



HEALTH SCIENCES

In silico affinity between analgesic/anti-inflammatory drugs and the transient receptor potential A1 to predict potential pharmacological managing approaches for bleaching sensitivity

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Abstract: Reducing in-office tooth bleaching sensitivity represents a challenge for professionals. Researchers have associated the block of the pain receptor TRPA1 with reducing bleaching sensitivity. However, the chemical affinity of analgesic/anti-inflammatory drugs to the TRPA1 needs to be verified. To perform a virtual screening of multiple drugs (analgesic and anti-inflammatory drugs) to verify chemical affinity for the TRPA1 receptor. The crystal structure of the TRPA1 receptor proteins was retrieved from the Protein Data Bank. The SMILES codes of the ligands were extracted from PubChem. The binding energy of the complex was obtained in ΔG - kcal/mol by AutoDock Vina[®] and replicated in the webservers SwissDock[®], DockThor[®], and CbDock[®]. LigPlus[®] confirmed the binding sites. Codeine and dexamethasone showed regularity among all servers, even showing binding energy values of -7.9 kcal/mol for codeine and -8.1 kcal/mol for dexamethasone. Codeine and dexamethasone may be potential drugs to manage tooth bleaching sensitivity if they reach the dental pulp TRPA1 receptor.

Key words: Computer simulation, dental whitening, pharmacology, drug treatment management.

INTRODUCTION

Despite the efficacy of in-office bleaching of vital teeth, bleaching sensitivity is the main side effect that causes individuals to abandon bleaching therapy (Reis et al. 2013, Coceska et al. 2015). Researchers have therefore sought to develop protocols to manage bleaching sensitivity, which can occur as a result of pulp inflammation caused by the permeation of hydrogen peroxide and its chemical by-products into the pulp chamber. Activation of nociceptors causes pain that persists for up to 48 hours after the procedure (Nyman et al. 2013). Therefore, knowledge of the specific nociceptor signalling pathways activated by tooth bleaching products has attracted attention (Giniatullin 2020).

Transient receptor potential (TRP) is a large channel family, of which transient receptor potential ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) are best known for their role in key hyperalgesia mechanisms (Liu et al. 2021), which are highly expressed in odontoblasts (El Karim et al. 2011, Asgar et al. 2015). TRPA1 has been shown to be activated by inflammatory mediators (Oyama et al. 2017) and hydrogen peroxide (Chen et al. 2011). A previous study (Costa et al. 2020) showed that TRPA1 triggers hyperalgesia and inflammation after tooth bleaching. Therefore, drugs that can inhibit TRPA1 activation in the dental pulp may be effective in treating in-office bleaching sensitivity.

The prophylactic use of oral analgesics and anti-inflammatory drugs has been investigated

as a way of preventing bleaching sensitivity. Systemic administration of ibuprofen 400 mg and 600 mg, etoricoxib 60 mg, dexamethasone 4 mg, naproxen 500 mg, acetaminophen 500 mg and etodolac 400 mg failed to eliminate bleaching sensitivity in the office from 1 hour to 48 hours after bleaching (de Oliveira et al. 2018, Costa et al. 2020). However, a significant reduction in bleaching sensitivity was observed in the drug group immediately after the procedure (de Oliveira et al. 2018). Furthermore, it has been shown that preemptive systemic administration of paracetamol/codeine prior to in-office tooth bleaching can reduce immediate bleaching sensitivity, in contrast to ibuprofen and placebo (de Oliveira et al. 2018). Knowing how these drugs interact with TRPA1 would help us understand their role in reducing immediate in-office bleaching sensitivity.

In silico evaluation through molecular docking has emerged as a method to screen the binding energy, binding type and amino acid residues present in the cluster between a protein and a ligand of many molecules (Benedikt et al. 2009, Ushanthika et al. 2019, Sette-de-Souza et al. 2021a). However, there are no data on the molecular docking of analgesic/anti-inflammatory drugs such as aceclofenac, codeine, dexamethasone, potassium diclofenac, sodium diclofenac, ibuprofen, naproxen, nimesulide, paracetamol, prednisone, rofecoxib, tramadol and valdecoxib to the TRPA1 receptor.

The hypothesis was tested that drugs used in clinical dentistry could block the nerve impulse transmitted by TRPA1, thereby reducing the pain caused by tooth bleaching in vital teeth. The binding energy, type of binding and amino acid residues present in the protein-binding complex between TRPA1 and A-967079 (antagonist), aceclofenac, codeine, dexamethasone, diclofenac potassium, diclofenac sodium, HC-030031 (antagonist), ibuprofen, naproxen,

nimesulide, paracetamol, prednisone, rofecoxib, tramadol and valdecoxib were analysed.

METHODS

Ethical aspects

As this is a computational analysis that does not directly involve the use, image or biological material from humans or animals, it did not require ethical approval from the Research Ethics Committee.

Study design

This computational study is based on primary data with a quantitative approach using observational molecular docking methods. The entire methodological protocol was carried out by a single trained researcher (M.J.F.C.). The factor studied was the type of drug on 15 levels: A-967079, aceclofenac, codeine, dexamethasone, diclofenac potassium, diclofenac sodium, HC-030031, ibuprofen, naproxen, nimesulide, paracetamol, prednisone, rofecoxib, tramadol and valdecoxib. The response variables were: (1) binding energy, (2) binding type, (3) and amino acid residues present in the protein-ligand cluster.

A number of drugs have been tested for TRPA1 antagonist activity. Some have shown therapeutic success in laboratory tests, such as HC-030031 (Eid et al. 2008), A-967079 (Chen et al. 2011). In general, HC-030031 antagonises the influx of calcium into the receptor (McNamara et al. 2007), similar to A-967079. Therefore, it would not make any difference to the methodological protocol of this research to use two different drugs. Therefore, the two drugs were used to perform a duplicate analysis.

Analysis methods

The AutoDock Vina[®] software prepared the molecules by creating three-dimensional maps

and generating appropriate dimensions. Web servers with other algorithms (Swissdock[®], Dockthor[®] and Cbdock[®]) were used to verify the reproducibility of the data.

The crystal structure of the TRPA1 receptor proteins (PDB ID: 6pqp) has been obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB; RRID: SCR_012820). These protein structures are expressed by humans (*Homo sapiens*). The SMILE codes of the chemical chains of the ligands were extracted from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and converted to PDB code in Open Babel (Open Babel, RRID: SCR_014920) (Sette-de-Souza et al. 2021b).

The crystal structure of the receptor protein and the ligand chain were prepared in AutoDock[®] software and the PDB codes were converted to PDBQT. The binding energy obtained in ΔG - kcal/mol of the receptor/ligand complex was determined by virtual screening using the AutoDock Vina[®] software with the aid of Perl[®]. The same analyses were reproduced in the web servers Swissdock[®], Dockthor[®] and Cbdock[®].

The LigPlus[®] software catalogued the binding sites of the protein-ligand complex (Sette-de-Souza et al. 2021c). Among the identified ligand clusters, those with the highest binding probability were extracted from previously published analyses, namely TRPA1 (Klement et al. 2013, Nakatsuka et al. 2013, Banzawa et al. 2014, Chen & Hackos et al. 2015, Paulsen et al. 2015). In the analysis of TRPA1 (PDB ID: 6pqp), the test with the antagonists known as A-967079 (Eid et al. 2008) and HC-030031 (Bautista et al. 2013) was used as a positive control.

The drugs in the common axis of analysis for all receptors were: eight non-steroidal anti-inflammatory drugs (aceclofenac, diclofenac potassium, diclofenac sodium, ibuprofen, naproxen, nimesulide, rofecoxib and

valdecoxib), two steroidal anti-inflammatory drugs (dexamethasone and prednisone) and three other analgesics (codeine, paracetamol and tramadol).

Data analysis

The data were analysed in the Microsoft Office Excel[®] 2016 spreadsheet with information on the protein-ligand complex: molecular affinity and system behaviour. The analyses performed consisted only of quantitative variables from which qualitative information on affinity through binding energy could be extracted.

RESULTS

Table I shows the binding affinity (ΔG -kcal/mol) of the protein-ligand complex for the TRPA1 receptor. The results obtained by the docking technique refer to an affinity score, expressed in ΔG -kcal/mol, which ranks the most favourable orientations of the interaction of the protein-ligand complex. Thus, reactions tend to be spontaneous, with a $\Delta G < 0$, meaning that the system has released energy for the reaction to occur. The lower the energy released for the reaction to occur, the higher the affinity of the complex.

The antagonist drug HC-030031 achieved the highest affinity in binding the complex (-8.3 kcal/mol) in the DockThor[®] server analysis. However, the drugs that regularly showed the highest affinities for all servers were codeine, followed by dexamethasone, tramadol and valdecoxib.

The dispersion values are shown in Figure 1. TRPA1 by AutoDock Vina[®] showed the lowest binding energy values.

Table II shows the results of the analyses performed using LigPlus[®], based on the AutoDock[®] software, with the data relating to the binding energy, the type of binding and the

Table I. Binding affinity of the receptor-ligand complex for the TRPA1 receptor.

	AUTODOCK VINA [®]	CBDOCK [®]	DOCKTHOR [®]	SWISSDOCK [®]
A-967079*	-6.2	-6.3	-7.4	-7
Aceclofenac	-5.8	-6.5	-6.6	-8.1
Codein	-7.5	-7.5	-7.5	-7.9
Dexametason	-6.8	-8.1	-7.6	-7.7
Diclofenac potassium	-5.9	-6.9	-6.3	-7
Diclofenac sodium	-5.9	-6.7	-6.2	-7.3
Hc-030031*	-6.1	-7.8	-8.3	-7.3
Ibuprofen	-4.9	-6.5	-6.1	-7
Naproxen	-5.7	-6.6	-6.5	-7.2
Nimesulide	-5.3	-7	-8	-7.3
Paracetamol	-4.2	-5.3	-6.9	-6.2
Prednisone	-7	-7.7	-8	-7.1
Rofecoxib	-6	-7.8	-8.1	-7.6
Tramadol	-5.5	-6.4	-7.8	-7.3
Valdecoxib	-6.1	-7.7	-8.2	-8.1

*Antagonist of TRPA1.

amino acid residue to which the drug bound in the analysed interaction. For some drugs, the binding energy is not the highest of the complex because it may not have shown binding with the amino acid residues identified in the cluster. Amino acid residues that showed direct binding have been assigned in the table and marked with *. Other unmarked amino acid residues are components of the cluster.

Although weaker, many hydrophobic interactions were observed with codeine and dexamethasone, which are essential for the high affinity with these drugs. Furthermore, the interaction with leucine 941 (Leu 941) and phenylalanine (Phe 909) residues is important because they are also found in the active sites of the antagonists.

DISCUSSION

The null hypothesis - that the binding energy, binding type and amino acid residues present in the protein-ligand complex between TRPA1 and the drugs are similar - was rejected because the drugs showed differences in binding energy, binding type and amino acid residues present in the protein-ligand complex. HC-030031 had the lowest binding energy of all the compounds screened. However, codeine and dexamethasone showed high standardised binding energy values for all servers tested. Therefore, they may have a potential therapeutic effect in the treatment of bleaching sensitivity when reaching the dental pulp.

Molecular docking is a computational method that uses mathematical algorithms to digitally calculate the interaction of a

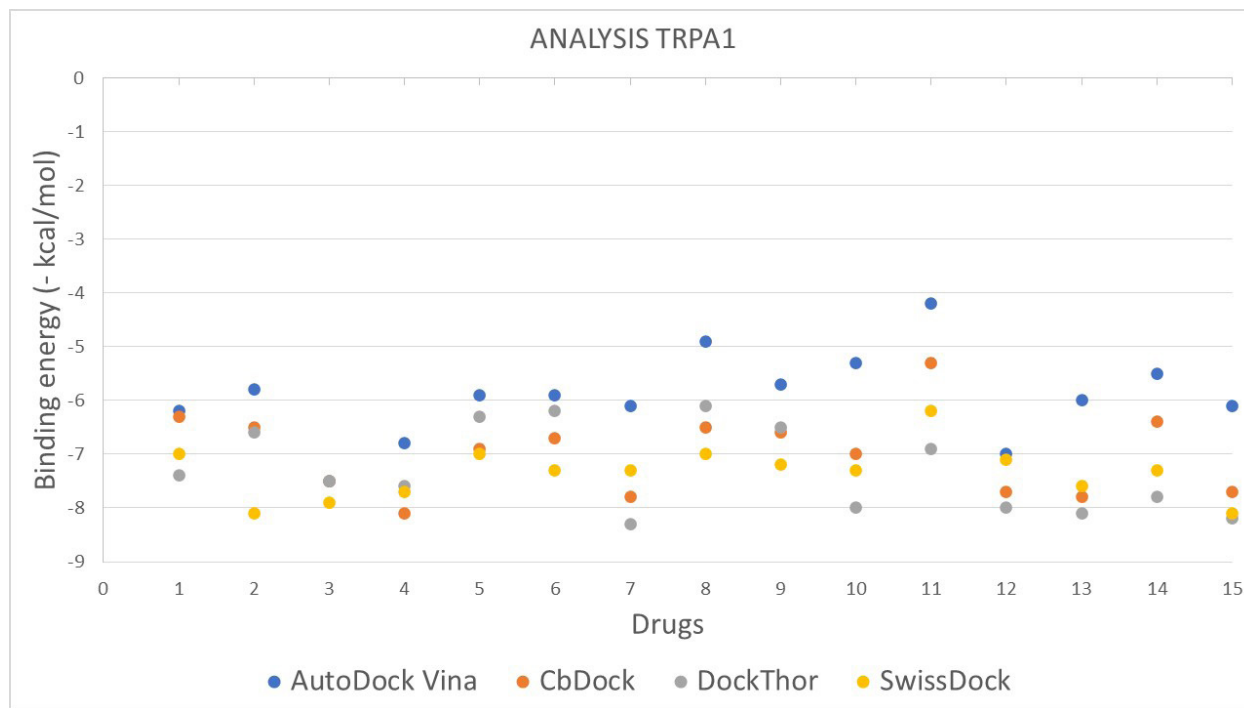


Figure 1. Dispersion values of TRPA1.

TRPA1: 1 - A-967079; 2 - Aceclofenac; 3 - Codein; 4 - Dexametason; 5 - Diclofenac potassium; 6 - Diclofenac sodium; 7 - HC030031; 8 - Ibuprofen; 9 - Naproxen; 10 - Nimesulide; 11 - Paracetamol; 12 - Prednisone; 13 - Rofecoxib; 14 - Tramadol; 15 - Valdecoxib.

protein-ligand complex. Several software packages (webservers) have been developed to improve the codes produced and to give researchers even more reliable results. Our results have been replicated in four different docking servers (AutoDock Vina®, CBDock®, Dockthor® and Swissdock®), allowing the visualisation of the variables in four scenes. As these are different algorithms, no comparative analysis is possible. However, the individual analysis of the results indicated by the binding energies did not show any significant discrepancies between the different drugs tested, revealing the standardisation of the basic formula of the algorithms in the different software.

TRPA1 is a channel permeable to monovalent and divalent cations that can depolarise the membrane and initiate calcium signalling in the cells in which it is expressed (Eid et

al. 2008). The responses that stimulate this receptor can be elicited by exogenous irritants such as hydrogen peroxide, resulting in pain and inflammation (Okunseri et al. 2015). TRPA1 plays an important role in dental pain as it is present in somatosensory afferent neurons of nociceptors containing sensory ganglia, such as the trigeminal ganglia (Eid et al. 2008).

There are already extensive results in the literature from clinical studies of tooth bleaching with the use of systemic medications such as codeine with paracetamol (Fernandes et al. 2017, de Oliveira et al. 2018, de Araújo et al. 2021). This use is justified because serum levels of prostaglandins are higher in the first hour after the painful stimulus, which significantly reduces sensitivity immediately after in-office bleaching (McConville 2017). However, despite the ease and availability of oral administration (McConville 2017), the same clinical studies of tooth

Table II. Binding energy, binding type, and amino acid residues present in the cluster for each receptor.

	Binding energy (ΔG - kcal/mol)	RESIDUES and BINDING TYPE	
	TRPA1	Hydrophobic (n)	Hydrogen bond (n)
A-967079	-4.1	Phe 909* (4), Ile 905 (1), Ile 906 (1)	-
Codeine	-5.5	Leu 941* (1), Ile 916 (1), Gly 914 (2), Tyr 918 (6), Arg 919 (2), Thr 945 (2)	-
Dexametason	-6.2	Leu 941* (3), Asn 917 (2), Tyr 918 (7), Leu 941 (3)	Arg 919 (1)
Hc-0300031	-5.2	Leu 941* (1), Tyr 918 (18), Glu 920 (1)	Asn 917 (2)
Ibuprofen	-4.4	Leu 941* (1), Ile 916 (2), Asn 917 (2), Thr 945 (1)	Arg 919 (2)
Naproxen	-4.8	Leu 941* (2), Ile 916 (2), Tyr 918 (9)	-
Nimesulide	-4.5	Leu 941* (2), Asp 915 (3), Tyr 918 (4)	Gly 914 (1), Ile 916 (1), Asn 917 (1),
Prednisone	-6.5	Leu 941* (1), Ile 916 (2), Asn 917 (2)	Tyr 918 (1), Arg 919 (2), Glu 920 (1)
Tramadol	-5.2	Phe 909* (8), Phe 877 (2), Leu 881 (2), Ile 905 (1)	-

*Amino acid residues found in the cluster.

bleaching conclude that the pain generated by the procedure cannot be fully exploited, either in the analysis of daily or global sensitivity (Fernandes et al. 2017, de Oliveira et al. 2018, de Araújo et al. 2021). Therefore, future perspectives should point to the use of local/topical drugs on the enamel, which could reach the pulp (Moura et al. 2022) and bind to the pain-activating receptors. Codeine and dexamethasone showed strong binding to TRPA1, forming up to 17 hydrophobic interaction bonds with residues of an active site of this receptor.

Codeine is used for the management of dental pain and appears in almost 51% of prescriptions in pain services due to its efficacy in the treatment of acute pain (Grabauer et al. 2018). It is a viable drug to be studied in other pain control programmes, mainly in the context

of tooth bleaching. The efficacy of codeine in the treatment of dental pain can be justified by the highest affinities to the TRPA1 receptor, as confirmed in our study. Furthermore, according to oral fluid analysis, codeine has a high concentration rate in saliva in repeated analyses for up to 4 weeks after serial use of the same sample (Coppla et al. 2018).

There are already extensive results in the literature from clinical studies of tooth bleaching with the use of systemic medications such as codeine with paracetamol (Fernandes et al. 2017, de Oliveira et al. 2018, de Araújo et al. 2021). This use is justified because serum levels of prostaglandins are higher in the first hour after the painful stimulus, which significantly reduces sensitivity immediately after in-office bleaching (McConville 2017). However, despite the ease and

availability of oral administration (McConville 2017), the same clinical studies of tooth bleaching conclude that the pain generated by the procedure cannot be fully exploited, either in the analysis of daily or global sensitivity (Fernandes et al. 2017, de Oliveira et al. 2018, de Araújo et al. 2021). Therefore, future perspectives should point to the use of local/topical drugs on the enamel, which could reach the pulp (Moura et al. 2022) and bind to the pain-activating receptors. Codeine and dexamethasone showed strong binding to TRPA1, forming up to 17 hydrophobic interaction bonds with residues of an active site of this receptor.

The hydrophobic effect observed between codeine and TRPA1 is caused by the interaction of the non-polar parts of the ligand and the active site at the time of complex formation, which increases the entropy of the system and favours the formation of the protein-ligand complex (Livadiotis & McComas 2021). Many hydrophobic subunits in both the peptides and drugs analysed are essential for ligand recognition by the receptor (Livadiotis & McComas 2021, Zhang et al. 2022). Thus, codeine and dexamethasone, if they can reach the pulp, may be promising drugs for eliminating the painful stimulus caused by clinical procedures that activate the TRPA1 channel in the pulp.

CONCLUSION

Analysis of the various pharmacological options may reveal a link with TRPA1. For example, codeine and dexamethasone, if they can reach the pulp, may be promising drugs to reduce the painful stimulus caused by clinical procedures that activate the TRPA1 channel in the pulp.

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