Free fatty acids impair steroidogenesis and promote apoptosis in leydig cells: A new link between metabolic dysfunction and hypogonadism

Celeste Lauriola, Valentina Annamaria Genchi, Sebastio Perrini, Annalisa Natalicchio, Luigi Laviola, Francesco Giorgino, Angelo Cignarelli

Dipartimento di Medicina di Precisione e Rigenerativa e Area Ionica; Università degli studi di Bari "A.Moro"
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Celeste Lauriola: celeste.lauriola95@gmail.com

Excess circulating fatty acids contributes to the association between metabolic disorders and hormonal alterations. Indeed, obesity and diabetes mellitus are frequently associated with functional hypogonadism characterised by reduced testosterone levels. Although a high-fat-diet is known to negatively affect testicular function, its specific impact on steroidogenesis remains unclear. Therefore, the aim of this study has been to investigate the effects of different FFAs, with or without human chorionic gonadotropin (hCG) stimulation, on steroidogenesis and apoptosis in a murine Leydig cell line (mLTC1). mLTC1 cells were exposed with increasing concentrations of palmitate (PA) or oleate (OA), in the presence or absence of 0.2 IU/mL hCG. The expression of the Steroidogenic Acute Regulatory (STAR) protein, a key marker of steroidogenesis, was evaluated by immunoblotting. Testosterone secretion was measured by ELISA, while apoptosis was evaluated by cleaved caspase-3 (C3C) protein expression using immunoblotting.

Exposure to PA significantly reduced hCG-induced STAR protein expression in a dose-dependent manner after 6h and 15h, respectively, compared with PA-free conditions. Similarly, exposure to OA reduced STAR protein expression at all concentrations tested (0.4-1 mM). Prolonged treatment with PA (96 hours) further compromised steroidogenic capacity, leading to a reduction in testosterone production. Furthermore, PA significantly increased C3C levels. Notably, hCG stimulation during the last 6h of incubation significantly reduced PA-induced C3C levels at all concentrations.

In conclusion, both PA and OA impair hCG-induced steroidogenesis, while PA additionally promotes Leydig cell apoptosis. These findings suggest a direct detrimental role of excess FFAs on testicular function in obesity and indicate a potential protective role of hCG in preserving Leydig cell viability under conditions of metabolic stress.

Effect of elexacaftor/tezacaftor/ivacaftor therapy on serum lipoprotein functions in adults with cystic fibrosis

Marcella Palumbo[1], Claudia Greco[2], Andrea Gramegna[3,4], Francesco Blasi[3,4], Massimiliano Ruscica[5,6], Francesca Zimetti[1], Maria Pia Adorni[2]

[1]Department of Food and Drug, University of Parma, Parma, Italy; [2]Unit of Neurosciences, Department of Medicine and Surgery, University of Parma, Parma, Italy; [3]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [4]Respiratory Unit and Cystic Fibrosis Adult Center, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [5]Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Milan, Italy; [6]Department of Cardio-Thoracic-Vascular Diseases, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
https://doi.org/10.56095/eaj.v5i1.131
Marcella Palumbo: marcella.palumbo@unipr.it

Cystic fibrosis is a genetic and multisystemic disease associated with a very poor quality of life and life expectancy. The introduction of the combined treatment with elexacaftor/tezacaftor/ivacaftor (ETI, Kaftrio) has extended the life expectancy of adults with cystic fibrosis (awCF), which could have an impact on the prevalence of certain chronic diseases, such as cardiovascular (CV) diseases. In this regard, in a recent work, it was observed that treatment with Kaftrio has a heterogeneous effect on CV risk factors, ameliorating some of them, such as chronic inflammation, and worsening others. Among the relevant factors determining CV risk, the capacity of HDL to promote cholesterol efflux (HDL-CEC), one of the main functions of this class of lipoproteins, has proven to be a better predictor than plasma HDL concentrations. In addition, the serum capacity to load macrophages with cholesterol (cholesterol loading capacity, CLC) represents an index of serum lipoproteins' pro-atherogenic potential.

This work aimed to evaluate the effect of six months of therapy with Kaftrio on serum lipoprotein functions, namely HDL-CEC and serum CLC, in 16 awCF, and in 8 sex and age-matched healthy controls. HDL-CEC through the main pathways was evaluated with a radioisotopic cell-based assay in specific cell models, and serum CLC was assessed fluorimetrically in human monocyte-derived macrophages THP-1.

Concerning plasma lipid profile, after treatment with Kaftrio, total cholesterol, LDL-C, and HDL-C significantly increased as compared to baseline ($p<0.001$, $p<0.001$, and $p=0.023$, respectively), reaching values comparable to those of healthy controls. Regarding HDL function, HDL-CEC mediated by the transporter ABCA1 was significantly lower in awCF at baseline compared to healthy controls (-14%, $p=0.0142$). Treatment with Kaftrio increased ABCA1 HDL-CEC compared to awCF at baseline (+7%, $p=0.02499$). Similarly, ABCG1 HDL-CEC was significantly lower in awCF at baseline compared to healthy controls (-22%, $p=0.0218$) while significantly higher after treatment compared to not treated awCF (+18%, $p=0.0255$). In both cases, Kaftrio restored HDL-CEC levels to values comparable to those of healthy controls.

No significant differences were found for serum CLC in awCF compared to healthy controls. Kaftrio did not have any significant impact on this parameter, despite the increased LDL-C levels observed after treatment.

In conclusion, Kaftrio treatment had a positive impact on the functional lipid profile as it increased ABCA1 and ABCG1 HDL-CEC without negatively affecting serum CLC. All these effects may contribute to reducing the CV risk in awCF.