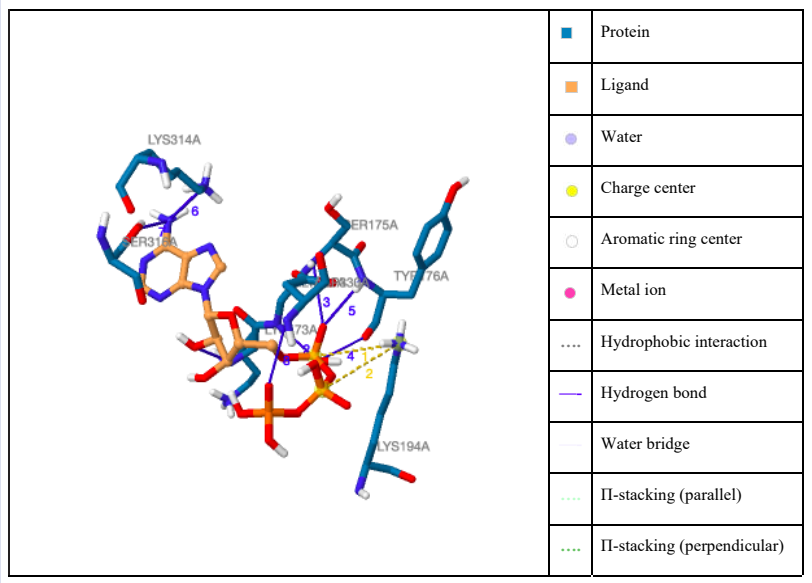

Figure 3: 3D visualization of ligands' molecular interaction CAMKK2 and its natural ligand, ATP.

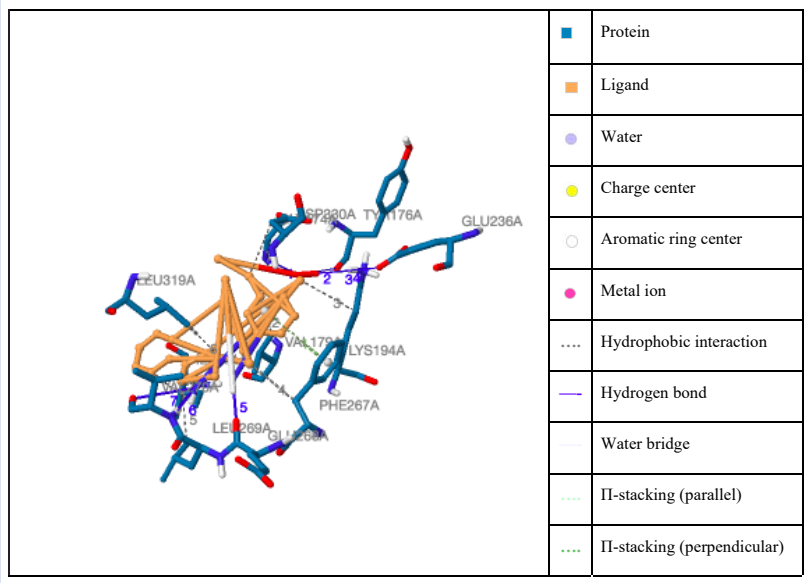

Figure 4: 3D visualization of ligands' molecular interaction of CAMKK2MT85 and its natural ligand, ATP.

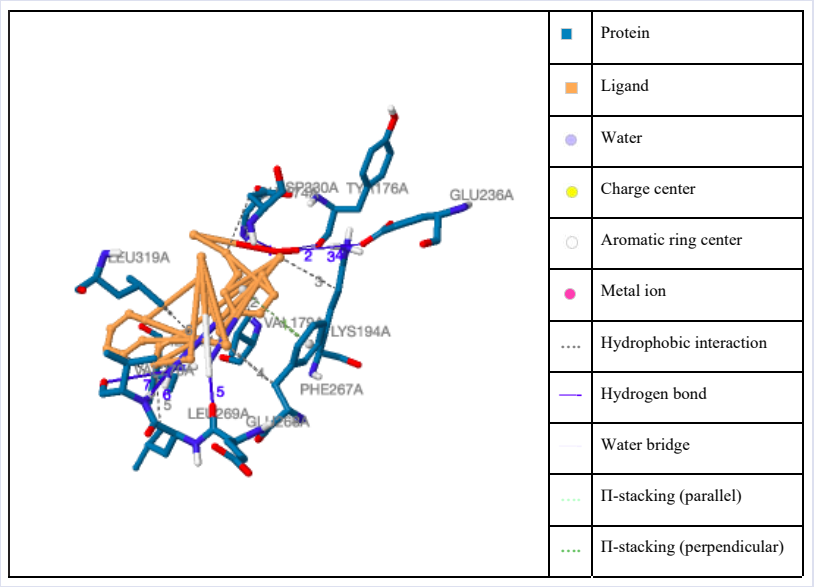

Figure 5: 3D visualization of ligands' molecular interaction of CAMKK2MT363 and its natural ligand, ATP.

CAMKK2 mutant variants of mutations 85 and 363 have binding energies of -6.00 kcal/mol and -5.90 kcal/mol.

DISCUSSION

Ligand Molecular Interaction

As Ca^{2+} enters the cell, it binds with calmodulin (CAM). Ca2+/CAM then binds and activates multiple enzymes. One of them is the calmodulin dependent protein kinases (CAMKs). There are three multifunctional CAMKs, i.e. CAMKI, CAMKII, and CAMKIV. In order to become fully activated, CAMKI and CAMKIV require phosphorylation and activation by CAMKKα/CAMKK1 or CAMKKβ/CAMKK2, respectively. CAMKI regulates multiple activities such as cell cycle progression, cell motility, cytoskeleton remodeling, and inflammation. CAMKIV regulates cell survival, gene expression, immune response, and mRNA splicing. CAMKK2 also activates AMP-activated protein kinase (AMPK). This complex acts in the hypothalamus to regulate energy balance. It also plays role in cytoskeleton remodeling, inflammation, and autophagy.[16]

CAMKK2 plays an important role in peripheral pain, which is caused by neural disruption that leads to persistent pain manifested in spontaneous pain, and hyperalgesia, and allodynia. One of the possible causes is thought to be the activation of the N-methyl-D-aspartate (NMDA) receptor. The activation of the receptor increases the influx of calcium ions into the cytosol therefore initiating the cascade, which includes CAMKK2.[17] A research has proven that CAMKK2 is involved in the transmission of nociceptive signals in the spinal cord.[18] Another study found that there is an increase in CAMK2 phosphorylation in the spinal cord after the injection of intradermal capsaicin in animal models. The study also proved that the addition of CAMKK2 inhibitor, i.e. KN93 and trifluoroperazine, alleviated the neuropathic pain in animal models. This further supports that the increase in CAMKK2 phosphorylation in the spinal cord is involved in pain modulation.[19]

According to the molecular docking result, the binding energy of the normal CAMKK2 protein with ATP as its native ligand (-5,27 kcal/mol) is stronger than the mutant variant CAMKK2MT85 and CAMKK2MT363 (-3.26 kcal/mol and -4.28 kcal/mol, respectively). This finding supports that the mutant variants, due to the aforementioned SNPs, lead to weaker CAMKK2 interaction. However based on Gurung et al. 2016, the binding energies of best docked compounds range in between -8.0 kcal/mol and -11.71 kcal/mol.[20] This finding is interesting as CAMKK2's binding energy with ATP as its natural compound was only -5.27 kcal/mol and did not reach the range.

Conversely, the result of the molecular docking between CAMKK2 and its inhibitor, i.e. STO-609 and trifluoperazine showed that the normal CAMKK2 protein variant had the lowest mean binding energy in comparison to the mutant variant 85 and 363. These findings indicate that CAMKK2 inhibitors, which were administered in order to decrease the incidence of HIV-SN, would eventually be weakened in the presence of SNP mutations on protein CAMKK2. This was not the case with the normal variant, where TFP and STO-609 could demonstrate strong bond, thereby serving their purpose as CAMKK2 inhibitors. As previously stated by Gurung et al., the binded CAMKK2 with KN-93, STO-609, and TFP all fulfilled the criteria. Meanwhile the mutated variants of CAMKK2 did not reach this range except for KN-93. Unlike the other inhibitors, KN-93 demonstrated the lowest mean binding energy with CAMKK2MT363.

Recent findings by He, 2021 on diabetic neuropathic pain (DNP) at model rats that were injected by KN-93 currently supports our current research. The research focused on KN-93 that act as CAMKK2 inhibitors relieving Streptozotocin-induced DNP in rats. Symptoms of DNP include paresthesia, hyperalgesia, allodynia and spontaneous pain. Pain will then be transmitted by the dorsal root ganglia (DRG) from peripheral afferents to the central nervous system. It was observed that p-CAMKII α levels increase in DRG of DNP rats and was co-expressed with P2X3. Administration of intraplantar KN-93 injection at minimum of 50 nmol relieved DNP and downregulated p-CAMKII α and P2X3 levels.[21] As it was discussed before, CAMKII plays a role in modulating nociceptive pain, where 50% of DRG rat neurons expressed CAMKII. The increase in calcium currents from internal storage have been observed in peripheral sensory neurons and DRG.[22] Western blot analysis also revealed that p-CAMKIIα levels elevated in L4, L5, and L6 DRGs but CAMKIIα levels did not change significantly. A previous study which is consistent in our findings also confirmed how KN-93 significantly relieves CAMKII activity.[23]

CONCLUSION

rs1132780 is an SNP found in the exon of CAMKK2 gene, which affects the incidence of neuropathy according to BPNST. It alters arginine into cysteine (A363S) on the 363rd sequence in the protein *domain kinase*.

Another SNP, rs3817190, was found in the exon of CAMKK2 gene. It affects the incidence of small fiber neuropathy as it converts the 85th amino acid sequence from threonine to serine (T85S). After molecular docking, the binding energy between the normal CAMKK2 protein variant with its native ligand is the lowest than the mutant variants. This finding means that the mutant variants have weaker CAMKK2 interaction, thereby increasing the incidence of HIV-SN. On another hand, the molecular docking between CAMKK2 and its inhibitors found that the normal protein has the lowest mean binding energy compared to the mutant variants. This finding means that the CAMKK2 inhibitor was eventually weakened by the SNP mutations. In vitro and in vivo studies are needed to confirm these findings.

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