Natural Defense Against THC Overdose
Type-1 Cannabinoid Receptors and the Functional Effects of Pregnenolone

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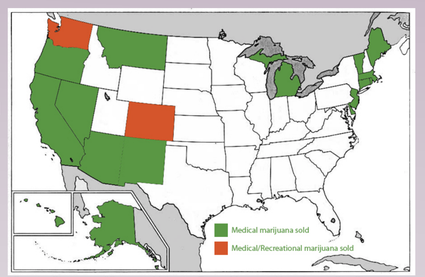
Introduction

Cannabis, often referred to as marijuana, is a drug produced from the Cannabis plant. Recently, marijuana has become an often debated topic as people work to legalize its use for both recreational (as in Colorado) and medical purposes. Marijuana is able to help relieve pain, but it can also lower performance in everyday tasks.

Negatives

- Poor coordination of movement
- Afterwards, users feel tired or depressed
- Increases heartbeat and risk of heart attack
- Inability to understand things clearly
- Personality and mood changes
- Long term: suppression of immune system



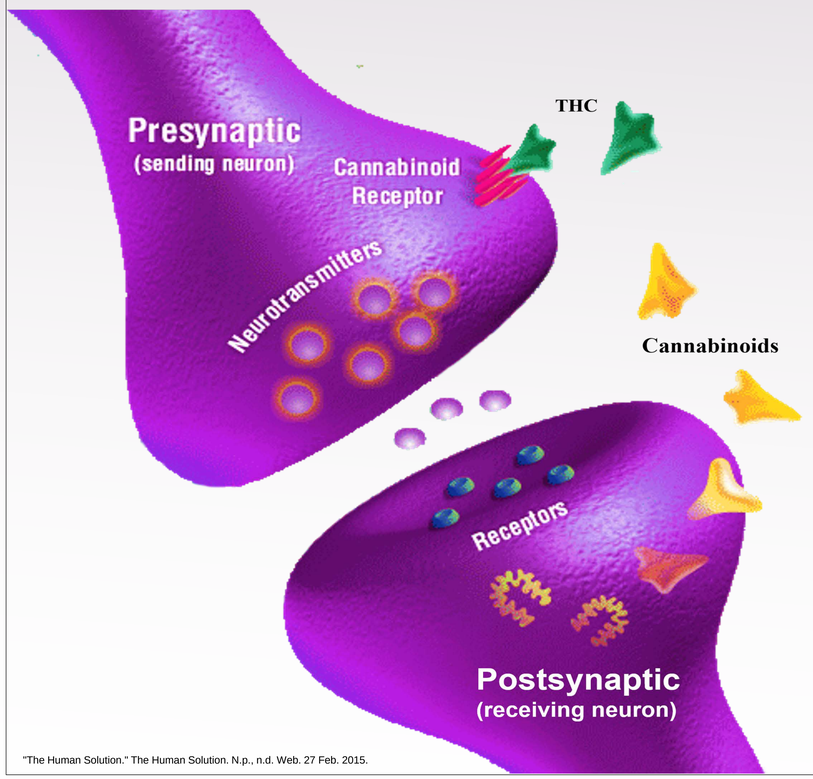
Sunata, Stephanie. "Colorado Votes for Rocky Mountain High, Illinois Still Struggles with the Issue of Medical Marijuana Use." Medill, 08 Nov. 2012. Web. 23 Feb. 2015.

Positives

- Can help control epileptic seizures
- May decrease anxiety
- Can slow progression of diseases such as Alzheimer's disease
- Has been used to treat nausea
- Active components of marijuana, cannabinoids, can potentially kill cancer cells

Endocannabinoid System

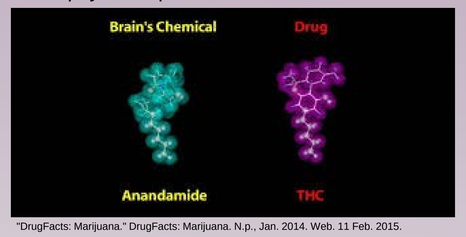
The endocannabinoid system plays a role in diverse conditions such as anxiety, addiction, eating and memory disorders. When synaptic activity occurs in the brain, presynaptic neurons release neurotransmitter that activates postsynaptic neurons. In certain brain regions, endocannabinoids are then produced by postsynaptic neurons and travel back across the synapse to activate CB_1 receptors on the presynaptic neurons. Activation of these receptors decreases neurotransmitter release.



"The Human Solution." The Human Solution. N.p., n.d. Web. 27 Feb. 2015.

THC, CB1 and Pregnenolone

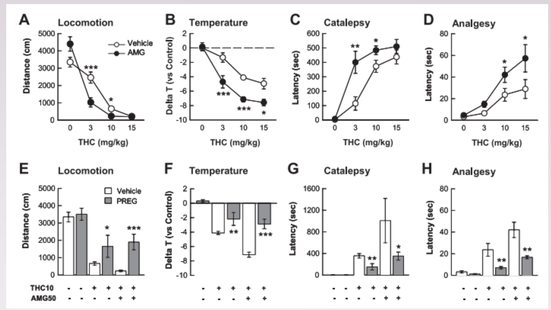
Tetrahydrocannabinol (THC), the active ingredient in marijuana, also activates the CB_1 receptor. THC and similar drugs have therapeutic potential in the treatment of pain, Alzheimer's disease, anxiety, arthritis, and cancer. A downside to the medicinal use of THC is that it also induces psychotropic effects.



"DrugFacts: Marijuana." DrugFacts: Marijuana. N.p., Jan. 2014. Web. 11 Feb. 2015.

Recently, it was discovered that pregnenolone binds to CB_1, where it acts as an allosteric modulator that decreases the effects of THC. An allosteric modulator is a molecule that modifies receptor function by binding somewhere other than the active site.

Cannabinoid Tetrad



Monique Vallée et al., (2014). Pregnenolone Can Protect the Brain from Cannabis Intoxication. Science 343: 94-98.

A series of four tests, known as the Cannabinoid Tetrad, are commonly used to measure the effects of THC. Vallée et al. performed these tests in mice treated with THC alone, THC + pregnenolone, or THC + AMG (an inhibitor of pregnenolone synthesis).

Locomotion Test: Using computerized video tracking, the total distance a mouse traveled over 15 minutes when placed in a square box was recorded. Results show that the distance traveled decreased when THC was present. The presence of pregnenolone, however, weakened the effect of THC (Fig. E) while blocking pregnenolone strengthened the effect of THC (Fig. A)

Temperature Test: A mouse's body temperature was measured. Body temperature decreased with THC. Pregnenolone moderated this effect (Fig. F), while when pregnenolone was blocked, the effect increased (Fig. B).

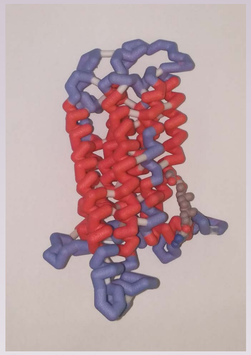
Catalepsy Test: Front paws of a mouse were placed on an elevated bar to measure time spent motionless. Mice treated with THC took longer to move off of the bar. Pregnenolone decreased the effect of THC (Fig. G), while blocking pregnenolone increased the effect of THC (Fig. C).

Analgesy Test: A mouse was placed on a 52 °C hot plate to measure latency, the amount of time it took the mouse to show signs of distress. Latency increased with THC treatment, but decreased with pregnenolone (Fig. H). Blocking pregnenolone increased the analgesic effect of THC (Fig. D).

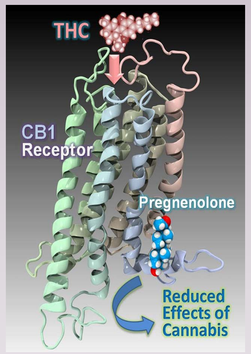
CB1 Receptor Model

Our model highlights the amino acids E133 and R409, which form hydrogen bonds with pregnenolone and are required for its binding to the allosteric site of CB_1.
Both of these amino acids are colored in cpk color and connected with a strut to our pregnenolone molecule. Other areas that are highlighted are color-coded as follows:

Alpha helixes are red.
Struts are colored white.
Non-motif portions are colored cornflower blue.



Reggio_cb1_inactive_pregnenolone-bound



Conclusions

Studying the interaction between CB_1 and pregnenolone provides:

1. A more complete understanding of the normal function of the endocannabinoid system
2. A potential strategy for the treatment of marijuana abuse or intoxication, whereby the effects of THC could be reduced by pregnenolone
3. The potential for targeting CB_1 with allosteric modulators for medicinal purposes

References

Monique Vallée et al., (2014). Pregnenolone Can Protect the Brain from Cannabis Intoxication. Science 343: 94-98.

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