

Modulation of Homeostatic Mechanisms to Reduce Biological Consequences of Radiation Exposure

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Are Cannabinoids Radioprotective Agents?

The Grant is designed to test the hypothesis that known protective effects provided by cannabinoids on a cellular level might be extended to include a more general organismic protection against radiation damage.

The experiments proposed in the grant application are designed to measure three biological endpoints:

1. organism survival
2. specific gene transcription
3. protein expression

as a function of x-irradiation with or without treatment with cannabinoids.

Why Cannabinoids?

Imbalances in these Body Systems are Homeostatically Regulated by Cannabinoids

Cardiovascular
Digestive
Endocrine
Excretory
Immunological
Nervous

Reproductive
Respiratory

Cannabinoids can have Profound Effects on Cell Survival

Pharmos News Releases

**"U.S. Army Finds Pharmos' Dexanabinol Effective in
Treating Damage Caused By Nerve Gas Exposure,"
Pharmos Corp.**

**Pharmos Files Investigational New Drug Application
for a Phase III Study of Dexanabinol to Treat TBI
(Traumatic Brain Injury)**

Cannabinoids often exhibit Biphasic Effects

Suzie Schweitzer, Karen Newell and Robert Melamede



Win 55,212-2 is a synthetic cannabinoid

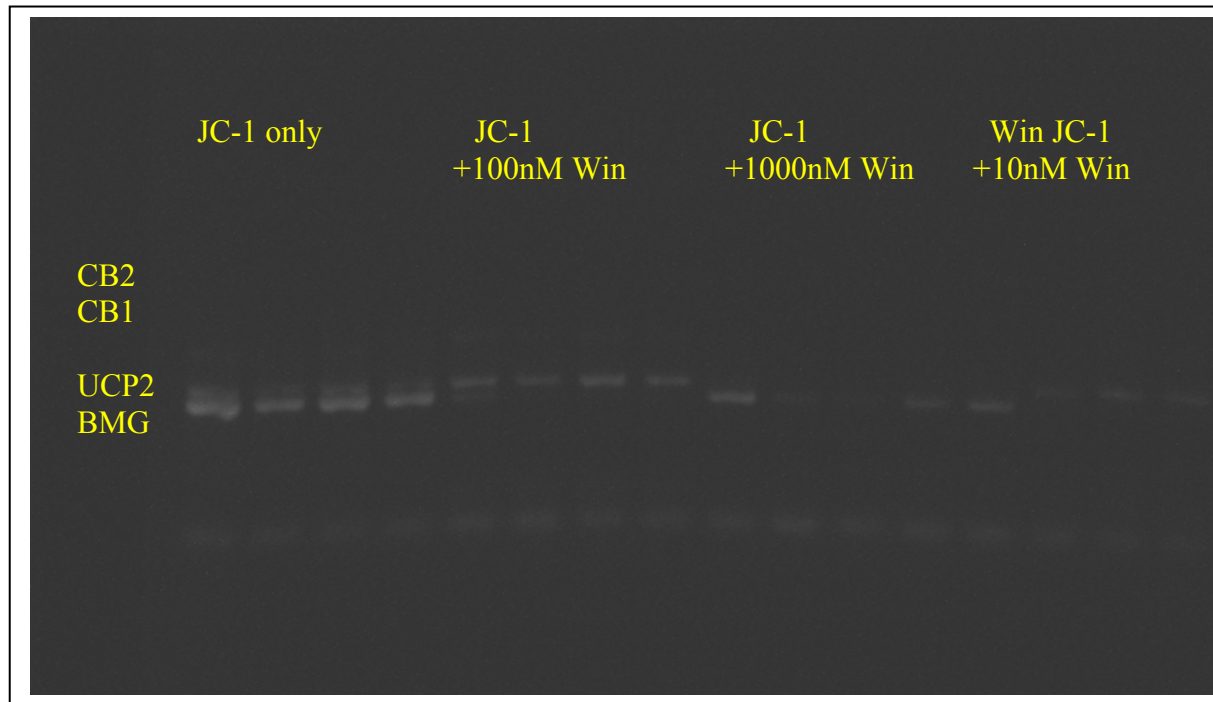
Cannabinoids often exhibit biphasic responses as seen in the adjacent figure. Before exposing mice to x-irradiation, in an effort to determine whether or not cannabinoids can provide organismic protection against x-irradiation, relevant effects of cannabinoids are first being examined in cell culture.

Cannabinoids function mostly through cannabinoid receptors of which there are two types. Then central receptors (Cb1) are found mostly in the brain whereas the peripheral receptors (Cb2) are largely immunological.

Win 55,212-2 has differing affinities for these receptors that may account for the often seen biphasic activities of cannabinoids.

Cannabinoids Regulate UCP-2 and Beta Microglobulin Genes

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The experiment shown in the adjacent figure (Figure 2) demonstrates that the addition of the synthetic cannabinoid Win 55,212-2 (10 or 100 nM) turns down the transcription of beta-2 microglobulin and turns up the transcription of ucp-2. We would expect these changes to protect these cells from dieing (increased ucp-2) and to make them less visible to the immune system (decreased beta-2 microglobulin).

Figure 1 shows these Win 55,212-2 concentrations are killing the majority of these cells.

Conclusion: The cells that survive treatment have been able to successfully up regulate ucp-2 and down regulate beta-2 microglobulin. Those that could not make this adaptation died

Summary:

Since cannabinoids act as homeostatic regulators of all body systems, and their activities span scales from subcellular to organismic, their actions are complex.

The outcome of co-administering cannabinoids and irradiation is likely to be dependant on the dose of either variable, as well as the genotype of the organism exposed.

Cannabinoids can protect cells as seen in brain cells or they can promote cell death as is often seen with cancer cells.

How these factors affect an organism as a whole will be the focus of future experiments.

The unique biochemistry of each individual may result in cannabinoid treatment benefiting some individuals exposed to radiation, while others might benefit from reducing their endogenous levels by the use of cannabinoid antagonists instead of agonists.