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# Endocannabinoid metabolism: The impact of inflammatory factors and pharmacological inhibitors

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## Akademisk avhandling

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**Abstract**

The endocannabinoid (eCB) system is an endogenous signaling system involved in homeostatic control of a variety of biological and pathological functions such as mood, pain, inflammation and tumour progression. The activity of the main eCBs *N*-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) is brief thus they are quickly degraded. Both AEA and 2-AG are substrates for cyclooxygenase-2 (COX-2). COX-2 is upregulated in inflammation, pain and in several tumours including prostate cancers, but it is not known whether COX-2 contribute significantly to eCB metabolism under these conditions. The enzyme primarily responsible for AEA degradation is fatty acid amide hydrolase (FAAH). Knockout of FAAH generates an analgesic phenotype and the expression of both FAAH and COX-2 has been correlated with prostate cancer severity and prognosis. Dual inhibition of FAAH and COX-2 to raise endogenous AEA levels is exploited as a therapeutic strategy for treatment of pain and the role of the eCB system in cancer may be of therapeutic value.

This thesis explores the role of COX-2 in AEA degradation, and the effect of inflammatory factors upon the expression and activity of eCB related enzymes in prostate cancer cell lines. Further, the FAAH and COX-2 inhibitory profiles of metabolites and derivatives of currently used NSAIDs was characterized. Both enantiomers of the flurbiprofen derivative flu-AM1 were equally potent as FAAH inhibitors and displayed a useful substrate selective COX-2 inhibition profile in enzyme assays, favoring eCBs as substrates rather than arachidonic acid. However, in intact cells (*R*)-flu-AM1 failed to affect AEA levels and the catabolic route. FAAH inhibitor URB597 and COX inhibitor flurbiprofen alone and together also failed to increase AEA levels in intact cells to any great extent. This suggests that the eCB turnover in these cells is rather slow and that the role of COX-2 in AEA uptake and degradation is minor, in these cells. Further inflammatory factors TNF $\alpha$ , IL-6 and lactic acid induced low pH affected the mRNA levels of 2-AG related enzymes leaving AEA rather unaffected.

**Keywords**

endocannabinoid, anandamide, 2-AG, fatty acid amide hydrolase, cyclooxygenase-2, prostate cancer, catabolism, inflammation, inflammatory factors.

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