Endocannabinoid/Endovanilloid System disregulation at the basis of glucocorticoid-induced bone loss

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Bone is a highly metabolically active tissue and its formation and resorption is at the base of bone remodeling, which continues throughout life. It is generally recognized that removal of bone isthe task of osteoclasts, while its neo-formation relies on osteoblasts. One of the most frequent pathologies against this tissue is osteoporosis (OP), characterized by decreased bone mass and an alteration of its architecture. The OP is distinguished into primary (postmenopausal or senile) and secondary (related to various diseases and taking drugs). The OP caused by glucocorticoids is the most common form of osteoporosis caused by drugs glucocorticoids are used for the therapy of many inflammatory and autoimmune diseases, although their administration for prolonged periods affects the bone cells activity leading to a bone mass reduction (Kim et al., 2005).
The (EC /EV) system comprises the cannabinoid receptors type 1 and 2 (CB1, CB2), the *Transient receptor protein cation channel* vanilloid subtype 1 (TRPV1) and their endogenous ligands, the hybrid EV/EC anandamide (AEA) and the EC 2-arachidonoylglycerol (2-AG) (Bab et al., 2008).
Recently we showed that the pharmacological manipulation of the endocannabinoid / endovanilloid system (EC / EV) is able to modulate osteoclast activity in vitro, suggesting the possibility of considering these receptors a new therapeutic target for the treatment of diseases related to resorption bone. In particular, we demonstrated that osteoclast differentiation and function can be modulated by CB2 as well as TRPV1 agonists/antagonists, suggesting that CB2 agonist together with TRPV1 blockers/desensitising compounds could represent promising new anti-resorptive agents (Idris et al., 2008) (Rossi et al. 2009) (Rossi et al. 2011)
To highlight a possible role of the EV/EC system in the glucocorticoid-induced OP, we have treated in vitro healthy woman derived OCs with Methylprednisolone (MP) in presence or not of CB2 or TRPV1 agonists/antagonists, analysing the effect on OCs function and morphology through a multidisciplinary approach.
MP induce a significant increase of the osteoclastic marker tartarte acid phosphatase (TRAP) expression levels, as well as of TRPV1, together with a significantly decrease of CB2.
MP significantly increase OCs number and activity.
Both the CB2 receptor agonist, JWH-133, and the vanilloid antagonist 5'-iodo-resinferatoxina (I-RTX) are able to significantly counteract all the MP-induced effects.
In conclusion, our results show, for the first time, that the glucocorticoid-induced OP may due also to the alteration of the EC / EV system. Drug cocktails or hybrid molecules, designed to stimulate CB2 receptors and block TRPV1 receptors simultaneously, may reduce the loss of bone mass induced by glucocorticoids, inhibiting glucocorticoid-dependent osteoclast hyperactivity.

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