

## Review Article

# The problem of obesity: is there a role for antagonists of the renin-angiotensin system?

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Obesity is a major health problem worldwide; it is associated with more than 30 medical conditions and is a leading cause of unnecessary deaths. Adipose tissue not only acts as an energy store, but also behaves like an endocrine organ, synthesising and secreting numerous hormones and cytokines. Angiotensin II (ANG II) is the biologically active component of the renin-angiotensin system (RAS). The RAS is present in adipose tissue and evidence suggests that ANG II is intimately linked to obesity. Indeed, ANG II increases fat cell growth and differentiation, increases synthesis, uptake and storage of fatty acids and triglycerides and possibly inhibits lipolysis. Evidence obtained using genetically modified animals has shown that the amount of body fat is directly related to the amount of ANG II, i.e., animals with low levels of ANG II have reduced fat stores while animals with excessive ANG II have increased fat stores. In humans, epidemiological evidence has shown that body fat is correlated with angiotensinogen, a precursor of ANG II, or other components of the RAS. Furthermore, blocking the production and/or actions of ANG II with drugs or natural substances decreases body fat. The decrease in body fat caused by such treatments predominantly occurs in abdominal fat depots and appears to be independent of energy intake and digestibility. Clearly, ANG II has an important role in the accumulation of body fat and the possibility exists that treatment of obesity will be enhanced by the use of natural or synthetic substances that interfere with ANG II.

**Key Words:** angiotensin, body fat, obesity, adipose, angiotensin-converting enzyme inhibitors

## Introduction

Obesity, the excess accumulation of body fat due to an imbalance between energy intake and output, is reaching epidemic proportions and is a major health hazard worldwide. It is linked to the aetiology of a number of conditions such as cardiovascular disease, hypertension, stroke and diabetes.<sup>1-4</sup> Over-consumption of unhealthy food and modern technology has resulted in an alarming increase in the incidence of obesity.<sup>5</sup> For example, in Australia, the prevalence of obesity has more than doubled over the past 20 years.<sup>6</sup> In the USA, more than half of the population are obese or overweight<sup>7</sup> with the prevalence of obesity doubling during the period from 1980 to 1999.<sup>8</sup> In China, there has been an increase, from 20.0% in 1992 to 29.9% in 2002, in overweight individuals.<sup>9, 10</sup> France also followed this trend; in 2003, 30% of the French adult population were overweight and 11% obese<sup>11</sup> compared to the 1997 figures of 23% and 7%, respectively.<sup>12</sup>

Various dietary, genetic and environmental factors are believed to be responsible for the aetiology of obesity. Within the last few decades, several studies have investigated a possible link between obesity and the renin-angiotensin system (RAS), a system involved in body fluid and cardiovascular homeostasis.<sup>13</sup> For example, insulin, a key factor in the control of food intake and body weight<sup>14</sup>, has been shown to stimulate angiotensinogen (AGT)

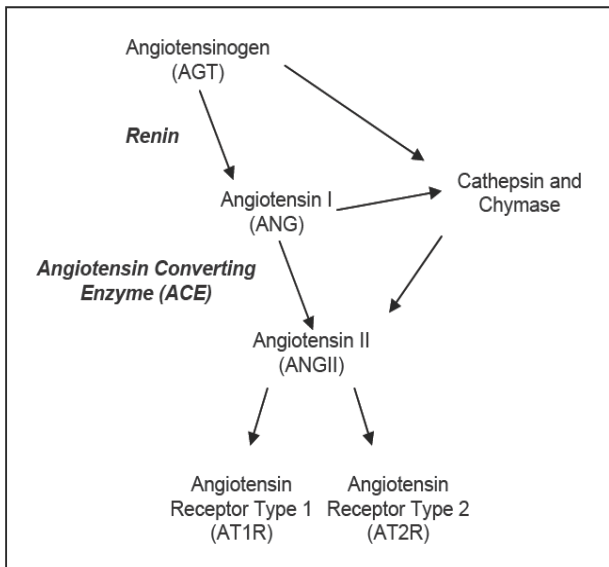
mRNA in human adipocytes<sup>15</sup> and 3T3-L1 adipocytes, adipocytes derived from Swiss albino mice.<sup>16</sup> Although there is some contradictory evidence, possibly due to differences between the species and/or models examined, there is still a considerable amount of data from both animal and human experiments suggesting that the RAS is involved in the regulation of body fat and is therefore an important factor in obesity.

## The RAS

In the classical RAS, AGT, a protein principally synthesised in the liver, is converted to angiotensin I (ANG I) by the action of renin, an enzyme mainly released from the kidney. ANG I reaches the lungs via the circulation, where it is converted into angiotensin II (ANG II) by angiotensin-converting enzyme (ACE). ANG II acts on the body through angiotensin receptors type 1 and type 2 (AT1R and AT2R) to increase blood pressure, thirst and fluid retention.<sup>13, 17-20</sup> All of the components of the RAS have been

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identified in adipose tissue.<sup>21-24</sup> Cathepsin and chymase, also found in human adipocytes, can catalyse the conversion of ANG I to ANG II.<sup>24-26</sup> It is unclear whether the production of ANG II in adipose tissue is due to the classical RAS system (ACE), the alternative enzymes or a combination of the two. Overall, the data clearly demonstrate the presence of a fully functional RAS in animal and human adipose tissue.<sup>26-29</sup> See Figure 1.



**Figure 1.** The renin angiotensin system; present in adipose tissue.

### Correlation of components of the RAS and body fat

Numerous reports have shown that components of the RAS are correlated with body fat. During early development and prior to there being a difference in body weight, obese Zucker rats had increased body fat and secreted significantly more AGT protein from adipose tissue than their lean littermates.<sup>30</sup> Evidence showing that secretion of AGT was not solely related to adipocyte hypertrophy suggested that locally produced AGT was involved in the development of adipose tissue. In mice, a high-fat diet for 20 weeks resulted in increased AGT transcription in abdominal fat (along with greater weight gain), suggesting that the level of AGT changed with the weight of the mice<sup>[31]</sup>. In rats that became obese on a moderately high fat diet, compared to rats that were obesity resistant or that were fed a low fat diet, AGT mRNA in retroperitoneal adipose tissue and AGT in the circulation were increased.<sup>32</sup> Increased levels of RAS components and activity have been reported in obese humans<sup>33-35</sup> and furthermore, these levels declined during weight loss.<sup>35, 36</sup> Subcutaneous and omental adipose tissue AGT mRNA was positively correlated with waist-hip ratio in overweight subjects<sup>37</sup> and polymorphism of the ACE gene has been linked to the incidence of obesity and alterations of body mass index (BMI).<sup>38</sup> However, there is some contradictory evidence. For example, it has been reported that AGT mRNA was decreased in the adipose tissue of obese compared to lean Zucker rats, yellow A<sup>vy</sup> mice, and the relationship between adipose tissue and AGT mRNA was variable in humans.<sup>16</sup> Interestingly, it has been reported that although relative to lean women, obese women had decreased expression of AGT in adipose tissue, they had

increased AGT in the circulation.<sup>36</sup> The existence of a negative feedback loop was suggested such that AGT expression in adipose tissue was decreased when plasma levels become high. Although there are some exceptions, there is evidence to suggest a positive correlation between levels of AGT or other components of the RAS and the level of body fat.

### Role of the RAS in adipocyte differentiation and lipogenesis

Adipocytes are crucial to energy balance. Adipose tissue mass is determined by adipocyte differentiation (the formation of new adipocytes from precursor cells) and adipocyte hypertrophy (increase in adipocyte cell size due to fat storage). The RAS has been implicated as a trophic factor in the differentiation of adipocytes. ANG II as well as other components of the RAS are elevated in differentiated cells.<sup>39</sup> In quiescent preadipocytes harvested from human adipose tissue, ANG II stimulated the progression of the cell cycle. This was blocked by losartan, an AT1R antagonist.<sup>22</sup>

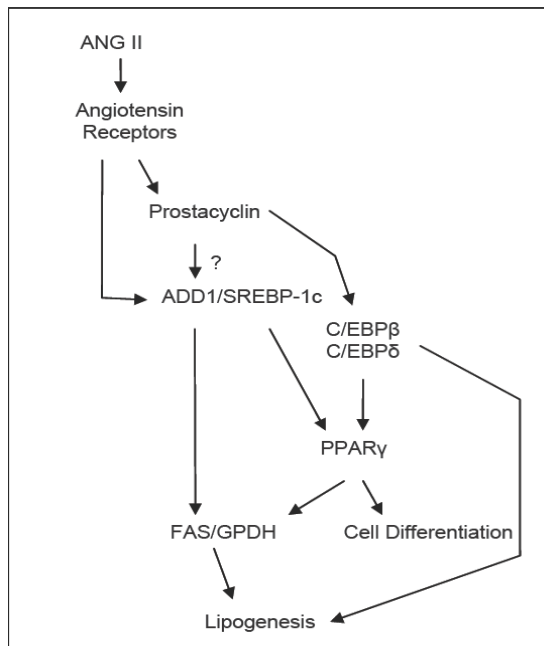
Evidence suggests that ANG II increases lipogenesis and the triglyceride content of adipocytes<sup>40</sup> (i.e., 3T3-L1 adipocytes). In regard to the mechanism by which ANG II increased the triglyceride content of the cells, it was observed that ANG II increased the activity of enzymes involved in lipogenesis, fatty acid synthase (FAS), an enzyme that catalyses the synthesis of palmitate from acetyl CoA and malonyl CoA in the presence of NADPH<sup>41</sup>, and glycerol-3-phosphate dehydrogenase (GPDH), the rate-limiting enzyme for triglyceride synthesis in adipose tissue. The increased activities of FAS and GPDH were blocked by antagonists of either AT1R or AT2R. Additionally, in experiments with human adipocytes, as in 3T3-L1 cells, ANG II increased both FAS and GPDH activities.

Some evidence suggests that the influence of ANG II on differentiation of preadipocytes to adipocytes and lipogenesis are mediated through its stimulation of peroxisome proliferators-activated receptor (PPAR)  $\gamma$ <sup>42</sup>, via pathways that includes a number of different transcription factors and/or prostacyclin (PGI<sub>2</sub>).<sup>43-46</sup> See Figure 2.

PGI<sub>2</sub> is the major metabolite of arachidonic acid in adipose tissue. It has been shown to cause adipose cell differentiation in isolated adipocytes and adipose tissue fragments derived from rats, mice and humans.<sup>47, 48</sup> Interestingly, ANG II, via AT2R, increased PGI<sub>2</sub> production in adipocytes but not preadipocytes; once produced, however, the PGI<sub>2</sub> stimulated differentiation of the preadipocytes to adipocytes<sup>44, 47</sup> PGI<sub>2</sub> regulates expression of early transcription factors of the family CCAAT/enhancer binding proteins, i.e., C/EBP $\beta$  and C/EBP $\delta$ .<sup>49</sup>

ANG II has been shown to cause the up-regulation of other transcription factors involved in adipocyte differentiation, e.g., adipocyte differentiation determination-dependent factor 1 (ADD1), sterol response element-binding protein 1 (SREBP1).<sup>50-53</sup>

PPARs are members of the nuclear hormone receptor superfamily, a group of nuclear proteins that mediate the effects of small lipophilic compounds on DNA transcription.<sup>54</sup> PPAR $\gamma$  is necessary and sufficient to promote fat cell differentiation and lipid accumulation.<sup>55</sup> PPAR $\alpha$ ,



**Figure 2.** Possible pathways by which angiotensin II stimulates cell differentiation and lipogenesis (ADD1, Adipocyte Differentiation Determination-dependent factor 1; ANG II, Angiotensin II; C/EBP, CCAAT Enhancer Binding Protein; FAS, Fatty Acid Synthase; GPDH, Glycerol 3-phosphate Dehydrogenase; PPAR, Peroxisome Proliferator Activated Receptor; SREBP-1c, Sterol Regulatory Element Binding Protein 1c).

most abundant in liver, mediates the regulation of enzymes involved in fatty acid oxidation (e.g., carnitine palmitoyl transferase (CPT) -1, acyl CoA oxidase (ACO)) while PPAR $\gamma$ , most abundant in adipose tissue, regulates enzymes involved in differentiation (e.g., GPDH), lipogenesis (e.g., acetyl CoA carboxylase (ACC), FAS, glycerol-3 phosphate acyl transferase (GPAT)) and in fatty acid uptake and trapping (e.g., lipoprotein lipase (LPL)), fatty acid transport protein CD 36).<sup>56</sup> PPAR $\gamma$  agonists (e.g., thiazolidinedione) stimulate adipogenesis and, in general, increase body fat.<sup>57-60</sup> Treatment of obese Zucker rats with irbesartan, an AT1R antagonist, reduced PPAR $\gamma$  and adipocyte differentiation<sup>61</sup>, a result consistent with the adipogenic effect of ANG II and PPAR $\gamma$ . However, as will be described below, other evidence suggests that irbesartan, as well as some other AT1R antagonists, e.g., telmisartan, are PPAR $\gamma$  partial agonists.

In spite of the evidence indicating that ANG II stimulates adipogenesis and lipogenesis, a contrary view of the role of ANG II has been proposed. Evidence based on work using human adipocytes suggested that ANG II was increased during adipogenesis and that ANG II, working via AT1 receptors, inhibited adipogenic differentiation while blockade of AT1R causing enhanced adipogenesis. It was proposed that the influence of ANG II was to inhibit the recruitment and differentiation of adipocytes<sup>62, 63</sup> while RAS antagonists promoted the recruitment and differentiation of adipocytes.<sup>64</sup> Thus, ANG II would cause an increase in fat cell size while antagonists would do the opposite. Differences in the influence of the RAS on hu-

man and animal adipogenesis have been cited as the explanation for the contradictory evidence. However, observations by Crandall<sup>22</sup> and Jones<sup>65</sup> using human adipose cells seem to question this interpretation. Furthermore, evidence obtained during *in vivo* microdialysis of human adipose tissue<sup>66, 67</sup> suggested that ANG II inhibited lipolysis. Clearly, further work is required to clarify the mechanisms responsible for the divergent results.

### Relationship between the RAS, body fat accumulation and body weight

Evidence from experiments involving genetically manipulated animals or from experiments in which the activity of the RAS was blocked suggests that the activity of the RAS is directly related to accumulation of body fat. For example, AGT-deficient mice (AGT-KO) gained less weight than their wild-type (WT) counterparts despite similar food intakes. The difference in body weights was attributed to hypotrophy of adipocytes and a corresponding decrease in adipose tissue mass. The AGT-KO and WT mice appeared to have similar metabolic rates but the AGT-KO mice displayed increased locomotor activity. Decreased lipogenesis and increased motor activity was thought to be responsible for the decrease in fat mass.<sup>68</sup>

AT2R-deficient mice (AT2R<sup>-/-</sup>) gained less weight than their wild-type (WT) counterparts when maintained on a high fat diet.<sup>69</sup> The reduced body weight gain of the AT2R-deficient mice was attributed to a lower food intake and increased energy expenditure; fat cell mass was unchanged, hypotrophy of adipocytes was accompanied by increased cell number. The AT2R-deficient mice had increased whole-body lipid oxidation associated with a decrease in FAS activity, PPAR $\gamma$  and in genes associated with the uptake and storage of fat (LPL, fatty acid transport protein aP2 (a protein involved in fatty acid uptake by adipocytes), CD36). Increased  $\beta$ -oxidation in muscle was suggested by increased PPAR $\alpha$ , fatty acid translocase, CPT-1 and uncoupling protein (UCP)-3. These results are consistent with the evidence showing that the ANG II-induced increase in FAS is mediated via AT2R in mice.<sup>40, 53</sup>

In contrast, transgenic mice that over-expressed AGT were shown to have a greater body weight than their control littermates. The difference in body weights was primarily due to a 2-fold increase in body fat mass achieved by adipocyte hypertrophy accompanied by hypoplasia of the adipose cells. The increased fat mass was associated with increased FAS activity and blood AGT levels. Food intake and motor activity of the transgenic mice were similar to those in the WT mice.<sup>70</sup>

The strongest evidence for a physiological role of the RAS in control of body fat comes from studies in which antagonists of the RAS have been administered. Although there have been some exceptions<sup>71-73</sup>, administration of an ACE inhibitor or a RAS antagonist has generally been shown to reduce body weight and/or body weight gain. Evidence has been obtained in experiments using spontaneously hypertensive rats, SHR<sup>74</sup>, Zucker obese rats<sup>75</sup>, and humans.<sup>76</sup> In addition to the decrease in body weight observed in the obese Zucker rats, ACE inhibition increased insulin-mediated glucose transport activity and GLUT 4 protein in muscle.<sup>75</sup> In rats fed a high fat diet<sup>77</sup>,

administration of telmisartan but not valsartan, decreased body weight and body fat (increased cell number and decreased cell size). The decreased body fat caused by telmisartan was due to increased energy expenditure; neither food intake nor motor activity were altered. Also, telmisartan increased expression of genes involved in mitochondrial function and energy metabolism. The explanation offered for the difference between telmisartan and valsartan was that although both telmisartan and valsartan are AT1R antagonists, only the telmisartan has partial PPAR $\gamma$  agonist activity. In mice maintained on a high fat diet, similar results were reported<sup>78</sup>, i.e., telmisartan decreased visceral adiposity and body weight without altering food intake or locomotor activity. The telmisartan treatment increased UCP1 mRNA, a marker of energy expenditure, in brown adipose tissue, and decreased triglyceride uptake into white adipose tissue, liver and skeletal muscle. Furthermore, telmisartan treatment decreased carbohydrate and increased fat metabolism.

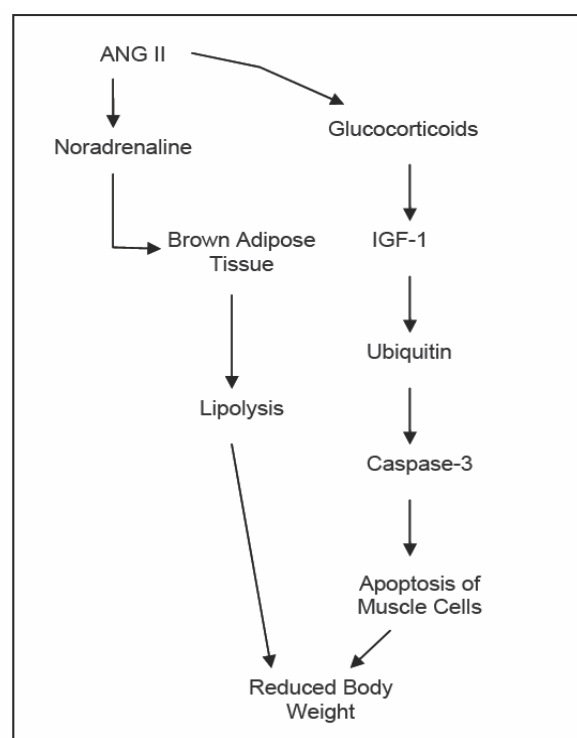
In addition to the abovementioned changes, the telmisartan treatment increased adiponectin mRNA in white adipose tissue. Increased adiponectin concentration has been observed with some ACE inhibitors, e.g., enalapril, and other AT1R blockers, e.g., irbesartan, losartan, candesartan.<sup>72, 79</sup> Adiponectin, an adipocytokine synthesized in white adipocytes and induced during differentiation, is an important signalling molecule between muscle and fat. Adiponectin levels are inversely related to BMI and insulin sensitivity.<sup>79-81</sup> Treatment with adiponectin stimulates UCP-1 mRNA in brown adipose tissue, consistent with a thermogenic action and increase in body temperature.<sup>82, 83</sup> Administration of adiponectin into the cerebrospinal fluid of mice increased Fos in the paraventricular nucleus of the hypothalamus, a key brain nucleus in energy homeostasis.<sup>83</sup> Food intake is not altered by adiponectin and decreased body weight is due to increased fatty acid oxidation and energy utilisation<sup>82-84</sup> via activation of AMP kinase.<sup>85</sup> Thus, although PPAR $\gamma$  is integral to adipocyte differentiation and lipogenesis, it also regulates adiponectin secretion.<sup>86</sup> Therefore, it is conceivable that the decrease in body weight caused by telmisartan is a consequence of the stimulation of adiponectin secretion by PPAR $\gamma$ .<sup>87-89</sup> Clearly, the contradictory roles proposed for PPAR $\gamma$  (e.g., stimulating mechanisms that result in an increase or a decrease body fat), suggest that explanation for the decrease in body weight caused by telmisartan is not straight-forward and, presumably involves the difference in the conformational changes and consequences of partial agonists in contrast to those of full agonists of PPAR $\gamma$ .<sup>90, 91</sup> Differential stimulation of PPAR $\gamma$  subtypes by different agonists/partial agonists may also be involved.<sup>92</sup>

Briefly, the RAS seems to affect body composition and weight regulation primarily via its influence on: (1) differentiation of pre-adipocytes to mature adipocytes, (2) promotion of transcription of the key lipogenic enzymes (e.g., FAS and GPDH), resulting in increased fatty acid synthesis and triglyceride storage, (3) inhibition of lipolysis, and (4) inhibition of adiponectin, via AT1R.<sup>79, 93</sup> Some evidence suggests that interference with ANG II production and/or action primarily reduces abdominal fat, the fat implicated in insulin resistance and diabetes.<sup>4, 94, 95</sup>

Interestingly, in addition to their well documented antioxidant effects, the naturally occurring polyphenols in tea have been shown to have ACE inhibitory activity.<sup>96</sup> In mice and rats maintained on high fat diets, green tea, green tea extracts or isolated catechin constituents of tea, in particular epicatechin gallate (EGCG), have been found to reduce adipose tissue mass and body weight<sup>97-99</sup> and to increase endurance, metabolic rate and  $\beta$ -oxidation in muscle and/or liver.<sup>100</sup> The decrease in body fat was associated with decreased expression of genes involved fatty acid and lipid metabolism (stearoyl-CoA desaturase (SCD)-1, GPAT, FAS, ACC-1) and the transcription factor, SREBP-1.<sup>97</sup> In vitro, EGCG inhibited adipocyte differentiation.<sup>97</sup> In human studies, drinking tea has been shown to increase energy expenditure and fat oxidation<sup>101</sup> and reduce body fat<sup>102-104</sup>, although not in all studies.<sup>105, 106</sup>

### Decreased body weight caused by infusion of ANG II: A paradox

Despite the overwhelming evidence that ANG II stimulates the synthesis and storage of fat and the observation that reduction or elimination of the RAS by pharmacological or genetic manipulation causes a decrease in body fat, ANG II administration has been shown clearly to cause weight loss in animals. Infusion of ANG II peripherally or into the brain of rats causes decreased body weight compared to saline-infused or pair-fed animals.<sup>107-111</sup> The decreased body weight has been observed to occur with or without decreased food intake and, therefore, has been attributed to increased energy expenditure (e.g., increased thermogenesis). There is some evidence that the increased energy expenditure is due to an ANG II-induced activation of the sympathetic nervous system and



**Figure 3.** Possible pathways by which angiotensin II causes decreased body weight (ANG II, Angiotensin II; IGF-1, Insulin-like Growth Factor 1)

release of noradrenaline<sup>107-109</sup>, independent of ANG II-induced hypertension.<sup>110, 111</sup> The increased activation of the sympathetic nervous system by ANG II is associated with lipolysis and the loss of body fat. Lipolysis and decreased adipocyte size has been shown to occur in subcutaneous and visceral fat.<sup>112</sup> The ANG II-induced lipolysis was blocked by losartan as well as by an adrenergic blocker.

ANG II-induced loss of body weight, however, has been attributed primarily to muscle wasting due to enhanced protein degradation. In this regard, ANG II stimulates glucocorticoid hormones that act to decrease insulin-like growth factor (IGF)-1 in blood and IGF-1 mRNA in skeletal muscle.<sup>113, 114</sup> Subsequently, via an ubiquitin-proteasome proteolytic pathway, there is an increase in caspase-3 which leads to apoptosis of the muscle cells.<sup>115</sup> See Figure 3.

Another possible mechanism by which ANG II could influence muscle wasting is through its influence on leptin, a cytokine synthesised in fat. Leptin is upregulated in obesity and promotes weight loss by decreasing food intake and increasing energy expenditure. In addition, leptin has effects in skeletal muscle, including an increase in fatty acid oxidation and decrease in muscle protein synthesis.<sup>80, 116</sup> Studies have shown that ANG II increases both leptin secretion from human adipocytes<sup>117</sup> and expression of the leptin (*ob*) gene in both human and 3T3-L1 adipocytes.<sup>40</sup> Thus, it is possible that the effects of ANG II on muscle degradation are mediated by leptin, however, ANG II has been shown to decrease muscle protein synthesis *in vitro*.<sup>118, 119</sup>

In a model of cancer cachexia, in which tumour growth was associated with decreased food intake and body weight and muscle wasting, antagonists of the RAS have been shown to decrease the loss of body weight and the loss of muscle mass and reduce tumour growth.<sup>119</sup>

One explanation for the paradoxical influence of infused ANG II, either systemically or into the brain, is that pathways not typically involved in the regulation of body weight are stimulated. That is, under normal circumstances, the physiological level of ANG II achieved in adipose tissue subsequent to its being stimulated, e.g., by insulin, will cause cell-differentiation and lipogenesis. In contrast, infused ANG II enhances the activity of systems typically involved in body temperature regulation, e.g., sympathetic nervous system, and in the response to stress, e.g., glucocorticoids. Thus, both body fat and body muscle are decreased in spite of any ANG II-induced adipogenesis. Interestingly, the body can adapt to the infused ANG II and it has been shown that after one week of ANG II treatment, body weight was decreased, however, after two weeks of treatment, the body weight of ANG II-treated rats was similar to that of control rats and lipogenesis in liver was increased in the ANG II-treated animals.<sup>120</sup>

### Conclusion

The presence of the major RAS components in adipose tissue, effect of ANG II on fat cell growth, differentiation, and synthesis, and the uptake and storage of fatty acids and triglycerides point to the importance of the RAS in body weight control. The evidence showing the ability of

compounds, both pharmacological and natural, that block the production of ANG II to decrease body fat, and that the loss of body fat caused by these treatments tend to occur in abdominal fat depots, indicate that further research into the natural and synthetic inhibitors of the RAS is required. The conflicting data, produced primarily in experiments in which ANG II is infused into the whole animal but also in experiments in which antagonists of the RAS are used, again points to the need for further research into systems and mechanisms influenced by the RAS and antagonists of the RAS. Research into understanding of the adipose tissue RAS and how it is influenced by the various treatments is crucial. At present, however, it seems clear that antagonists of the RAS, both natural and pharmacological, have the potential to become vital to the treatment of the ever increasing problem of obesity and insulin resistance.

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