The adipokine *chemerin* increases vascular reactivity to ET-1 via activation of ERK1/2

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Introduction: Obesity and cardiovascular diseases are associated with vascular dysfunction and elevated levels of pro-inflammatory cytokines. ET-1 is considered to play a major role on vascular dysfunction associated with these pathological conditions. *Chemerin* is a pro-inflammatory cytokine secreted by the adipose tissue. The mechanisms by which adipokines interfere with the vascular function as well as the effects of *chemerin* on vascular reactivity are not fully understood. Therefore, this study investigated the effects of *chemerin* on vascular reactivity and the mechanisms by which it modifies vascular function. We hypothesized that *chemerin* increases vascular reactivity to ET-1 via activation of MAPKs, a major signaling pathway activated by ET-1 in the vasculature.

Methods: Endothelium-intact and endothelium-denuded thoracic aortic rings (2-3mm) from 10-12 week-old male Wistar rats were used to record isometric contractions (DMT Wire Myograph; Krebs buffer pH 7,4; 37ºC; 5% CO_2 - 95% O_2). Vessels were incubated with *chemerin* (0.5ng/mL or 5ng/mL; for 1 or 24 h) and cumulative responses to ET-1 (10^{-12} - $3x10^{-8}$ M) were determined, in the presence of vehicle (distilled water) or ERK1/2 inhibitor (PD 98059, 1µM, 30 min before the incubation with *chemerin*). Vascular protein expression of ERK1/2 was also determined in aortic rings incubated with *chemerin* (0.5ng/mL; 1 and 24 h) plus ET-1 (10^{-7} M; 10 min)

Results: *Chemerin* (0.5ng/mL; n=5-6) augmented ET-1-induced vasoconstriction [pD_2 = 1h: 10.5±0,2 vs. 9,1±0,04 vehicle (PBS 0,1% BSA) (p<0,05); 24 h: 10.9±0,1 vs. 8.7±0,02 vehicle (p<0,05). Endothelium removal further augmented *chemerin* effects. The potentiation of ET-1-induced vasoconstriction by *chemerin* (0,5ng/mL, 1h) was abolished by ERK1/2 inhibition [pD_2= 9.1±0,6 (p<0,05)] (see Figure). *Chemerin* (0,5ng/mL) induced vascular ERK1/2 phosphorylation [arbitrary units: 1.5±0.04 *vs*. 1.0±0.07 control; n=6, 1h (p<0,05)] and also potentiated ET-1 induced ERK1/2 phosphorylation [arbitrary units: 1.59±0.25 *vs*. 1.0±0.09 ET-1; n=4-5, 1h (p<0,05); 1.27±0.16 *vs*.1.0±0.17 ET-1; n=6, 24h (p<0,05)]

Conclusions: The adipokine *chemerin* increases vascular contractile responses to ET-1 via activation of ERK1/2 signaling. These effects may contribute to obesity- and ET-1-associated vascular dysfunction.

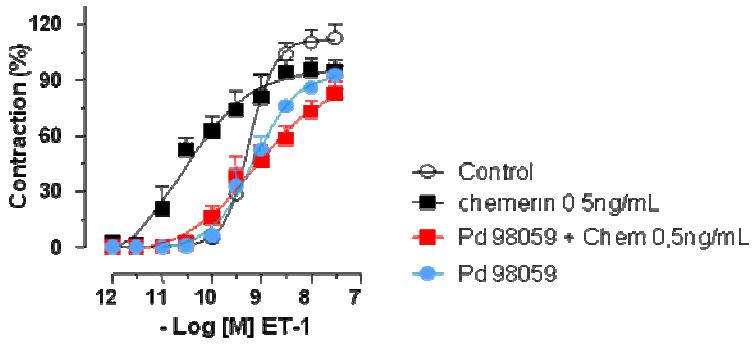

Figure 1. Cumulative concentration-response curves to ET-1 in endothelium-intact thoracic aortas incubated with *chemerin (*1 h) plus vehicle or Pd98059 (ERK1/2 inhibitor, 1 µM).