CALIFORNIA STATE SCIENCE FAIR
2013 PROJECT SUMMARY

Name(s)

Masih A. Babagoli

Project Number

S1703

Project Title

Structure-Activity Relationship Exploration of Fatty Acid Amide Hydrolase Inhibitors

Abstract

Objectives/Goals

The goal was to find a fatty acid amide hydrolase inhibitor that is both effective and restricted from the central nervous system. Such a compound would enable raising endocannabinoid, substances associated with having analgesic and anti-inflammatory effects, levels just in the periphery.

Methods/Materials

Brain and liver samples were collected from mice previously administered the compounds in different doses. Each compound at each dose was tested in one trial with triplicates (n=3). Samples were placed into vials containing lysis buffer, homogenized, and centrifuged at 2100 rpm for 12 min at 4°C, and the supernatants were collected (S1 fraction).

In order to quantify the protein, BCA quantification assays were performed. They were analyzed with a plate spectrophotometer with optical density being an indicator for the protein concentration.

An ex vivo assay to determine FAAH activity was performed by incubating each sample containing 50 µg of FAAH for 30 minutes with H3-anandamide. Samples were analyzed with scintillation counter.

Results

Four compounds (ARN354, ARN715, ARN716, and ARN14038) were tested. Each was a derivative of a single compound but just with a different substituent in the para- position of the proximal phenyl ring. When administered orally at a dose of 1 mg/kg, ARN715 did not exhibit good oral bioavailability, while the other 3 compounds did. Only ARN354, ARN716, and ARN715 showed to be peripheral inhibitors. On the other hand, ARN 14038 was not restricted to the periphery. Lastly, ARN354 and ARN716 gained access to the brain when co-administered with Ko-143 (a selective inhibitor of the ABC-transporter abcg2).

Conclusions/Discussion

My hypothesis was correct. Manipulating the specified position did change the peripheral distribution of the compounds. Results showed that the hydroxyl group is necessary for the peripheral character of these compounds. Increasing the polarity also significantly limits the compounds' abilities to penetrate blood brain barrier. ARN 715 -- with a carboxyl group -- was unable to enter the central nervous system. Lastly, the loss of peripheral character comes with the elimination of an H-bond donating group, as ARN 14038 -- with the methoxy group -- was able to evade recognition by abcg2. Additionally, this compound had the lowest polarity, enhancing its ability to move across the barrier.

Summary Statement

This project was aimed at finding a fatty acid amide hydrolase inhibitor that is both effective and restricted from the central nervous system.

Help Received

Project was done under Dr. Moreno-Sanz at UCI. He did much of the experimental design. He also administered the drugs and collected the samples. After that, I did most of the work in analyzing the samples and was actively involved in all processes of the experiments, including data analysis.