Early Postnatal Administration Of Oleanolic Acid Attenuates The Development Of Non-Alcoholic Fatty Liver Disease In Fructose Fed Adult Female Rats.

**Trevor T. Nyakudya**¹ ³, Emmanuel Mukwevho², Pilani Nkomozepi³, Elaine Swanepoel³
Kennedy H. Erlwanger¹

¹School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Parktown, 2193, Johannesburg, South Africa
²Department of Biology, Faculty of Agriculture, Science and Technology, University of the North West, Mmabatho, Mafikeng, 2735, South Africa
³Department of Human Anatomy and Physiology, Faculty of Health Sciences, University of Johannesburg, Doornfontein, 2028, Johannesburg, South Africa

The early postnatal period is a critical “window” of developmental plasticity. Dietary manipulations in this phase are associated with the long-term effects on the development of metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD) in adulthood. High fructose diets have been implicated in the rise of the incidence and prevalence of MetS and NAFLD. Current research is exploring the potential use of phytochemicals such as oleanolic acid (OA) to promote metabolic programming that will impart positive health benefits later in life. Oleanolic acid, a biologically active phytochemical compound, has anti-diabetic and anti-obesity effects. We investigated the effects of early postnatal administration of OA on the subsequent development of diet-induced metabolic dysfunction and NAFLD in female Sprague Dawley rats.

Seven-day old Sprague-Dawley suckling female rats (N=94) were gavaged daily with 10 ml/kg of either; 0.5% Dimethylsulphoxide (vehicle control), OA (60mg/kg), metformin (MET; 500mg/kg), high-fructose diet (HFD; 25% w/v), MET+HFD or OA+HFD for 7 days. The rats were weaned onto normal rat chow and plain drinking water on day 21. In adulthood (day 56), half of the rats in each treatment group were either continued on plain drinking water or received a 20% fructose solution (w/v) as drinking fluid for eight weeks (day 112). Body mass gain, fasting glucose, triglyceride, and oral glucose tolerance test were measured before termination. On termination (day 112) serum and liver tissue samples were collected to determine the effect of OA on surrogate biomarkers of liver function, alanine aminotransaminase (ALT) and alkaline phosphatase (ALKP), cholesterol, adiposity, hepatic lipid storage and hepatic histomorphometry. Livers were formalin fixed, automatically processed, paraffin embedded and sectioned at 4µm with a rotary microtome. Representative sections from each animal were stained with H&E (for hepatocellular changes), Masson’s Trichome (for connective tissue) and Periodic Schiff’s (for glycogen).

Fructose consumption in adulthood following treatment with fructose in the early postnatal period resulted in an increase in body mass, cholesterol and serum triglycerides (P<0.05). Unlike OA and OA+HFD, fructose consumption both neonatally and in adulthood increased hepatic lipid storage and plasma concentrations of liver biomarkers, ALT and ALKP (P<0.05). Non-alcoholic fatty liver disease activity scores (NAS) for inflammation, steatosis and area fractions for fibrosis were significantly higher in the HFD group compared to other groups (P<0.05). However, there were no significant differences among OA, OA+HFD, Control and MET+HFD (P>0.05). All treatments did not have a significant effect on glucose tolerance (P>0.05). Neonatal administration of OA reduced excessive fructose-induced hepatic lipid accumulation in the rats (P<0.05).
Although fructose administration had adverse effects on hepatic function in female rats, neonatal interventional treatment with OA was found to program hepatic function so as to protect against impaired hepatic lipid metabolism in adulthood. Therefore, OA is a phytochemical that exhibit great potential in the prevention of dysfunctional hepatic lipid metabolism and NAFLD.