Author/s:
Snelson, M;Tan, SM;Thallas-Bonke, V;Sourris, K;Ziemann, M;El-Osta, A;Cooper, M;Forbes, J;Coughlan, M

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Thermally Processed Diet-Induced Albuminuria, Complement Activation and Intestinal Permeability Are Attenuated by Resistant Starch in Experimental Diabetes

Matthew Snelson,[1] Sih Min Tan,[1] Vicki Thallas-Bonke,[1] Karly Sourris,[1] Mark Ziemann,[2] Assam El-Osta,[1] Mark Cooper,[1] Josephine Forbes,[3] and Melinda Coughlan[1]

[1]Monash University; [2]Deakin University; and [3]University of Queensland

Objectives: The primary objective of this study was to ascertain whether thermally processed diets influence albuminuria and intestinal permeability via alterations in the complement cascade. A secondary objective was to see whether these pathological alterations could be ameliorated by a gut-targeted dietary intervention, resistant starch.

Methods: Six-week-old Sprague Dawley rats were randomised to receive a control (CON; AIN93G), thermally processed diet (TPD) (AIN93G baked at 160°C for 1h) or TPD with daily gavage of either 10 mg/kg/d alagebrium chloride (ALA), an inhibitor of advanced glycation end products or daily gavage of 2mg/kg/d PMX-53, a C5a receptor inhibitor for 24 weeks. Six-week-old diabetic mice (db/db) received the CON diet or TPD with or without 12.5% resistant starch (RS) for 10 weeks. Albumin, MCP-1 and C5a were measured by ELISA. Endotoxin was measured using a limulus amoebocyte lysate kit. Intestinal permeability was assessed *in vivo* by the clearance of FITC-labelled dextran. Transcriptomic profiling of renal cortex was determined by RNA-Sequencing.

Results: The TPD increased albuminuria, plasma endotoxin and MCP-1 which were ameliorated with ALA or PMX-53. TPD increased urinary C5a, which was decreased with ALA. In db/db mice, RS supplementation of the TPD reduced albuminuria and intestinal permeability. Gene set enrichment analysis showed an upregulation in the complement cascade in TPD db/db mice, which was normalized by RS. Similarly, RS supplementation reduced urinary C5a in TPD-fed db/db mice.

Conclusions: These results demonstrate that thermally processed diets lead to worsening albuminuria via activation of the complement cascade. These results also indicate that resistant starch supplementation may ameliorate some of the negative effects observed with excessive intake of thermally processed.

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