EDITORIAL COMMENT

Endocannabinoid Inhibition
A New Cardioprotective Strategy Against Doxorubicin Cardiotoxicity*

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It has been almost 40 years since the quinone-containing anthracycline doxorubicin was first isolated from cultures of Streptomyces peucetius var. caesius (1), and it remains one of the most effective and commonly used drugs for treatment of a variety of solid and hematologic malignancies. There is a strong correlation between total dose and antitumor efficacy; however, soon after its discovery a second effect became evident: patients treated with doxorubicin developed cardiomyopathic changes. This serious side effect has significantly limited its potential clinical utility (2). Initial reports documented the highest risk for doses above \(450 \text{ mg/m}^2\) (3). However, with improved methods of detecting subtle changes in cardiac function, (e.g., alterations in left ventricular wall stress [4]), the incidence of doxorubicin cardiotoxicity is now appreciated to be much higher than previously suspected. Alterations in wall stress have been documented in 65% of long-term survivors of childhood cancer, even at doses as low as \(228 \text{ mg/m}^2\) (5).

It was initially believed that most anthracycline cardiomyopathies developed late after therapy; however, there is increasing recognition that acute injury plays an important role in chronic doxorubicin cardiomyopathy. Recent studies, using sensitive echocardiographic indexes rather than symptoms, show that 90% of children manifest some abnormality in cardiac function during their first year of doxorubicin therapy (6). These data suggest that patients develop subclinical cardiotoxicity rather than true “latency” between drug exposure and onset of symptoms (5).

Despite much research, the cardiotoxicity associated with doxorubicin remains a challenge. There have been important advancements in understanding the basic mechanisms involved in its cardiotoxic effects, in making an early diagnosis using sensitive indexes of left ventricular performance, and in developing more effective surveillance strategies for those receiving the drug. A diverse array of therapeutic strategies has emerged; however, new avenues of research involving potential novel mechanisms may provide alternative pathways by which to mitigate the cardiotoxicity.

Fortunately, the mechanism of doxorubicin’s toxicity in cancer cells is thought to be different from its toxicity in myocardial cells. There are several modes by which doxorubicin induces cell damage: interference with DNA synthesis, interference with DNA helicase activity, inhibition of topoisomerase II, DNA aduct formation and cross-linking, generation of free radicals, direct membrane effects, and the induction of apoptosis. The direct effects of doxorubicin on DNA are thought to mediate its antitumor toxicity (7), whereas the generation of free radicals and membrane effects are thought to mediate its cardiotoxicity. Doxorubicin can also generate free radicals in cancer cells; however, this probably occurs only at supratherapeutic drug concentrations (8,9). That cardiomyocytes may be particularly susceptible to doxorubicin’s free radical effects may be partially explained by data showing that cardiomyocytes have low levels of catalase activity (10), that myocardial glutathione peroxidase decreases after doxorubicin administration (11), and that doxorubicin undergoes redox cycling in mitochondria, increasing the generation of free radicals. The high volume fraction of mitochondria in the heart may thus be linked to its vulnerability, because mitochondria are one of the major targets of doxorubicin’s toxicity (12–15).

Additional differences between the response of cancer versus myocardial cells to doxorubicin may be explained by signaling pathways that play opposing roles depending on the cell type in which they are acting; for example, in myocytes doxorubicin-induced activation of nuclear factor-kappa B is proapoptotic, whereas in cancer cells nuclear factor-kappa B is antiapoptotic. Similarly, in myocytes activation of jun N-terminal kinase, signaling through activating transcription factor-3, is antiapoptotic, whereas in cancer cells jun N-terminal kinase, signaling through AP1, is proapoptotic (9).

After the initial injury, several additional mechanisms have been implicated in the progression of doxorubicin cardiotoxicity, including the dysregulation of iron homeostasis (16), changes in intracellular \(\text{Ca}^{2+}\), alterations in mitochondrial respiratory chain function (17, 18), alterations in beta-adrenergic receptor signaling (19,20), differential activation of various mitogen-activated protein kinase family members (21), alterations in AKT signaling (22), alterations in \(\text{Na}^+\)-\(\text{K}^+\) adenosine triphosphatase and \(\text{Ca}^{2+}\) adenosine triphosphatase, and imbalance in intracellular electrolytes (23). This growing list emphasizes the complex and multifaceted pathophysiology of doxorubicin cardiotoxicity, but also suggests that doxorubicin cardiomyopathy is an excellent model in which to study cellular crosstalk pathways involved in...
both cell survival and cell death applicable to many forms of cardiac disease.

In this issue of the *Journal*, Mukhopadhyay et al. (24) present evidence for the role of endocannabinoid system inhibition in the protection against doxorubicin cardiotoxicity. The endocannabinoid system is a complex signaling pathway that includes endogenous cannabinoid ligands, their receptors, and several proteins implicated in their synthesis, release, transport, and degradation. In addition to its actions in the control of several central nervous system functions, the endocannabinoid system plays a role in cardiovascular and metabolic regulation and has been linked to obesity and cardiometabolic risk (25,26). Cannabinoid receptors are members of the transmembrane G protein-coupled receptor superfamily, and the cloning of 2 receptors, CB1 and CB2, has been reported, although there may be additional subtypes (27,28). The CB1 receptors are abundant in the brain but are also present at much lower concentrations in a variety of tissues, whereas CB2 receptors are expressed primarily in the immune and hematopoietic systems (27). Mukhopadhyay et al. (24) report the efficacy of the CB1 antagonists rimonabant or AM281 in protecting against the cardiotoxicity induced 5 days after treatment with a single high dose of doxorubicin. In control mice, dP/dt, stroke work, ejection fraction, cardiac output, and the load-independent end-systolic pressure–volume relationship index Emax were all decreased and left ventricular end-diastolic pressure was increased. These measures of cardiotoxicity were all attenuated in mice pretreated with either CB1 antagonist (but not with CB2 antagonists). In vitro, the toxicity of doxorubicin in H9c2 cells was also prevented by CB1 antagonists. Finally, anandamide, a natural ligand of the CB1 receptor, was elevated in the myocardium after doxorubicin administration, suggesting activation of the endocannabinoid system.

These data provide support for the role of the endocannabinoid system as a potentially novel target for the protection against doxorubicin cardiotoxicity. Unfortunately, the present study does not provide sufficient data to fully understand the mechanism for the beneficial effects of CB1 inhibition. Further investigation of the signaling pathways associated with endocannabinoid/doxorubicin interaction will be required as well as studies to determine whether inhibition of CB1 receptors has an effect on the antitumor efficacy of doxorubicin. Additional CB1 and CB2 agonists and antagonists as well as the use of CB2 knockout mice (29,30) will be useful tools in confirming the current results and placing these in a mechanistic framework. Finally, because there may be mechanistic differences between acute versus chronic doxorubicin cardiotoxicity, studies using CB1 antagonists during chronic administration of a lower dose of doxorubicin will be important. Developing a better understanding of the role of this novel receptor system in mediating cardioprotection may have benefits that extend beyond doxorubicin cardiotoxicity to other forms of cardiac injury.

**REFERENCES**


