The primary psychoactive ingredient in cannabis is Δ9-tetrahydrocannabinol (THC). It exerts its effects by stimulating the type 1 cannabinoid receptor (CB1). CB1 is the most expressed G-protein-coupled receptor in the brain, activated by endocannabinoids. It plays a key modulatory role in pleasure, motivation, cognition, and pain. About 20% of individuals who use cannabis develop a cannabis use disorder. This term describes the continued use of cannabis despite impairment in psychological, physical, or social functioning. Despite a growing demand, there is no effective treatment for cannabis use disorder. The consortium of authors led by scientists from the United States and France conducted phase 1 and phase 2a of randomized trials to investigate a new signaling-specific inhibitor of type 1 CB1, AEF0117, as a potential treatment for cannabis use disorder.

The same group of scientists demonstrated before that the steroid pregnenolone is released in response to high concentrations of THC and binds to a specific site of CB1. Without modifying ligand binding, pregnenolone inhibits intracellular responses triggered by CB1 activation, such as mitogen-activated protein kinase phosphorylation and mitochondrial respiration, but it does not alter CB1-mediated changes in cyclic adenosine monophosphate, a typical cellular effect of CB1 agonists.

Although pregnenolone was identified as a potential therapeutic tool, it is believed that it is not a viable option because of its short half-life and rapid conversion into other active steroids with potentially adverse effects. Therefore, a new pharmacological class called ‘signaling-specific inhibitor of the CB1’ (CB1-SSi) has been developed. This class was called CB1-SSi to distinguish it from known inhibitors, orthosteric antagonists, and negative allosteric modulators that act by blocking (antagonists) or decreasing (negative allosteric modulators) the access of ligands to the receptor. Orthosteric antagonists/inverse agonists inhibit all receptor activity, impair endocannabinoid function, and produce serious adverse effects.

The authors noted that CB1-SSi does not alter the orthosteric binding of ligands. CB1-SSi can be regarded as a subclass of biased allosteric modulators, which can inhibit the effects of a receptor agonist without exhibiting any psychoactive effects *per se*. This provides a significant advantage for the use of the first CB1-SSi drug, AEF0117, as a potential treatment for cannabis use disorder.

The AEF0117 was shown to decrease THC-related behavioral disorders without producing significant adverse effects in mice and non-human primates. AEF0117 did not show any adverse effects in safety tests, did not increase plasma endocannabinoid levels, and was not converted into pregnenolone’s downstream steroids, testosterone, and allopregnanolone in

experimental animals.

About the study

Phase 1 trial

In phase 1, healthy volunteers were randomized to two AEF0117 ascending-dose cohorts (*n* = 8 per cohort): single-ascending-dose and multiple-ascending-dose. The majority of volunteers were men (90–91%), black (67–85%), and non-Hispanic (83–90%). Both cohorts had a similar mean age (36.8–38.1 years) and body mass index (25.2–25.7 kg/m^2).

In both groups, the administration of AEF0117 was safe and well-tolerated. There were no drug-related adverse events, except for one episode of pruritus and cutaneous rash after the first administration of AEF0117 at a dose of 0.6 mg in the individual from the multiple-ascending-dose study. Treatment for this person was discontinued.

AEF0117 did not change mood ratings or behavioral measures compared to the placebo. Psychometric assessment by the Columbia-suicide severity rating scale and Addiction Research Center inventory did not show any trends.

AEF0117 was not converted into other steroids, such as testosterone, dehydroepiandrosterone, allopregnanolone, cortisol, estradiol, and progesterone, and there was no increase in endocannabinoids after a single administration of AEF0117.

Phase 2a trial

In phase 2a, the authors conducted a randomized, double-blind, placebo-controlled, multiple-dose-escalation study to investigate the effects of AEF0117 on cannabis use disorder. The study included 29 volunteers who were cannabis smokers with cannabis use disorder. The severity of cannabis use disorder was mild in 34% of participants, moderate in 45% of participants, and severe in 21% of participants. The mean age of participants was 32 years, ranging from 21 to 44 years.

Two doses of AEF0117 (0.06 mg and 1 mg) were tested in two ascending-dose cohorts (0.06 mg, $n = 14$, and 1 mg, $n = 15$). Participants completed two 5-day inpatient periods separated by a ≥ 14-day outpatient washout. They received AEF0117 or a matching placebo in a counterbalanced order during the two testing periods. Each day, participants took capsules at 9:00 and then smoked a controlled amount of cannabis 3.5 hours later. They smoked on average 2.9 g of cannabis per day.

AEF0117 significantly reduced the positive subjective effects of cannabis by 19% (at a dose of 0.06 mg) and 38% (at a dose of 1 mg) in volunteers with cannabis use disorder compared to placebo.

At a higher dose of 1 mg, AEF0117 reduced the self-administration of cannabis. This observation is consistent with the dose range seen in animals, where 15 µg/kg of AEF0117 (corresponding to 1 mg in humans) was needed to reduce self-administration, whereas 1.5 µg/kg (corresponding to 0.06 mg in humans) was sufficient to inhibit other THC-related behaviors.

Conclusion

This study showed that AEF0117 reduced the positive subjective effects of cannabis and self-administration of cannabis in individuals with cannabis use disorder in comparison to placebo.

AEF0117 is the first member of a novel pharmacological class of inhibitors, called CB1-SSi, that change the activity of the target receptor in a signaling-specific manner. Since these drugs reproduce the effects of a natural mechanism to counteract CB1 overactivation, they can inhibit the effects of THC without altering the basal activity of the CB1. It seems that AEF0117 decreases the abuse-related effects of cannabis not affecting normal behavior or activities. This provides a significant advantage for the use of AEF0117, as a potential

treatment for cannabis use disorder.

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