

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

**Endogenous annexin-A1 is a protective determinant in high-fat diet (HFD)-induced insulin resistance and diabetic nephropathy**

**This is a pre print version of the following article:**

*Original Citation:*

Endogenous annexin-A1 is a protective determinant in high-fat diet (HFD)-induced insulin resistance and diabetic nephropathy / Purvis, Gsd; Chiazza, F; Solito, E; Collino, M; Thiemermann, C.. - In: DIABETIC MEDICINE. - ISSN 0742-3071. - 34(2017), pp. 174-175.

*Availability:*

This version is available <http://hdl.handle.net/2318/1657443> since 2018-01-14T18:22:53Z

*Published version:*

DOI:10.1111/dme.42\_13304

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

# Endogenous Annexin-A1 is a Protective Determinant in HFD-induced Insulin Resistance and Diabetic Nephropathy

Gareth S.D. Purvis<sup>1</sup>, Fausto Chiazza<sup>2</sup>, Massimo Collino<sup>2</sup>, Egle Solito<sup>1</sup> and Chris Thiemermann<sup>1</sup>

 Author Affiliations

1. <sup>1</sup>William Harvey Research Institute, Queen Mary University of London, London, United Kingdom
2. <sup>2</sup>Department of Drug Science and Technology, University of Turin, Turin, Italy

## Abstract

---

**Introduction** Type-2 diabetes mellitus is a key driver of cardiovascular disease often leading to renal failure, infarction or stroke. Here we investigate the role of Annexin-A1 (ANXA1), an endogenous anti-inflammatory peptide, in a mouse model of high-fat diet (HFD) induced insulin resistance and diabetic nephropathy.

**Methods** 10-week old male C57BL/6 (wild-type) and ANXA1 null (ANXA1<sup>-/-</sup>) mice were fed a normal (chow) diet or high-fat high-sugar (HFD) diet for 10 weeks. Mice were administered either human recombinant (hr) ANXA1 (1 µg hrANXA1, HEPES buffer, i.p.) or vehicle (100 µl HEPES buffer, i.p.) from weeks 5–10 of dietary manipulation.

**Results** When compared to WT-mice fed on chow diet, WT-mice fed on HFD exhibited significantly lower serum levels of ANXA1 (1.259±0.01 vs. 1.154±0.03 ng/ml, P<0.05) and reduced ANXA1 expression in the kidney (0.96±0.02 vs. 0.30±0.04 O.D, P<0.05). When compared to WT-mice fed on chow diet, WT-mice fed on HFD and subjected to OGTT demonstrated a significant impairment in their oral glucose tolerance test (OGTT; AUC analysis: 84.42±4.51 vs. 110.70±3.89, P<0.05), which was improved with hrANXA1 treatment (110.70±3.89 vs. 89.40±0.99, P<0.05). The OGTT of ANXA1<sup>-/-</sup> mice fed on HFD was significantly worse than that of WT-mice. When compared to WT-mice fed on chow diet, WT-mice fed on HFD demonstrated a significant increase in albumin-to-creatinine (ACR) ratio (20.75±2.434 vs. 56.10±5.80 mg/mg, P<0.05), suggesting the development of proteinuria, which was improved with hrANXA1 treatment (56.10±5.80 vs. 35.28±6.04 mg/mg, P<0.05). ANXA1<sup>-/-</sup> mice fed on HFD demonstrated a significant increase in ACR compared to WT-mice fed on HFD (56.10±5.80 vs. 79.38±4.33 mg/mg, P<0.05) suggesting more severe proteinuria. When compared to WT-mice fed on chow diet, WT-mice fed on a HFD had decreased phosphorylation Ser<sup>188</sup> of RhoA in the liver (1.00±0.004 vs. 0.575±0.002 O.D, P<0.05) and kidney (0.95±0.02 vs. 0.030±0.04 O.D, P<0.05) which was associated with increased phosphorylation of MYPT1 (liver, 1.15±0.006 vs. 4.15±0.07 O.D, P<0.05; kidney, 1.025±0.09 vs. 2.60±0.09 O.D, P<0.05). Both of these signalling events was prevented by treatment with hrANXA1. Interestingly, ANXA1<sup>-/-</sup> mice demonstrated

constitutively activated RhoA and phosphorylation of MYPT1 suggesting that ANXA1 could be a major regulator of this GTPase activity.

**Conclusion** We have shown for the first time that ANXA1 expression is reduced in a mouse model of HFD-induced insulin resistance and diabetic nephropathy. This down-regulation removes an important tissue-protective factor allowing for exacerbation of renal dysfunction, which can be attenuated with treatment with hrANXA1. Most notably, hrANXA1 reduces both the metabolic derangements and the renal dysfunction associated with T2DM.

**Support or Funding Information**

This work is funded by the British Heart Foundation grant number FS/13/58/30648.