L JCET LECTURE, 19.12.2014, 9.00

Mineralocorticoid Receptor in the adipose organ: new perspectives for the treatment of Metabolic Syndrome

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In the last 7 years our group has contributed to explore the role of Mineralocorticoid Receptor (MR) in the adipose tissue and vascular dysfunction. We demonstrated for the first time that MR plays a pivotal role in adipose differentiation induced both by mineralocorticoids and glucocorticoids. In fact, we showed that chronic exposure to aldosterone in 3T3-L1 and 3T3-F442A cells induces remarkable changes in morphological, biochemical and molecular markers of differentiation, through specific activation of MR.

We have also recently confirmed that pharmacological blockade of the MR inhibits critical pathways controlling adipose differentiation in 3T3-L1 cells, via inhibition of clonal expansion and by interfering with the transcriptional control of adipose conversion through inhibition of PPARγ expression. Importantly, we showed that MR antagonism is able to block adipocyte differentiation *ex vivo* also in human primary preadipocytes from different fat depots, giving the MR a clearly relevant role in the pathophysiology of adipose dysfunction in humans.

Our laboratory also showed that aldosterone increases expression of Intercellular Adhesion Molecule 1 (ICAM-1) gene in human ECs and in turn promotes leukocyte adhesion to human coronary ECs, effects abolished by the MR antagonist or by MR knock down. These data suggest a novel mechanism by which aldosterone may influence ischemic cardiovascular events.

In order to better understand the pathophysiology of MR activation in adipocytes and endothelial dysfunctions, andthe role of MR antagonism as a therapeutic option for the prevention of the metabolic complications of obesity, we are currently performing studies *in vivo* and *ex-vivo* on animal models of diet-induced obesity and atherosclerosis.

We have recently shown that MR antagonists improve glucose tolerance in a model of diet-induced obesity in mice, and counteract the effects of high-fat diet on white adipose mass and adipocyte size and function.

Indeed modulation of MR activity in adipose tissue has promise as a novel therapeutic approach to treat obesity and its related metabolic complications. More extensive clinical studies are deemed necessary to explore the potential therapeutic applications of MR blockers in the prevention and treatment of metabolic syndrome.

Biographical note

Dr. MassimilianoCaprio, is the head of the Laboratories of Cardiovascular Endocrinologyat the Research Center of IRCCS San Raffaele Pisana in Rome, and works as a consultant diabetologist at the University of Rome Tor Vergata. He has an internationally recognized expertise in the exploration of the roles of mineralocorticoid receptor (MR) activation in diabetes and metabolic syndrome. Dr. Caprio has contributed a large amount of work on the pathophysiology of adipose proliferation and endothelial inflammation due to excessive mineralocorticoid activation,

Dr. Caprio is author of more than50 publications in peer-reviewed journals, and has been often invited to give lectures by severalacademic institutions and meetings all over the world. He has been recipient of prestigious research grants as a PI:Fondation pour la Recherche Medical (France), Italian Ministery of Health (Progetto Giovani Ricercatori 2009 – Ricerca Finalizzata 2011), Italian Ministery of Foreign Affairs (Progetti Grande Rilevanza Italy-USA 2011), Bayer Schering Pharma (2008). He is reviewer forseveral journals (Circulation, ATVB, Endocrinology, J Clin Endocrinol Metab, PLOS ONE, Int J Cardiol, Cardiovascular Diabetology, etc).

Most relevant publications:

1. Marzolla V, Armani A, Zennaro MC, Cinti F, Mammi C, Fabbri A, Rosano GM, **Caprio M**. The role of the mineralocorticoid receptor in adipocyte biology and fat metabolism. Mol Cell Endocrinol. 2012 Mar 24;350(2):281-8

2. **Caprio M**, Antelmi A, Chetrite G, Muscat A, Mammi C, Marzolla V, Fabbri A, Zennaro MC, Fève B. Antiadipogenic effects of the mineralocorticoid receptor antagonist drospirenone: potential implications for the treatment of metabolic syndrome. Endocrinology. 2011 Jan;152(1):113-25

3. Zennaro MC, **Caprio M.**, Fève B. Mineralocorticoid receptors in the metabolic syndrome. Trends Endocrinol Metab. 2009 Nov;20(9):444-51

4. **Caprio M**, Newfell BG, la Sala A, Baur W, Fabbri A, Rosano G, Mendelsohn ME, Jaffe IZ. Functional mineralocorticoid receptors in human vascular endothelial cells regulate intercellular adhesion molecule-1 expression and promote leukocyte adhesion. Circ Res. 2008 Jun 6;102(11):1359-67

5. **Caprio M**, Fève B, Claës A, Viengchareun S, Lombès M, Zennaro MC. Pivotal role of the mineralocorticoid receptor in corticosteroid-induced adipogenesis. FASEB J. 2007 Jul;21(9):2185-94. Epub 2007 Mar 23

6. Armani A, Marzolla V, Rosano G, **Caprio M**. Mineralocorticoid vs glucocorticoid receptors: solo players or team mates in the control of adipogenesis? Int J Obes (Lond). 2014 Apr 30 [Epubahead of print]

7. Marzolla V, Armani A, Feraco A, De Martino MU, Fabbri A, Rosano G, **Caprio M**. Mineralocorticoid receptor in adipocytes and macrophages: A promising target to fight metabolic syndrome. Steroids. 2014 May 10 [Epub ahead of print] Review

8. Armani A, Cinti F, Marzolla V, Morgan J, Cranston GA, Antelmi A, Carpinelli G, Canese R, Pagotto U, Quarta C, Malorni W, Matarrese P, Marconi M, Fabbri A, Rosano G, Cinti S, Young MJ, **Caprio M**. Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. FASEB J. 2014 Aug; 28(8):3745-57