

# The Differential Effect of Opioids on Breast Cancer Cell Pro-Survival and Pro-Apoptotic Pathways

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Opioid administration is a common practice for pain management in cancer patients undergoing chemotherapy. It is important, then, to understand how opioids affect cancer cells. Previous studies have shown conflicting results with some depicting that opioids increase apoptosis in cancer cells and others showing that opioids actually enhance cancer cell proliferation. Thus, the purpose of this project was to determine the cell response that opioids induce in cancer cells and to understand whether pro-survival or pro-apoptotic pathways are activated. To do this, MCF-7 breast cancer cells were treated with DAMGO, a synthetic opioid with high  $\mu$ -opioid receptor specificity. In addition, cells were treated with buffer as a control, naloxone (an opioid antagonist), and naloxone plus DAMGO. Through western blot analysis of the cell lysate samples, activation of proteins ATF4, AKT1, Bax, AMPK, and ERK1/2 were found. Samples treated with DAMGO were found to have overexpression of ATF4 and Bax proteins and increased phosphorylation of AKT1 and ERK1/2. Overexpression of ATF4 indicates the activation of the integrated stress response (ISR) by DAMGO, whereas the overexpression of Bax and phosphorylation of AKT1 indicate the induction of pro-apoptotic and pro-survival pathways, respectively. The phosphorylation of AMPK also indicates the activation of the AMPK stress pathway. These results may explain why previous conflicting results have been seen, due to the activation of the ISR which can lead to either cell recovery or cell death. The results found also indicate that pro-apoptotic pathway activation is linked to ISR activation. In addition, the phosphorylation of AMPK and increased level of Bax suggests that opioids may cause stress in cancer cells through mitochondrial damage.