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ETHANOL DYSREGULATES MYOBLAST METABOLIC FUNCTION IN ASSOCIATION WITH DECREASED DIFFERENTIATION

BACKGROUND: Myopathy, or loss of muscle mass, affects nearly half of individuals with alcohol use disorder. Regeneration of skeletal muscle requires myoblasts to proliferate, differentiate into multinucleated myotubes, and fuse in a process termed myogenesis. Myogenesis is supported by metabolic shifts. We hypothesized that chronic in vitro ethanol treatment would interfere with metabolic shifts during proliferation and impair myoblast differentiation.

METHODS: Myoblasts were isolated from vastus lateralis muscle collected from alcohol-naïve adult male (n=5) and female (n=5) rhesus macaques. To assess metabolism, cells were proliferated for 3 days with or without 50 mM ethanol and subjected to a Mito Stress Test (Agilent) to measure oxygen consumption (OCR) and extracellular acidification (ECAR) rates. OCR reflects oxygen utilization and ECAR is an index of glycolytic activity. To assess differentiation, cells were proliferated for 3 and differentiated for 5 days with or without 50 mM ethanol. Cells were fixed and stained. Images were captured at 20x and analyzed for fusion index, myotubes per field, and total nuclei.

RESULTS: During the proliferative phase, ethanol significantly ($p < 0.05$) increased myoblast maximal OCR and decreased ECAR. Ethanol also decreased fusion index, myotubes per field, and total nuclei after 5 days of differentiation. The difference in ECAR at baseline was associated with the percent difference in fusion index and myotubes per field.

CONCLUSION: These results demonstrate that ethanol decreased glycolytic metabolism during the proliferative phase. Furthermore, maximal OCR was increased with ethanol, suggesting the potential to respond aerobically to increased energetic demands. The baseline reduction in ECAR with ethanol was related to the ethanol-mediated impairment in differentiation. These findings suggest that metabolic phenotype may underlie impaired differentiation with ethanol, which has important clinical implications for muscle regeneration in those affected by myopathy.

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