

Chemerin as a novel target for the alleviation of CKD induced muscle weakness

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People with non-dialysis dependent CKD (NDD-CKD) often experience muscle wasting and dysfunction, limiting physical activity and resulting in a downward spiral of atrophy and disuse, reduced quality of life and increased risk of morbidity and mortality. Understanding this process and developing interventions to alleviate muscle loss is of great interest, and in this regard the link between adipokines and muscle loss is under-researched. An adipokine termed Chemerin has been shown to correlate strongly with CKD disease progression and has also been shown to be involved in inflammatory signalling processes. With chronic inflammation recognised as a contributory factor in NDD-CKD muscle loss, we sought to 1. define Chemerin systemically in NDD-CKD and, 2. investigate its potential effects on the skeletal muscle of these patients. Retrospective analyses of Chemerin concentrations were performed by ELISA on stored plasma and urine samples from 71 NDD patients and 32 age and sex matched controls. Correlation analysis was conducted to explore the relationships between Chemerin and markers of disease severity and body composition. To investigate the role of Chemerin on skeletal muscle, human derived muscle cells (HDMCs) were harvested from skeletal muscle biopsies and the cells matured in cell culture. Mature skeletal muscle myotubes were exposed to multiple doses of Chemerin and subsequently harvested for downstream analysis. This included identification of the proposed receptors ChemR23, GPR1 and CCLR-2 as well as quantifying the effects of Chemerin on intracellular signalling related to protein degradation. Both urine and plasma Chemerin concentrations were significantly raised in NDD-CKD patients in comparison controls (162.00 vs. 66.08 ng/ml respectively, $p < 0.0001$). Plasma Chemerin was negatively correlated with eGFR ($r = -0.57$, $p < 0.0001$) and positively correlated with both BMI ($r = 0.26$, $p = 0.009$) and % body fat ($r = 0.28$, $p = 0.008$). Utilising cell culture we were able to identify two of the three proposed receptors of Chemerin in skeletal muscle myotubes, termed ChemR23 and GPR1. Myotubes exposed to an acute dose of Chemerin displayed a dose dependent significant increase in the mRNA expression of the pro-inflammatory markers TNF- α , IL-6 & MCP-1 ($p \leq 0.05$). Our work shows increased plasma and urine Chemerin levels in NDD-CKD, which correlates with disease severity. Further to this, utilising in-vitro methodology we have been able to show that Chemerin stimulates increases in intramuscular inflammation which has been shown previously to drive protein degradation. Our work provides a novel insight into a potential role for Chemerin in CKD induced muscle wasting, and implicates it as a potential future therapeutic target to resolve such muscle losses in this population. Future work will seek to define a specific mechanism for such effects in order to further our understanding of the role of adipokines in CKD induced muscle dysfunction.