MiRA1a, a novel synthetic THC analog, improves cognition

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Introduction

There has been a dramatic rise in the use of Marijuana (i.e. Cannabis Sativa), with Marijuana legalized for medical and recreational purposes in 39 and 19 states, respectively. 52 million Americans (1 in 6) consumed marijuana by the end of 2022, which is an 86% increase from just 10 years ago. [1]

Despite the increased use of Marijuana, Delta-9-tetrahydrocannabinol (THC), thought to be primarily responsible for the intoxicating effects of Marijuana, still has a number of known side effects. Chief among these include cognitive impairment and anxiety/paranoia.[2]

Recent studies have suggested that cognitive impairment from long-term Cannabis use during childhood can lead to an IQ point decline, and among adults there is a significant increase in the risk of car crashes including those resulting in fatalities.[3]

The effect of THC on anxiety and paranoia are biphasic, with low doses being therapeutic and high doses being anxiogenic.

Mira1a, a novel synthetic analog of THC, was developed to address the side effects of THC, which resulted in the surprising finding of improved, rather than impaired, cognition with treatment.

Methods

We tested the effects of Mira1a in the cAMP Hunter™ eXpress CNR1 (CB1) CHO-K1 GPCR Assay, the Elevated Plus Maze (EPM), and trace fear conditioning (TFC). The cAMP Hunter™ eXpress CNR1 (CB1) CHO-K1 GPCR Assay assessed the agonist profile of Mira1a compared to THC. The EPM assessed the effect of MiRA1a on anxiety related behavior. The TFC assessed the effect of MiRA1a on cognition[4].

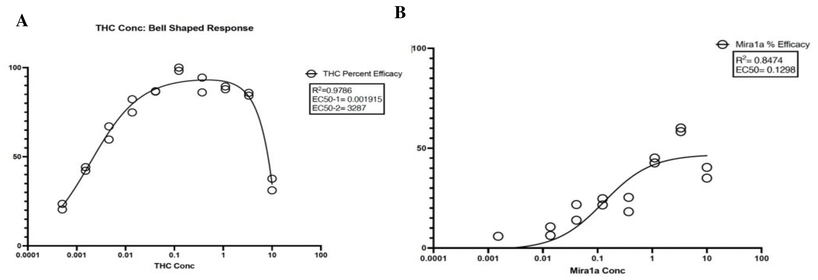
Agonist Assay: Using the cAMP Hunter™ eXpress system, Chinese Hamster Ovary Cells (CHO) expressing CNR1 (encoding CB1 Receptors) and Gi were treated with forskalin and tested with THC vs Mira1a across a range of concentrations. The resulting inhibition of cAMP levels were measured.

Elevated Plus Maze (EPM): 8-12-week-old male C57Bl/6 mice (n=5/group) were administered intraperitoneal (i.p.) injections of vehicle (0 mg/kg) or Mira1a (50 mg/kg). 30 minutes following injection, mice were tested in the elevated plus maze.

Trace fear conditioning test (TFC): The TFC consisted of three phases: habituation, training, and testing. On day 1, female mice (n=6-7/group) were habituated to the arena, and on day 2 they were trained to associate a 30 second tone followed with a foot shock (.5mA, 2s) after a 20 second delay. On day 3 mice were treated with MiRA1a vs vehicle 30 min prior to measuring freezing in response to being placed in the same context as where they were shocked.

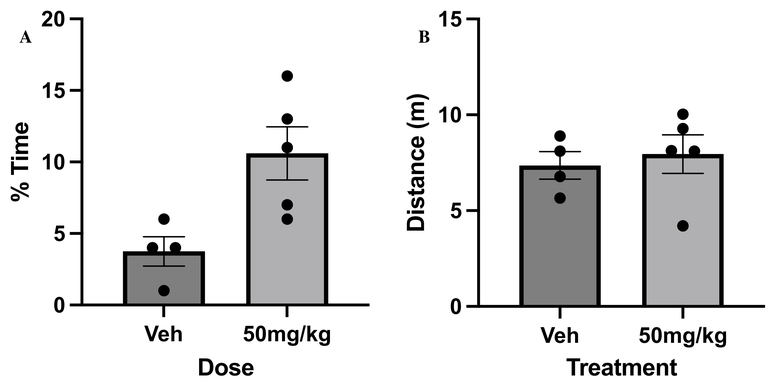
Results

Binding assay for THC compared to MiRA1a



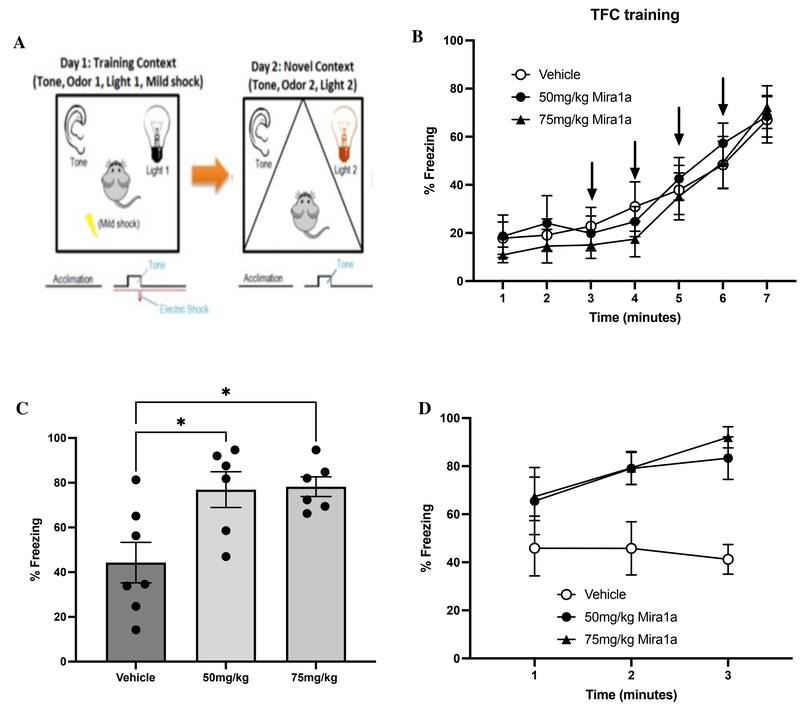
1. THC had a biphasic dose response curve with respect to changes in cAMP levels, reaching a maximal (100%) inhibition of cAMP levels at around 130 nM and then a progressive drop in inhibition of cAMP at higher THC concentrations (A). The EC50 for the initial increase in inhibition of cAMP for THC was 2 nM. Mira1a displayed a response of a mixed agonist/antagonist, reaching a maximal cAMP effect at 50% and having an EC50 of 123 nM. (B)

Performance in an anxiety related task following Mira1a administration



2. MiRA1a had a potent anxiolytic effect in comparison to vehicle. The data showed a significant increase in time spent in the open arm following administration of MiRA1a (p=0.02) in comparison to vehicle (A). There was no difference in distance travelled in MiRA1a treated mice compared to vehicle, indicating a lack of sedation or intoxication (B).

Performance in Cognitive Task following Mira1a administration



3. The TFC data showed that during training—which was done in the absence of any drug treatment—all mice learned equivalently as indicated by the same degree of increased freezing (B). The following day, MiRA1a or vehicle was administered, and freezing in response to context recognition showed significantly increased % freezing (p=<0.0001) in mice given 50mg/kg or 75mg/kg MiRA1a compared to vehicle (C and D).

Summary

- **In the agonist assay, MiRA1a displayed that it was a mixed agonist/antagonist.**
  THC displayed a biphasic dose response (increasing 100% then declining) as a CB1 agonist. This biphasic response of THC might be the pharmacodynamic correlate of the biphasic effects of THC on anxiety. Mira1a displayed that it was a mixed agonist/antagonist, reaching a 50% maximal cAMP inhibition at the highest doses tested. This suggests that Mira1a may be devoid of anxiogenic side effects.

- **MiRA1a has potent anxiolytic effects, as demonstrated in the EPM.**
  EPM demonstrated that Mira1a had potent anxiolytic effects, even at high concentrations. One explanation for the lack of increased anxiety could be explained by the dose response curve for MiRA1a compared to THC at the CB1 receptor.

- **MiRA1a administration leads to increased cognitive performance in the TFC**
  Mira1a--instead of impairing cognition, like THC, or merely having no effect on cognition-- demonstrated an increase of cognitive performance in the Trace Fear Conditioning test. Notably, the effect was seen in healthy wildtype mice. Since Mira1a was not present during conditioning but only during cognitive testing on the following day, the effect of MiRA1a is to increase cognitive performance in the absence of increases in memory. To our knowledge there has never been a similarly robust effect in normal mice by another treatment reported previously. The potential application of MiRA1a for dementia is being explored.

Health Equity

Though African Americans continue to be underrepresented in cognitive aging research, there is substantial evidence that when compared with age-matched Caucasians they are at increased risk for dementia. The potential application of Mira1a to enhancing cognition in patients with dementia would help address this unmet need of cognitive aging disparity. [5]

References

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