Effect of hypoxia on adiponectin pathway in murine and cellular models: which involvement in COPD-associated cardiovascular risk ?

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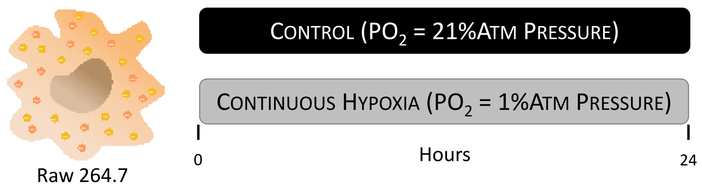
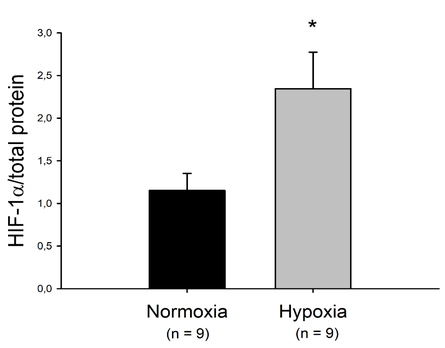
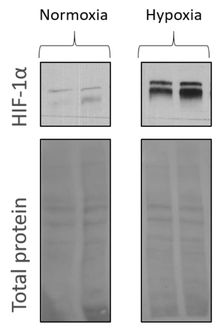
Context : Hypoxaemia is a pathophysiological condition frequently observed in severe COPD patients (Chronic Obstructive Pulmonary Disease). It initiates compensatory mechanisms mainly mediated by a family of transcription factors (Hypoxia Inducible Factors HIFs). Hypoxaemia was suggested to modulate Adiponectin plasmatic (Ad_{pl}) level, its multimer (Ad-mer) distribution and protein abundance of its receptors (AdipoR) in target tissues. Due to its anti-diabetic, anti-inflammatory and anti-atherosclerotic properties, we postulate that alteration of Ad pathway could participate to metabolic troubles and cardiovascular (CV) co-morbidities in COPD patients.

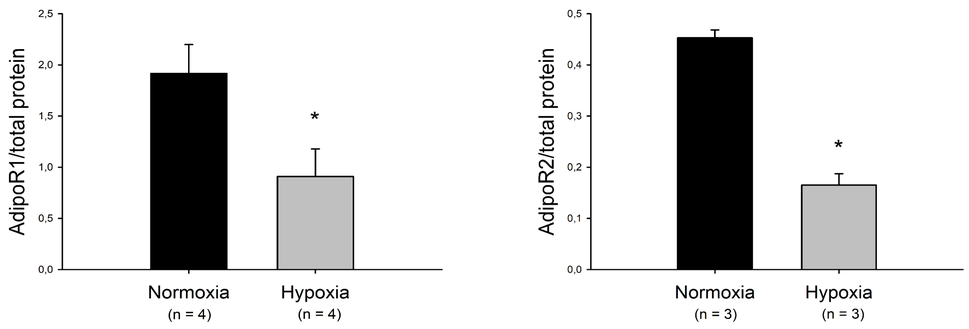






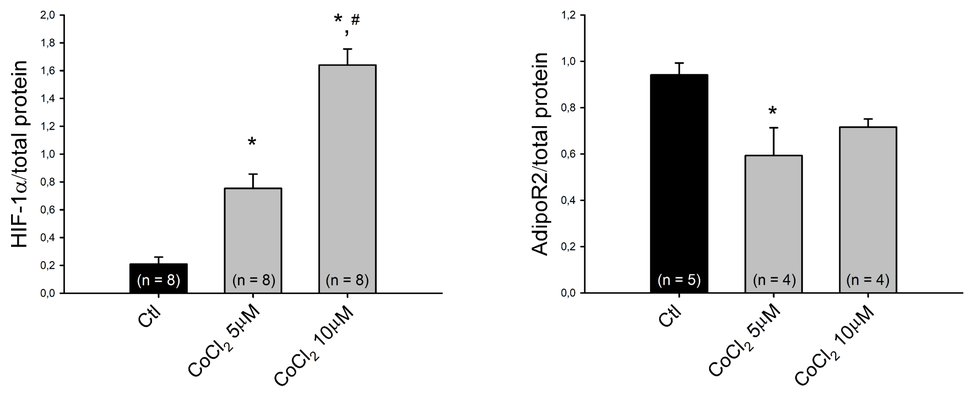
Effect of hypoxia on HIF-1α abundance in RAW macrophages. HIF-1α/total protein ratio was determined by a PAGE-SDS followed by a Western blot. HIF-1α/total protein ratio was obtained after densitometric analysis. * p<0.05, vs normoxia, T-test.

Impact of hypoxia on AdipoR protein level

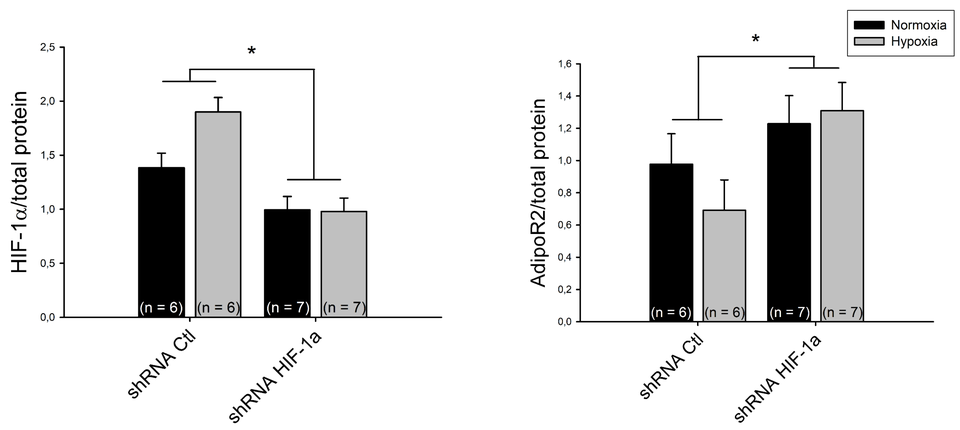


Effect of hypoxia on AdipoR1/2 protein levels in macrophages. AdipoRs/total protein ratio were determined by a denaturant PAGE-SDS followed by a Western blot. AdipoR1/total protein ratio and AdipoR2/total protein ratio were obtained after densitometric analysis. * p<0.05, vs normoxia, T-test.

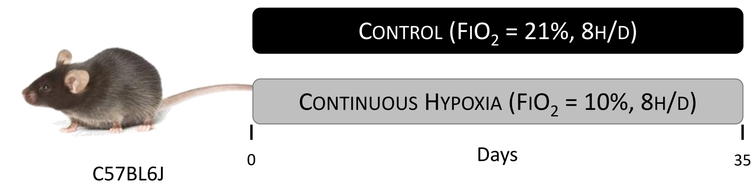
Contribution of HIF-1α on the effect of hypoxia on AdipoR2 protein level

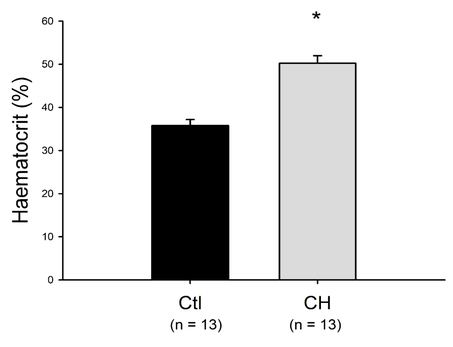


HIF-1α and AdipoR2 protein levels in macrophages exposed to $CoCl_2$, a hypoxia- mimetic agent. HIF-1α/total protein and AdipoR/total protein ratio were determined by a denaturant PAGE-SDS followed by a Western blot. HIF-1α/total protein ratio and AdipoR2/total protein ratio were obtained after densitometric analysis. * p<0.05, vs Ctl ; # p<0.05, vs $CoCl_2$ 5 µM, One-Way Anova.



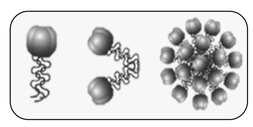
HIF-1α and AdipoR2 protein levels in macrophages transfected with a plasmid encoding a shRNA targeting HIF-1α. HIF-1α/total protein and AdipoR/total protein ratio were determined by a denaturant PAGE-SDS followed by a Western blot. HIF-1α/total protein ratio and AdipoR2/total protein ratio were obtained after densitometric analysis. * p<0.05, vs shRNA Ctl, Two-Way Anova.

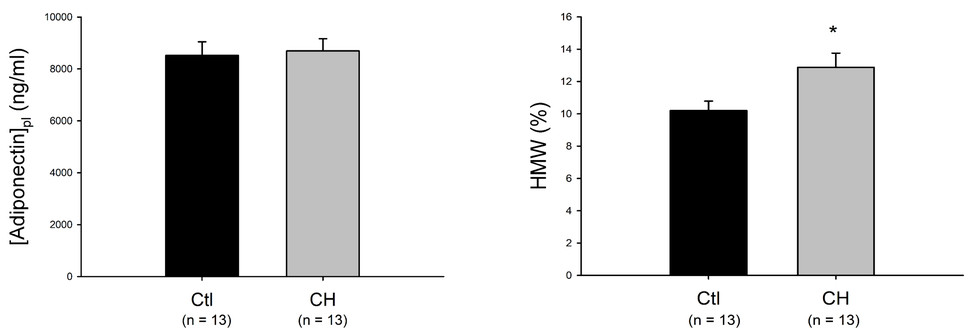




Effect of hypoxia on haematocrit. Haematocrit was evaluated in mice exposed to normoxia (Ctl) or chronic hypoxia (CH) * : p < 0,001, vs Ctl, T-test.

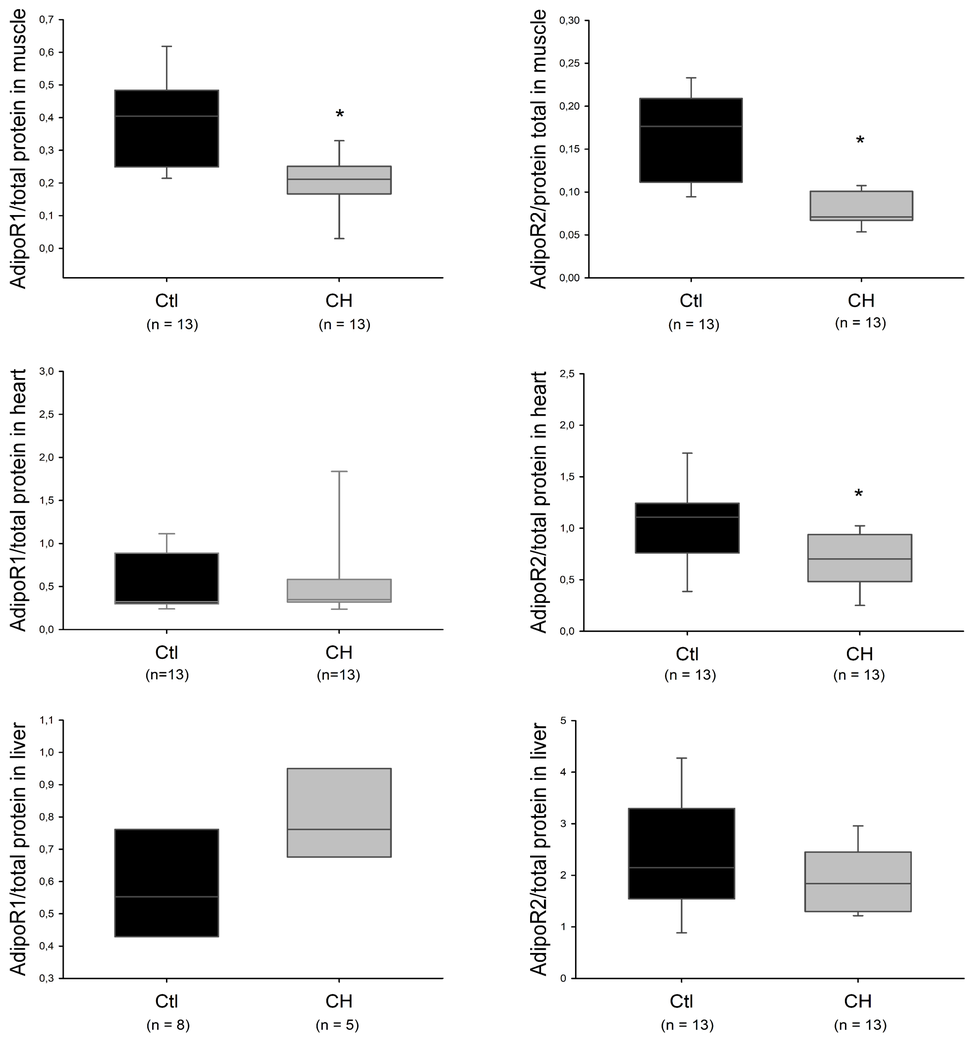
Impact of hypoxia on Ad_{pl} level and Ad-mer distribution





Circulating Ad and Ad-mer distribution analysis. Ad plasmatic level was measured by ELISA. The relative abundance of the high (HMW), medium (MMW) and low (LMW) molecular weight forms were determined by a non-denaturant PAGE-SDS followed by a Western blot. HMW/total Ad ratio was obtained after densitometric analysis. * p<0.05, vs Ctl,T-test.

Impact of hypoxia on AdipoR protein level



AdipoR1/2 protein levels in skeletal muscle, heart and liver. AdipoRs/total protein ratio were determined by a denaturant PAGE-SDS followed by a Western blot. AdipoR1/total protein ratio and AdipoR2/total protein ratio were obtained after densitometric analysis. * p<0.05, vs Ctl, Rank Sum Test.

In conclusion, chronic hypoxaemia, per se, modifies Ad oligomerisation state and AdipoR protein level *in vivo* and in macrophages *in vitro*. These effects could be partly linked to HIF-1α activation during adaptive response to hypoxia and could influence the cardiovascular risk in hypoxaemic COPD patients.

We acknowledge V. Jenart and B. Blairon for technical assistance. Molecular analyses were funded by the FRMH (Fonds pour la Recherche Médicale dans le Hainaut). The ISPPC (Intercommunale de Santé Publique du Pays de Charleroi) provided funding for the conception of device inducing hypoxia. MP held PhD fellowships from the University of Mons. The macrophage cell line RAW 264.7 cells was kindly provided by the Laboratory of Cellular Biochemistry and Biology from the University of Namur.