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 (Ad₉₉) 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.

Impact of hypoxia on AdipoR protein level

Effect of hypoxia on AdipoR1/2 protein levels in macrophages. AdipoR1/2 total protein ratio were determined by a denaturant PAGE-SDS followed by a Western blot. AdipoR1/2 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 CoCl₂, a hypoxia-mimetic agent. HIF-1α total protein and AdipoR2/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 Chi, # p<0.05, vs CoCl₂, 5 μM, One-Way Anova.

Impact of hypoxia on Ad₉₉ 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 Chi, T-test.

Impact of hypoxia on AdipoR protein level

HIF-1α and AdipoR2 protein levels in skeletal muscle, heart and liver. AdipoR2/total protein ratio were determined by a denaturant PAGE-SDS followed by a Western blot. AdipoR1/2 total protein ratio and AdipoR2/total protein ratio were obtained after densitometric analysis. * p<0.05, vs Chi, 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.

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