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Molecular mechanisms regulating skeletal muscle homeostasis: effects of V1a AVP receptor over-expression

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The maintenance of a working skeletal musculature is conferred by its capacity to regenerate after mechanical or pathological injury. Most muscle pathologies are characterized by the progressive loss of muscle tissue due to chronic degeneration combined with the inability of the regeneration machinery to replace damaged myofibers. Cachexia or muscle wasting is characterized by a loss of adipose and muscle mass associated with a compromised muscle regenerative ability. Arg-vasopressin (AVP) is a potent myogenesis promoting factor and activates both the calcineurin and CaMK pathways, whose combined activation leads to the formation of transcription factor complexes in vitro. The local over-expression of V1a AVP receptor (V1aR) in injured muscle results in enhanced regeneration. V1aR over-expressing muscle exhibits early activation of satellite cells and regeneration markers and accelerated differentiation. Here we investigated the role of V1aR over-expression in animals undergoing cachexia as a result of muscle over-expression of a specific cytokine (TNF). In these conditions, the local V1aR over-expression counteracts the negative effects of cachexia on muscle, as demonstrated by morphological and biochemical analysis. In particular, the presence of V1aR results in increased Pax-7, myogenin and myosin expression levels both in wild type and in cachectic muscles. The positive effects of V1aR on muscle homeostasis are due to the promotion of the calcineurin-IL-4 pathway and to the inhibition of atrophic genes expression mediated by FOXO phosphorylation.

This study highlights a novel in vivo role for the AVP-dependent pathways which may suggest a potential gene therapy approach for many diseases affecting muscle homeostasis.

References

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Key words

Skeletal muscle, cachexia, regeneration, TNF.