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ORIGINAL ARTICLE

5-HTR$_{2B}$ and SLC6A3 as potential molecular targets of sertraline in the treatment of major depressive disorder: the use of bioinformatics and its practical implication

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Abstract
Major depressive disorder (MDD) is known to be a highly limiting and disabling disorder worldwide. The main management for this disorder is based on pharmacological therapy with antidepressants, especially in moderate to severe presentations. Among these, selective serotonin reuptake inhibitors (SSRIs) are, at the moment, the most widely prescribed class. Individualized pharmacological therapy presents itself as a powerful tool to reduce the course of the disorder, especially if one takes into account the potential molecular targets and the relationship of these targets in MDD pharmacotherapy. To explore this possibility, using bioinformatics approaches, we combined two reverse molecular screening approaches, followed by traditional docking simulations to identify potential molecular targets specifically for sertraline. According to our results, sertraline presented 17 potential targets, 4 in common within both inverse screening approaches, and were analyzed in our study: 5-HTR$_{2B}$ (5-hydroxytryptamine receptor 2B subtype), SLC6A2 (norepinephrine transporter), SLC6A3 (dopamine transporter) and SLC6A4 (serotonin transporter). Traditional docking simulations revealed higher interaction energies of 5-HTR$_{2B}$ and SLC6A3 with the sertraline molecule. In addition, both proteins are directly or indirectly related to the modulation of serotonin and dopamine, as well as the rate of response to SSRIs. Therefore, we suggest that the interaction of sertraline with the 5-HTR$_{2B}$ and SLC6A3 proteins points to a multimodal mechanism of pharmacological action, especially for the treatment of MDD.

Keywords Bioinformatics · Biomarker · Inverse screening · Major depressive disorder · Psychopharmacology

1 Introduction

Major depressive disorder (MDD) is one of the most common causes of years lived with disability (Rehm and Shield 2019), totaling more than 264 million individuals affected, less than half of whom have access to treatment (World Health Organization 2020). MDD presents itself as a common and often debilitating mood disorder, usually associated with cognitive deficits, high levels of functional disability (Pan et al. 2019) and with a decrease in the quality of life to those affected (Malhi and Mann 2018). Highly prevalent among individuals with MDD, suicidal ideation is as high as 60% (Hasin et al. 2018), a major risk factor for suicide, the most tragic consequence of depression.

MDD is characterized, according to the DSM-5 diagnostic criteria (APA 2013), by a period of (at least) 2 weeks of depressed mood or loss of interest and pleasure, associated with other symptoms that occur on a daily basis, such as abnormalities of neurovegetative functions (alteration of appetite or weight, altered sleep), psychomotor activity (loss of energy, agitation or slowness) and cognition (feelings of worthlessness, hopelessness or inappropriate guilt), as well as anxiety and suicidal ideation. In practice, its detection, diagnosis and management often pose challenges to physicians due to the heterogenetic longitudinal characteristics (van Eeden et al. 2019). Thus, the initial objective when treating MDD is the complete remission of depressive symptoms; in general, this objective

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can usually be achieved with the use of psychological, pharmacotherapeutic or combination therapy (Gartlehner et al. 2017; Kennedy et al. 2016; Parikh et al. 2016).

Subjects experiencing moderate to severe episodes of MDD need antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are a choice class of and most widely prescribed drugs based on consistent superiority over placebo in the treatment of MDD (Hieronymus et al. 2016). According to some guidelines, some SSRIs have modest superiority for treatment response, particularly sertraline (Kennedy et al. 2016) which, moreover, presents a considerable acceptability when compared to other antidepressants (Cipriani et al. 2018).

The pharmacological effect of sertraline relies on the selective and potent inhibition of serotonin reuptake, promoting the inhibition of the serotonin transporter (SERT) (Hiemke and Härtter 2000), which removes serotonin from the synapse and delivers it to the presynaptic neuron, contributing to the significant increase of serotonin in the synaptic cleft (Baudry et al. 2019). In addition to this effect, sertraline has two mechanisms that set it apart from other drugs in the same class: it acts by inhibiting the dopamine active transporter (DAT) (Sanchez et al. 2014) and by binding to sigma 1 receptors (Fishback et al. 2010). It is important to note that the blockade of SERT by chronic administration of SSRIs is associated with an increase in the expression of neurotrophins, which leads to a rise in the transcription of neurotrophic factors, including the brain-derived neurotrophic factor (BDNF), associated with an increase in synaptogenesis, neurogenesis and neuronal resilience (Duman et al. 2021). The usual therapeutic dose is 100 mg/day, with a maximum of 200 mg/day (Kennedy et al. 2016).

Aiming at this pharmacological action, the proposition of potential molecular targets to which sertraline interacts would raise elements of therapeutic response, promoting an individualized approach, limiting the course and favoring the prognosis of the disorder. To explore this possibility, computational techniques can be used to identify the structural conformations and binding affinities of proteins with a specific molecule to predict which molecular targets have higher affinity between the molecule and the binding site (Naga Madhavilatha and Rama Mohan Babu 2019). Among these methods, we highlight traditional and inverse molecular docking. The first is based on a process of fitting a small molecule into a protein binding site (Saikia and Bordoloi 2019), whereas the second can predict a potential receptor binding site for a specific small molecule (Lee et al. 2016; Xu et al. 2018).

In the present work, we applied structural bioinformatics techniques to describe potential molecular targets that could be involved in the pharmacological response of sertraline.

2 Methods

2.1 Comparative modeling

To obtain the tertiary structures for SLC6A2 and SLC6A3, we used a comparative modeling approach implemented in the Modeller 9v24 program (Šali and Blundell 1993). The structure of the *Drosophila* dopamine transporter (PDB ID 4XP4) (Wang et al., 2015) was used as template to build models for SLC6A2 and SLC6A3. The protocol used to perform the molecular modeling experiments comprehends the generation of ten models to build the structure of each molecular target. All models were submitted to the DOPE energy scoring function (Shen and Sali 2006) implemented in the MODELLER 9v10 program aiming to select the best structures. In addition, MolProbity was used to verify the stereochemical quality of the models. Intermolecular hydrogen bonds (HB) were calculated and displayed with the program (Stierand et al. 2006). In addition, QMEANDisCo score was also applied to estimate the overall quality of the models (Studer et al. 2020). All images were generated using PyMOL (The PyMOL Molecular Graphics System, Version 1.5.0.4 Schrödinger, LLC).

2.2 Molecular docking

Inverse virtual screening approaches were applied using two open access prediction programs: SwissTargetPrediction, version 2019 (Daina et al. 2019) and similarity ensemble approach (SEA) (Wang et al. 2016); these servers were used to predict potential molecular targets for sertraline to assess potential interactions of this molecule with the active site and create a map of similarity between targets. The four targets used for the docking simulations were SLC6A2 (noradrenaline transporter), SLC6A3 (dopamine transporter), SLC6A4 (serotonin transporter) and 5-HTR_{2B} (5-hydroxytryptamine receptor 2B subtype). Once the potential targets were identified, AutoDock4.2 was used to perform traditional docking simulations to evaluate the conformation and binding affinities of sertraline against the selected targets. The crystallographic structures of SLC6A4 and 5- HTR2B were obtained from PDB (ID 5I6X and 4IB4, respectively), and the structures of SLC6A2 and SLC6A3 were built based on a comparative modeling approach. To ensure that the sertraline molecule was properly docked, a 3D-grid with dimensions $60 \times 60 \times 60$ with spacing of 0.375 Å was used to define the active site of each molecular target. The grid center was defined independently for each protein: SLC6A2 (x: 106.15, y: 146.83, z: 29.26), SLC6A3 (x: −8.78, y: −1.36, z: 26.97), SLC6A4 (x: −32.31, y: −21.11, z: 2.11) and 5-HTR_{2B}.

(x: 22.32, y: 18.58, z: 13.98). All molecular docking processes were carried out with 100 independent runs for each docking simulation, an initial population of 150, a maximum number of 500,000 energy evaluations, and a maximum number of 27,000 generations. Mutation and crossover were applied to the population at rates of 0.02 and 0.80, respectively.

2.3 Consensus scoring

Molecular docking programs are known to present higher accuracy to describe the best conformation of a small molecule into a protein binding site; however, its drawback is the estimation of binding affinities. Therefore, to better characterize the molecular target with the highest affinity for sertraline, we applied a consensus scoring function (Huang and Zou 2010). All conformations obtained from the traditional docking simulations were evaluated using a combination of four independent scoring functions: RankScore (Fan et al. 2011), PoseScore (Moal et al. 2013), PRODIGY (Vangone and Bonvin 2017) and AutoDock4.2. Therefore, the most likely targets with which sertraline interacts were calculated based on a simple average of its binding energies.

2.4 Molecular dynamics simulations

To investigate the stability of the best complexes obtained from molecular docking experiments, molecular dynamics (MD) simulations were performed using the GROMACS 2020.4 package (van der Spoel et al. 2005). Ligands were prepared using the Avogadro software. Hydrogens were added for a 7.4 pH and energy minimization was performed using the MMFF94 force field and steepest descent algorithm. Parameterization of the ligands was performed using ACPYPE (Sousa da Silva and Vranken 2012). Protein topology file was created using the Amber99SB force field and TIP3P water model (Jorgensen et al. 1983). Systems were solvated in a cubic box that extended 10 Å from the surfaces of the macromolecule, and ions were added to neutralize the system charges when needed. Periodic boundary conditions were applied, and the number of particles, the pressure, and the temperature were kept constant (NPT ensemble). The V-rescale (Bussi et al. 2007) thermostat was employed to maintain the system at constant temperature using a coupling time of 0.1 ps, and the Parrinello-Rahman barostat was used to ensure that the system pressure was maintained at 1 bar. The LINCS (Hess et al. 1997) algorithm was implemented in order to constrain all of the covalent bonds involving hydrogen atoms, and the system evolved in time steps of 2 fs, for a total runtime of 50 ns. Van der Waals interactions were computed using a 12 Å cutoff. The particle-mesh Ewald method was applied to calculate electrostatic contributions in a grid with 1.2 Å spacing. Trajectories were visualized in PyMOL and analyses were performed with the Geo-Measures v0.9 PyMol plugin (Kagami et al. 2020) and GROMACS built-in tools.

3 Results

Structural bioinformatics techniques were applied to gain insight and suggest potential molecular targets for the pharmacological therapy of sertraline. To identify the molecular targets with high probability to interact with the sertraline molecule, two independent programs were used; SwissTargetPrediction and SEA. During the first phase of this work, 49 proteins were described by SwissTargetPrediction and 19 by SEA as potential targets. Research was also performed over the literature to analyze whether these molecular targets (obtained from the inverse screening) have been previously associated, directly or indirectly, to MDD. According to these results, we selected 17 molecular targets that were common to both programs and ranked with the highest probability scores (Table 1). The top four results, 5-HTR2B (5-hydroxytryptamine receptor 2B subtype), SLC6A4 (serotonin transporter), SLC6A2 (norepinephrine transporter) and SLC6A3 (dopamine transporter), were selected for the following analysis due to the metabolic pathway they belong and possible association to the clinical outcome.

Before the evaluation of the difference in binding affinity among the selected targets and sertraline, we built a structure model for the SLC6A2 and SLC6A3 proteins, which lack structures experimentally determined. The structure of the dopamine transporter from *Drosophila melanogaster* (Uniprot ID Q7K4Y6) was used as template for modeling the atomic coordinates of the SLC6A2 and SLC6A3 targets, since their sequence identity with the template were 59.0% and 54.8%, respectively. The analysis of the Ramachandran diagram plots revealed that the models present over 94.5% (SLC6A2) and 97.0% (SLC6A3) of residues in most favorable regions. In addition, QMEANDiscCo results show global score values of 0.74 ± 0.05 and 0.72 ± 0.05 for the structures, corroborating with the stereochemical quality analysis and allowing us to use these structures for traditional docking simulations.

According to docking results, all complexes present a favorable binding energy, indicating that the sertraline molecule could bind to the active site of the selected targets (Table 2). However, the highest affinities were found for the SLC6A3 and 5-HTR_{2B} proteins. Figure 1A, B highlight the residues involved in anchoring of the sertraline molecule into the binding pocket of the 5-HTR_{2B} protein. The presence of ergotamine into the binding site of the 5-HTR_{2B} crystallographic structure allows us to compare the binding mode of our docking result. It is interesting to observe that ergotamine and sertraline share three amino acid residues

Table 1 Possible molecular targets of sertraline of high similarity found in the two servers

Common target name	Description
SwissTargetPrediction	
SLC6A2	Norepinephrine transporter
SLC6A4	Serotonin transporter
SLC6A3	Dopamine transporter
CHRM4	Muscarinic acetylcholine receptor M4
HTR2B	Serotonin 2b (5-HT2b) receptor
ADRA2A	Alpha-2a adrenergic receptor
ADRA2C	Adrenergic receptor alpha-2
ADRA2B	Alpha-2b adrenergic receptor
CHRM5	Muscarinic acetylcholine receptor M5
CHRM2	Muscarinic acetylcholine receptor M2
CHRM1	Muscarinic acetylcholine receptor M1
HTR2A	Serotonin 2a (5-HT2a) receptor
HTR2C	Serotonin 2c (5-HT2c) receptor
KCNH2	HERG
SIGMAR1	Sigma opioid receptor
CYP2C19	Cytochrome P450 2C19
MC5R	Melanocortin receptor 5
Similarity Ensemble Approach (SEA)	
SLC6A3	Sodium-dependent dopamine transporter
SLC6A2	Sodium-dependent noradrenaline transporter
SLC6A4	Sodium-dependent serotonin transporter
HTR2B	5-hydroxytryptamine receptor 2B
SIGMAR1	Sigma non-opioid intracellular receptor 1
KCNH2	Potassium voltage-gated channel subfamily H member 2
ADRA2B	Alpha-2B adrenergic receptor
HTR2A	5-hydroxytryptamine receptor 2A
CHRM5	Muscarinic acetylcholine receptor M5
ADRA2C	Alpha-2C adrenergic receptor
HTR2C	5-Hydroxytryptamine receptor 2C
CHRM4	Muscarinic acetylcholine receptor M4
ADRA2A	Alpha-2A adrenergic receptor
MC5R	Melanocortin receptor 5
CHRM1	Muscarinic acetylcholine receptor M1
CHRM2	Muscarinic acetylcholine receptor M2
CYP2C19	Cytochrome P450 2C19

that participate in hydrogen bonding (Asp135) and hydrophobic contacts (Val13 and Met218). This result corroborates with the consensus scoring function, regarding the potential interaction between 5-HTR_{2B} and sertraline. Figure 1C, D presents the binding mode of sertraline into the SLC6A3 active site. Even though the structure of SLC6A3 does not present a reference molecule into the binding site, we observed that sertraline shows a similar binding pattern when compared to 5-HTR_{2B}. Therefore, we suggest that 5-HTR_{2B} and SLC6A3 are potential molecular targets of sertraline.

The analysis of radius of gyration (RoG) revealed that all complexes were stable during the simulation time. Figure 2 presents the behavior of RoG to all complexes. The 5-HTR_{2B}:sertraline complex presents the RoG values ranging from 2.02 to 2.11 nm, whereas among the SLC6 complexes, the SCL6A3:sertraline shows the lowest values. However, none of these complexes present large variations along the simulation. Regarding the root mean square deviation (RMSD) and the surface accessible surface area (SASA) analysis of the sertraline into each binding pocket, it is possible to observe that there are no large conformational changes between the docking pose and the ligand stability monitored during the simulation (Figure S1A and S1B).

Table 2 Binding energies of ligand–target interaction with sertraline

Proteins	Autodock[a]	RankScore[b]	PoseScore[c]	PRODIGY[d]	Consensus[e]
5HTR2B	– 8.98	– 7.03	– 27.70	– 8.70	– 13.10
	– 8.94	– 11.06	– 32.34	– 8.80	– 15.29
SLC6A2	– 8.06	– 7.98	– 22.34	– 8.70	– 11.77
SLC6A3	– 9.80	– 1.58	– 28.22	– 9.60	– 12.30
	– 9.59	– 7.54	– 34.93	– 9.50	– 15.39
SLC6A4	– 10.02	0.44	– 24.32	– 8.90	– 10.70

hydroxytryptamine receptor 2B subtype; SLC6A2: solute carrier 6-member 2-norepinephrine transporter; SLC6A3: solute carrier 6-member 3-dopamine transporter; SLC6A4: solute carrier 6-member 4-serotonin transporter

[a]Used to predict the ligand–receptor interactions

[b]Used to estimate the binding energy, by ranking the target complexes with different small molecules

[c]Used to create a rough estimate of a ligand's fitting orientation at the active binding site of a protein

[d]Used to predict the binding affinity between protein complexes

[e]It is a technique used in docking studies to combine the individual scoring functions

4 Discussion

The monoamine (serotonin, noradrenaline and dopamine) transporters have a hallmark role in the pathogenesis of MDD (Malhi and Mann 2018) and are extensively distributed in the brain (Aggarwal and Mortensen 2018). The monoamine transporters (MAT) are one of four subgroups of the human solute carrier 6 (SLC6) family transporter protein. This subgroup is composed of norepinephrine (NET, SLC6A2), dopamine (DAT, SLC6A3) and serotonin (SERT, SLC6A4) transporters (Salatino-Oliveira et al. 2018) and exhibits a high degree of sequence similarity (Shumay et al. 2010). Despite distinct pharmacological properties, each presynaptic MAT has considerable affinity for different amines due to the similarities among them (Cheng and Bahar 2019). For example, NET and DAT efficiently transport both norepinephrine and dopamine (Mulvihill 2019); SERT also transports dopamine (Larsen et al. 2011). The results related to the actions of DAT and SERT suggest, through the primary substrate-binding site, allosteric binding site, and cholesterol and ion-binding sites, a future challenge for the functional and pharmacological roles (Aggarwal and Mortensen 2018; Cheng and Bahar 2019).

The serotonergic pathway plays an essential role in antidepressant response. After all, sertraline works by inhibiting SERT (Sangkuhl et al. 2009), which modulates brain function and behavior by regulating the duration and intensity of synaptic serotonin signaling (Nikolova et al. 2014). Several studies also recognize the relationship between norepinephrine systems and MDD, being the norepinephrine transporter one of the main treatment routes for this disorder (Moriguchi et al. 2017). The dopaminergic system, in addition, may have an important stabilizing and integrative influence on brain circuits (Grace 2016) and recent studies also have demonstrated that it plays a role in many psychiatric conditions, including MDD (Salatino-Oliveira et al. 2018). Current evidence suggests that disruptions in the systems that provide control of the brain dopaminergic system are linked to the pathophysiology of depression (Grace 2016), especially the dysregulation of the reward-related circuitry (Belujon and Grace 2017) and the cognitive and pharmacological mechanisms of treatment response (Peciña et al. 2017).

The polymorphism in serotonin receptor and transporter genes is considered an important factor in therapeutic response, serving, in addition, as a useful predictor of clinical outcome (Staeker et al. 2014). Two types of functional polymorphisms have been reported in the serotonin transporter gene (*SLC6A4*): (1) serotonin transporter long promoter region (5-hydroxytriptamine transporter long promotor region - 5-HTTLPR) related to the binding of antidepressant to SERT and (2) the variable number tandem repeat (VNTR) that decreases the SERT expression and the inhibition of serotonin reuptake (Dogan et al. 2008). The first one has been shown to influence the response-time to sertraline, especially in patients that are homozygous for the 5-HTTLPR long form (L allele) (Durham et al. 2004; Mushtaq et al. 2012; Poweleit et al. 2019). As we look at other mechanisms, there seems to be significant increase on *SLC6A4* DNA methylation in patients who experienced MDD when compared to healthy controls (Won et al. 2016). Li and coworkers (Li et al. 2019) found that *SLC6A4* hypermethylation was associated with MDD, as it may reduce *SLC6A4* expression, resulting on the decrease of serotonin reuptake (Chen et al. 2017) and on the increase of affective vulnerability (Li et al. 2019). Thereby, an important function of *SLC6A4* was observed, both genetically and epigenetically.

Serotonin (5-hydroxytryptamine - 5-HT) receptor 2B subtype (5-HTR_{2B}) was identified in the late 1980s (Belmer et al. 2018) and is a member of the 5-HT2 subfamily of 5-HT receptors, which includes 5-HTR2A and 5-HTR2C (McCorvy et al. 2018). Expressed centrally and peripherally, only modest levels of 5-HTR_{2B} can be detected in the brain (Doly et al. 2008) in the raphe nucleus, especially in the serotonergic neurons (Belmer et al. 2018) and in the glial cells (Hertz et al. 2015). Even though the receptor function in the brain is mainly unknown (Goldman et al. 2010), 5-HTR_{2B} receptor has been involved in maladaptive behaviors, such as impulsivity and addiction, and in the response to antidepressants and psychostimulants, pointing toward putative interactions with the dopamine system (Doly et al. 2017).

A few studies have shown that 5-HTR_{2B} has critical importance on the effects of SSRI, perhaps by modulating

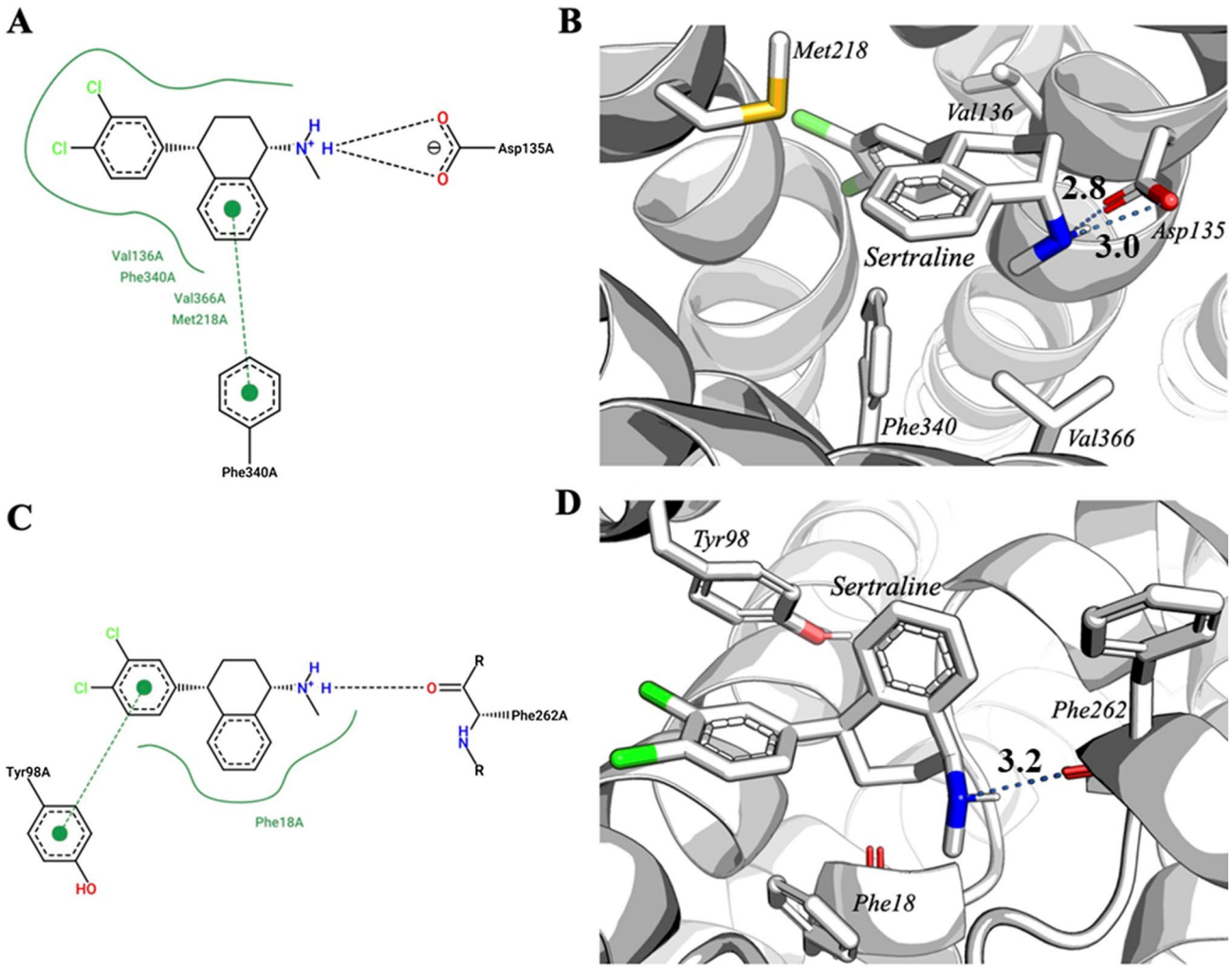

Fig. 1 Binding mode of the sertraline molecule into the binding site of 5-HTR_{2B} and SLC6A3 proteins. A general 2D representation of the binding mode between the molecule of sertraline and the proteins 5-HTR_{2B} and SLC6A3 are presented in (**A**) and (**C**), respectively. The best docking conformation for the complexes 5-HTR_{2B}:sertraline and SLC6A3:sertraline are represented in (**B**) and (**D**), respectively. The overall structures of both proteins are shown as a cartoon. The sertraline molecule and residues that participate in hydrogen bonding and hydrophobic contact are represented as sticks and colored according to the CPK scheme. Image generated with PoseView and PyMOL

serotonergic tone, due to its relatively high affinity for these drugs (Diaz et al. 2012; Hertz et al. 2015) through the regulation of extracellular levels of serotonin (Diaz and Maroteaux 2011). Using an animal model, Diaz and coworkers observed that, by genetically or pharmacologically inactivating 5-HTR_{2B}, the action of SSRI can be abolished (Diaz et al. 2016, 2012; Diaz and Maroteaux 2011). Using a forced swimming test (FST), a classical test for acute antidepressant activity with good reliability and predictive validity, the authors observed that knockout mice for the 5-HTR_{2B} gene did not respond to SSRI, suggesting that the absence of this receptor impairs the serotonergic drug response system. This finding is supported by the fact that a 5-TH2B receptor agonist induced an SSRI-like response, suggesting that this receptor is necessary for the acute effect of this antidepressant class and might modulate serotonergic tone (Diaz et al. 2016, 2012). In line with this observation, 5-HTR_{2B} positively regulates serotonin neurons and this has important implications on the serotonin-releasing effect of SERT-targeting drugs, such as SSRI (Banas et al. 2011; Belmer et al. 2018; Diaz et al. 2012; Diaz and Maroteaux 2011). Furthermore, the activation of 5-HTR_{2B} leads to dopamine release in the nucleus accumbens (NAcc) (Doly et al. 2008), showing the ability of this receptor to regulate SERT function and serotonin and dopamine release (Doly et al. 2009; Launay et al. 2006).

This statement is supported by our findings, which showed the high ligand affinity of the sertraline molecule with this receptor. Bringing into clinical practice, this can be corroborated as we observed that sertraline, at clinical

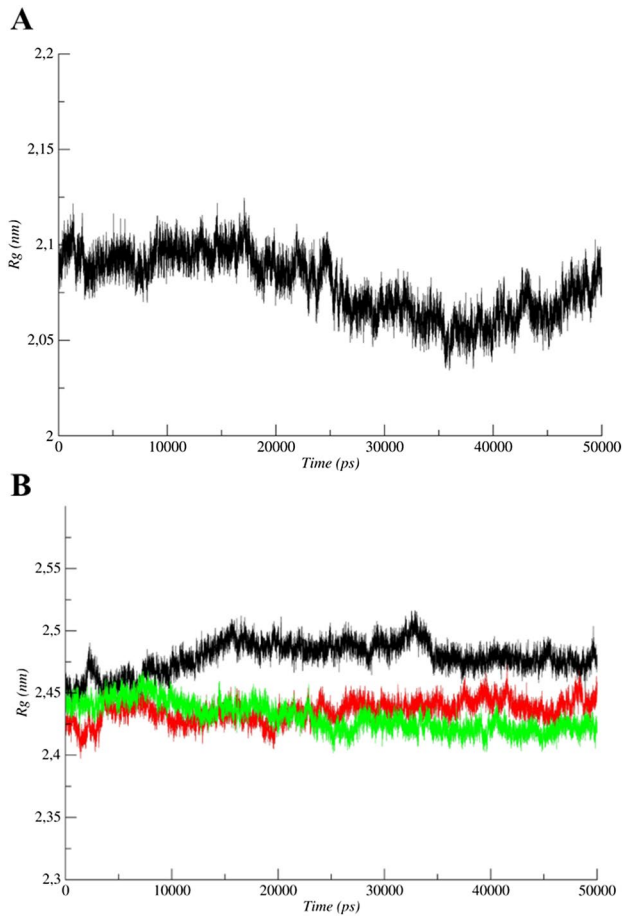

Fig. 2 Radius of gyration of the best complexes. **A** RoG of 5-HTR2B:sertraline complex. **B** RoG of SLC6A2:sertraline (black line), SLC6A3:sertraline (red line) and SLC6A4:sertraline (green line). Image generated with Xmgrace

dosages, showed the ability to increase extracellular dopamine concentration in NAcc, in contrast to the other SSRIs (Kitaichi et al. 2010). Although the precise role of 5-HTR_{2B} in 5-HT neurons remains poorly understood (Belmer et al. 2018), these findings could shed light on a new tractable target toward treating MDD based on a unique mechanism to SSRIs, especially sertraline.

The major regulator of dopamine signaling is DAT, which modulates synaptic concentration, availability and function of this neurotransmitter (Shumay et al. 2010). This transporter is expressed in all dopamine neurons, especially in the striatum and NAcc, where its density is higher (Salatino-Oliveira et al. 2018).

Van De Giessen and coworkers found that the polymorphisms in the DAT1 gene are associated with the availability of this transporter in the human brain, especially in the striatal DAT expression (Van De Giessen et al. 2009). D'Souza and coworkers also suggested that DAT1 had an influence on children's depressive symptoms (D'Souza et al. 2016). Another study found that a polymorphism in the DAT gene (SCL6A3) influenced a rapid response to antidepressant therapy (Kirchheiner et al. 2007). A recent review showed several findings associating SCL6A3 to psychiatric disorders. Nevertheless, due to the common and rare variants of the phenotypes, there is discrepancy in the effects of SCL6A3 (Salatino-Oliveira et al. 2018).

Using an animal model, Bahi and Dreyer showed that DAT knockdown, especially in the NAcc, decreased anxiety and attenuated depression-related behaviors (Bahi and Dreyer 2019). When clinically evaluated, it was observed that two important symptoms of depression, anhedonia and amotivation, appear to be related to dysfunctions in the dopaminergic system (Grace, 2016). The hallmark symptom of this disorder is anhedonia, especially in clinical presentations well known as melancholic depression (Belujon and Grace, 2017; Parker et al. 2013). It could be possible that, by engaging additional targets, such as serotonin and dopamine systems, broader therapeutic benefits can be achieved.

The interaction of the sertraline molecule with its specific targets may be related to the improvement on the course of the disorder, as well as its response and remission. On the other hand, individuals who are experiencing inadequate response to antidepressant therapy, about 30–50%, are subjected to broader pharmacological interventions, using a combined pharmacological therapy where the interaction of drugs with the most varied receptors can guarantee a broad and robust pharmacological response (Rafeyan et al. 2020). Several studies proposed to evaluate molecules with the most varied binding sites to promote this coverage. On the other hand, studies in the field of bioinformatics indicate an evaluation of existing molecules, proposing a structural model of conformation and connection with specific actions. This context was used in this study using a single molecule, which presents the potential molecular targets with which sertraline interacts and its relationship with the treatment of MDD.

The serotonergic and dopaminergic modulation proposed by both activation of 5-HTR_{2B} and activation pathway of SLC6A3 can explain the effectiveness of sertraline in the treatment of MDD. This synergistic performance profile causes the drug to act by modulating two of the main neurotransmitters involved in MDD, suggesting a close relationship between the response/remission rates to the drug and its potential in the treatment of this common disorder.

In conclusion, according to our results, 5-HTR_{2B} and SLC6A3 proteins were identified as potential targets, since they present higher affinity to the sertraline molecule and also due to its stability in the binding sites. Here, we suggest that sertraline has a high affinity to 5-HTR2B and SLC6A3 proteins, proposing the relationship between these data and the potential multimodal treatment effectiveness of this drug. These exploratory findings could assist future research using

bioinformatics and its practical implication in the development of further treatment strategies. Therefore, our findings could point to a multimodal mechanism of pharmacological action, especially for the treatment of MDD.

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Declarations

Conflict of interest The authors declare no competing interests.

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