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Growth and differentiation factor-11 is developmentally regulated in skeletal muscle and inhibits myoblast differentiation

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ABSTRACT

Growth and differentiation factor-11 (GDF-11) is a secreted protein that is closely related to myostatin, a known inhibitor of skeletal muscle development. The role of GDF-11 in regulating skeletal muscle growth remains unclear and the pattern of expression during post-natal growth has not been reported. Therefore, we sought to determine the expression of GDF-11 during post-natal growth and its effect on myoblast proliferation and differentiation. We collected *gastrocnemius* muscles from male and female mice at 2, 3, 4, 6, 12, 20 and 32 weeks of age (n = 6 per sex and age). In addition, *gastrocnemius* muscles were col- lected from male wild-type and myostatin knockout mice at 4, 6, 12 and 20 weeks of age (n = 6 per age and genotype). RNA was extracted and reverse tran- scribed. Northern analysis identified an expected 4.4 kb mRNA transcript for GDF-11 in *gastrocnemius* muscles of mice. The concentration of GDF-11 mRNA, as determined by quantitative PCR, was increased in *gastrocnemius* muscles from 2 to 6 weeks—a period of rapid postnatal muscle growth—and remained higher in male than female mice from 4 to 20 weeks of age ($P < 0.05$). Interestingly, the mRNA concentration of GDF-11 and its cognate receptors (ActRIIA, ActIIB and Alk5) were increased in *gastrocnemius* muscles of myostatin knockout compared with wild-type mice ($P < 0.05$), which may suggest a compensatory mecha- nism for the lack of myostatin. In support, recombi- nant GDF-11 inhibited differentiation of C2C12 mur- ine myoblasts and those isolated from myostatin knockout and wild-type mice ($P < 0.05$). Inhibited dif-ferentiation of C2C12 myoblasts was associated with decreased mRNA expression of early and late mo- lecular markers of differentiation (MyoD, myogenin, IGF-II, desmin and MyHC, $P < 0.05$). Our results suggest that GDF-11 regulates growth of skeletal muscles by inhibiting myoblast differentiation in an autocrine/paracrine manner and, perhaps, also plays a role in regulating sexually dimorphic growth.

KEYWORDS

GDF-11, Developmental Expression, Post-Natal Muscle Growth, Sexual Dimorphism, Myoblast Differentiation

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