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Can Adrenomedullin be a potential Osteoarthritis treatment?

A. Chatron-Colliet , F. Velard , D. Côme, N. Hafsia, H. Lin , H. K. Ea, F. Lioté.

BACKGROUND & METHODS

Chondrolysis, chondrocyte apoptosis and local inflammation are described to exacerbate osteoarthritis (OA) development. We therefore aimed to investigate the effects of adrenomedullin (AM) and its truncated peptide (22-52AM) on *in vitro* and *in vivo* OA models.
Both have exhibited anti-apoptotic and anti-inflammatory properties in collagen-induced arthritis (CIA) in mice.

IN VITRO METHODS

Bovine articular chondrocytes (BACs) → Normoxia / Hypoxia (3%O2)
- ① AM and receptor complex CLR/RAMP-2 protein levels (EIA, immunofluorescence). cAMP production to assess the receptor functionnality
- ② Pro-apoptotic treatment (Fas-L) ± AM

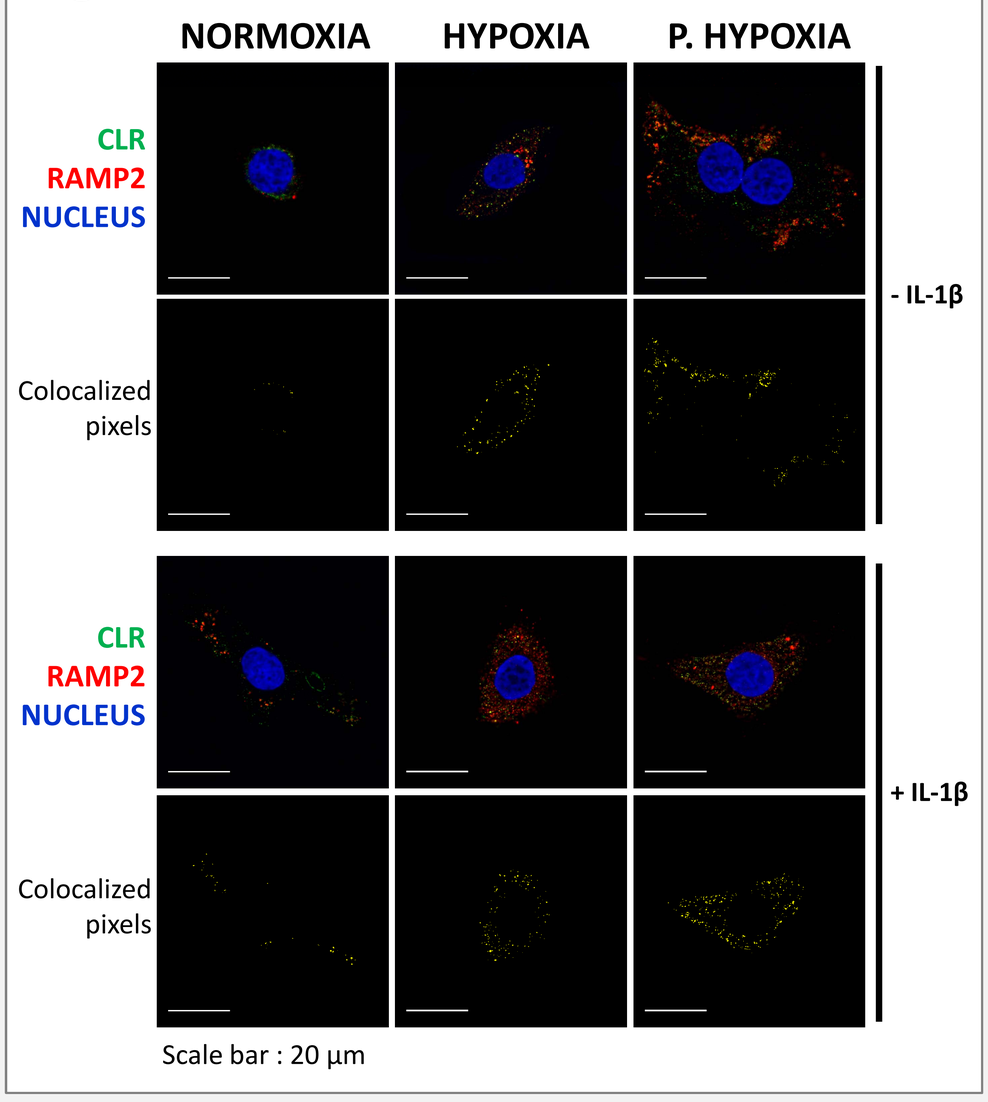
IN VIVO METHODS

③ Murine OA instability model (meniscectomy) → AM / 22-52AM → Sacrifice and histology assays (Safranin-O and TUNEL)

IP injections, 3 times a week, 8 weeks

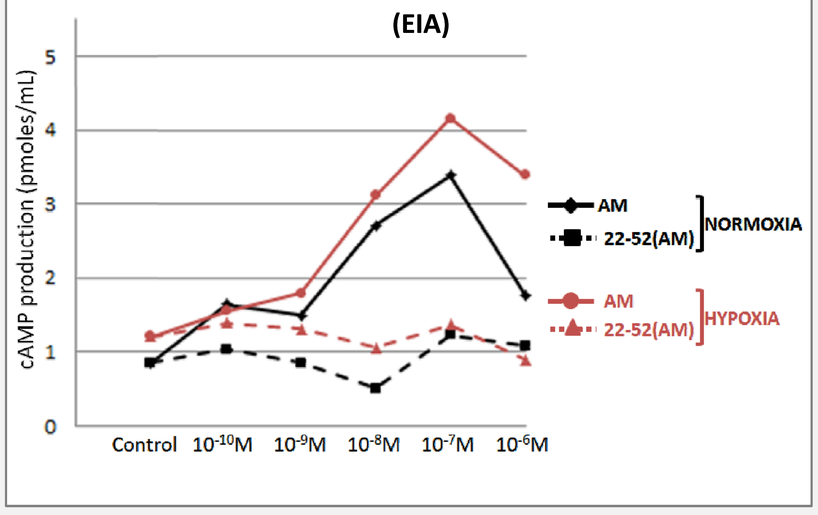
IN VITRO RESULTS

① AM RECEPTOR COMPONENTS LOCALIZATION

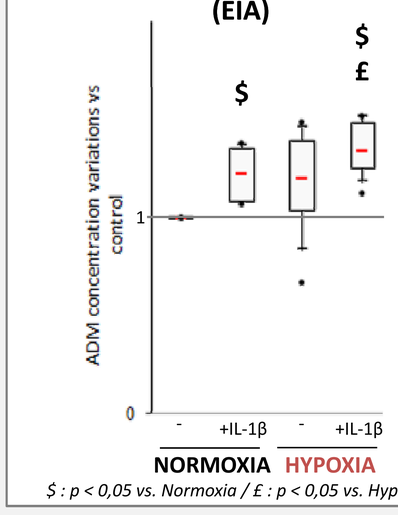


Scale bar : 20 µm

② cAMP PRODUCTION (EIA)



③ AM SECRETION (EIA)



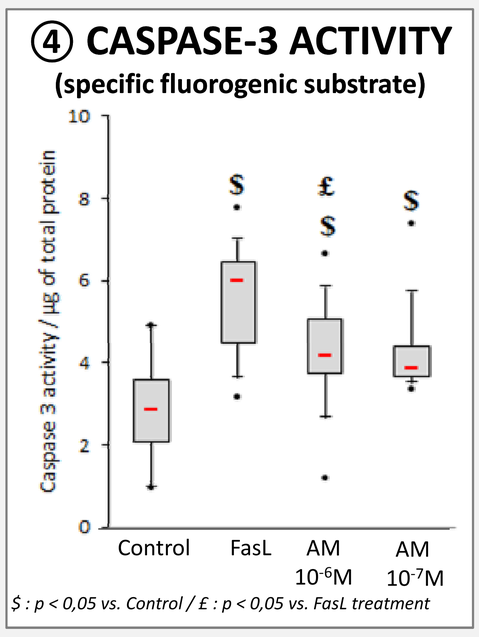
$: p < 0,05 vs. Normoxia / £ : p < 0,05 vs. Hypoxia

① AM and its receptor components are constitutively expressed in BACs. In physiological hypoxic environment, **CLR-RAMP2 association is enhanced**, as visualized by colocalized pixels. Moreover, inflammatory environment increases extensively this association. ② **IL-1β stimulation also induces an increased AM secretion** in chondrocyte conditioned media and cAMP production suggests that AM receptor is functional, both in normoxia and hypoxia (③).

④ Exogenous AM treatment (10^{-6}M) leads to a **decreased caspase-3 activity**, assuming AM could modulate chondrocyte apoptosis during OA.

Given the AM effects and the AM receptor functionality, we address AM as a preventive OA treatment *in vivo*.

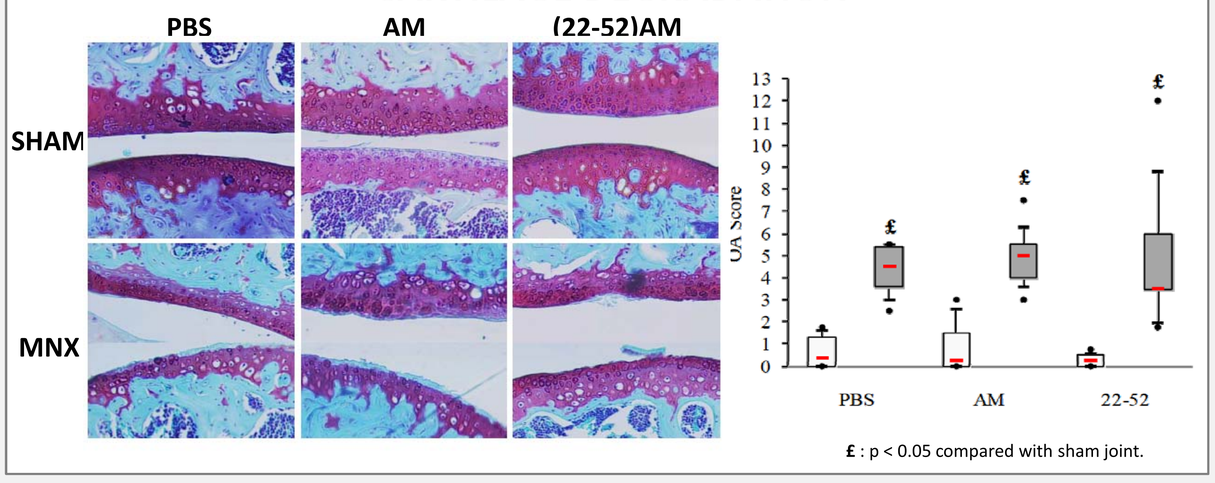
④ CASPASE-3 ACTIVITY (specific fluorogenic substrate)



$: p < 0,05 vs. Control / £ : p < 0,05 vs. FasL treatment

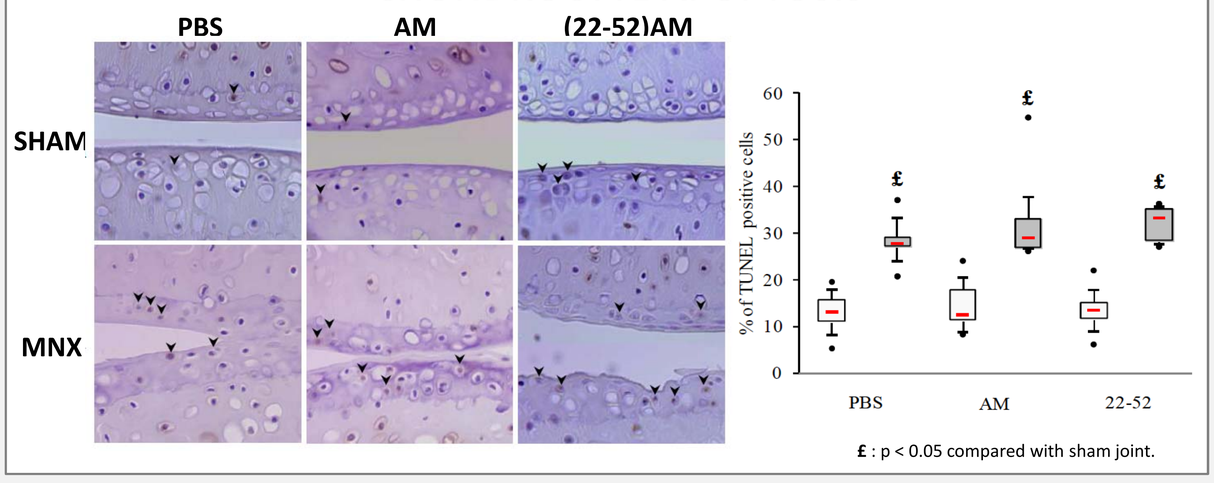
IN VIVO RESULTS

CARTILAGE DEGRADATION



£ : p < 0.05 compared with sham joint.

CHONDROCYTE APOPTOSIS



£ : p < 0.05 compared with sham joint.

Neither AM nor (22-52)AM have a protective effect on apoptosis and chondrolysis.

CONCLUSION

In « physiological environment », BACs were able to produce both ADM and functional receptor components. In addition, ADM treatment prevented FasL-induced apoptosis in hypoxia.

Contrary to our expectations based on the CIA model, ADM or its derived peptide 22-52ADM administered systemically did not disclose any effect on OA progression. Direct intra-articular effects of ADM might be investigated.

CONTACT

Aurore Chatron-Colliet, PHD, Inserm U606, Paris: aurore.chatron-colliet@inserm.fr
Prof. Frédéric Lioté, MD, PHD, Inserm U606, Hôpital Lariboisière, Paris: frederic.liote@lrb.aphp.fr