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SHORT COMUNICATION

Investigating the Interaction between SSRI Drugs and Human Serum Albumin: Unraveling the Key Players in Antidepressant Delivery

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KEYWORDS

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ABSTRACT: Antidepressant drugs are medications used to treat various types of depressive disorders. They work by altering the balance of chemicals in the brain called neurotransmitters, which are involved in regulating mood. Selective Serotonin Reuptake Inhibitor (SSRI) is a class of antidepressant drugs that specifically target the neurotransmitter serotonin in the brain. They work by blocking the reuptake of serotonin, which increases the concentration of serotonin in the synaptic gap between neurons. HSA plays a crucial role as a transport protein, facilitating the delivery of hormones and various other ligands to their specific destinations within the body. The interaction of SSRI drugs with HSA and their binding mechanism in the HSA-SSRI system has not been extensively studied so far. The primary objective of this study is to investigate the binding affinity (BA) of SSRI drugs with HSA and identify the amino acids that bind to the antidepressant drug. The HSA protein structure (PDB ID: 1AO6) has been downloaded from the Protein Data Bank, and the SSRI antidepressant drugs structure were generated using ChemDraw. Our docking results showed that the SSRI drugs had a significant binding affinity (BA) (more negative than -5.0) with the HSA protein. Among them, the highest BA was found with vilazodone (-8.6), and the lowest BA was observed with escitalopram (-6.1). This suggests that SSRI drugs can bind to the HSA protein, potentially facilitating their transport through the bloodstream. HSA binding can also influence the drug's free concentration, which is the active form available for interaction with its target receptors in the brain.

INTRODUCTION

Psychological Disorders include a broad spectrum of conditions that impact various aspects of an individual's well-being, emotions, and behaviors. These disorders can include major depressive disorder, post-traumatic stress disorder, bipolar disorder, obsessive-compulsive disorder, generalized anxiety disorder, and many others [1]. Antidepressant medications are commonly prescribed for the treatment of certain psychological disorders, particularly depressive disorders. They can also be prescribed for other conditions such as anxiety disorders, obsessive-compulsive disorder (OCD), and certain types of phobias [2]. The utmost frequently recommended class of antidepressants is Selective Serotonin Reuptake Inhibitors (SSRIs). SSRIs work by blocking the reuptake of serotonin, a neurotransmitter associated with mood regulation, in the brain [3]. This leads to increased levels

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of serotonin in the synaptic gap between neurons, which can help alleviate depressive symptoms. Some examples of SSRIs include escitalopram (Lexapro), sertraline (Zoloft), paroxetine (Paxil), fluoxetine (Prozac), Vilazodone (Viibryd) [4]. These medications are usually taken orally in the form of tablets or capsules. The exact physiological process of antidepressant drugs is not yet fully understood [5]. However, understanding the interaction between these drugs and plasma proteins is crucial because it directly affects their pharmacodynamics and pharmacokinetics properties in the human body [6]. The interaction between drug proteins and plasma proteins helps determine therapeutic efficacy, drug distribution, bioavailability, solubility in plasma, reduction of toxicity, and protection against oxidation [7-9]. Human serum albumin (HSA) is a key plasma protein with important physiological functions. It plays a critical role in transporting various molecules and metabolites [9]. HSA is a monomeric globular plasma protein consisting of three homologous domains (I-III-A and B subdomains), which provide multiple binding sites for several different drugs [10]. As a result, HSA acts as a fundamental functional drug carrier. The binding of therapeutic drugs to HSA is typically reversible and involves weak interactions, including hydrogen bonding, hydrophobic forces, ionic interactions, and van der Waals interactions [11]. To date, the binding mechanism between SSRI drugs and HSA has not been thoroughly investigated. In this study, we utilized molecular docking approaches to explore the binding properties of SSRI drugs with HSA under physiological conditions [12]. By examining the SSRI-HSA interactions, we aim to elucidate the molecular-level binding mechanism and provide insights into the pharmacokinetics and pharmacodynamics of these drugs. Understanding the SSRI-HSA interactions can also aid in the development of new therapeutic drugs optimized for their delivery within the human body. Overall, investigating the binding of SSRI drugs to HSA helps advance our knowledge of their interactions at a molecular level and contributes to the improvement and optimization of therapeutic drugs.

MATERIALS AND METHODS

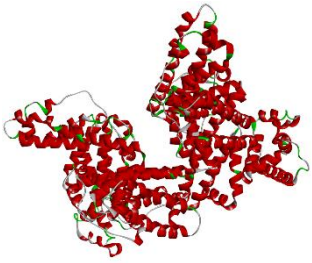
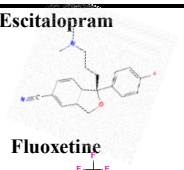
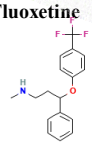
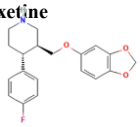
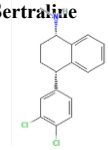
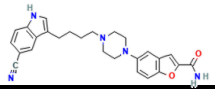
Protein and ligand structure preparation

In this study, we selected the HSA protein structure with the PDB ID 1AO6 as a reference for the binding analysis with SSRI drugs. The ChemDraw Ultra 2.0 software was utilized to generate the molecular structures of the specific SSRI drugs being investigated. This software allows for the creation and depiction of chemical structures. For predicting the binding affinity between HSA and the SSRI drugs, we employed the AutoDock Vina 1.2.0 tool [13]. By obtaining binding affinity values, we can gain insights into the strength of the interactions and potential binding modes between HSA and the SSRI drugs. This information contributes to our understanding of their interaction and transportation through the bloodstream.

AutoDock Vina 1.2.0

In this study, five types of SSRI drugs were docked using the Autodock tool. The docking protocol was applied separately for each ligand when docked with the HSA protein. The ligand structures were converted from SDF to PDB format using PyMOL 2.5.5. Initially, water molecules were removed, and polar hydrogen bonds were added. Kollman charges were then incorporated. The docking protocol and corresponding parameters are listed in Table 1. After preparing the macromolecules, AutoDock Vina was executed through the Windows command prompt.

Table 1. Customized parameters and coordinates for the molecular docking were determined based on the specific requirements of the study.

Protein	Ligand	Grid box	Coordinates
	**Escitalopram** 	126 x 126 x 126	X = 25.79 Y = 7.38 Z = 13.34
	Fluoxetine 	114 x 122 x 126	X = 24.905 Y = 7.696 Z = 11.977
	Paroxetine 	126 x 112 x 126	X = 24.215 Y = 8.054 Z = 21.423
	Sertraline 	126 x 112 x 126	X = 24.215 Y = 8.054 Z = 21.423
	Vilazodone 	126 x 112 x 126	X = 21.9 Y = 8.054 Z = 21.423

RESULTS

Using the HSA protein structure, the docking was performed by having SSRI drugs as ligand. All the analysed ligand showed strong binding affinity to the active sites of HSA (Figure 1). For instance, vilazodone showed highest affinity (-8.6 kcal mole^{-1}) while escitalopram showed the lowest affinity (-6.1 kcal mole^{-1}) respectively. The binding affinity, hydrogen bonding, and PI interactions were mentioned in Table 2. The interaction of amino acids with the selected ligands has been showed in Figure 2.

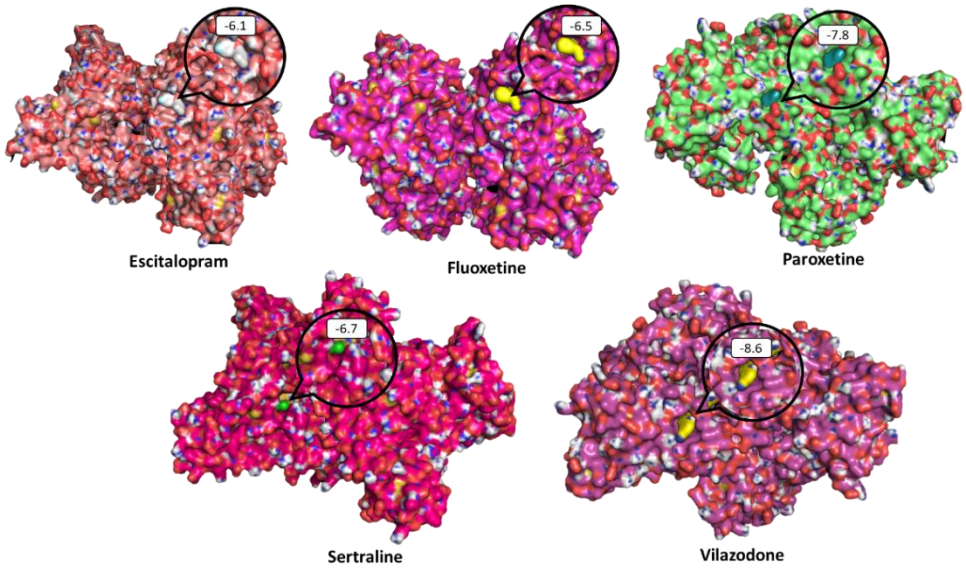


Figure 1. Molecular docking of the SSRI ligand to the HSA protein was performed to analyze their interaction and binding affinity.

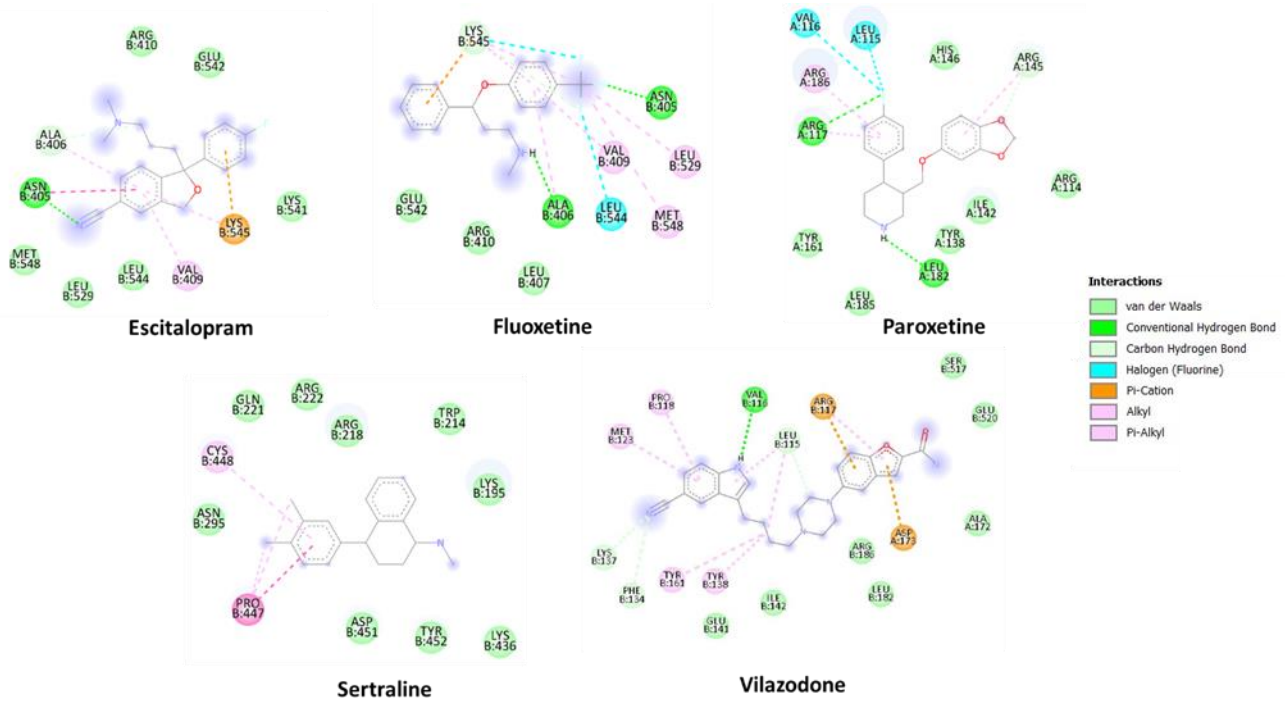


Figure 2. The interaction SSRI ligands with HSL protein.

Table 2. Binding affinity and interacting amino acids with selected ligands.

Compound	Formula	Binding affinity	Hydrogen bond	PI-interaction
Escitalopram	$C_{20}H_{21}FN_2O$	-6.1	1 bond with ASN B: 405	LYS B:545, ALA B:406, VAL B:409
Fluoxetine	$C_{17}H_{18}F_3NO$	-6.5	2 bonds with ALA B: 406, ASN B: 405	VAL B: 409, LEU B: 529, MET B: 548
Paroxetine	$C_{19}H_{20}FNO_3$	-7.8	2 bonds with ARG A: 117, LEU A: 182	ARG A: 145, 186
Sertraline	$C_{17}H_{17}Cl_2N$	-6.7	-	CYS B:448, PRO B: 447
Vilazodone	$C_{26}H_{27}N_5O_2$	-8.6	1 bond VAL B: 116	PRO B: 118, MET B: 123, TYR B: 138, 161, LEU B: 115, ARG B: 117

DISCUSSION

The interaction between human serum albumin (HSA) and SSRI drugs is an important area of study in pharmacology. HSA is a major protein found in the blood plasma, and it serves as a carrier for various substances, including drugs, hormones, and fatty acids [9, 13]. Understanding the binding of antidepressant drugs to HSA can provide insights into their distribution, metabolism, and elimination in the body [14]. When antidepressant drugs are administered orally or intravenously, they enter the bloodstream and can bind to HSA as they circulate throughout the body. This binding to HSA can affect the pharmacokinetics of the drugs, including their absorption, distribution, and elimination processes [15].

The binding of antidepressant drugs to HSA can influence their free concentration, which is the active form available to interact with target receptors in the brain and exert therapeutic effects [16]. HSA binding can also impact the drug's half-life, bioavailability, and tissue distribution. Studying the interaction between antidepressant drugs and HSA can involve techniques such as in vitro binding assays, fluorescence spectroscopy, and molecular modelling approaches [17]. These methods provide insights into the binding affinity,

binding sites, and molecular interactions between the drugs and HAS [18]. In this study, vilazodone demonstrated the highest affinity (-8.1 kcal $mole^{-1}$) with HSA, and it has been associated with more side effects compared to other SSRIs [19]. On the other hand, escitalopram exhibited the lowest affinity among the SSRI drugs, although it still possessed a binding affinity of more than -6.1 BA [20]. Therefore, it is suggested that researchers should prioritize drug development for neurological disorders that have a lower binding affinity with HSA. Additionally, understanding the binding of antidepressant drugs to HSA can be helpful in predicting potential drug-drug interactions [21]. If an antidepressant drug competes with another drug for binding to HSA, it may alter the free concentration and therapeutic efficacy of both drugs. This knowledge is crucial for healthcare professionals to ensure appropriate dosing and avoid potential adverse effects. Moreover, studying the binding of antidepressant drugs to HSA can aid in the development of novel drug formulations or delivery systems. By considering the binding properties, drug researchers can design formulations that optimize drug release, enhance drug stability, or improve drug targeting to specific tissues [22].

CONCLUSIONS

In conclusion, investigating the interaction between antidepressant drugs and HSA provides valuable insights into their pharmacokinetics, drug-drug interactions, and potential applications in drug formulation. This knowledge contributes to the understanding of how these medications are transported and processed in the body, ultimately supporting the development of more effective and targeted antidepressant therapies. Further research in this area will continue to shed light on the complex interplay between antidepressant drugs and HSA, contributing to the development of safer and more effective antidepressant therapies. Ultimately, understanding the interaction between antidepressant drugs and HSA aids in maximizing their therapeutic benefits and minimizing potential adverse effects.

Conflict of interests

No conflict.

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