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The Anti-proliferative Effect Of N-3 Fatty Acids And N-3 N-acylethanolamines In Breast Cancer Cells Is Mediated Through Cannabinoid Receptors And Fatty Acid Amide Hydrolase

Jisun Lee, Klaus Wahle, Maria Cascio, Roger Pertwee, Steven Heys, Iain Brown. Aberdeen University, Aberdeen, UK

There is evidence to suggest that omega-3 polyunsaturated fatty acids (n-3 PUFA) such as EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are associated with a lower incidence of breast cancer. Omega-6 PUFAs are thought to have cancer promoting effects, yet endocannabinoid derivatives of n-6 PUFA have anticancer effects (Kim et al., 2009). We wished to assess the effects of n-3 PUFA ethanolamide derivatives (n-3 NAE) on the proliferation of breast cancer cells MDA-MB-231 and MCF-7, and determine the role of CB_1 and CB_2 receptors and the presence of FAAH (fatty acid amide hydrolase). Cells were treated with EPA, DHA and their ethanolamides EPEA and DHEA respectively. Cell viability assay (MTT) was used to confirm that n-3 PUFAs and n-3 NAEs dose dependently inhibited growth of both MDA-MB-231 and MCF-7 cells. Statistical analysis was carried out using Student's T-test and shown as IC50 concentrations μM) +/- SEM). EPEA was significantly more potent than EPA in inducing cell death in both MDA-MB-231 (65.82 ± 5.43 and 171.32±6.92, $p \leq 0.01$ respectively) and MCF-7 (76.22±4.70 and 187.87±1.34, $p \leq 0.01$ respectively) cells after 24 hours incubation. DHEA was also significantly more potent than DHA in inducing cell death in both cell types (68.52±5.02 and 70.12±5.39, $p \leq 0.001$ respectively) after 24 hours. Both MDA-MB-231 and MCF-7 cells expressed $CB_{1/2}$ as determined by western blot (n=3), however only MCF-7 expressed FAAH. The selective inhibitor of FAAH (JNJ 1661010) only enhanced the effect of DHEA after 48h incubation. $CB_{1/2}$ receptor antagonists (AM281 and AM630 alone or combined) decreased the effect of n-3 NAE in breast cancer cell lines. These results suggest that anti-tumour effects of n-3 NAEs work via $CB_{1/2}$ receptors in breast cancer cell lines. DHEA is maybe metabolised differently from EPA, DHA and EPEA. Alternatively the anti-tumour effect of DHEA may be due to another metabolite of DHEA, when it is metabolised by FAAH, which is produced when FAAH is inhibited. These results confirm the anti-proliferative effects of n3- NAEs and suggest a role of cannabinoid receptors and FAAH in breast cancer cells.

Kim J et al, BMC Cancer 9:216, 2009