Opposing tissue-specific roles of angiotensin in the pathogenesis of obesity, and implications for obesity-related hypertension

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Littlejohn NK, Grobe JL. Opposing tissue-specific roles of angiotensin in the pathogenesis of obesity, and implications for obesity-related hypertension. Am J Physiol Regul Integr Comp Physiol 309: R1463–R1473, 2015. First published October 21, 2015; doi:10.1152/ajpregu.00224.2015.—Metabolic disease, specifically obesity, has now become the greatest challenge to improving cardiovascular health. The renin-angiotensin system (RAS) exists as both a circulating hormone system and as a local paracrine signaling mechanism within various tissues including the brain, kidney, and adipose, and this system is strongly implicated in cardiovascular health and disease. Growing evidence also implicates the RAS in the control of energy balance, supporting the concept that the RAS may be mechanistically involved in the pathogenesis of obesity and obesity hypertension. Here, we review the involvement of the RAS in the entire spectrum of whole organism energy balance mechanisms, including behaviors (food ingestion and spontaneous physical activity) and biological processes (digestive efficiency and both aerobic and nonaerobic resting metabolic rates). We hypothesize that opposing, tissue-specific effects of the RAS to modulate these various components of energy balance can explain the apparently paradoxical results reported by energy-balance studies that involve stimulating, versus disrupting, the RAS. We propose a model in which such opposing and tissue-specific effects of the RAS can explain the failure of simple, global RAS blockade to result in weight loss in humans, and hypothesize that obesity-mediated uncoupling of endogenous metabolic rate control mechanisms can explain the phenomenon of obesity-related hypertension.

angiotensin; energy; hypertension; metabolism; obesity

THE RENIN-ANGIOTENSIN SYSTEM (RAS) is well-recognized for its contributions to cardiovascular control physiology. The RAS exists as a classic, circulating hormone system, but also locally within individual tissue types as a paracrine, autocrine, and even intracrine signaling modality (29, 36, 48). Circulating RAS activity positively correlates with body mass in both human and animal models (7, 20, 31, 34, 38, 82), and weight loss in humans is associated with reduced RAS activity (31, 134). As detailed below, genetic and pharmacological manipulation of components of the RAS in rodents results in altered energy balance and/or sensitivity to weight gain. This is mediated through various combinations of effects on ingestive behavior, digestive efficiency, physical activity, and resting metabolic rate (Table 1), though the actions of the RAS on these contributors to energy balance appear to be site and ligand/receptor specific. Collectively, these findings lead to the hypothesis that the RAS is a critical contributor to the development of obesity and obesity-associated cardiovascular dysfunctions such as hypertension.

Obesity and Obesity-Related Hypertension

According to the American Heart Association’s annual statistical update, 30% of children and 70% of adults in the United States are now overweight or obese (90). Simultaneously, roughly 33% of Americans experience hypertension, and there is gross overlap between these two groups (90). Evidence tends to support a causal role for obesity in the pathogenesis of hypertension, as weight loss interventions such as chronic orlistat use can reduce blood pressure (118). Despite substantial investments by various governmental, industrial, and nonprofit organizations, the cardiovascular research community is poised to fall far short of the highly publicized American Heart Association 2020 Impact Goal (to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%) (78), almost exclusively due to obesity and related metabolic disease (61). Thus it is clear that improving cardiovascular health depends on improving metabolic health.
### Table 1. Examples of the effects of genetic and pharmacological targeting of RAS components on metabolic functions

<table>
<thead>
<tr>
<th>Targeted RAS Component</th>
<th>Manipulation (Ref)</th>
<th>Model</th>
<th>Weight Gain or Adiposity</th>
<th>Energy Intake</th>
<th>Energy Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>Global knockout (127)</td>
<td>C57BL/6 mouse</td>
<td>↓</td>
<td>**</td>
<td>⬆</td>
</tr>
<tr>
<td>Angiotensinogen</td>
<td>Global knockout (83)</td>
<td>ICR-CD1 mouse</td>
<td>↓</td>
<td>**</td>
<td>??</td>
</tr>
<tr>
<td>AT1/AT1A receptor</td>
<td>Global knockout (65)</td>
<td>C57BL/6 mouse</td>
<td>↓</td>
<td>⬆</td>
<td>↓</td>
</tr>
<tr>
<td>AT2 receptor</td>
<td>Global knockout (147)</td>
<td>C57BL/6 mouse</td>
<td>↓</td>
<td>⬆</td>
<td>↓</td>
</tr>
<tr>
<td>Mas receptor</td>
<td>Global knockout (114)</td>
<td>FVB/N mouse</td>
<td>↓</td>
<td>↔</td>
<td>?</td>
</tr>
<tr>
<td>Peptides</td>
<td>Subcutaneous ANG II</td>
<td>SD rat (infusion (16))</td>
<td>↓</td>
<td>↔</td>
<td>?</td>
</tr>
<tr>
<td>Global transgenic (47)</td>
<td>C57BL/6 mouse</td>
<td>↑</td>
<td>??</td>
<td>??</td>
<td>?</td>
</tr>
<tr>
<td>ICV ANG II infusion (104)</td>
<td>SD rat (young)</td>
<td>↓</td>
<td>↔</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Brain-specific transgenic (46)</td>
<td>C57BL/6 mouse</td>
<td>↓</td>
<td>↔</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>DOCA-salt (45)</td>
<td>C57BL/6 mouse</td>
<td>↓</td>
<td>↔</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

???, Not determined; ↑, increased; ↓, decreased; ++, no change; (↑ ?), possible increase; (↓ ?), possible decrease; (++?), possible no change. ICV, intracerebroventricular.

### Obesity as a Chronic Energy Imbalance

Obesity can be conceptualized as the consequence of a chronic imbalance between energy input and output. At the population level, it has been estimated that as little as a 7.2 kcal/day imbalance between energy input and output is sufficient to account for the current human obesity epidemic in the United States (51). When compared with a standard 2,000 kcal/day diet, 7.2 kcal/day represents <0.5% of total daily energy turnover and is the equivalent to ingesting one teaspoon of ketchup or roughly four Tic Tac candies, or failure to perform seven sit-up exercises per day. While this estimate represents a gross oversimplification that assumes no compensatory changes in various systems during sustained weight gain, an excess 7.2 kcal/day accumulation in the body over 40 years would equate to 26 to 58 lbs. (11 to 26 kg) if converted directly to lean (1 g/4 kcal) or fat (1 g/9 kcal) tissue. Such gains are in line with observed excess weight gain in adults in the United States (71). Regardless of the exact precision of the 7.2 kcal/day estimate, however, the very small magnitude of the gap highlights the sensitivity and reliability of the physiological systems in place to control energy balance. Thus it follows that relatively small adjustments in any aspect of energy balance may represent favorable means of correcting obesity. We hypothesize that the RAS is integrally involved in the regulation of all aspects of energy balance, but also that this control is mediated through complex, opposing, and tissue-specific actions.

### RAS in Energy Balance: Behaviors Versus Biological Processes

At the most basic level, obesity is due to an imbalance between energy “input” and “output,” which includes behavioral mechanisms such as food intake and physical activity and biological mechanisms such as gastrointestinal absorption efficiency and resting metabolism. Energy homeostasis at the whole animal level is achieved through modulation of both “input” and “output,” though this is often inappropriately oversimplified and paraphrased as merely adjusting “diet” and “exercise.” In subsections below, we detail the site-, ligand-, and receptor-specific effects of the RAS upon individual components of energy balance.

### Food Intake

Caloric intake (food ingestion) is unquestionably a major contributor to energy balance, as this behavior precedes the expenditure of the calories in question and maximally limits the energy to be balanced. Not surprisingly, the modulation of intake behavior (“dieting” behavior and pharmacological appetite suppressants) are frequently the first approaches used to combat obesity. As of late 2015, there are four FDA-approved, appetite-suppressant drugs available in the United States. Qsymia (phentermine/topiramate) is a combination of a phenethylamine (similar to methamphetamine) and an anticonvulsant that was approved in 2012, though postapproval cardiovascular safety trials are underway. Belviq (lorcaserin) is a serotonin 5-HT2C agonist also approved...
in 2012, though it is considered a Schedule IV drug by the United States Drug Enforcement Administration (DEA) because of hallucinogenic properties. Contrave (bupropion/naltrexone) is a combination norepinephrine-dopamine reuptake inhibitor-nicotinic receptor antagonist and opioid receptor antagonist that was approved in 2014, and its postapproval safety evaluation is ongoing. Saxenda/Victoza (liraglutide) is a glucagon-like peptide-1 receptor agonist approved in 2014, and its postapproval safety evaluation is ongoing. Saxenda/Victoza (liraglutide) is a glucagon-like peptide-1 receptor agonist that was approved in 2014, and its complete mechanism is not yet clearly documented. Collectively, over the last few years this array of new appetite-suppressant compounds has hit the American market, and the medical community is bracing to see if these new compounds are sufficiently efficacious to risk various potential side effects.

The RAS is known to modulate food intake behavior. Infusion of exogenous angiotensin II either peripherally or centrally results in reduced food intake, presumably through actions within the hypothalamus. Cassis et al. (17) found that in rats, chronic peripheral infusion of angiotensin reduced body mass primarily through suppression of food intake. Similarly de Kloet et al. (26) found that in rats, intracerebroventricular (ICV) infusion of angiotensin reduced food intake, and this was associated with increased expression of anorexie hormones in the hypothalamus. Using FVB mice, Yoshida et al. (146) found that peripheral and central delivery of angiotensin both caused reduced food intake and suppressed orexigenic gene expression in the hypothalamus. Jointly, these findings indicate an important role of angiotensin actions to suppress food consumption both peripherally and centrally.

The involvement of various angiotensin II receptor subtypes in the control of ingestive behavior is complicated. Ohnata et al. (95) examined the involvement of AT1 and AT2 receptors in the anorexic behavior induced by ICV delivery of angiotensin II. This group determined that genetic or pharmacological inhibition of the AT2 receptor abolished the anorexic effect, whereas manipulation of the AT1 receptor had much smaller effects (95). New colocalization studies from de Kloet et al. (28) have documented expression of AT2 receptors with GABA- and acetylcholine-synthetic enzymes in brain regions well recognized as contributing to ingestive behavior, including the nucleus of the solitary tract, the area postrema, and the median preoptic nucleus. Thus it appears that AT2 receptors may play a dominant role in the control of food intake by the RAS within the brain. Conversely, de Kloet et al. (27) identified that deletion of the AT1 receptors within the paraventricular nucleus increased food intake. However, various studies have implicated AT1 receptor subtypes and its second-messenger systems in the control of sodium intake behavior (23, 24), and therefore future studies must be carefully designed to delineate sodium seeking behavior versus energy seeking behavior.

Digestive Efficiency

Total caloric intake is bounded by caloric ingestion (a behavior), but this value is scaled from 0 to 100% by the modulation of digestive efficiency (a biological function). Various pathological states (e.g., diarrhea, gastric motility disorders, or malabsorption disorders), medical interventions (e.g., various bariatric surgeries), and dietary components (e.g., fiber, sodium, carbohydrates, fats) modulate digestive efficiency. Furthermore, the gut microbiota also majorly contributes to the regulation of digestive efficiency (30, 66, 128). It follows that investigations into the control of energy balance in vivo require assessments of digestive efficiency to fully account for caloric input, and that targeting digestive efficiency may prove effective as an antiobesity therapy. Indeed, the longest-running FDA-approved antiobesity drug available in the United States is orlistat (tetrahydrolipstatin), approved for prescription use in 1999 and now sold over the counter as Alli. The molecular mechanism of orlistat’s efficacy is to reduce digestive efficiency by inhibiting pancreatic lipase activity in the gastrointestinal tract. It has been suggested, however, that the major mechanism of weight loss in human users is actually the learned avoidance of fatty foods. This behavioral modification (changes in food choices away from fatty foods toward predominantly carbohydrate-laden foods to avoid unpleasant side effects) may also explain the limited long-term efficacy of orlistat, as roughly half of initial weight lost with the use of this compound is regained within a few years (130).

As Garg et al. (37) recently reviewed, virtually all components of the RAS are expressed throughout the gastrointestinal tract in rodents as well as humans. Angiotensinogen is expressed in the small intestine, colon, and stomach (13, 52, 139); renin is expressed in intestines and colon (57, 117); angiotensin-converting enzymes (ACE) 1 and 2 are expressed in the intestine and colon (10, 53, 54, 57, 129); and angiotensin receptors AT1 and AT2 are expressed in the intestine (33, 121, 122). It is interesting to note that the highest human tissue concentrations of ACE and ACE2 expression are in the gastrointestinal tract (54, 129).

Functionally, manipulation of the RAS can have large effects on digestive efficiency. Takahashi et al. (127) demonstrated that mice deficient for renin exhibit reduced digestive efficiency that correlated with reduced lipase/collipase expression in the pancreas and decreased weight gain during high-fat feeding. In addition, our group recently examined the effect of dietary sodium on weight gain during high-fat feeding in wild-type mice (135). Weight gain in C57BL/6J mice with a 45% high-fat diet was suppressed in a dose-dependent manner by dietary sodium. This was not mediated through any changes in food intake, physical activity, or resting metabolism but instead appeared to be completely dependent on the suppression of digestive efficiency. Chronic infusion (replacement) of angiotensin II reversed the digestive efficiency-suppressing effect of high dietary sodium, and the effect was reconstituted specifically by antagonism of AT2 (not AT1) receptors. Finally, digestive efficiency was suppressed in mice lacking AT2 receptors on either the FVB/NCtrl or C57BL/6J backgrounds. Thus an increased appreciation for the role of the RAS in the control of digestive efficiency may lead to the development of novel therapeutics. Furthermore, involvement of the RAS in its control should bring increased attention and scrutiny of digestive efficiency (a major and often-ignored regulator of energy input) to studies of energy balance.

Physical Activity

A common strategy to induce weight loss is to increase energy expenditure via exercising. Physical activity has numer-
ous beneficial effects including reducing adiposity and the risk for cardiovascular disease. After initial weight loss, physical activity is considered necessary for weight maintenance. Although most overweight or obese individuals are successful in losing weight through diet and exercise behaviors, studies have shown that only approximately 20% of these individuals maintain the weight loss for at least 1 yr (84, 138). A major problem in showing the benefits of exercise is the lack of long-term adherence (63). Animal models have shown that exercise reduces energy intake and increases energy expenditure (79, 123). However, in normal weight humans exercise causes compensatory increases in ingestive behaviors (58). Therefore, it is unclear how exercise influences food intake and preference or energy expenditure. Furthermore, there is still debate on the beneficial effects of different types of exercise such as aerobic versus resistance training (80). Thus approaches to increase adherence to exercise regimens and increased understanding of the costs and benefits of specific types of exercise are needed to improve the maintenance of weight loss at the population level.

Massiera et al. (82, 83) observed that mice harboring a null allele for angiotensinogen have increased locomotor activity, and that mice with adipose-specific manipulation of angiotensinogen also exhibit altered spontaneous locomotor activity. Therefore, the RAS appears to modulate locomotor activity; however, further studies are needed to better understand this effect. For example, other genetic or pharmacological manipulations of the RAS have not been reported to exhibit significant effects on physical activity. Rodents with global ACE deficiency, pharmacological blockade of ACE or AT1R, or angiotensin II treatment have not been linked to changes in locomotor activity (15, 62, 65, 106, 112). In contrast, Takada et al. (126) found that olmesartan treatment improved exercise capacity in mice fed a high-fat diet (126). Thus control of spontaneous locomotor activity by the RAS is possible, but the nuances of this mechanism are unclear.

Interestingly, any interaction between physical activity and the RAS appears to be bidirectional because exercise can alter the RAS. Gomes-Santos et al. (42) found that exercise training in rats reduced plasma angiotensin II and increased angiotensin-(1–7) levels. In addition to changes in the circulating RAS, rodent studies have shown that chronic exercise can lead to a reduction in brain and cardiac RAS activity (3, 5, 100). Additional studies to clarify whether exercise directly modulates the RAS versus whether this modulation is secondary to improved cardiovascular or metabolic control and reduced adiposity are warranted.

Resting Metabolism

Just as food consumption behavior is only one component of energy input, exercise behavior is only one component of energy expenditure. A large fraction of the calories expended by endothermic organisms is spent in the form of resting metabolic rate (RMR). Depending on the equation used to estimate RMR [an estimate of basal metabolic rate (BMR)] and the level of physical activity of the subject (i.e., extreme athlete versus sedentary), RMR accounts for between 60 and >90% of the total energy expenditure (75, 85, 111). Thus this biological controller of energy expenditure represents yet another potential therapeutic target for obesity. Debatably the single most potent antiobesity drug ever used clinically was 2,4-dinitrophenol (DNP). This compound is a mitochondrial proton ionophore, acting as an artificial uncoupling protein to destroy the proton gradient across the inner membrane of mitochondria (125). As cells scramble to utilize available fuel sources to rebuild the proton gradient, energy is lost in the form of heat. The drug indiscriminately affects all cell types and exhibits highly undesirable pharmacokinetic properties that can lead to cataracts and even death. The clinical use of DNP has a fascinating history, and it has the dubious honor of helping to precipitate the passage of the United States Federal Food, Drug and Cosmetic Act of 1938, which gave the FDA its legal powers to ban dangerous drugs such as DNP (49). Recent studies using oral, extended-release formulations of DNP have demonstrated the utility of this compound (presumably through its actions to increase RMR) to protect the liver of rats from nonalcoholic fatty liver disease (101). Collectively, the previous use of DNP in humans and its beneficial effects in various disease models serve as potent proof-of-principle demonstrations that increasing RMR represents a robust method to combat obesity and other metabolic diseases. We simply need safer drugs, which will come from a deeper understanding of the biological controllers of RMR.

Contributions of the RAS to the control of RMR have been demonstrated using genetic and pharmacological methods. Genetic deletion of renin (127), ACE (65), the angiotensin AT1A receptor (70), and the angiotensin AT2 receptor (147) are all associated with increased RMR. Pharmacological inhibition of ACE by captopril (137) or antagonism of AT1A receptors by candesartan (150) both appear to increase RMR. In contrast, genetic disruption of the angiotensin-(1–7) receptor Mas may reduce RMR (114). These studies collectively implicate the RAS in the control of RMR, but as we detail below, there appear to be site-specific and antagonistic effects of the circulating versus tissue versions of the RAS in RMR control.

Notably, most studies investigating a role for RMR energy balance utilize easily accessible, turn-key instrumentation such as oxygen/carbon dioxide respirometry to assess the impact of manipulations upon metabolic rate. Unfortunately these methods rely upon assumptions that are simply untenable, such as a lack of physiological significance of anaerobic (fermentation and nitrogenous) metabolic rates (68, 75, 85). In contrast, other methods such as direct calorimetry, which account for all forms of metabolism, have been also been used to investigate the effects of RAS manipulation upon RMR. Using a custom-built combined direct calorimeter (to measure total RMR) and respirometer (to measure aerobic RMR), we recently documented that genetic disruption of the angiotensin AT2 receptor in FVB/NCrI mice has a robust effect on “nonaerobic” RMR (the difference in results between direct calorimetry and respirometry and logically a measure of the combination of anaerobic processes) (12). Interestingly, we also found that placing wild-type C57BL/6J mice on a 45% high-fat diet (a manipulation previously shown to have stimulatory effects on the circulating and adipose RAS) also has a major suppressive effect on “nonaerobic” RMR (11). Such findings are strikingly similar to those reported from humans by Pittet et al. (102, 103) who used a combined direct calorimeter and respirometer to examine resting metabolism (at rest after a 12-h fast) in lean and obese humans. Studies published by this group in the mid-1970s demonstrated that this “nonaerobic” RMR contrib-
uted roughly 6–12% of the total RMR in lean men and women. Obese women, in comparison, exhibited a complete loss of the “nonaerobic” fraction of total RMR (102). Similarly, Seale and Rumpler (116) demonstrated that total daily energy turnover by respirometric methods underestimated the values calculated using isotope dilution methods by 16% (~425 kcal/day). Together these studies support the concept that respirometry/aerobic RMR is ignoring some pathophysiologically relevant component of energy expenditure in humans (51). Collectively then, it is reasonable to hypothesize that the RAS may contribute to the control of both the aerobic (i.e., processes that can be measured by respirometry) and “nonaerobic” (i.e., processes to which respirometry-based methods are blind) RMR. Improved methodologies to assess both aerobic and “nonaerobic” components of RMR stand to greatly challenge our understanding of the control of resting energy expenditure by the RAS and other hormone systems and may identify “nonaerobic” processes, which are modulated by the RAS, as novel and robust targets for obesity therapeutics (11, 67).

The applicability of studies of RMR in rodents toward our understanding of human RMR control is often questioned. Many studies have illustrated allometric scaling principles across species; for example, it has been demonstrated that the relationship between metabolic rate and organism mass follows a simple positive scaling function across species differing in body mass by a factor of ~10^18 (39). Nonetheless, before the late 2000s, because brown fat had not yet been identified in adult humans, and the function of this tissue in adaptive thermogenic mechanisms in rodents had long been known, it was assumed that resting metabolic processes would function quite differently. Then in 2009 several studies identified functional brown adipose tissue in adult humans following acute cold exposure (22, 133). Subsequently, molecular analyses have aimed to clarify the identity and to understand the function of such “brown/beige/brite” adipose in humans (25, 92, 141). Thus the similarities across species appear to be strong, supporting the continued use of rodent species to dissect the physiology of RMR. Careful consideration must always be given, however, to species-specific differences in thermoregulatory setpoints such as differences in upper- and lower-critical temperatures when translating findings between species (1).

**Opposing, Tissue-Specific Metabolic Regulatory Actions of the RAS**

Descriptions of the metabolic effects of global RAS disruption in rodents have led many to hypothesize that inhibiting the RAS may have beneficial antiobesity effects in humans. Unfortunately, almost no published studies support this concept, as pharmacological RAS interference largely fails to modulate body mass in humans (2, 31, 55). One study examining the effects of ACE inhibitors perindopril, enalapril, losartan, and telmisartan in obese hypertensive human subjects documented significant beneficial effects on body mass index, waist-hip ratio, and body fat percentage (93). Unfortunately, many more studies have failed to document beneficial effects of candesartan (43, 76), valsartan (86), ramipril (8), irbesartan (9), telmisartan (60, 89, 120), and olmesartan (81) in humans.

One hypothesis for the lack of consistent beneficial metabolic effects of indiscriminant RAS inhibition on obesity in human patients is rooted in the established independent (and occasionally opposing) effects of local paracrine tissue versions of the RAS, versus the circulating hormone version of this system. For example, within the brain, all components of the RAS are expressed and regulated independently of the circulating and peripheral tissue versions of this system (48, 73). Delivery of angiotensin II into the brain via ICV cannula results in increased RMR and reduced body mass (26, 104, 105). When animals are treated with chronic delivery of the steroid deoxycorticosterone and maintained on a high dietary sodium regimen (the DOCA-salt model), the brain RAS is stimulated while the circulating RAS is suppressed (115). We previously demonstrated that treating wild-type C57BL/6J mice with DOCA-salt resulted in a robust increase in RMR, and that inhibiting AT1 receptors within the brain attenuated this effect (45). Ongoing work in our lab focuses on the dissociation of controlling blood pressure versus energy balance by the RAS within the brain (19). Similarly, mice with transgenic hyperactivity of the brain RAS (sRA mice) exhibit increased RMR that is correlated with suppressed circulating RAS activity (46). As expected, inhibition of β-adrenergic signaling in sRA mice attenuated RMR, implicating the sympathetic nervous system in the elevated energy expenditure of these animals. Surprisingly, however, we discovered that chronic replacement of circulating angiotensin II levels via subcutaneous infusion also completely normalized RMR of sRA mice. Complementing these findings, Yiannikouris et al. (144, 145) has demonstrated that adipose tissue produces RAS components in sufficient amounts to contribute to blood pressure control. These data together highlight critical, opposing effects of the circulating RAS and local brain RAS in the control of RMR. Perhaps the failure of whole body RAS inhibition to oppose obesity in humans stems from the effects of anti-RAS compounds to simultaneously modulate both stimulatory and inhibitory tissue-specific mechanisms, resulting in no net change in energy balance (Fig. 1). By way of analogy, simultaneously and firmly depressing both the accelerator and brake pedals of an automobile has little net effect on the movement of the vehicle, yet the engine may burn out. In much the same way, indiscriminately activating or suppressing the RAS may have no net effect on energy balance, yet the cardiovascular system may pay a hefty price for such stimulation.

Above we have documented potent, opposing tissue-specific effects of the RAS on components of energy balance. In particular, the effects of the RAS appear to largely oppose the effects of the circulating and adipose RAS. One resulting hypothesis to explain the failure of RAS blockade to reduce body mass in humans focuses on the compartmental distribution of RAS inhibitors in overweight/obese human patients that are examined in such clinical studies. Very few of the RAS inhibitors can cross an intact blood-brain barrier (BBB). Captopril exhibits low permeability through the BBB in normo- tensive Wistar rats (64). Outside the circumventricular organs, lisinopril and benazepril also appear to exhibit low permeability through the BBB, though high doses of perindopril do exhibit a low level of permeability in selected regions (18). Candesartan appears to readily cross the BBB, whereas losartan, irbesartan, and telmisartan all exhibit much lower permeability (21, 40, 41, 132). While losartan exhibits low permeability through the BBB, the active metabolite EXP 3174 may
Fig. 1. Renin-angiotensin system (RAS) and energy balance. Energy balance is maintained by the regulation of behaviors (food ingestion and physical activity) and biological mechanisms (digestive efficiency and resting metabolism), and very small but sustained imbalances mediate human obesity. The RAS has been documented to exhibit modulatory effects on each of these major contributors to energy balance. The complex, simultaneous, and frequently opposing modulation of all of these systems by angiotensin may explain why simple RAS inhibition does not reliably cause weight loss in humans. (−), Inhibition; (+), stimulation; (?), remains unclear.

Fig. 2. Hypothesized mechanism for the uncoupling of resting metabolic rate control by the circulating RAS, leading to obesity-related hypertension. Increased adiposity causes increases in leptin and the circulating RAS, both of which stimulate brain RAS activity. The brain RAS, through arginine vasopressin (AVP) and sympathetic nervous activity (SNA), stimulates blood pressure (BP). Elevated BP causes a reflexive suppression of the circulating RAS. Reduced circulating RAS activity and SNA synergistically act to increase resting metabolic rate, which ultimately antagonizes obesity. We hypothesize that the obesity-associated increase in circulating RAS activity uncouples the control of resting metabolism by the brain RAS, resulting in maintained stimulation of blood pressure, but loss of feedback inhibition of adiposity and weight gain, which presents clinically as obesity-related hypertension.

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more efficiently cross (110). Critically, these assessments of BBB permeability have been performed almost exclusively in lean, otherwise healthy animals. The tacit assumption that the BBB is intact and functioning normally in obese or obese hypertensive patients is probably inappropriate.

RAS components themselves, and the various pharmacological modulators of the RAS, are all known to affect BBB permeability. Astrocyte-derived angiotensin II acts via AT1 receptors on BBB endothelial cells to modulate permeability (140). Interestingly, angiotensin-(1–7) (142) and the activation of AT2 receptors (88) also modulate permeability. Peripheral angiotensin II infusion in mice also frequently results in increased BBB permeability, which is reduced in AT1a knockout mice (91, 98) or by tempol (149). The effect of angiotensin II to increase BBB permeability is also amplified with coadministration of nitro-L-arginine methyl ester (69). Angiotensin II acts directly on microvessel endothelial cells and this effect can be ameliorated by telmisartan but not the AT2 antagonist PD-123,319 (35). Dahl salt-sensitive rats exhibit increased BBB permeability, and a nondepressor dose of olmesartan reduces permeability (98, 99). Spontaneously hypertensive rats exhibit disrupted BBB, resulting in increased permeability and increased angiotensin II extravasation into brain tissue; this can be corrected with losartan but not hydralazine treatment (6). Similar to losartan, candesartan also reduces BBB permeability (74, 97). Enalapril appears to reduce permeability following middle cerebral artery occlusion-induced ischemia (96), whereas captopril increases permeability in normotensive rats (119). Interestingly, DOCA-salt hypertension does not appear to grossly modulate BBB permeability (108, 109), which may reflect the tissue-specific effects of DOCA-salt treatment on RAS activity.

Alterations of the BBB not only occur with hypertension but also with metabolic disorders including obesity and diabetes. Mice fed high-fat diets exhibit deterioration of the BBB (59, 131). Body mass is also positively correlated with markers of reduced BBB function in elderly women (50). Although leptin transport across the BBB is reduced in obesity (14), leptin is a large peptide (146 amino acids) and likely not reflective of changes in permeability to other smaller peptides (such as the 8 amino acid angiotensin II) and small nonpeptide modulators of the RAS. Streptozotocin-induced Type 1 diabetes results in increased BBB permeability in rats, which can be reversed by candesartan treatment (4). KKA(y) Type 2 diabetic mice exhibit increased BBB permeability that is reversed by telmisartan; blocking the activation of PPAR-γ via GW9662 blocked this beneficial effect (87). Losartan was less effective than telmisartan to reduce BBB permeability, and GW9662 had no modulatory effects on the losartan effect. Collectively these data are consistent with the hypothesis that a dysfunctional BBB during obesity and obesity-related hypertension may eliminate beneficial compartmentalization of RAS hyper- versus hypoactivity, resulting in loss of tissue-specific metabolic control by the RAS. Future studies investigating the utility of RAS modulators that cannot cross “weak-
Hypothesis: Uncoupled Feedback and Obesity-Related Hypertension

Obesity is correlated with increased circulating RAS activity, increased levels of various other hormones such as leptin, and increased sympathetic nerve activity (SNA) (32, 143–145). Angiotensinogen derived from adipose tissue is increased in obese humans (143), and RAS components from adipose tissue contribute to blood pressure control (144, 145). Circulating RAS activity is a well-established stimulant of the brain RAS (94). Similarly, work from the Mark group (56) demonstrated that SNA responses to leptin were completely dependent on AT1 receptors in the brain, as ICV infusion of losartan attenuated SNA activity responses to leptin injection, to both intercapsular brown adipose and kidney. These data highlight the dependence of thermogenic and renal SNA responses to various obesity-related stimuli upon brain AT1 signaling. As we previously documented, the brain RAS (through AT1 signaling) is critically involved in the stimulation of RMR (45, 46), and this stimulation requires suppression of the circulating RAS via increased blood pressure (46, 47, 77). Thus it is conceivable that obesity uncouples the hypertension-mediated suppression of the circulating RAS, thereby disrupting the stimulation of RMR by obesity (Fig. 2). Ultimately, these effects would culminate in unchecked weight gain and increased blood pressure.

Conclusions and Ongoing Questions

The lack of a unique “obesity-specific” mechanism of hypertension is highlighted by the finding that normal-weight hypertensive, overweight hypertensive, and obese hypertensive patients have the same blood pressure responses to antihypertensive medications (107). In the early 1970s, Laragh and colleagues (72) documented the relative abundance of essential hypertensive patients with high-, normal-, and low-circulating renin. These studies and several subsequent replications have demonstrated that roughly 16% of hypertensive patients exhibit high-renin hypertension (where the RAS is presumably the primary cause of the hypertension), whereas roughly 57% exhibit normal and 27% exhibit low circulating levels of renin. We posit that comorbid obesity and hypertension may represent an enrichment of the high-RAS hypertensive population, in which elevated RAS activity (in the context of an obesigenic environment) may spill over and contribute to the pathogenesis of obesity.

Herein we hypothesize a relatively simple model of the pathogenesis of obesity and obesity-related hypertension that may result from opposing, tissue-specific effects of the RAS on energy balance. The RAS is involved in the control or regulation of all of the cardinal metabolic processes (food intake behavior, digestive efficiency, physical activity, and resting metabolism; Fig. 1), and the production of RAS components by (and action upon) adipose tissue may ultimately explain the pathogenesis of obesity and the paradox of why stimulation of the RAS and inhibition of the RAS can both result in a negative energy balance. Much more work is needed to understand the mechanisms by which the RAS contributes to energy homeostasis, and how it functions in concert with cardiovascular control, to develop potent dual antihypertensive/antiobesity therapeutics.


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Review


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