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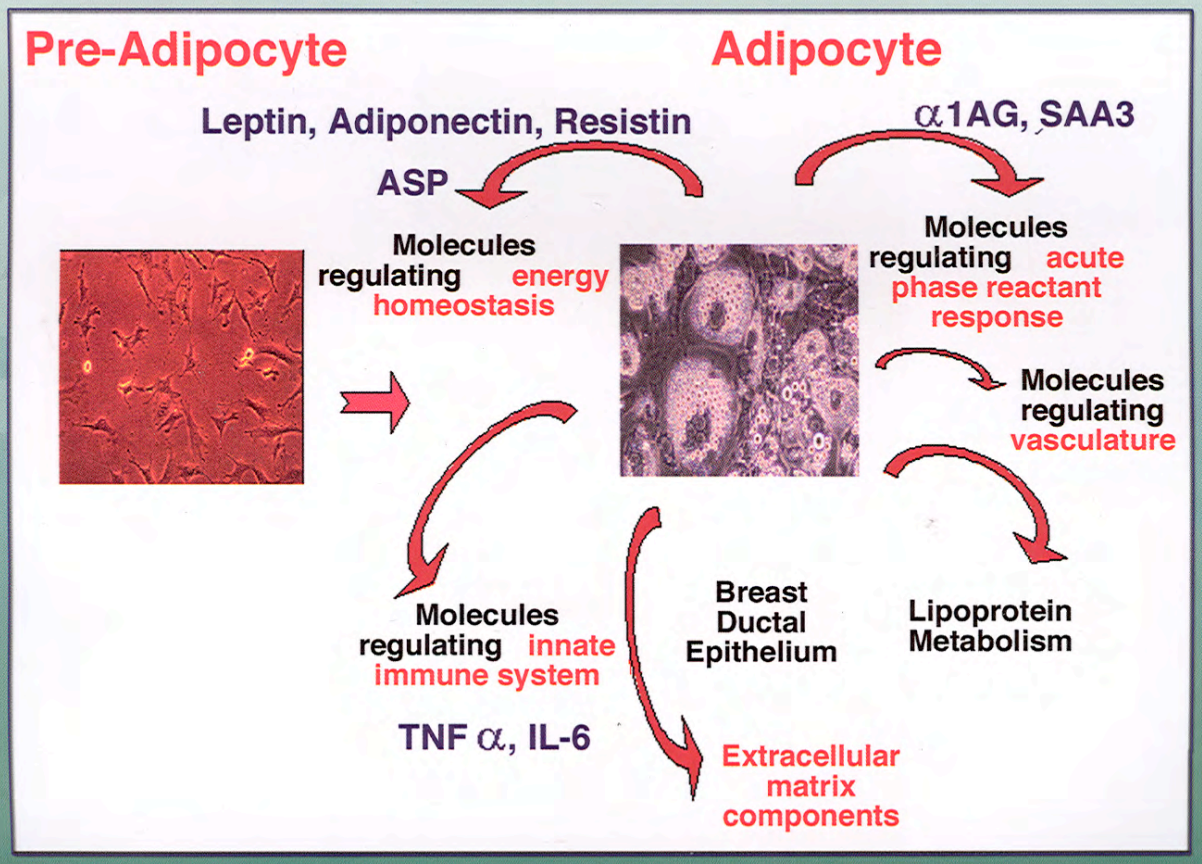

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Adiponectin, an Adipocyte-Derived Hepatic Insulin Sensitizer Regulation During Development

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Abstract

A large body of clinical data, supported by genetic and pharmacological evidence, has demonstrated potent insulin-sensitizing effects of the adipocyte-derived secretory factor adiponectin. In adults, plasma adiponectin is generally negatively correlated with BMI and positively correlated with systemic insulin sensitivity. Only a limited number of studies have been performed in newborns, children and adolescents. Here we summarize the results from these recent findings in younger cohorts and discuss these results in context of the much vaster literature on adiponectin levels in lean, obese and diabetic adults.

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Introduction

The recent past has provided us with many new insights into the physiological role of adipocytes. We now realize that adipose tissue is not only a storage compartment for triglycerides, but also an endocrine tissue, releasing several factors into plasma with distant sites of action and involved in a number of physiological processes, such as the innate immune response, vascular remodeling and whole body energy homeostasis (1). Adipose tissue secretes key modulators of insulin sensitivity that include hormonal as well as lipid factors. Adipocytes play a significant role in shaping FFA levels in circulation. Excessive levels of FFAs have been shown to impact negatively upon insulin sensitivity in skeletal muscle and liver glucose metabolism and have potent negative effects on β cell function. Inflammatory factors and acute phase reactant proteins constitute another major class of adipose tissue-derived factors that are prominently upregulated in the obese and insulin resistant state (1).

More recently, two new factors exclusively secreted by adipocytes, resistin (2,3) and adiponectin (also named Acrp30, AdipoQ and GBP28) (4) have been identified. Pharmacological and genetic evidence pinpoints these two factors as major players in the adipo-hepatic axis where they act as mediators of insulin sensitivity. Elevated levels of resistin trigger insulin resistance (5), whereas adiponectin increases insulin sensitivity by the enhancing of insulin-mediated suppression of hepatic glucose production (6). Both proteins form larger homo-oligomers and in both cases the assembly state of the protein complex is of critical importance for function. Adiponectin resembles complement factor C1q, comprising an N-terminal collagenous domain and a C-terminal globular domain. The C-terminal structure is similar to that of TNFα (7). The basic building block of the protein is a homotrimer, formed initially through interactions between the globular domains and further stabilized by the collagenous triple helix. Through interactions within the collagenous domain, these trimers can associate into hexamers and higher-order structures composed of 2 to 3 hexamers. With a total concentration of 5-20 nM, adiponectin exists in the circulation in two discrete oligomeric structures: a hexamer or low molecular weight form (LMW form) and a higher order structure or high molecular weight form (HMW form) (8). Adult mice and humans display sexually dimorphic plasma levels with higher levels of the total adiponectin found in females (9).

Adiponectin: physiological effects

Circulating adiponectin, obesity and insulin sensitivity are generally closely linked (10). This study highlighted for the first time the inverse correlation between fat mass and circulating adiponectin levels. Hotta et al subsequently reported a similar reduction of adiponectin levels in type 2 diabetic patients, independent of body mass index (BMI) (11). More recently, Weyer et al (12) and Mynarcik et al (13) confirmed the association of obesity and type 2 diabetes with hypoadiponectinemia in Pima Indians and in HIV-positive patients. Conversely, weight loss in humans and mice (9,14)

leads to a significant increase in adiponectin plasma levels and a concomitant increase in insulin sensitivity. Moreover, the locus encoding the adiponectin gene has been identified as a susceptibility gene for insulin resistance and type 2 diabetes (15-17).

Adiponectin levels in the newborn

A recent study by Sivan and colleagues examined the levels of adiponectin in the early neonatal period and reported a number of surprising observations (18). Adiponectin can easily be detected in cord blood and is present at very high levels, in the order of 3 to 4-fold higher than in adults and children. The levels correlated positively with birth weight, but no gender difference could be observed. Interestingly, the cord blood levels did not correlate with maternal adiponectin levels, suggesting that a unique regulatory program is in place in newborns. Despite these rather unique aspects of adiponectin regulation in the newborn, the very high levels observed are consistent with the high degree of insulin sensitivity in neonatals. Adiponectin levels remain high even 4 days post partum, further underlining that circulating adiponectin in the newborn is derived from endogenous fat depots and does not originate in the placenta. Similar conclusions were drawn by Lindsay and colleagues (19). They also report that neonatal levels are independently controlled from the levels in the mother and significantly higher in the neonates. In addition, they extended the analysis to offspring of type 1 diabetic mothers (ODMs) which are at high risk for future development of metabolic disorders. Adiponectin levels were slightly lower in ODMs. The levels increased with later gestational ages. Since the ODMs were born on average slightly earlier, the difference may be at least in part due to the shorter gestational period. Unlike in adults, adiponectin levels in both studies were unrelated to fasting insulin, adiposity and leptin levels.

Children born small for gestational age have decreased levels of adiponectin

A study by Cianfarani and colleagues focused on small for gestational age (SGA) children (20). Intrauterine growth retardation is a significant risk factor for the development of insulin resistance and type 2 diabetes later in life. Adiponectin levels are significantly reduced in SGA children (aged 8 to 10 years) compared to short, normal or obese children. This was particularly pronounced for SGA children with catch-up growth as opposed to those with non-catch-up growth. However, it is at this stage not clear whether the adiponectin levels in that SGA age group have any predictive power for the development of insulin resistance and associated cardiovascular co-morbidities.

Adiponectin levels during childhood – relationship to obesity

Asayama and colleagues have measured adiponectin levels in obese children and assessed whether weight loss has an impact on circulating levels (21). Not unexpectedly, serum adiponectin levels were significantly lower in obese children (average age 10 years) with a strong inverse correlation with visceral adipose mass. Children subjected to a weight loss program who reduced adiposity over the course of the program displayed significant increases of serum adiponectin levels.

Weiss and colleagues (22) looked at adiponectin levels in adolescent obesity from the perspective of intramyocellular lipid content. In addition, detailed insulin sensitivity measurements were available from euglycemic-hyperinsulinemic clamp studies. The authors report strong inverse correlations between adiponectin, triglyceride and intramyocellular lipid levels. Adiponectin levels were proportional to insulin sensitivity, independent of total body fat and central adiposity. These authors conclude that within their adolescent cohort, adiponectin exerts its insulin sensitising effects primarily through the modulation of intramyocellular lipids and plasma triglycerides.

Huang and colleagues (23) focused on a female adolescent population (average age 16 yrs) in the context of blood pressure measurements. They report significant correlations between both systolic and diastolic blood pressure measurements. Upon adjustment for age, anthropometric and metabolic factors, a significant correlation with systolic blood pressure remained, further underlining the general relationship between adiponectin levels, metabolic syndrome and cardiovascular disease.

Our own unpublished observations (Philippe Froguel and Philipp E. Scherer) show decreased levels of adiponectin during puberty with decreasing values during the different Tanner stages, consistent with the decrease in overall insulin sensitivity during that period.

Effects of race and gender during childhood

There is relatively little known about racial differences with respect to adiponectin levels. A recent study by Retnakaran and colleagues focused on a South Asian cohort (24). South Asians display an increased risk of Type 2 diabetes mellitus (DM) and coronary artery disease (CAD) compared with other ethnic groups. A study was performed in 180 women undergoing oral glucose tolerance testing in late second or early third trimester to investigate the relationship between adiponectin and glucose tolerance in pregnancy. Even after adjustment for age, prepregnancy body mass index, weight gain in pregnancy, previous history of GDM, family history of

DM, fasting insulin and glucose intolerance, mean adiponectin remained significantly lower among South Asians compared with either Caucasians or Asians. This suggests that adiponectin levels can vary significantly based on ethnic background and suggests that variations in adiponectin levels may at least in part explain ethnic differences with respect to susceptibility to type 2 diabetes and cardiovascular risk factors. Degawa-Yamauchi focused on a population of African-American boys (25). African-Americans adults are at increased risk for obesity, type 2 diabetes and cardiovascular disease. In agreement with other studies, these authors find overall decreased levels of adiponectin in young obese subjects. Overall, African-American boys display reduced adiponectin levels compared to Caucasians independent of obesity, again an observation consistent with an increased predisposition of this group towards greater risk of diabetes.

Measurements of circulating adiponectin

The vast majority of clinical studies published to date measure total adiponectin levels with one of several commercially available assays. However, our recent observations suggest that measurement of the different forms of adiponectin (the high molecular weight form (HMW) and the low molecular weight form (LMW)) may be superior to the measurements of the total levels (26). Human insulin resistant subjects have a significantly decreased HMW/total adiponectin ratio compared to lean controls, even when adjusted to the same total adiponectin levels. These observations give rise to the hypothesis that the relative levels of the HMW form, rather than the total amount of adiponectin, may be a more accurate indicator of insulin sensitivity. Purified HMW and LMW complexes, when isolated in separate fractions, showed that only the HMW form was able to decrease serum glucose, suggesting that the HMW form is the biologically active form of the protein in liver. We defined a novel index, the adiponectin sensitivity index (SA), which is defined as the relative level of HMW per total adiponectin (26). Monitoring the changes in SA (i.e. ΔSA) offers an excellent parameter to assess improvements in insulin sensitivity. We have monitored these changes in the context of thiazolidinedione-mediated improvements in insulin sensitivity. Across a range of studies, monitoring ΔSA emphasizes that changes in this parameter can account for the response of almost every single patient with respect to insulin sensitivity and offers a parameter far superior to that of total adiponectin levels. However, short of a high throughput assay, we recommend to continue to measure total adiponectin levels and only resort to the more labor-intensive biochemical subfractionation in cases where the total levels fail to provide statistically significant assessments.

Conclusions

In summary, the basic rules of adiponectin physiology established in the adult population hold up during child development. Adiponectin levels start out at very high levels during the neonatal period, decrease to levels comparable to adult levels during childhood, decrease further during puberty and then rebound to normal adult levels that display a linear increase with age. The levels at all stages including childhood and adolescence, correlate very well with measurements of insulin sensitivity during the respective period. Spranger and colleagues determined that basal adiponectin concentrations in plasma were lower among individuals who later developed type 2 diabetes than among controls (27). High concentrations of adiponectin in adults are associated with a substantially reduced relative risk of type 2 diabetes even after adjustment for other risk factors. However, additional studies will have to address the question whether measurements of adiponectin levels during childhood have similarly potent predictive power as in adults for the future development of type 2 diabetes and cardiovascular disease.

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