The Cannabinoid Receptor (CB₁): Like a teenager, misunderstood and full of potential

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The Brown Deer High School SMART (Students Modeling A Research Topic) Team has designed a model of CB₁ using 3D printing technology to help visualize the interactions between CB₁ and its agonists and antagonists.

New Opportunities for Cannabinoids

As of January 1st, 2018, eight states have legalized the recreational use of marijuana, while 21 states have legalized its medical use¹ (Figures 1A and 1B). Regardless of attitudes toward recreational use, constituents of marijuana (Cannabis sativa, C. indica) known as cannabinoids are potentially useful in treating pain and inflammation, stress and anxiety disorders, and possibly seizures disorders. Diseases such as obesity and substance abuse disorders may be treated by agents that block the actions of cannabinoids. While there are pharmaceuticals that help with these health issues, often times people will abuse them to get “high.” Ultimately the goal is to create new drugs that will only be useful as a therapeutic and won’t be used recreationally.

The Structure of CB₁

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The Cannabinoid Receptor (CB₁): 1CB₁ is a seven transmembrane-domain, G-protein coupled receptor (GPCR) found on presynaptic neurons throughout the brain (Fig. 2). Various ligands bind to these alpha helices throughout the protein. Agonists such as tetrahydrocannabinol (THC) and other cannabinoids bind with CB₁ in the area of alpha helices 3, 6, and 7, at Phe268 and Phe379. Antagonists such as AM6538 or rimonabant bind with CB₁ in the area of alpha helix 2 at Phe170 and Phe174. An interesting aspect of this receptor is all the amino acids at the active site are non-polar, making the interactions with CB₁ and its ligands very hydrophobic or “greasy.” An “ionic lock” holds helices 3 and 6 close together, with a positively charged Arg214 and a negatively charged Asp338. Agonists have the ability to force the helices apart when they bind to CB₁, opening the “ionic lock” and activating the receptor. With the receptor activated, a coupled G protein can send a message internally within the cell (Fig. 3).

Antagonist in the Active Site

When the medical capabilities of CB₁ are fully understood, it could potentially be useful in treating pain and inflammation, stress and anxiety disorders, and possibly seizure disorders. By peripherally restricting agonists and antagonists to work in certain places, researchers can have the agonists and antagonists target only the desired organs. The ultimate goal of CB₁ research is to develop a pharmaceutical that is not addictive and will be taken for medical reasons only, as opposed to recreational reasons (Fig. 8).

Cannabinoid Receptor 1 (CB₁)

ε and δ

Figure 1B: Marijuana Legalization Status¹

<table>
<thead>
<tr>
<th>State</th>
<th>Legalization Status</th>
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<tbody>
<tr>
<td>Medical marijuana broadly legalized</td>
<td></td>
</tr>
<tr>
<td>Marijuana legalized for recreational use</td>
<td></td>
</tr>
<tr>
<td>No broad laws legalizing marijuana</td>
<td></td>
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</tbody>
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Figure 1A: Medical marijuana logo. (n.d.). Retrieved 15 Feb. 2018 from https://www.medical-marijuana.com/

Figure 2: The Human Brain

Figure 3: G Protein Activation

Figure 4: Tetrahydrocannabinol

Figure 5: Rimonabant

Figure 6: Alpha helices 1, 4, and 5 (purple) and the National Institutes of Health Clinical and Translational Science Award (NIH-CTSA UL1RR031973) for their support in funding the 2017-2018 SMART Team program.

Conclusion

When the medical capabilities of CB₁ are fully understood, it could potentially be useful in treating pain and inflammation, stress and anxiety disorders, and possibly seizure disorders. By peripherally restricting agonists and antagonists to work in certain places, researchers can have the agonists and antagonists target only the desired organs. The ultimate goal of CB₁ research is to develop a pharmaceutical that is not addictive and will be taken for medical reasons only, as opposed to recreational reasons (Fig. 8).

Citations

7. Tian Hua, et al. (2016). Crystal Structure of the Human Cannabinoid Receptor CB₁ (GenBank Accession No.: PDB 5TGZ) and the National Institutes of Health Clinical and Translational Science Award (NIH-CTSA UL1RR031973) for their support in funding the 2017-2018 SMART Team program.