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Downregulation of RAGE may contribute to pain associated with obesity and diabetes

A. Aibinu, S. Dolan. HEALTH AND LIFE SCIENCES, GLASGOW CALEDONIAN UNIVERSITY, GLASGOW, UNITED KINGDOM.

Introduction: *The downstream effects of adipokine activity such as pathogenesis of inflammation which contribute to pain are well established but exact mechanisms are unclear. Previous studies have shown altered expression of pro-inflammatory adipokines in spinal cord from obese rats,[1] leading to the hypothesis that adipokines may play a role in pathogenesis of pain with obesity and diabetes.*

Methods:*Responses to thermal and mechanical stimulation, metabolic profile and adipokine expression were measured in: 1) a diet-induced obesity model where adult male Wistar rats (340-360g) were fed a high fat diet (HFD; 22%) or normal diet for 16 weeks (n= 6/group), and 2) a diabetes model where adult male Wistar rats (285-345g) were fed a HFD (22%) diet or normal diet for 16 weeks and injected intraperitoneally (i.p) with either streptozotocin (STZ; 30 mg/kg) or vehicle (n=6/group). Animals were euthanised and spinal cord, white adipose tissue (WAT) and plasma collected. Blood glucose, insulin, cholesterol and triglycerides were measured, and expression of key adipokines lipocalin-2 and RAGE (receptor for advanced glycation end products) characterised using real-time PCR, Western blotting and ELISA.*

Results: *Obese rats were significantly heavier than controls (556 ± 18 g vs. 503 ± 11 g; $P < 0.05$, t-test), with elevated serum insulin levels (n=5, $P < 0.05$ vs. controls; t-test) but cholesterol, triglycerides and glucose levels were unchanged. Diabetic rats did not have significant weight gain compared to controls but were hyperglycaemic (n=6, $P < 0.001$ vs. controls; t-test), had elevated serum cholesterol and triglycerides (n=6, $P < 0.01$ vs. controls; t-test) and reduced insulin levels (n=6, $P < 0.01$ vs. controls; t-test). Nociceptive responses were unchanged in obese rats but diabetic rats displayed hypersensitivity to thermal stimuli (n=6, $P < 0.05$ vs. controls; t-test). Lipocalin-2 was constitutively expressed in WAT, spinal cord and serum but expression remained unchanged in both models. RAGE was also constitutively expressed in all tissues; mRNA levels were downregulated in WAT of obese rats (5-fold, n=5 $P < 0.02$ vs. controls; t-test), and protein levels significantly lower in serum of diabetic animals (3-fold, n=3 $P < 0.05$ vs. controls; t-test).*

Conclusion: *RAGE is known to contribute to the development of diabetic vascular complications[2] and altered expression observed in this study matched to thermal hypersensitivity with diabetes suggests a role in pain modulation.*

References *1. Iannitti T. et al. (2012). Experimental Physiology **97**: 85-95 2. Miura J. et al. (2004) J Diabetes Complicat **18**: 53-59*