THE ANTI-INFLAMMATORY PROTEIN ANNEXIN A1 AS NEW PHARMACOLOGICAL APPROACH TO COUNTERACT THE DELETERIOUS EFFECTS OF DIET-INDUCED METABOLIC DERANGEMENTS.

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We have recently contributed to demonstrate the causative relationship between chronic low-grade inflammation and insulin resistance development, showing a key role for selective pro-inflammatory signaling pathways [1,2]. However, the role of anti-inflammatory molecules in the cross-talk mechanisms leading to obesity and insulin resistance has never been studied. Thus, this study was designed to investigate (I) the role of the endogenous anti-inflammatory protein Annexin A1 (ANXA1), and (II) the effects of therapeutic administration of human recombinant ANXA1 (hrANXA1) in an animal model of diet-induced type 2 diabetes mellitus.

Male C57/BL6 wild-type (WT) mice and ANXA1-/- knockout (KO) littermates were fed control diet (n=10 WT, n=5 KO) or high-fat diet (HD; n=25 WT, n=13 KO) for 10 weeks. Sub-groups of HD-fed WT (n=11) and ANXA1-/- KO (n=5) mice were treated with hrANXA1 (40 µg/kg i.p. five days/week) during the last 6 weeks of dietary manipulation.

HD-feeding increased plasma triglycerides (41.38±4.35 mg/dl) and impaired glucose homeostasis (fasting glycaemia 13.86±0.66 mmol/L) in WT mice, when compared to WT mice exposed to control diet (respectively 29.83±1.31 mg/dl, $p<0,05$ vs. HD-fed WT; 7.68±0.29 mmol/L $p<0,001$ vs. HD-fed WT). The diet-induced metabolic abnormalities were worsen in HD-fed ANXA1-/- KO mice (respectively 67.89±7.92 mg/dl, $p<0,05$ vs. HD-fed WT; 17.76±0.86 mmol/L, $p<0,001$ vs. HD-fed WT). Most notably, they were dramatically reduced by hrANXA1 administration to either WT mice (respectively 21.18±4.29 mg/dl, $p<0,05$ vs. HD-fed WT; 9.09±0.44 mmol/L, $p<0,001$ vs. HD-fed WT) or KO mice (respectively 57.80±8.12 mg/dl, $p<0,05$ vs. HD-fed KO; 9.68±0.19 mmol/L, $p<0,001$ vs. HD-fed KO). Histological analysis showed a moderate degree of cytoplasmic vacuolar degeneration in the kidney of both WT and KO HD-fed mice. hrANXA1 administration prevented the proximal convoluted tubule damage in both WT and KO mice. The improved glucose tolerance by hrANXA1 was, at least in part, mediated by enhancing the insulin-related signaling pathway in both liver and gastrocnemious of HD-fed mice, as shown by Western blot analysis on phosphorylated and total IRS-1, Akt and GSK-3β. Interestingly, dietary manipulation resulted in significant increase in the activity of the RhoA-Rho kinase (ROCK) pathway in the gastrocnemius of both WT and KO mice and this effect was markedly prevented by chronic administration of hrANXA1. As the RhoA pathway has been recently implicated in the development of insulin resistance and related obesity-induced cardiac dysfunction, our results demonstrate, for the first time, that ANXA1 may protect against the diet-induced impairment of a key mechanism leading to insulin resistance and related organ injury. Overall, these findings suggest a new pharmacological strategy that could possibly lead to the development of innovative therapeutic agents for insulin resistance and target organ dysfunction. Further preclinical and clinical studies are needed to better explore this possibility and to investigate/ensure the safety of this innovative pharmacological approach.

References

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