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Pharmacological prospection of cannabidiol analgesic action through molecular docking: interactions with voltage-gated sodium channel Nav1.7

Prospecção farmacológica da ação analgésica do canabidiol através de docking molecular: interações com o canal de sódio dependente de voltagem Nav1.7

Prospección farmacológica de la acción analgésica del cannabidiol a través del acoplamiento molecular: interacciones con el canal de sodio dependiente de voltaje Nav1.7

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Abstract
Objective: to analyze the interaction of cannabidiol (CBD) with Nav1.7 and compare it with carbamazepine (CBZ) through molecular docking. Methodology: a quantitative and experimental research, of the *in silico* type, which used CBD (CID: 644019) and CBZ (CID: 2554, standard drug blocker), anticonvulsant used in chronic pain, on the Nav1.7 channel (PDB: 6N4I), as target protein. Docking simulations were obtained using the Dockthor®, analyzed and visualized using UCSF Chimera®. The results of the CBD and CBZ simulations were arranged in order of highest affinity with the channel protein. The affinities scores were compared using the Student t-test in the GraphPad Prism®, where p values $p < 0.05$ were considered significant. Results: 1,000,000 evaluations of the possible interactions of CBD and CBZ with Nav1.7 were carried out, which the best three with the lowest binding energy (kcal/mol) were selected. The predicted binding affinity scores of Nav1.7 protein and CBD, and CBZ were - 8.61 ± 0.008 and - 8.47 ± 0.27, respectively. Comparing these values, it was noted that affinities did not difference significant ($p = 0.31$), which is reflected in the similar positions of each one in the channel and possible therapeutic potency. CBD is hydrogen bonded to THR180 residue with the distance of 1.86 Å. Conclusions: cannabidiol binds to Nav1.7, being able to block it. These data support the clinical use of cannabidiol as an analgesic through the neuronal inhibitory pathway.
Keywords: Cannabidiol; Analgesic; Drug design; Voltage-gated sodium channel Nav1.7.

Resumo
Objetivo: analisar a interação do canabidiol (CBD) com Nav1.7 e comparar com a carbamazepina (CBZ) através de docking molecular. Metodologia: trata-se de uma pesquisa quantitativa e experimental, do tipo *in silico*, que utilizou

como substâncias testes, o CBD (CID: 644019) e a carbamazepina (CID: 2554, bloqueador controle), anticonvulsivante padrão utilizado na dor crônica, sobre o canal Nav1.7 (PDB: 6N4I), como proteína alvo. Os experimentos de docking molecular foram obtidos usando o portal online Dockthor®, analisados e visualizados pelo UCSF Chimera®. Os resultados das simulações do CBD e da CBZ foram estabelecidos em ordem de maior afinidade com a proteína canal. As afinidades foram comparadas utilizando teste "t" de Student no programa GraphPad Prism®, onde valores de $p < 0,05$ foram considerados significantes. Resultados: foram realizadas 1.000,000 avaliações das possíveis interações do CDB e CBZ no Nav1.7, destas as três melhores, com menor energia de ligação (kcal/mol) ou melhor afinidade, foram selecionadas. O CBD e CBZ apresentaram afinidade de - 8,61 ± 0,008 e - 8,47 ± 0,27 kcal/mol, respectivamente. Comparando-se esses valores, notou-se que não houve diferença estatística significante ($p = 0,31$), o que se reflete posicionamentos similares de cada um no canal e também possível potência terapêutica. O CBD fez uma ligação de hidrogênio com o resíduo THR180 com uma distância de 1,86 Å. Conclusões: o canabidiol se liga ao Nav1.7, sendo capaz de bloqueá-lo. Estes dados fundamentam o uso clínico do canabidiol como analgésico pela via inibitória neuronal.
Palavras-chave: Canabidiol; Analgésico; Modelagem de drogas; Canal de sódio dependente de voltagem Nav1.7.

Resumen
Objetivo: analizar la interacción del canabidiol (CBD) con Nav1.7 y compararla con la carbamazepina (CBZ) a través del acoplamiento molecular. Metodologia: trata-se de uma pesquisa quantitativa e experimental, do tipo *in silico*, que utilizou como substâncias testes, o CBD (CID: 644019) e a carbamazepina (CID: 2554, bloqueador controle), anticonvulsivante padrão used na dor crônica, sobre o canal Nav1.7 (PDB: 6N4I), como proteína alvo. Los experimentos de acoplamiento de foraminíferos moleculares obtenidos mediante el portal en línea Dockthor®, analizados y visualizados por UCSF Chimera®. Os resultados das simulações do CBD y da CBZ foram estabelecidos ordem of maior afinidade com a protein canal. Como afinidades por el uso de la prueba "t" de Student en el programa GraphPad Prism®, los valores de $p < 0,05$ fueron considerados significativos. Resultados: foram realizó 1.000,000 avaliações das possíveis interações do CDB e CBZ no Nav1.7, destas as três melhores, com menor energia de ligação (kcal/mol) ou melhor afinidade, foram selecionadas. O CDB y CBZ presentan una afinidad de - 8,61 ± 0,008 e - 8,47 ± 0,27 kcal/mol, respectivamente. Comparando-se esses valores, notou-se que não houve diferença estatística significante ($p = 0,31$), o que se reflete posiciones similares de cada um no canal e também possível potência terapêutica. El CBD hizo un enlace de hidrógeno con el residuo THR180 con una distancia de 1,86 Å. Conclusiones: o canabidiol se liga ao Nav1.7, sendo capaz de bloquear-lo. Estos dados son fundamentales o el uso clínico del canabidiol como analgésico pela vía inibitória neuronal.
Palabras clave: Cannabidiol; Analgésico; Diseño de fármacos; Canales de sodio activados por voltaje Nav1.7.

1. Introduction

Cannabis sativa is a herbaceus plant from Cannabaceae (Carlini, 2006). It has been used to treat many disease, including pain (Hudson & Puvanenthirarajah, 2018; Skaper & Di Marzo, 2012). This specie presents hundreds of compounds, which have been called as phytocannabinoids. The primary active components are Δ9-tetrahydrocannabinol (THC), imparts psycho-activity, and cannabidiol (CDB), without psycho-activity. Those components have been shown to promote pain relief in animal models (Romero-Sandoval et al., 2018; Casey et al., 2017; Hill, 2015). Recently, the use of CBD as an anticonvulsant agent have been related (Vitale, Iannotti & Amodeo, 2021; Devinsky et al., 2017a,b; Devinsky et al., 2016).

CBD's lack of activity in various disorders that involves membrane excitability, have been known as CBD targets, including voltage-gated sodium (Nav) channels, voltage-gated potassium (Kv) channels, voltage-gated calcium (Cav) channels, and transient receptor potential (TRP) channels (De Petrocellis et al., 2011; Ghovanloo et al., 2018; Patel et al., 2016; Ross et al., 2008; Sait et al., 2020). In special, the Nav function has been suggested to be associated with many conditions in which CBD has shown efficacy (Dravet, 2011; Devinsky et al., 2017a).

Nav channels are hetero-multimeric proteins composed of large ion conducting α-subunits and smaller auxiliary β-subunits (Catterall, 2012; Ghovanloo & Ruben 2020). Lastly, certain gain-of-function mutations in Nav1.7 cause multiple pain disorders (Bankar et al., 2018; Emery et al., 2016; Dib-Hajj et al., 2007; Dib-Hajj et al., 2010). The inhibitory effects of CBD on Nav1.1 to Nav1.7 were characterized using voltage-clamp electrophysiology of cells and neurons (Ghovanloo et al., 2018). Docking analyses have shown CBD effects on Nav1.1, 1.2 and 1.4 (Ghovanloo et al., 2021; Sait et al., 2020), however, the method of interaction with Nav1.7 is still unknown. Moreover, molecular docking studies provided atomic level details on

protein-ligand interactions (Teixeira et al., 2021). Thus, this work proposes to verify the cannabidiol interactions with Nav1.7 and compare to carbamazepine in the molecular mechanism by docking studies.

2. Methodology

A quantitative and experimental research (Pereira et al., 2018) with an *in silico* approach (Teixeira et al., 2021) was performed used CBD (CID: 644019) and carbamazepine (CID: 2554), a drug blocker Nav, both obtained from PubChem. For docking studies, the structure of Nav1.7 was retrieved from Protein Data Bank (ID: 6N4I). The output conformers from Dockthor®, a receptor-ligand docking program, were ranked in order of increasing affinity with the protein (Magalhães et al., 2014). The evaluations were obtained using the co-ordinates of the grid boxes were: x = 97.3135; y = 249.151; z = 214.9925). Twenty four poses were generated for each docking experiment. Docking poses were analyzed and visualized using UCSF Chimera®.

The predicted binding affinity scores (Aff) were obtained and compared using Student t-test in the GraphPad Prism® software, where values $p < 0.05$ were significant.

3. Results and Discussion

From 1,000,000 evaluations into CBD or CBZ and Nav1.7, the best three were selected because they presented the lowest binding energy (kcal/mol), confirming high affinity. The predicted binding affinity scores of Nav1.7 protein and CBD, and CBZ were - 8.61 ± 0.008 and - 8.47 ± 0.27, respectively (Table 1). The values were compared and no difference statistically was observed ($p = 0.31$), therefor CBD and standard drug showed similar affinity with Nav1.7. If the binding energy of molecular docking is < -5 kcal/mol, the binding is likely to be reasonably stable, which indicates that both ligand and receptor can spontaneously bind without external force (Du et al., 2022). The first study that showed the Nav channels to be among CBD's targets was in 2016. Over the past few years, Ghovanloo et al. (2018) showed that CBD inhibited Nav1.1 to 1.7 currents, which they used voltage-clamp electrophysiology of cells and neurons.

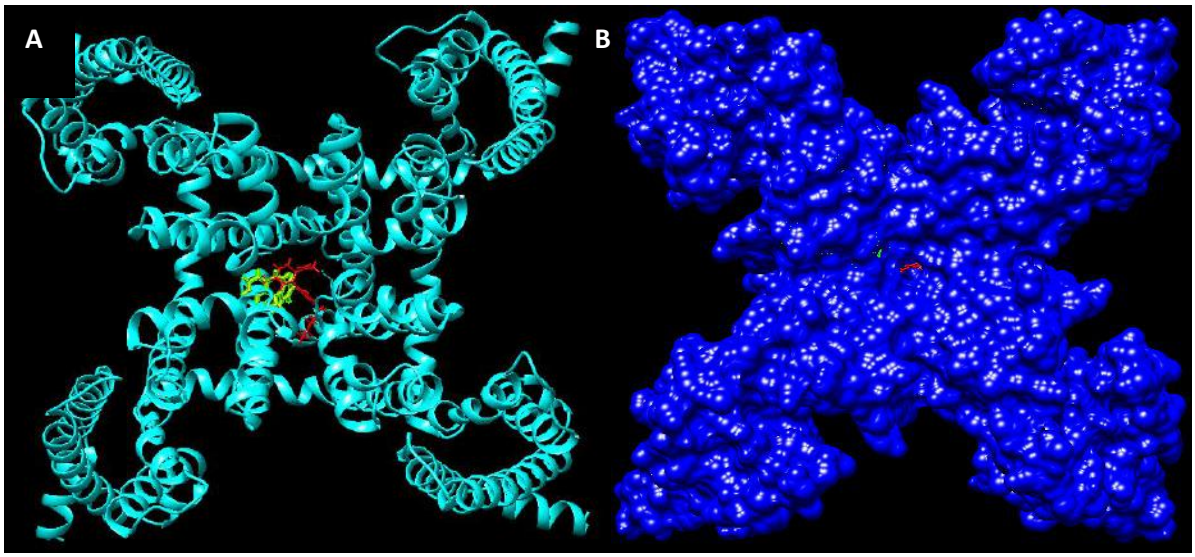
Table 1 - Biding affinity of the CBD and CBZ on NAV1.7.

	Biding affinity (kcal/mol)
CBD	- 8.61 ± 0.008
CBZ	- 8.47 ± 0.27

Student t-test, $p = 0.31$. Source: Authors (2023).

Docking simulations revealed CBD`s and carbamazepine's localization in channel grid (Figure 1A), which corresponds at a blocking pore (Figure 1B). Analyzing the 3D structure, both drugs presented a different position in Nav1.7, although it showed similar binding affinity. High-resolution X-ray crystallography of a bacterial Nav channel showed that CBD indeed interacts inside the Nav pore (Sait et al., 2020), which was similar to results observed in Nav1.1 and Nav1.4 (Ghovanloo et al., 2021).

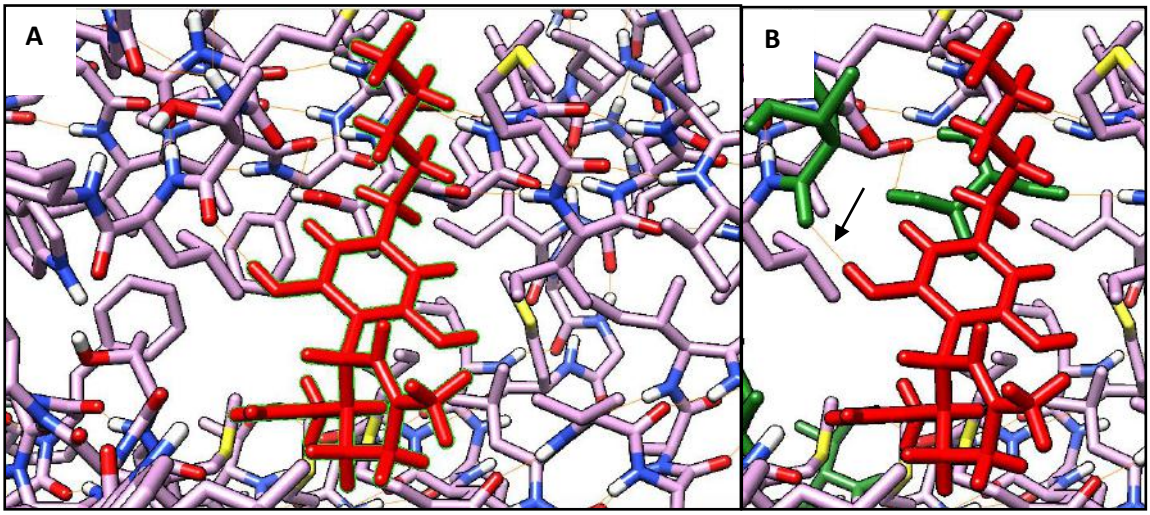
Figure 1. CBD and CBZ binding pose inside Nav1.7.



Being: CBD' (red) and CBZ' (yellow) chemical structure inside channel 3D (green) and hydrophobicity surface (B).
Source: Authors (2023).

The main hydrophobic interactions of CBD and residues Nav1.7 are shown in Figure 2A. Other docking details as CBD is hydrogen bonded to THR180 residue with the distance of 1.86 Å (Figure 2B). Differently, the hydrogen bond between CBD and a bacterial Nav channel involves the M175 residue (Sait et al., 2020). However, CBZ did not present hydrogen bond, it made hydrophobic interactions only. By analyzing all data, it suggests that CBD may be most steady inside channel pore than CBZ which justified the CBD to be closed and specific. On the other hand, the CBD could be better tolerated than CBZ in neuropathic pain and epilepsy.

Figure 2 - Interaction of CBD inside the binding site of NAV1.7 using 3D representations.



Being: CBD' (red) interactions with residues (A); black arrow shown hydron bond (orange) with THR180 residue (green) (B).
Source: Authors (2023).

Nevertheless, CBZ has been related to different cognitive and psychomotor features, mainly in attention and language domains such as deterioration in information processing speed and attention, detrimental effects on memory, and worse

arithmetic performance (Witt & Helmstaedter, 2013; Eddy et al., 2011; Forsythe et al., 1991; Kang et al., 2007; Shehata et al., 2009; Wesnes et al., 2009), our data have shown that CBD's mode interaction on Nav1.7 could be alternative to minimize those side effects. Since the use of selective Nav1.7 antagonists together with either drugs has the potential for side effect-free analgesia (Emery et al., 2016).

4. Conclusion

The cannabidiol interacts with Nav1.7, which it able to block. These findings reinforce clinical apply cannabidiol as analgesic by neural inhibition.

However, further studies with analysis others are necessary in the future.

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