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A pilot study on measuring the activity level of fatty acid amide hydrolase (FAAH) in human blood

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Background: There are multiple reports describing levels of endocannabinoids and congeners in human plasma, many of which show changes associated with physiological and pathological conditions, such as food intake and obesity. But as yet, there are no investigations into how the activity levels of FAAH and MAGL enzymes might change between individuals. Therefore, this study is designed to fill this gap by investigating the activity level of FAAH in blood and the factors that could affect it compared to Monoacylglycerol lipase (MAGL) enzyme.

Methods: Overnight fasting blood samples were taken from 18 healthy subjects. The blood samples were collected at three visits and the period between each experimental visit was 15 days. Radiometric assays of FAAH and MAGL (using N-arachidonoyl-[3H]-ethanolamine and 2-oleoyl-[3H]-glycerol as substrates, respectively) were conducted with the use of pharmacological tools to define more closely the involvement of these enzymes. Enzyme activities were normalised to the equivalent volume of blood from which they were derived and expressed as mol/min/mL blood in order to allow analysis of the relative contribution to blood endocannabinoid hydrolysis.

Results: erythrocytes contained a higher proportion of FAAH activity compared to other blood fractions. In contrast, platelets contained a higher proportion of MAGL activity, at nearly 86% of the total MGL activity in the whole blood. Specific inhibitors were used to emphasise that FAAH was a predominant enzyme for AEA hydrolysis in erythrocyte membrane. JNJ1661010[2], and URB597[3] (previously described as a selective FAAH inhibitors) caused complete, a potent inhibition (pIC_{50} value of 6.8 ± 0.4 and 8.5 ± 0.1 respectively). In contrast to FAAH, there were other serine hydrolysis enzymes in addition to MAGL responsible for [^{3}H]-2OG hydrolysis in erythrocyte. JJKK-048[1], a selective inhibitor of MAGL, produced an incomplete inhibition (40.9 ± 3% control, pIC_{50} 7.9 ± 0.2). Interestingly, the results from this study suggest that the mechanism that regulates FAAH in human are similar in each volunteers.

Conclusions: FAAH and MAGL activities are differentially expressed in blood fractions, and their activity level may reflect different roles in these fractions. Additional enzyme activities are able to hydrolyse 2-OG, which have yet to be characterized. This is the first study to determine the potency of selective FAAH enzyme inhibitors in human blood samples

References:

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