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EDITORIAL

Involvement of the renin-angiotensin system in obesity: Older and newer pathways

Two decades ago Siiteri [1] called the experts' attention on the endocrine activities of adipose tissue. Since then, a bulk of clinical and experimental studies have unravelled the complex nature of the so-called ''adipose organ''. It has been recognised that adipocytes are equipped with all the ''machinery'' necessary to the production of various substances, and that they express this potential to an extent depending on both physiological stimulation and pathological conditions [2]. These substances are able to exert powerful effects both locally and systemically; among them, the best known are the regulators of appetite or satiety for food, such as leptin, growth factors and pro-inflammatory molecules, e.g. IL-6 and TNF-α, but also anti-inflammatory and vasoprotective substances like adiponectin, and others with important effects on the hemostatic balance, such as PAI-l [2–5].

Renin-angiotensin system (RAS) in adipose tissue

Perhaps among the most unexpected findings is the fact that adipose tissue is able to synthesise the components of the renin-angiotensin system [2–4]. As a matter of fact, angiotensinogen (AGT) expression has been demonstrated in adipose tissue and its increase is now considered a late marker of adipocyte differentiation. In addition, increased AGT secretion appears to be a characteristic feature of obesity and, according to recent evidence, AGT expression seems higher in visceral than in subcutaneous adipose tissue in both normal weight and overweight individuals [6,7]. A number of factors appear to affect AGT gene expression, e.g. fatty acids and glucocorticoids [8,9], peroxysome-proliferator agonist receptors PPARδ and PPARγ [10], glucose [11], insulin [12] and isoproterenol stimulation [13], but also the fasting or repleted state [14]. ACE expression has also been found in adipose tissue and appears to be greater in human visceral tissue than in subcutaneous adipose tissue [7]. Controversy still exists as to whether the locally observed renin accumulation derives from local de novo synthesis [15,16] or from uptake of the enzyme from the circulation [7,17–24]. The occurrence of angiotensin II (Ang) receptors in adipose tissue has also been recognised in rodent models and in human adipocytes [17,19,25,26]. Human preadipocytes and mature adipocytes seem to express almost exclusively AT1R [7,17,27], and increased expression of this receptor has been reported in obesity, particularly in visceral adipocytes [28].

Because adipose tissue is provided with all the mechanisms required for the production of Ang, it is generally assumed that the active product of RAS is produced within the adipose tissue, although direct evidence of its *in vivo* formation has yet to be obtained. Ang is actually found in the culture media of both preadipocytes and adipocytes, and its production increases during human preadipocyte differentiation [29,30]. In addition to adipocytes, adipose tissue contains a number of other cell types, including vascular smooth muscle cells, lymphocytes, sympathetic nerve fibers and fibroblast-like elements (preadipocytes), on which local Ang may exert its effects but which could themselves contribute to local Ang production [31]. Furthermore, since adipocytes are almost ubiquitous in the body, it is possible that Ang released by adipocytes contributes to the action of systemic RAS in different organs.

It has been demonstrated that circulating RAS components are increased in obesity [32–38] and that, vice versa, weight loss reduces systemic

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RAS activity in man [32]: thus, it is reasonable to speculate that RAS components expressed in adipose tissue may also be secreted into the systemic circulation, thus contributing to the occurrence of cardiovascular complications of obesity, particularly high blood pressure.

All together these data are in favour of an important role of adipose tissue RAS in obesity and obesity related disorders. This contention has recently received further support by the results of studies investigating the possible relationship between genetic variation in RAS and individual susceptibility to develop overweight or obesity.

RAS genetic polymorphism and obesity

Recently it has been established that genes influence obesity either directly or by acting on eating patterns [39—41]. Although the data on the relationship between genetic variation in RAS, body mass and body fat distribution are still controversial [42—44], the results of two recent studies have provided reasonably strong support to the hypothesis that genetic variation in RAS components may influence personal susceptibility to obesity. In older participants of the Olivetti Heart Study, which involved an unselected sample of male population in southern Italy, a greater prevalence of overweight and abdominal adiposity was observed in carriers of the ACE D/D genotype [45]. Furthermore, in a subgroup of the same population, followed for 20 years, a significantly larger increase in body weight occurred in the DD compared with the ID + II group. Notably, in previous studies, individuals carrying the DD genotype had substantially higher plasma and tissue ACE activity compared with II homozygotes [46,47]; moreover, Cooper and associates found a positive correlation between plasma ACE activity and BMI [48]. Another study by Cooper and coworkers investigated the relationship between 13 allelic variants of the ACE gene with the risk of obesity in three different Black populations. Haplotype analysis revealed that one haplotype deriving from the combination of five allelic variants in the promoter area was overtransmitted from parents to the overweight or obese offspring. This haplotype was associated with significantly greater systemic ACE activity and was in linkage disequilibrium with the I/D polymorphism, the D allele being present in as many as 85% of the haplotype carriers [49].

In addition to the association with obesity, there is also circumstantial evidence in favour of a relationship between RAS genetic polymorphism, muscular performance and insulin resistance [50—57].

Adipose tissue RAS: effects on adipocyte differentiation

An important feature of adipose tissue RAS could be its role in the process of adipocyte differentiation and, in turn, of body-fat accumulation. In apparent contrast with earlier observations in mice, it has been reported that Ang might have an inhibitory effect on insulin-stimulated human preadipocyte differentiation [30] and that overexpression of the AGT gene is followed by both an increase in adipocytes size and failure to differentiate [15]. In accordance with these findings is the evidence that co-culture of mature and maturing adipocytes also inhibits adipogenic differentiation, suggesting that enhanced AGT expression and Ang production by mature adipocytes exert a negative paracrine feedback on new adipocyte recruitment [24]. Therefore, it appears as if Ang II, locally produced by mature adipocytes, slowed down further differentiation of adipocyte precursors in man, an action which may have substantial effects on insulin sensitivity by decreasing the percentage of small insulin-sensitive adipocytes in comparison to larger mature and relatively insulin-resistance cells [58]. As a consequence of this phenomenon, the physiological function of adipose tissue to buffer the daily influx of dietary fat is reduced [59], causing a tendency for triglycerides to accumulate in other organs such as the liver [10,17] and the skeletal muscle [60—62]. This increased ectopic triglyceride accumulation is closely associated with reduced insulin sensitivity [16,63], the so-called *lipotoxicity theory*. This theory is strengthened by the observation made in lipodystrophy, a condition determined by the absence of adipocytes, in which the obligated triglyceride flux to the liver and skeletal muscle is likewise paradoxically associated with insulin resistance and increased rate of type 2 diabetes [64]. In keeping with these concepts stand the results of a number of randomized controlled trials indicating that RAS blockade by ACE inhibitors or AT1R blockers improves insulin sensitivity and reduces the risk for type 2 diabetes [60—62].

Adipose tissue RAS and inhibition of lipolysis

In this framework, in the last few years growing attention has also been paid to the possible effects of