Acetyl-L-carnitine attenuates hypersensitivity in an alcohol/high-fat diet induced rat chronic pancreatitis model

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Background: Diets rich in alcohol and saturated fats are factors contributing to the development of pancreatitis, an unbearably painful disease. The present study utilizes a chronic pancreatitis model induced solely by feeding an alcohol and high fat diet (AHF) to otherwise normal rats, recapitulating these high-risk human behaviors.

Purpose/Hypothesis: The overall goal was to determine the efficacy of acetyl-L-carnitine (ALC), a naturally occurring amino acid already marketed as a dietary supplement, evidenced to have anti- inflammatory, anti-nociceptive, and anti-apoptotic properties, for reducing pain-like behaviors and pathological changes.

Methods: Adult male Fischer 344 rats were fed the AHF diet containing 6% ethanol and 30% vegetable oil as well as 8 g of lard daily. Mechanical sensitivity was characterized weekly by probing the abdomen and the footpads with 3 different von Frey filaments using the up-down method. A 10-min temperature place preference test (44 vs. 21ºC) determined heat sensitivity. In experimental week 12 prolonged 3 week daily treatment with 100 mg/kg ALC (p.o.) was started. Finally glucose tolerance was tested by measuring blood glucose concentrations before and after injection of 2 g/kg glucose after a 6 h fast prior.

Results: Rats fed AHF were hypersensitive in weeks 3-15; i.e. abdominal withdrawals were significantly increased (1.2 g force: control: 3-4, AHF: 7-8 responses), mechanical thresholds of the footpads decreased (controls: 17.3±0.7, AHF: 4.9±0.4 g), and less time spent on 44ºC (control: 333±29, AHF: 246±21 s). ALC reversed mechanical hypersensitivity to baseline levels in rats with AHF pancreatitis. No tolerance was noted during treatment duration. ALC did not alter heat sensitivity nor change control rats' behavior. Blood glucose test in week 15 elicited peak concentrations of 167±26 mg/dl in AHF vehicle treated rats while ALC treated AHF pancreatitis rats and controls peaked 30% lower. Blood serum TBARS analysis revealed that AHF diet resulted in a 135% increase of lipid peroxidation that was reduced to control rat levels with ALC treatment (control: 2.9±0.2 nmol/ml). Expression of Ki67, a cell proliferation biomarker used to identify aberrant/carcinogenic growth, was doubled in the pancreas of AHF fed rats and reduced to control levels with ALC treatment. Overall pathology was also improved.

Conclusions: These results identify ALC as an efficacious pharmacological intervention for the treatment in a stable chronic pancreatitis model. Its ability to activate multiple beneficial signaling pathways decreases inflammation and nociception, thus facilitating tissue regeneration, suggesting potential efficacy for the treatment of clinical patients.