

P011 Alcohol-induced oxidative damage
H. Everitt; *V. R. Preedy; V. B. Patel

*University of Westminster; *Kings College, London*

Alcoholic liver disease (ALD) is the leading cause of liver disorders in the Western world. Understanding the pathological mechanisms throughout the progression of ALD is paramount to improving treatment. Alcohol metabolism can occur by two main pathways; alcohol to acetaldehyde by alcohol dehydrogenase (ADH) or via the inducible enzyme cytochrome P450 2E1. Acetaldehyde is further metabolised to acetate by acetaldehyde dehydrogenase (ALDH). Alcohol metabolism via the ADH pathway increases the intracellular NADH/NAD⁺ ratio. Elevated NADH is thought to increase mitochondrial reactive oxygen species (ROS) formation. We investigated the role of alcohol, acetaldehyde and altered NADH production in a model of acute alcohol-induced oxidative stress by blocking ALDH with cyanamide in rats. Investigations were carried out on liver cytosolic and mitochondrial fractions. Alcohol alone and inhibition of ALDH increased the formation of 4-hydroxynonenal protein adducts, suggesting increased lipid peroxidation from elevated ROS production. We also observed increased levels of the apoptosis-inducing enzyme caspase-3 in animals treated with alcohol alone and in animals pre-treated with cyanamide followed by alcohol. The increase with cyanamide pre-treatment was not as great as the increase from alcohol alone. This data suggests that raised acetaldehyde is not the primary cause of mitochondrial injury, but instead, it is the production of NADH linked to elevated ROS levels.