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MYOGENIC DIFFERENTIATION AND MUSCLE HOMEOSTASIS: NOVEL ROLES OF VASOPRESSIN

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The neurohypophyseal nonapeptide arg-vasopressin (AVP) and related peptides constitute a novel family of positive regulators of terminal differentiation of myogenic cell lines and primary satellite cells. By interacting with V1 type receptor, AVP induces activation of phospholipases C and D, regulates cAMP levels, increases cytosolic Ca^{2+} concentration and up-regulates Myf-5 and myogenin expression, both at the mRNA and at the protein level. In a chemically defined medium, which eliminates the interference of serum components, AVP activates both the calcineurin and the CaMK signaling pathways, whose combined activation leads to the formation of multifactor complexes and is required for the full expression of the differentiated phenotype *in vitro*.
To better clarify the physiological role of AVP in skeletal muscle, we analyzed the AVP effects on muscle regeneration induced by cardiotoxin injection. In particular, to increase skeletal muscle sensibility to circulating AVP, in the absence of systemic effects related to administration of the hormone itself, we over-expressed the V1a AVP receptor in mouse tibialis anterior muscle by electroporation-mediated gene delivery *in vivo*. The local over-expression of the V1aR in injured muscle results in enhanced regeneration. V1aR over-expressing muscle exhibits: early activation of satellite cells and regeneration markers, accelerated differentiation, increased cell population expressing hematopoietic stem cell markers and its conversion to the myogenic lineage. We demonstrate that V1aR over-expressing muscle increases calcineurin and IL-4 expression levels, and induces the phosphorylation of FOXO trascription factors, inhibiting the expression of atrophic genes. This study highlights a novel *in vivo* role for the AVP-dependent pathways which may represent a potential gene therapy approach for many diseases affecting muscle homeostasis.