

obtained in 7 of these subjects before and after infusion for analysis of IGF-I mRNA and Akt phosphorylation. Blood was obtained serially every 10 minutes during the infusion for GH, IGF-I, insulin and glucose assessments. GH infusion increased plasma GH and forearm blood flow by 66% ($p < 0.001$), but did not change plasma IGF-I concentrations, muscle IGF-I mRNA expression, or muscle Akt phosphorylation—therefore suggesting a lack of IGF-I action in muscle. Additionally, human aortic endothelial cells (HAECs) were incubated with GH (30 ng/mL) in vitro for 3 or 6 hours. GH did not alter endothelial nitric oxide synthase (eNOS) protein content, but induced a time-dependent increase of the phosphorylation of eNOS. This study demonstrated that GH exerts an acute vascular effect, independent of both systemic and local IGF-I production and that this effect probably occurs via direct action on GH receptors and eNOS in the vascular endothelium.

Li G, del Rincon P, Jahn LA, et al. Growth hormone exerts acute vascular effects independently of systemic or muscle insulin-like growth factor I. *J Clin Endocrinol Metab.* 2008;93:1379-1385.

Editor's Comment: *Endothelial dysfunction appears to explain much of the increased cardiovascular risk of GH deficiency. GH seems to play an important role in the regulation of peripheral vascular resistance and vascular reactivity; these effects appear to be mediated*

by the activation of the NO pathway. GH deficiency is associated with decreased systemic NO formation and decreased forearm release of nitrite and cyclic GMP during acetylcholine stimulation, as well as a decreased peak hyperemic response to ischemia, which reverts to normal during GH replacement. Significant endothelial dysfunction—as determined by an impaired endothelium-dependent brachial artery dilatory response to occlusion ischemia and by abnormalities of several biochemical markers of endothelial cell activation—has been reported in adolescents and adults with GH deficiency.^{1,2} It is not clear whether these effects are a result of a direct effect of GH on the vascular endothelium or whether they are dependent on systemic and local IGF-I production. This study seems to indicate that the acute vasodilatory effect of GH is exerted independent of IGF-I, very possibly through GH receptor mediated eNOS activation.

Roberto Lanes, MD

References

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2. Elhadd TA, Abdu TA, Oxtoby J, et al. Biochemical and biophysical markers of endothelial dysfunction in adults with hypopituitarism and severe GH deficiency. *J Clin Endocrinol Metab.* 2001;86:4223-4232.

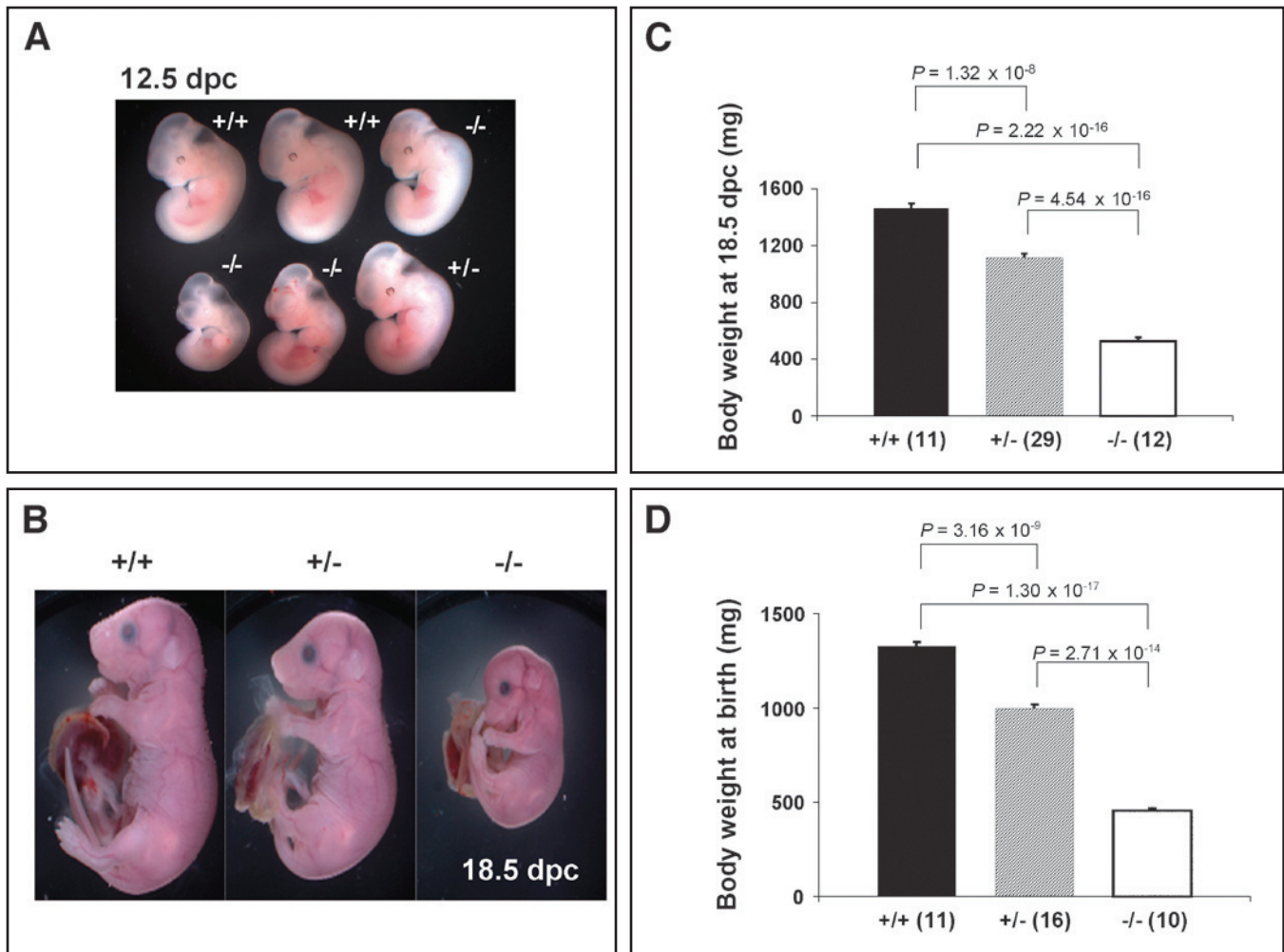
Nedd4 Controls Animal Growth by Regulating IGF-I Signaling

Nedd4 (Neural precursor cell expressed developmentally down regulated 4 - OMIM 602278, chromosome 15q) is a cytoplasmic ubiquitin ligase that regulates protein movement and structure thereby its function or directs a protein into ubiquitin-proteasomal degradative pathway. Cao et al demonstrated that Nedd4 is essential for transduction of intracellular signals initiated by insulin and insulin-like growth factor (IGF)-I and the localization of the insulin receptor (IR, OMIM 147670, chromosome 19p13.2) and the IGF-I receptor (IGF1R, OMIM 147370, chromosome 15q25-q26) to the cell plasma membrane. Nedd4 does not bind to IR or IGF1R directly, but links to an adaptor protein, Grb10 (Growth factor receptor-bound protein10, OMIM 601523, chromosome 7p12-p11.2), which in turn is bound by IR and IGF1R. Grb10 inhibits movement of these receptors to their localization sites in the plasma membrane and thereby impairs function of IR and IGF1R. This effect is opposed by the binding of Nedd4 to Grb10. Cao and colleagues generated Nedd4 knockout (KO) mice. Nedd4^{-/-} mice died during gestation or shortly after birth due to immature lung development and aeration (Figure); their linear growth and weight were severely impaired by embryonic day 12.5. Heterozygous Nedd4^{+/-} mice were also small at birth and through post-natal age 3 months (the end of the study period). In vitro, the proliferation of Nedd4^{-/-} fibroblasts was impaired relative to that of

wild-type fibroblasts due to decreased progression through the cell cycle at phases G₀ and G₁. IGF-I and insulin mediated intracellular signaling was substantially reduced in Nedd4^{-/-} and Nedd4^{+/-} fibroblasts and could be restored by expression of Nedd4 in these cells. However, in Nedd4^{-/-} fibroblasts, the expression and translation of IR and IGF1R were normal, but the receptors did not reach the cell surface, an abnormality that could also be reversed by expression of Nedd4 in these cells. Further studies demonstrated that the amount of Grb10 was increased in Nedd4^{-/-} fibroblasts and that “knockdown” of Grb10 by small interfering RNA (siRNA) restored insulin and IGF-I signaling in Nedd4^{-/-} fibroblasts. The investigators concluded that Nedd4 positively regulates IGF-I and insulin signaling by enhancing the movement of their receptors to the cell surface. Nedd4 does so by dis-inhibiting the inhibitory effect of Grb10 on this process—perhaps by controlling the rate of degradation of Grb10 itself through the ubiquitin-proteasomal system.

Cao XR, Lill NL, Boase N, et al. Nedd4 controls animal growth by regulating IGF-1 signaling. *Sci Signal.* 2008;1:ra5. [DOI:10.1126/scisignal.1160940]

Editor's Comment: *This study has identified another intracellular signal transduction site (Nedd4-Grb10) to examine when a patient with severe growth retardation due*



Nedd4^{-/-} mice die immediately after birth, and *Nedd4*^{+/-} and *Nedd4*^{+/-} mice exhibit intrauterine growth retardation. No mice homozygous for disruption of the *Nedd4* gene were found 2 or 3 weeks after birth. Ratios of heterozygotes and homozygous mutants were thus assessed at earlier time points: (A) 12.5 dpc, (B and C) 18.5 dpc, and (D) immediately after birth. Both heterozygotes and homozygous mutants showed signs of intrauterine growth retardation as early as 12.5 dpc (A) and at late gestation [18.5 dpc (B) and (C)]. At the time of birth [postnatal day 1 (D)], the body weights among three genotypes differed significantly: *Nedd4*^{-/-} body weight averaged 64 to 68% lower relative to that of wild-type littermates; heterozygote body weight averaged about 15 to 20% reduction in body weight relative to that of wild-type littermates. In (C) and (D), the numbers of animals used for the analyses are shown in parentheses; the body weight was significantly different between groups of mice, with P values indicated. Reprinted with permission Cao XR, et al. *Sci Signal*. 2008;1: ra5. Copyright © AAAS 2008. All rights reserved.

to insensitivity to IGF-I and an intact IGF1R is encountered. A polymorphic variant or mutation in either one of these proteins might also account for impaired intrauterine

growth in some small-for-gestational age neonates.

Allen W. Root, MD

Growth Hormone Deficiency: Transient or Permanent?

In this multicenter study, Berberoglu and colleagues tried to assess the need for continuation of growth hormone (GH) treatment in adulthood after growth is completed and also to evaluate factors that would predict persistent GH deficiency (GHD). A total of 70 (31 female, 39 male) GHD patients were included in the study; 52 patients (74%) had isolated GHD and 18 patients (26%) had multiple pituitary hormone deficiency (MPHD). The initial diagnosis was based on a peak GH level <10 ng/mL in 2 pharmacological tests. GH treatment was discontinued in these patients when growth velocity during the

previous year decreased to less than 2 cm and the bone age had reached greater than 14 years in girls, and greater than 16 years in boys, and after completion of puberty. All patients were re-tested by insulin tolerance test (ITT) at least 6 weeks after discontinuation of the replacement treatment. Serum insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 concentrations were determined at the same time. If GH peak during ITT was <3 ng/mL, the patient was diagnosed to have severe permanent GHD.

Among the patients with isolated GHD, 9 patients