Growth hormone and the Obesity Hormones: focus on adiponectin

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Adiponectin

- Insulin sensitizing, anti-inflammatory adipokine
- Involved in tissue remodeling, cell adhesion, cell proliferation and growth
- Levels are low in obesity and diabetes and increase with weight loss
Regulation of Adiponectin

• 30 Kda protein has amino terminal signal sequence, variable region, collagen domain and carboxy terminal globular domain
• Post translational modifications after secretion from adipocytes: hydroxylation, glycosylation.
• Single monomers associate to form trimers that polymerize through collagenous domain into hexamers of LMW, MMW molecules, or 12-18 multimers (HMW).
Full length vs. globular domain

- Full length adiponectin cleaved by elastase from monocytes to generate globular form
- Full length and globular domain have distinct biologic effects.
- Globular domain may contribute to insulin mimetic action of adiponectin.
Adiponectin Isoforms

- HMW (18mers): high correlation to insulin sensitivity; most biologically active form.
- MMW (hexamer) Increase after hypocaloric diet along with LMW.
- LMW (trimer) Increase following bariatric surgery
- Globular forms
C-terminal, which is resident in the extracellular side (int). The expression of both receptors is inversely regulated by insulin both in physiological and pathophysiological conditions such as fasting/refeeding, insulin deficiency and hyperinsulinemia and correlates with adiponectin sensitivity ([1], [2]). Recent observations suggest that in myocytes the level of expression of adiponectin receptors increases in pro-inflammatory conditions, probably through a redox mechanism, while it is unaffected by muscle differentiation ([3]). In addition to these receptors, T-cadherin was suggested as a possible cell-surface-binding protein for full-length and oligomeric adiponectin, although it does not participate in adiponectin cellular signalling ([4]). An association between T-cadherin and adiponectin has been recently observed in breast cancer. In this paper the authors suggest a role for T-cadherin in sequestering adiponectin in the vasculature, where the T-cadherin-adiponectin interaction could play a key role in the control of vascular function by regulating the molecular cross-talk between tumour cells and the stromal compartment ([5]).

Although the signalling pathway triggered by adiponectin receptors is not yet completely elucidated, several signalling...
Adiponectin Signal Cascades

- APPL1 transduces Adiponectin signal via AMPK
- AMPK leads to: decreased hepatic gluconeogenesis and Tg content and increased muscle glucose uptake and fatty acid oxidation
- Activation of hypothalamic AMPK stimulates food intake, decreases energy spent during fasting, and acts as a “general starvation signal”.
Secretion of adiponectin oligmers

• Tightly controlled in ER by molecular chaperones:
  • Erp44 sequesters oligomers to inhibit their release
  • Erol-Lalpha: permits release of HMW complexes trapped by Erp44
Adiponectin receptors

- AdipoR1 (highly expressed in skeletal muscle in man), AdipoR2 (liver)
- Adiponectin receptors are also present in adipose tissue and in pancreatic beta cells.
- Growth hormone and PRL differentially regulate adiponectin receptor mRNA in cultured human adipocytes in vitro
Role of Adiponectin

• Adiponectin treatment of mice increases fatty acid oxidation in muscle, lowers serum glucose, suppresses hepatic glucose production.

• Treating obese mice with adiponectin reduces triglycerides and lowers insulin resistance.

Nilsson L. BBRC 331(2005)1120-1126
In vitro effects of growth hormone on adiponectin

• Both growth hormone and prolactin significantly suppress human adipose tissue adiponectin secretion in vitro.
IGFBP-3 effects on adiponectin

- IGFBP-3 treatment suppresses adiponectin expression in 3T3-L1 adipocytes in culture and reduces insulin-stimulated glucose transport
- Systemic administration of IGFBP-3 to 7 day old Sprague-Dawley rats causes a 40% decline in glucose utilization and glycogen synthesis.

Kim HS, Pediatric Research, 2007
GH-tg and GHR deficient mice

- Adiponectin levels in GH-tg mice are suppressed and primarily mirror insulin sensitivity rather than fat mass.
- GHR deficient mouse has increased adiponectin despite increased interscapular fat.

Adiponectin in Human GHI

- Adiponectin levels, primarily HMW, in both male and female GHI patients, are 2-3 fold higher than those of matched subjects of similar age, gender, and adiposity.
- Treatment with rhIGF-1 fails to suppress adiponectin

Kanety H, European J Endocrinol, 2009
Prenatal adipose development

- Adipose tissue present from 14 weeks gestation
- Most adiposity accrues during 3rd trimester
- Adiponectin is present in brown and white adipocytes, diaphragmatic and iliopsoas skeletal muscle, arterial wall smooth muscle, perineum, and renal capsule… (all mesenchymal tissues)
Neonatal Fat

- 15% body fat in neonates
- Visceral fat increases from 4% at birth to 11% in 4-8 year old child.
- 90% newborn fat is subcutaneous by MRI
- Term females fat mass > males
Adiponectin and Fetal Growth

• Adiponectin is measurable in cord blood by the 24th week of gestation
• Its levels increase from <1.9 ug/mL at 24 weeks to 20 ug/mL at term.
• Cord blood adiponectin correlates with the ratio of fetal to placental weight.
• Cord adiponectin also correlates with birth weight, BMI, and ratio of birth weight to length
High neonatal adiponectin

- Fetuses in late gestation and newborns have significantly lower numbers of GH receptors compared with the postnatal state.
- Does this finding contribute to high levels of neonatal adiponectin?

Adiponectin and early growth

- HMW adiponectin = main isomer in cord blood
- In multiple regression analysis, cord HMW adiponectin concentrations predict birth weight and birth weight to length ratio
- HMW adiponectin/leptin ratio correlates with weight gain in first 7 months of life
- Cord blood adiponectin is inversely associated with weight gain in the first 6 months of life and predicts an increase in central adiposity at age 3
- Matzoros CS, Pediatrics 123, 2009
LEPTIN/ADIPONECTIN RATIO IN MID-INFANCY

Fig. 1: Leptin/adiponectin ratio by weight gained since birth.
Breast milk adiponectin and growth

- Most breast milk adiponectin in HMW form
- Longitudinal study of healthy breast fed term infants over 6 months:
- Higher milk adiponectin associated with lower infant weight-for-age Z-score and weight-for-length Z score, but not length for age Z-score, adjusted for covariates

Woo JG, Breastfeeding Medicine, 2009
Maternal adiponectin during pregnancy

• The proportion of maternal serum adiponectin in HMW form, (S(A)), is independently and inversely associated with infant birth weight

Growth hormone and adipocytes

• Growth hormone receptors are expressed in pre-adipocytes and adipocytes.
• GH stimulates proliferation of pre-adipocytes but inhibits differentiation into mature adipocytes.
• GH deficient children have fewer and larger fat cells compared to normals.
hGH effects on adipocytes

- GH appears to be the main regulator of IGF-1 mRNA expression in adipose tissue.
- IGF-1 mRNA levels in adipose tissue are similar to those found in liver.
- Hypophysectomy markedly reduces IGF-1 mRNA in rat adipocytes.

Peter MA, Endocrinology, 1993, 133: 2624-2631
Adiponectin and growth

- In a group of 95 short pre-pubertal Scandinavian children (mean age 9.0 years) treated with hGH:
  - Adiponectin concentrations at start of hGH treatment correlated positively with first year growth response.

  Andersson B, Hormone Research, 2008
Adiponectin and growth

Adiponectin declined significantly with hGH treatment despite reduction in fat mass

• High baseline adiponectin was associated with a greater growth response if other independent variables were held constant

• Decrease in adiponectin after 3,12 months of hGH treatment correlated to growth response.

• No correlation between adiponectin and insulin resistance during first year of treatment.
Adiponectin and growth

• SGA children with catch up growth have lower HMW adiponectin than those who do not catch up.
• Hypoadiponectinemia may relate to or predict development of visceral adiposity and insulin resistance.
Adiponectin in SGA children

• Decline in adiponectin in hGH treated short SGA kids reflects the fall in HMW adiponectin (less subcutaneous adiposity over time)

• An elevated ratio of visceral to subcu fat could explain lower HMW adiponectin in SGA babies

Adiponectin and LGA

- Subjects born LGA develop higher BMI, waist circumference, BP, and HOMA than AGA at ages 23-25 years (case control study of a prospective cohort followed from birth)
- -1139A ADIPQ polymorphism in the adiponectin gene regulatory region is associated with an increased chance of LGA birth and higher adiponectin in early adulthood
  
Adiponectin in PWS

• PWS subjects have higher percent body fat by DEXA and lower % lean mass compared to obese controls.

• Plasma adiponectin levels are significantly higher in PWS than in obese controls

• PWS subjects have less insulin resistance proportionate to their obesity status than subjects with simple obesity.

Adiponectin in GHD children treated with hGH

- Adiponectin concentrations in GHD Italian children, mean age 11.6 years, were similar to those in a normal control group at baseline.

- Following one year of hGH treatment, BMI and leptin declined while adiponectin was unchanged.

Ciresi A, Europ J. Endocrinology, 2007
Adiponectin in growth hormone deficient adults

- In a cohort of growth hormone deficient adults, baseline ghrelin levels were lower in GH deficient subjects compared to controls, but not adiponectin levels.
- After one year of hGH therapy, adiponectin levels increased significantly as BMI and BF% declined.

Ciavoli C, Clinical Endocrinology, 2004
In Conclusion

- Adiponectin appears to be closely related to parameters of fetal and placental growth
- The interaction of adiponectin, body fat stores, insulin and insulin sensitivity, relate to growth and growth hormone during childhood.
- The role of adiponectin as a determinant or marker of human growth merits further investigation.