Reactive Oxygen Species in Choline Deficiency Induced Carcinogenesis and Nitrone Inhibition

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Reactive oxygen species and free radical processes have been considered important in cancer development for many years. Much research demonstrates that the choline-deficiency induced hepatocarcinogenesis model prominently involves reactive oxygen species. We present a summary of results obtained in our original studies of this model over the last 4 years. We have shown that alpha-phenyl-*tert*-butyl nitrone (PBN) and some of its hydroxylated derivatives (the 4- and 3-hydroxylated compounds) prevent hepatocarcinogenesis in this model. Mechanistic studies have demonstrated that isolated mitochondria from the livers of rats fed the choline-deficiency defined amino acid diet produce significantly much more H_2O_2 per NADH reducing equivalents oxidized. Based on these observations, we postulate that the inhibiting action of PBN involves suppression of H_2O_2 production of mitochondria and generally decreasing the oxidative stress within the preneoplastic lesions. The net effect of the activity of the nitrone compounds appears to be due to their ability to shift the apoptosis/neoplastic tendency balance toward apoptosis of the cells within the preneoplastic lesions. This is considered to be the primary reason the size of the preneoplastic lesions are significantly decreased and why the nitrones are potent anti-carcinogenic agents in this model.