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Cannabidiol interactions in the voltage-gated calcium channel by molecular docking: its role in the neuronal inhibitory mechanism

Interações do canabidiol no canal de cálcio dependente de voltagem por docking molecular: papel no seu mecanismo inibitório neuronal

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Abstract

Objective: to analyzer the interactions of cannabidiol in the $Ca_V3.2$ through molecular docking. Methodology: this is a research with *in silico* approach, which CBD and gabapentin (GBP) were employed as test substances, and $Ca_V3.2$ channel the target protein. Molecular docking experiments were realized by Dockthor. The drugs simulations were classified in order of highest affinity in the channel. The binding energy scores were linked using Student t-test by GraphPad Prism software, the values were significantly different when $p < 0.05$. **Results:** the spatial positions into CBD or GBP and $Ca_V3.2$ were 1.000,000 conformers. Our data showed that the binding energies of $Ca_V3.2$ channel and CBD or GBP were - 6.493 ± 0.07 and - 6.842 ± 0.19 kcal/mol, respectively. Those values did not show statistically difference ($p = 0.08$), suggesting that both drugs bind similarly the $Ca_V3.2$, however both chemicals connected the distinct sites. **Conclusions:** CBD binds to $Ca_V3.2$, which corroborates its blockade channel. Those data support the analgesic effect of CBD through the neuronal inhibitory pathway.

Keywords: Cannabidiol; Drug analgesic; Drug design; Voltage-gated calcium channel.

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Resumo

Objetivo: analisar as interações do canabidiol (CBD) no $Ca_V3.2$ através de docking molecular. Metodologia: trata-se de uma pesquisa do tipo *in silico*, que o CBD e a gabapentina (GBP) foram utilizadas como substâncias teste e o canal $Ca_V3.2$ como proteína alvo. Os experimentos de docking molecular foram realizados no Dockthor. As simulações dos fármacos foram classificadas em ordem de maior afinidade no canal. As energias de ligação foram comparadas usando o teste "t" no programa GraphPad Prism, os valores foram significantemente diferentes quando $p < 0,05$. **Resultados:** as posições entre CBD e GBP foram 1.000,00 conformações. Os dados mostraram que as energias de ligação no $Ca_V3.2$ e CBD ou GBP foram - 6,493 ± 0,07 kcal/mol e - 6,842 ± 0,19 kcal/mol, respectivamente. Esses valores não apresentaram diferença estatística significante ($p = 0,08$), mostrando que ambos têm afinidade similar no canal, apesar de posicionamentos distintos. Conclusões: o CDB se liga ao CaV3.2, o que corrobora o bloqueio deste canal. Estes dados fundamentam o efeito analgésico do CDB pela via inibitória neuronal.

Palavras-chave: Canabidiol; Analgésico; Modelagem de drogas; Canal de cálcio dependente de voltagem.

INTRODUCTION

Pain is defined as an uncomfortable emotional and sensitive experience, associated or similar to potential or real tissue lesion.[1-2] The patient is affected by pain consequences, because health activities, social life and workday are limited.[3] Despite high prevalence of disorder related to pain, it effective handling is a challenge.[4]

A putative analgesic is the cannabidiol (CBD), a phytocannabinoid presents at *Cannabis sativa*. CBD acts without psychoactive and is not cognitive depressive, which promotes drug safe.[5,6]

CBD have been applied in many diseases that involves membrane excitability, therefore its targets including channels, such as voltage-gated sodium (Na_V) channels, voltage-gated potassium (K_v) channels, voltage-gated calcium (Ca_V) channels, and transient receptor potential (TRP) channels.[7-11]

The low voltage-gated calcium channel family is important in the peripheral processing of nociceptive signals since they play a crucial role in controlling neuronal excitability.[12] Three subtypes of Ca_V channels have been identified, namely $Ca_V3.1$, $Ca_V3.2$, and $Ca_V3.3$. Gene regional distribution analysis demonstrated that the $Ca_V3.2$ subtype is predominantly found at sites essential for pain transmissions.[13,14] Blockers of Cav3.2 are putative candidates to treatment of chronic and acute pain.[15-19] CBD was able to abolish fully conductance via Ca_V 3.1, 3.2 and 3.3 T-type channels using patch clamp electrophysiology, although mechanism molecular details of CBD on Ca_V has not been elucidate yet.[9] Therefore, molecular docking insights understand the function-structure relation in a pharmacological target and its ligand-protein binding.[20]

GBP is a synthetic analogue of the neurotransmitter gamma-aminobutyric acid with anticonvulsant activity, a blockade neuronal Ca_V and has also become popular alternatives to opioids for pain and are widely recommended as first-line agents for the treatment of neuropathic pain.[21,22] GBP presents molecular formula $C_9H_{17}NO_2$ and molecular weigth 171.24 g/mol, the CBD has $C_{21}H_{30}O_2$ and 314.5 g/mol.[23]

This study aimed to analyzer the CBD interactions in the $Ca_V3.2$ channel by molecular docking insights, and to compare the GBP.

METHODS

The research was quantitative and experimental, with an *in silico* network. The chemical structures of CBD (CID: 644019) and GBP (CID: 3446), a drug Ca_V blocker, were downloaded from the PubChem database and the 3D structure of $Ca_V3.2$ from the PDB database (ID: 6N4I). The channel protein and chemicals were molecularly docked by Dockthor® and classified in order the highest affinity with the channel.[24] The simulations were processed from the grid boxes co-ordinates (x = 178.5415, y = 169,681 and z = 193.33). The docking poses selected and H-bonding were visualized by UCSF Chimera® software.

The binding energy scores were linked using Student t-test by GraphPad Prism®, the values were significantly different when $p < 0.05$.

RESULTS AND DISCUSSION

The spatial positions into CBD or GBP and $Ca_V3.2$ were 1,000,000 conformers. The top three were selected, and the binding energy of each drug and the channel was calculated and shown in Table 1. It is generally determined that the molecular docking is more stable if presents lower biding energy.[25] Our data showed that the binding energies of $Ca_V3.2$ channel and CBD or GBP were - 6.493 ± 0.07 and - 6.842 ± 0.19 kcal/mol, respectively (Table 1). Those values did not show statistically difference, suggesting that both drugs bind similarly the $Ca_V3.2$. In fact, the energy scores are < − 5 kcal/mol, it determines the spontaneous biding into ligand and receptor.[26]

Table 1. Docking binding energy of CBD and GNP in the CaV3.2.

Ligand	Affinity (kcal/mol)
CBD	- 6.493 ± 0.07
GBP	- 6.842 ± 0.19

Being: p = 0.08 (CBD vs. GBP).

* CBD: cannabidiol; GBP: gabapentin

The best CBD`s and GBP's position were presented in Fig. 1, which may be correspond to blockade channel (Fig. 1B). Visualizing the 3D structures, both chemicals connected the

distinct sites in $Ca_V3.2$, however they exhibited same binding energy (Table 1). In similar manner, CBD and carbamazepine showed same energy on $Na_V1.7$.[27] Others phytocannabinoids, as cannabigerolic acid and cannabidivarin, have been shown inhibit $Ca_V3.2$ using whole-cell patch clamp recordings.[28]

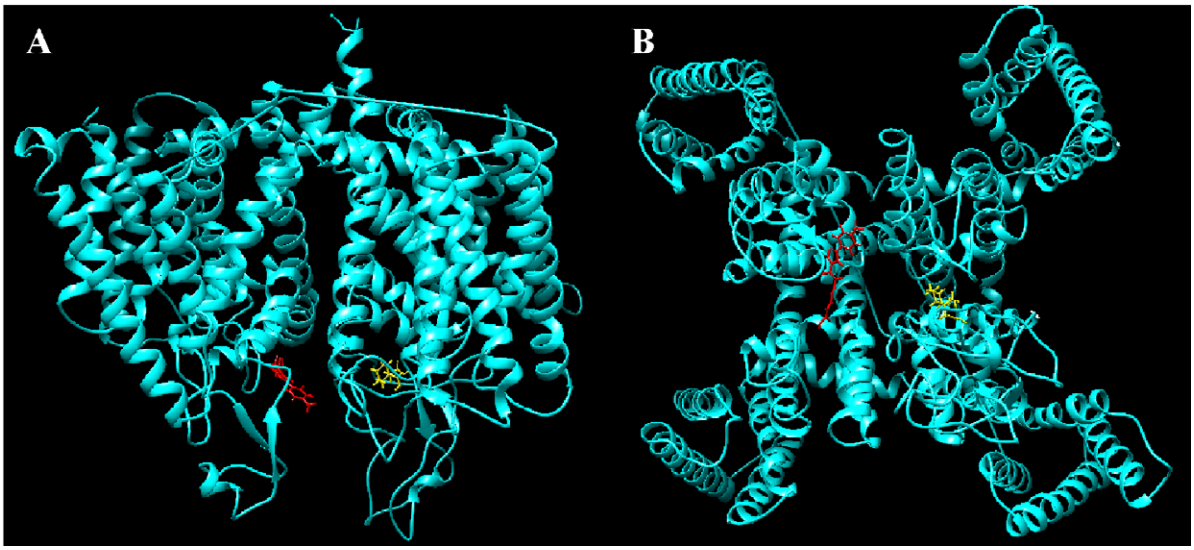

Figure 1 – CBD and GBP site in the CaV3.2. Being: CaV3.2 shown from the side (A) and cytoplasmic (B) view. CBD' (red) and GBP' (yellow) conformation inward protein 3D (cyan).

The helices of CaV3.2 and CBD binding sites are presented in Figure 2A. Specifically, the CDB makes H-bond with ASP690, ASP421 and LYS423 residue (Fig. 2B), whose the distance were 2.38, 1.42 and 1.88 Å, respectively. However, GBP did not present H-bond with residue (data not shown), suggesting it has less stability than CBD in CaV3.2. The CBD binding site and others channels have been different, such as NaV1.7 involves the THR180 and a bacterial NaV channel the M175 residue.[10,27]

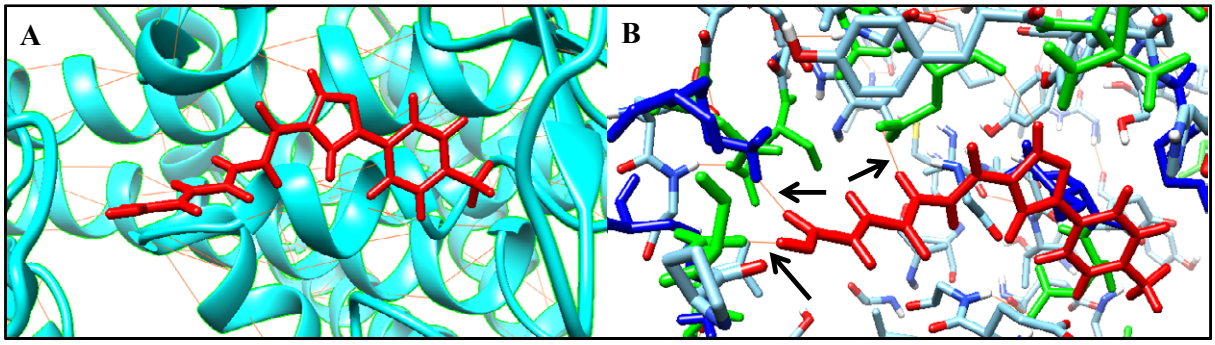

Figure 2 – Sight of CBD binding sites in CaV3.2. Being: CBD' (red) interactions (A); H-bond and ASP690, ASP421 (green), or LYS423 (blue) are presented orange (black arrow) (B).

GBP acts by blockade neuronal CaV and is a recommended first-line agent for treating neuropathic pain, despite its efficacy rate is reportedly low, and the risk of adverse events is high. [29,30] On the other hands, our data shown that CBD mechanism in CaV3.2 may be an analgesic alternative. The binding are capable of blocking the entry of calcium into the neuronal terminal, which prevents neurotransmitter exocytosis, and thus, communication for the conduction of the painful stimulus.

CONCLUSIONS

The cannabidiol interacts CaV3.2 channel residues, corroborating its blockade, while gabapentin interacts with others residues. Those findings reinforce neuronal inhibition promoted by cannabidiol that may be an alternative drug to treat neuropathic pain. It can be used as a reference for future research.

CONFLICT OF INTERESTS

Not applicable

AUTHOR CONTRIBUTIONS

GEJA, GJSJ, NNM and **GNM**: scientific Initiation students who developed the article. **AEAC**: collaborating professor who reviewed the article. **LCLF and JLVS**: advisors who designed and reviewed the article.

REFERENCES

1. Witte W, Stein C. History, Definitions and Contemporary Viewpoins. In: Kopf A, Patel NB, editores. Guia para o gerenciamento da dor em configurações de poucos recursos. Seattle; IASP; 2010:3-8p.
2. Cipriano A, Almeida D, Vall J. Perfil do paciente com dor crônica atendido em um ambulatório de dor de uma grande cidade do sul do Brasil. Rev Dor. 2011;12(4):297-300.
3. Picavet HS, Schouten JS. Dor musculoesquelética na Holanda, prevalências, consequências e grupos de risco, estudo DMC (3). Dor. 2003;102(1-2):167-78.
4. Polacek C, Christopher R, Mann M, Udall M, Craig T, Deminski M, Sathe NA. Percepções dos profissionais de saúde sobre os desafios do manejo da dor crônica. Am J Manag Care. 2020;26:e135–e139.
5. Silva LMN, Lopes DC, Silva EC. O uso fitoterápico do canabidiol no tratamento de dores crônicas: Uma revisão de literatura. SEMOC–Semana de Mobilização Científica-Economia Circular: o novo paradigma para a sustentabilidade, 2021.

6. Bih CI, Chen T, Nunn AVW, Bazelot M, Dallas M, Whalley BJ. Molecular Targets of Cannabidiol in Neurological Disorders. *Neurotherapeutics* 2015;12:699–730.

7. De Petrocellis L, Ligresti A, Moriello AS, Allarà M, Bisogno T, Petrosino S, Stott CG, Di Marzo V. Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. British Journal of Pharmacology. 2011;163(7):1479–1494. https://doi.org/10.1111/j.1476-5381.2010.01166.x

8. Ghovanloo MR, Shuart NG, Mezeyova J, Dean RA, Ruben PC, Goodchild SJ. Inhibitory effects of cannabidiol on voltage-dependent sodium currents. The Journal of Biological Chemistry. 2018:293(43),16546–16558. https://doi.org/10.1074/jbc.RA118.004929

9. Ross HR, Napier I, Connor M. Inhibition of recombinant human T-type calcium channels by Delta9-tetrahydrocannabinol and cannabidiol. The Journal of Biological Chemistry. 2008;283(23),16124–16134. https://doi.org/10.1074/jbc.M707104200

10. Sait LG, Sula A, Ghovanloo MR, Hollingworth D, Ruben PC, Wallace BA. Cannabidiol interactions with voltage-gated sodium channels. eLife. 2020;9:e58593. https://doi.org/10.7554/eLife.58593

11. Patel RR, Barbosa C, Brustovetsky T, Brustovetsky N, Cummins TR. Aberrant epilepsy-associated mutant Nav1.6 sodium channel activity can be targeted with cannabidiol. Brain. 2016;139(8):2164–81.

12. Zamponi GW, Striessnig J, Koschak A, Dolphin AC. The physiology, pathology, and pharmacology of voltage-gated calcium Channels and their future therapeutic potential, Pharm. Rev. 2015;67(4):821–870.

13. Choi S, Na HS, Kim J, Lee J, Lee S, Kim D, Park J, Chen CC, Campbell KP, Shin HS. Attenuated pain responses in mice lacking Ca(V)3.2 T-type channels. Genes Brain Behav.2007;6(5):425–431. 12

14. Talley EM, Cribbs LL, Lee JH, Daud A, Perez-Reyes E, Bayliss DA. Differential distribution of three members of a gene family encoding low voltage-activated (Ttype) calcium channels, J. Neurosci.: Off. J. Soc. Neurosci. 1999;19(6):1895–1911.

15. Kamau PM, Li H, Yao Z, Han Y,Luo A, Zhang H, Boonyarat C, Yenjai C, Mwangi J, Zeng L, Yang S, Lai R, Luo L. Potent CaV3.2 channel inhibitors exert analgesic effects in acute and chronic pain models. Biomedicine & Pharmacotherapy. 2022;153:113310.

16. Jarvis MF, Scott VE, McGaraughty S, Chu KL, Xu J, Niforatos W, Milicic I, Joshi S, Zhang Q, Xia Z, A peripherally acting, selective T-type calcium channel blocker, ABT-639, effectively reduces nociceptive and neuropathic pain in rats, Biochem. Pharmacol. 2014;89(4):536–544.

17. Ziegler D, Duan WR, G. G, Thomas JW, Nothaft W. A randomized doubleblind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. Pain. 2015;156(10):2013–2020.

18. Lee M. Z944: a first in class T-type calcium channel modulator for the treatment of pain, J. Peripher. Nerv. Syst. 2014;19(2):S11–S12.

19. Snutch TP, Zamponi GW. Recent advances in the development of T-type calcium channel blockers for pain intervention, Br. J. Pharmacol. 2018;175(12):2375–2383.

20. Teixeira LR, Silva Júnior JJ, Vieira PHS, Canto MVG, Figueirêdo AGM, Silva JLV. Tamoxifen inhibits the anion channel induced by Staphylococcus aureus α-hemolysin: electrophysiological and docking analysis. RSD [Internet], 2021;10(2):e13010212326.

21. Peckham AM, Evoy KE, Ochs L, Covvey JR. Gabapentin for off-label use: evidence-based or cause for concern? Subst Abuse. 2018;12:1178221818801311.

22. Goodman CW, Brett AS. A clinical overview of off-label use of gabapentinoid drugs. JAMA Intern Med. 2019;179:695–701.

23. PubChem. National Library of Medicine. https://www.hhs.gov/

24. Magalhães CS, et al. A dynamic niching genetic algorithm strategy for docking of highly flexible ligands. Information Sciences. 2014;289:206–24.

25. Liu ZL, Li L, Ma HL, Zhong QS, Ke JY, Zhang H. Mechanism of action of Zhishi Daozhi decoction in the treatment of diarrhea based on network pharmacology and molecular docking. Drug Combination Therapy. 2023;5(1):1-8. https://doi.org/10.53388/DCT20230003

26. Du G, Qu X, Hu J, Zhang Y, Cai Y. Identification of Taohong Siwu Decoction in Treating Chronic Glomerulonephritis Using Network Pharmacology and Molecular Docking. Natural Product Communications. 2022;17(11):1-12.

27. Silva Júnior GJ, Arruda GEJ, Lira NBD, Lira NBD, Costa AEA, Morioka CY, Silva JLV. Pharmacological prospection of cannabidiol analgesic action through molecular docking: interactions with voltage-gated sodium channel Nav1.7. RSD [Internet]. 2023;12(3):e30340292.

28. Mirlohi S, Bladen C, Santiago MJ, Arnold JC, McGregor I, Connor M. Inhibition of human recombinant T-type calcium channels by phytocannabinoids in vitro. British Journal of Pharmacology. 2022;179(15):4031–4043.https://doi.org/10.1111/bph.1584

29. Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. J Biol Chem. 1996;271:5768–76.

30. Russo M, Graham B, Santarelli DM. Gabapentin - Friend or foe?. Pain Practice. 2023;23:63–69.