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Research Article

In Silico Binding Affinity Study of Lisinopril and Captopril to I/D Intron 16 Variant of Angiotensin Converting Enzyme Protein

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ABSTRACT

ACE gene polymorphism is thought responsible to the difference of response to ACE inhibitor therapy in hypertensive patients. The inhibitory potency of ACE inhibitors are mainly determined by differences in the binding affinity. This study was conducted to investigate the inhibitory potency of lisinopril and captopril by analyzing the binding affinity of ACE protein to lisinopril and captopril *in silico*. Binding affinity was obtained from molecular docking using AutodockVina. Docking calculation showed lisinopril has the higher binding affinity to the C-domain than N-domain ACE, means that lisinopril was found to be more effective to inhibit D variant of ACE protein activity. In case of captopril, captopril showed the same binding affinity of captopril in both N- and C-domain (-6.1 kcal/mol). This result implied that captopril could bind to I and D variant of ACE protein with the same affinity. In conclusion, lisinopril and captopril apparently showed a difference inhibitory potency between I and D variant of ACE, as proven by calculated binding affinity.

Keywords: ACE, Binding affinity, Lisinopril, Captopril

INTRODUCTION

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase that generates an active vasopressor angiotensin II and inactivates the vasodilator bradykinin[1]. ACE protein has two domains (N-domain and C-domain), each possesing a functional active site with Zn binding sequence motif HEXXH[2,3]. Our previous study suggested that *Alu* insertion in the intron 16 results in the presense of premature termination codon, so the protein only has one active site in the N–domain, while the D allele still has two active sites. This variation is thought responsible to the difference of response to ACE-inhibitors between the two alleles. However, binding of a substrate at one active site makes the other site unavailable for either the same or a different substrate[4]. Several ACE-inhibitors employed clinically show some different inhibitory potencies towards the two active sites that are mainly determined by differences in the binding affinity[5,6]. Several studies have conducted to investigate the association of *ACE* gene I/D polymorphism, either with hypertension or ACE-inhibitor response[6-8]. To our knowledge, there is no study conducted in Indonesia to investigate the potency of ACE-inhibitors in hypertensive patients with *ACE* gene I/D polymorphism. Therefore, this study was conducted to investigate the potency of lisinopril and captopril in hypertensive patients with *ACE* gene I/D polymorphism by analyzing the binding affinity of ACE protein to lisinopril and captopril *in silico*.

MATERIAL AND METHODS

Sample Preparation

The 3D structure of lisinopril-N domain ACE complex (2C6N), lisinopril-C domain ACE complex (1O86), and captopril-C domain ACE (1UZF) were retrieved from protein data bank, PDB (http://www.rcsb.org). Then, those complexes were separated using UCSF Chimera software (https://www.cgl.ucsf.edu/chimera). Captopril obtained from 1UZF complex separation was then used in molecular docking of captopril and N domain ACE.

Molecular Docking

Molecular docking of lisinopril and captopril with ACE protein was performed using AutoDock Vina, PyRx software[9]. Autodock Vina was used due to its accuracy and it speed, which is approximately two orders of magnitude faster than its predecessor, AutoDock 4[10]. As there is only one domain that functionally active[4], molecular docking was performed between lisinopril and captopril with each domain ACE separately. To get the predicted binding affinity, we redocked lisinopril and N-domain ACE (2C6N), lisinopril and C-domain complex (1O86), captopril and tACE complex (1UZF)[11-13]. The grid maps we used are 15.767 x 10.854 x 16.102, 13.209 x 15.914 x 19.217, 7.537 x 6.8335 x 10.969 in the dimensions of x, y, and z using 1.000Å spacing, respectively. For captopril and N-domain ACE complex, as there is no crystal structure of the complex, we used 2C6N grid maps. The predicted binding affinity (kcal/mol) is calculated based on the scoring function used in AutoDock Vina. A more

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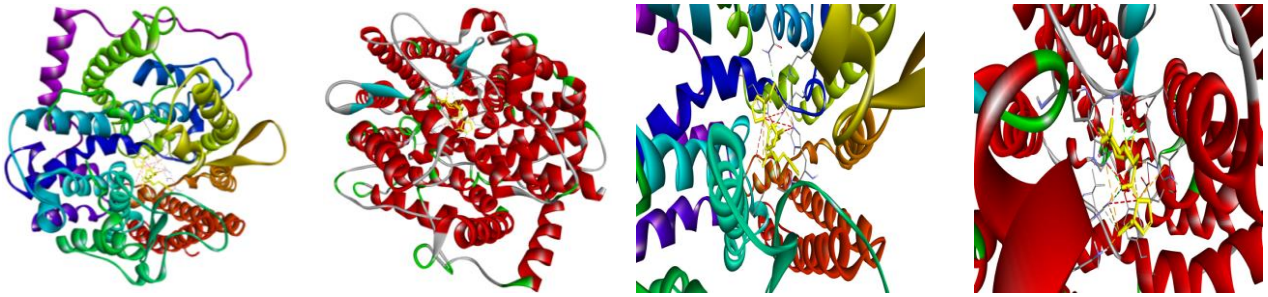

Figure 1: 3D representation of molecular docking between lisinopril and N-domain ACE (left), lisinopril and C-domain ACE (right).

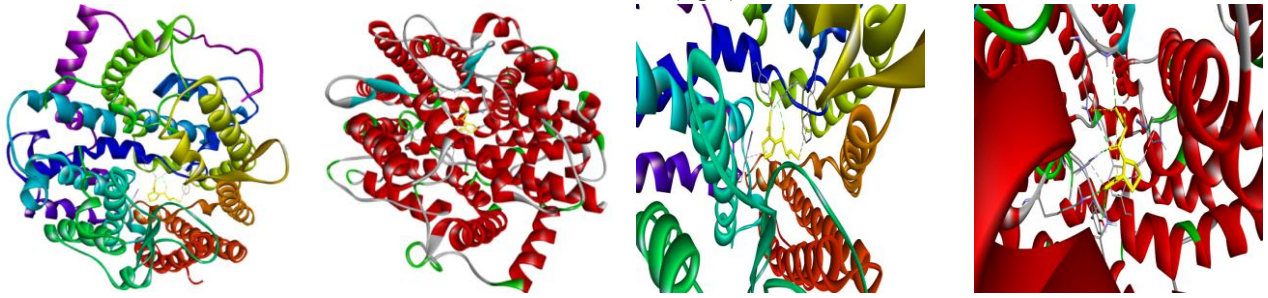

Figure 2: 3D representation of molecular docking between captopril and N-domain ACE (left), captopril and C-domain ACE (right).

Table 1: Binding Affinity of Lisinopril and Captopril with N- and C-domain ACE.

ACE inhibitor	Binding affinity (kcal/mol)	
	N-domain	C-domail
Lisinopril	-7.3	-8.8
Captopril	-6.1	-6.1

negative binding affinity indicates stronger binding. The scoring function in AutoDock Vina is divided into two parts: i) a conformation-dependent part that can be seen as a sum of intramolecular and intermolecular contributions, including steric, hydrophobic, and hydrogen bonding interactions, and ii) a conformation-independent part that depends on the number of rotatable bonds between heavy atoms in the ligand. Each contribution (steric, hydrophobic, hydrogen bonding, and number of rotatable bonds) is given a different weight in the AutoDock Vina scoring function[10].

DISCUSSION

The concept of free energy is used to determine the binding affinity of protein-ligand complex in docking studies. The negative or low value of free energy indicates the strong binding affinity between protein-ligand complex and that the ligand is in the most favourable conformation[14]. Therefore, in the present study, we determined the binding affinity of both lisinopril and captopril to I/D intron 16 variant of Angiotensin Converting Enzyme protein. Our previous study indicates that *Alu* insertion in the intron 16 ACE gene leads to the absence of C-domain ACE, thus the protein only has N-domain, whereas the D variant has both C- and N-domain. As there is only one domain that functionally active[4], molecular docking was performed between lisinopril and captopril with each domain ACE separately. Our docking calculation indicates that lisinopril has the higher binding affinity for C-domain ACE, means that lisinopril was found to be more effective to inhibit D variant of ACE protein activity. This is consistent with biological experiment, which suggested that Ki of

RESULTS

Binding Affinity of Lisinopril and Captopril with N- and C-domain ACE

To know the difference of inhibitory potency of lisinopril and captopril in I and D variant, we performed molecular docking between lisinopril with N- and C-domain ACE (Fig.1) and captopril with N- and C-domain (Fig.2). The binding affinity of lisinopril was found higher in complex with C-domain than N-domain, while captopril showed the same binding affinity in N- and C-domain (Table 1).

lisinopril is lower in C-domain than N-domain[15]. Although N- and C-domain ACE shared ~60% homology, there are some residue differences in the active side of both domain[12]. Glu 162 in the C-domain ACE is replaced by Asp140 in N-domain. This substitution results in an increased distance between the side chain of Asp140 and lysine side chain of lisinopril, thus the binding affinity of lisinopril to N-domain ACE was lower[3]. Captopril bound to N- and C-domain with the same affinity (-6.1 kcal/mol). Our result is consistent with previous study that stated captopril was able to bind to the two domain ACE with similar affinity[16]. This result means that captopril could bind to the two domain ACE and implied that captopril could bind to I and D variant of ACE protein with the same affinity. However, previous study showed that Ki value of captopril was lower in N-domain ACE than C-domain ACE[15]. Given that binding affinity of captopril to N-domain ACE was the same with N-domain, the modest N-domain selectivity of captopril remains unclear[11].

CONCLUSION

In conclusion, lisinopril and captopril apparently showed a difference inhibitory potency between I and D variant of ACE, as proven by calculated binding affinity. We found that lisinopril binds to C-domain ACE with the higher affinity than N-domain, means that the inhibitory potency of lisinopril was higher in D variant than I variant of I/D *ACE* gene polymorphism. In case of captopril, the affinity formed from interaction between captopril with N- and C-domain ACE was the same, indicating that captopril showed the same inhibitory potency for both I and D variant of ACE protein.

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