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The renin-angiotensin system in the arcuate nucleus controls resting metabolic rate

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Abstract

Purpose of review: Obesity represents the primary challenge to improving cardiovascular health, and suppression of resting metabolic rate (RMR) is implicated in the maintenance of obesity. Increasing evidence supports a major role for the renin-angiotensin system (RAS) within the brain in the control of RMR.

Recent findings: The angiotensin II (ANG) Agtr1a receptor co-localizes with the leptin receptor (Lepr) primarily within cells of the arcuate nucleus (ARC) of the hypothalamus that also express Agouti-related peptide (Agrp). This sub-population of Agtr1a receptors is required for stimulation of thermogenic sympathetic nervous activity and RMR, but not the suppression of food intake or increasing blood pressure, in response to various stimuli including high fat diet, deoxycorticosterone acetate + salt, and leptin. Agtr1a is localized to a specific subset (SST3) of Agrp neurons within the ARC.

Summary: The RAS within the ARC is implicated specifically in RMR control, primarily through Agtr1a localized to the SST3 subset of Agrp neurons. Ongoing research is focused on understanding the unique anatomical projections, neurotransmitter utilization, and signal transduction pathways of Agtr1a within this subset of neurons. Understanding these projections and molecular mechanisms may identify therapeutic targets for RMR and thus obesity, independent of blood pressure and appetite.

Keywords

Resting metabolism; Energy expenditure; Agtr1a; Angiotensin

Introduction

Obesity remains a major health concern and economic burden for the global populace. Despite decades of efforts to halt disease progression, the World Health Organization has published that approximately 39% of the world's population is either overweight (body mass

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index (BMI) 25 to 30) or obese (BMI >30), translating into a global health burden of >$2 trillion dollars USD (1, 2). A recent study examining the association between BMI and mortality in the United States concluded that the increase in BMI between 1998 to 2011 has reduced the life expectancy at age 40 by 0.9 year in 2011, and warns that continued increases in BMI will jeopardize future gains in life expectancy (3). Obesity is a major risk factor for type II diabetes mellitus as well as cardiovascular diseases, including hypertension (4). The link between obesity and hypertension was first noted in a prospective data analysis from the Framingham Heart Study in the late 1960s (5). Alarmingly, subsequent studies have reported that while ~34% of humans with normal BMI exhibit hypertension, approximately 78% of humans with obesity are diagnosed with hypertension (6). Thus, improvements in cardiovascular outcomes are expected, secondary to the identification of actionable therapeutic target(s) central to the development and maintenance of obesity. This review therefore aims to outline the rationale for pursuing the study of resting metabolic rate (RMR), and the current understanding of the role of the brain renin-angiotensin system in RMR control.

Suppression of resting metabolic rate in the pathogenesis and maintenance of obesity

The obesity epidemic is attributable to the complex interplay among social factors, genotypes and phenotypes, which ultimately lead to an imbalance between energy intake and energy expenditure. Beyond diet and exercise, many anti-obesity interventions (including bariatric surgery and pharmacological agents to suppress caloric intake) exist, yet there are currently no safe and effective drugs available that stimulate resting energy expenditure.

Resting metabolic rate (RMR), the rate of energy expenditure at rest, accounts for approximately 70% of all energy expended by healthy humans. Long-term follow-up studies examining energy balance of obese adult humans who have undergone intensive behaviorally-mediated weight loss identify the adaptive suppression of RMR as the single dominant factor in weight maintenance & regain (7). Given this evidence, it is unsurprising that most anti-obesity therapeutics currently approved by the FDA (eg - orlistat, lorcaserin, liraglutide, etc.), which act to reduce food intake or fat absorption, fail to elicit a sustained meaningful reduction (<6%) in body weight (8). In contrast, numerous studies have touted the efficacy of 2,4-dinitrophenol (2,4-DNP), a potent RMR stimulator, as proof-of-concept evidence for RMR stimulation as a robust approach to weight loss despite the dangerous pharmacokinetics of this particular compound that preclude its use clinically (9, 10). While evidence implicates RMR suppression in the pathogenesis and maintenance of obesity and the utility of stimulating RMR as a powerful anti-obesity therapeutic approach, the underlying cellular and molecular processes controlling RMR remain unclear.

Research over the past two decades examining the genetic basis of obesity has identified loss-of-function mutations in several key components of the leptin/melanocortin pathway in patients with hyperphagia and severe early-onset obesity, including the adipose-derived hormone leptin, the leptin receptor (*LEPR*), pro-opiomelanocortin (*POMC*), and the

melanocortin 4 receptor (*MC4R*). The most commonly mutated gene implicated in monogenetic obesity is *MC4R*, encoding the melanocortin 4 receptor, with a prevalence of ~6% in severely obese patients (11). Central MC_4R activation by α-melanocyte stimulating hormone induces powerful satiety signals to inhibit feeding behavior, as well as increase sympathetic output to stimulate energy expenditure (12). Critically, however, sympathetic activation by MC_4R agonists such as LY2112688 also increases blood pressure (BP) and heart rate, thereby limiting the therapeutic use and continued development of first-generation MC_4R agonists for obesity treatment (13, 14).

Recent studies evaluating the efficacy and safety profile of the second-generation MC_4R agonist, Setmelanotide, in obese patients with *POMC*, *LEPR*, or *MC4R* deficiency demonstrate that it suppresses hyperphagia and body weight without adverse cardiovascular effects (15–17). It has been suggested that the MC_4R-mediated modulation of food intake and body mass are dependent on $G_{\alpha q}$ signaling, while cardiovascular responses appear to require $G_{\alpha s}$ signaling (15–23). The finding that differential second messenger signaling pathways are activated by MC_4R to elicit metabolic versus cardiovascular effects illustrates a critically important concept: Biased activation of the melanocortin system, to selectively engage specific second-messenger signaling cascades in *MC4R*-expressing cells, and/or activate only specific subsets of *MC4R* neurons, may hold great therapeutic potential – but greater understanding of the relevant signaling network(s) is required.

The Renin-Angiotensin System

The renin-angiotensin system (RAS) exists as a circulating hormone system as well as a local paracrine signaling system within various tissues including brain and adipose. Angiotensin II (ANG) activates at least two G-protein Coupled Receptors (GPCRs), the ANG type 1 (AGTR1) and type 2 (AGTR2) receptors. In contrast to humans, there two isoforms of Agtr1 within rodents –Agtr1a and Agtr1b (24–26). It has been established that Agtr1a is essential for the BP response effects of the brain RAS, whereas Agtr1b receptors are critical for the dipsogenic effects of central ANG action within rodents (27). While the role of the RAS in cardiovascular control has been well defined, growing evidence demonstrates a multimodal role for the RAS in energy homeostasis, and more specifically, RMR control (28). Activation of Agtr1a in the brain stimulates energy expenditure through increasing RMR, but activation of Agtr2 in adipocytes suppresses RMR (29, 30).

The sympathetic nervous system orchestrates a complex homeostatic control of white adipose tissue (WAT) and brown adipose tissue (BAT) in response to caloric availability by modulating the sympathetic outflow to these fat depots. In response to thermal (cold) challenge, BAT dissipates chemical energy as heat, thus serving as a critical site for heat production. The thermogenic capacity of BAT corresponds to the presence of uncoupling proteins encoded by the *UCP1* gene. By uncoupling respiration from ATP production, uncoupling proteins dissipate the energy of substrate oxidation as heat (reviewed in (31)). As noted above, *Agtr2* activation in adipocytes suppresses RMR, which is mediated in part by abrogating norepinephrine-induced UCP1 production (30).

The brain RAS is required for RMR control by various stimuli. Inhibition of angiotensin converting enzyme with captopril or blockade of Agtr1a with losartan within the brain, or whole-body genetic knockout of *Agtr1a* all result in loss of thermogenic sympathetic nerve activity (SNA) responses to acute injections of leptin (32). *Agtr1a* is expressed by neurons within the arcuate nucleus (ARC) which also express *Lepr* and *Agrp*. Genetic disruption of *Agtr1a* in *Lepr*- or *Agrp*-expressing cells abolishes thermogenic SNA and RMR responses to leptin, high-fat diet (HFD), and deoxycorticosterone acetate (DOCA)-salt stimuli (33). Because pharmacological inhibition of the brain RAS attenuates BP responses to these types of stimuli (34–36), it was surprising to discover that BP responses to DOCA-salt remained intact in mice lacking *Agtr1a* in *Lepr*-expressing cells. This establishes a specific role for the subpopulation of Agrp neurons, and *Agtr1a* expressed on this subset of neurons, in RMR control, and implicates other populations of *Agtr1a*-expressing neurons in BP control. Although Agrp neurons are known to play in the control of feeding behavior, we consistently fail to detect any alterations in food intake behaviors in mice lacking *Agtr1a* within *Lepr*- or *Agrp*-expressing cells. Collectively, these observations identify divergent mechanisms by which ANG in the brain contributes to the control of RMR versus BP, and identifies the brain RAS as a major integrator of RMR control through its actions on leptin-sensitive ARC Agrp neurons. Further, the determination that Agtr1a on Agrp neurons contributes to RMR control without effect upon food intake or BP led us to hypothesize the existence of distinct ANG-sensitive ARC Agrp neuronal subtype(s) essential for RMR control but decoupled from food intake behaviors and BP control. In support of this hypothesis, *in silico* reanalysis of a publicly-available single-cell RNA-sequencing dataset describing the transcriptomes of cells within the mouse hypothalamus, identifies at least two distinct populations of Agrp neurons: the “GABA14” and “SST3” subtypes (37, 38). Intriguingly, only the SST3 subtype of Agrp neurons expresses *Agtr1a*, and this cell type exhibits one of the highest levels of expression of *Agtr1a* among all cell types within the mouse hypothalamus. The presence of neurons coexpressing *Agrp* and *Sst* has also been reported by Campbell and colleagues (39). Notably, deletion of *Crhr1* from all AgRP neurons resulted in alterations in thermogenesis without effects on food intake and body weight, and *Crhr1* is highly expressed within $Agrp^{+}Sst^{+}$ neurons, underscoring the potential for this subtype of Agrp neurons in metabolic control (39, 40). The existence of the “GABA14” and “SST3” Agrp neuronal subpopulations has prompted our team to propose a series of questions to further understand the specific contributions of these cells to energy homeostasis:

Do GABA14 and SST3 subtypes of Agrp neurons project to different brain nuclei to control specific physiological effects?

Agrp neurons are critical controllers of appetite, and respond to circulating satiety and hunger signals such as leptin and ghrelin. In addition to expressing *Agrp*, these neurons also express neuropeptide Y (*Npy*) as well as the genes to produce and package γ-aminobutyric acid (GABA). In response to leptin, Agrp neuronal activity is decreased, and *Agrp* and *Npy* production are suppressed. This results in the disinhibition of *Mc4r*-expressing second-order neurons, and the suppression of feeding (41). Further, a role for Agrp neurons in energy expenditure control has been suggested with the observation that mice with specific deletion

of the vesicular GABA transporter in Agrp neurons are resistant to HFD-induced weight gain, due to increased oxygen consumption (42).

While the presynaptic inputs to Agrp neurons of the ARC have been identified, the targets of efferent projections from these neurons involved in RMR control remain relatively unresolved (43). As we have recently reviewed, Agrp neurons send projections to numerous nuclei implicated in energy balance control, including the PVN, the dorsomedial nucleus of hypothalamus (DMH), the lateral hypothalamic area (LHA), ventromedial hypothalamus (VHL), the preoptic area (POA), the locus coeruleus (LC) as well as the periaqueductal gray (PAG) (44). The PVN is implicated in the control of feeding and BP (45, 46). Thus, it is plausible that the GABA14 subset of Agrp neurons projects to second order neurons of the PVN critical for feeding control and/or BP control, while the ANG-sensitive SST3 subset of Agrp neurons projects to a unique set of second order neurons specifically involved in RMR modulation. To the best of our knowledge, however, there have been no studies examining differential efferent projections from subpopulations of Agrp neurons which differentiate RMR, BP, and food intake. Future studies designed to specifically elucidate the distinguishing molecular features, projections, and relative utilization of neurotransmitters between GABA14 and SST3 Agrp neurons are needed (Figure 1).

What is the second-messenger signaling cascade activated by Agtr1a within the RMR-modulating “SST3” subtype of Agrp neurons?

As noted above, our recent publications implicate the brain RAS in RMR control through actions at the *Agtr1a* specifically expressed on ARC Agrp neurons. The “SST3” subtype of Agrp neurons but not the GABA14 subtype of Agrp neurons expresses *Agtr1a*. This receptor is a prototypical GPCR that can couple to $G_{\alpha q}$, $G_{\alpha i1}$, $G_{\alpha i2}$ and $G_{\alpha 12/13}$ pathways (Figure 2). Using site-directed mutagenesis, Shibata and colleagues identified a conserved sequence within second intracellular loop of the human AGTR1 critical for association with both $G_{\alpha q}$ and $G_{\alpha i}$, whereas the last 50 amino acids of the cytoplasmic tail coupling to $G_{\alpha i}$ but not $G_{\alpha q}$ (47). The observation that Agtr1a couples to both $G_{\alpha q}$ and $G_{\alpha i}$ is consistent with earlier mapping studies of G protein coupling sites in the rat Agtr1a by Shirai et al (48). The SST3 cell expresses genes encoding $G_{\alpha i}$ (*Gnai1, Gnai2*) and $G_{\alpha q}$ (*Gnaq*) (37), and thus it is possible that Agtr1a may couple to either (or both) of these pathways to control RMR.

Typically, activation of $G_{\alpha q}$ results in increased intracellular calcium ($[Ca^{2+}]_i$), whereas $G_{\alpha 12/13}$ activates Rho/Rho-kinase signaling cascades, and $G_{\alpha i}$ decreases intracellular cyclic-adenosine monophosphate (cAMP) levels. Thus, the molecular, cellular and physiological output of Agtr1a activation critically depends upon which G-protein it couples. This coupling interaction is often both tissue- and cell-type dependent. In vascular smooth muscle cells (VSMC), Agtr1a can couple to $G_{\alpha q}$ and $G_{\alpha 12/13}$, as its activation results in $[Ca^{2+}]_i$-mediated activation of myosin light chain kinase as well as Rho/Rho-kinase-dependent myosin light chain phosphatase inhibition, respectively (49, 50). More recently, using bioluminescence resonance energy transfer biosensors, Saulière et al. further confirmed the ability of ANG, as well as the biased agonist [^{1}Sar^{4}Ile^{8}Ile]-angiotensin II (SII), to facilitate the coupling of Agtr1a to both $G_{\alpha q}$ and $G_{\alpha i}$, and induce the G-protein independent

recruitment of β-arrestin, in cells with exogenous as well as endogenous *Agtr1a* expression (51). Agtr1a can also transactivate receptor tyrosine kinases, such as the epidermal growth factor receptor to facilitate VSMC hypertrophy and migration (52, 53). The complex intracellular signaling cascades afforded by Agtr1a activation also include serine/threonine and tyrosine kinases, including ERK, PI3K, JAK and c-SRC. As it is beyond the scope of this review, we wish to direct interested readers to a recent review highlighting the novel Agtr1a signaling partners by Forrester and colleagues (54).

Termination of G-protein signaling can be accelerated by Regulators of G-protein Signaling (RGS), which are GTPase activating proteins that function as endogenous terminators of $G_{\alpha i}$ and $G_{\alpha q}$ second-messenger signaling by increasing the intrinsic GTPase activity of G_{α} subunits to facilitate the GTP-to-GDP exchange (55–57). Rgs2 is a potent suppressor of Agtr1a signaling in various cell types, and it is the dominant isoform expressed within Agrp neurons (37, 58). Roles for Rgs2 and $G_{\alpha i2}$ in the modulation of RMR have been suggested from studies demonstrating that mice expressing an RGS-insensitive $G_{\alpha i2}$ mutant allele exhibit increased energy expenditure, whereas Rgs2-deficient mice are resistant to weight gain (59, 60). We therefore hypothesize specific roles for $G_{\alpha i2}$ and Rgs2 within Agrp neurons to mediate and modulate Agtr1a signaling, and studies are ongoing (Figure 3).

Is there a role for dysregulated Agtr1a signaling in the pathogenesis of obesity and selective leptin resistance?

A phenomenon, termed “selective leptin resistance (SLR),” is observed in experimental animal models fed a HFD and in morbidly obese humans without concurrent deficiency in leptin (reviewed in (61)). Further, higher circulating leptin levels are documented in patients who have regained lost weight following an energy-restriction-based intervention as compared to patients who have been successful in maintaining weight loss (62). With SLR following 10 weeks of HFD feeding, mice are desensitized to the metabolic actions (ie – thermogenic adipose SNA) of leptin, while the cardiovascular responses (eg – renal SNA) are preserved (63). While molecular mechanism(s) underlying SLR remained undefined, several possibilities have been hypothesized. First, the inability for leptin to cross the blood brain barrier (BBB) limits its access to specific portions of the central nervous system and neuronal targets. Thus, site-specific alterations in BBB permeability/transport of leptin may contribute to SLR. Second, dysregulation of leptin and/or its multiple independent second-messenger signaling pathways within specific neurons may also contribute to the development of SLR. Our recent work underscores a pivotal role for the Agtr1a in ARC Agrp neurons in RMR stimulation in response to various stimuli, including HFD and leptin (33). Given the critical role of RMR suppression in the maintenance of obesity (7), and the specific role of Agtr1a in this neuronal population in RMR but not BP control (33), we hypothesize a role for dysregulated Agtr1a signaling (possibly including dysregulated $G_{\alpha i2}$ and Rgs2) in SST3 neurons in the pathogenesis of obesity and SLR, and therefore ultimately obesity-associated cardiovascular disease.

Conclusions

The brain RAS is critically involved in energy homeostasis, in addition to its well-documented roles in cardiovascular control. The Agtr1a receptor within a subset of ARC Agrp neurons is critical for RMR stimulation in response to many stimuli, but is not required for cardiovascular control by the brain RAS. Understanding the molecular and neuroanatomical characteristics of the Agtr1a-expressing subset of Agrp neurons, and the unique signal transduction pathway(s) for Agtr1a in these specific cells, will provide essential insights into the fundamental control of RMR necessary for the development of safe and efficacious new anti-obesity therapeutics.

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Key Points

- Suppression of resting metabolic rate (RMR) is implicated in the maintenance of obesity, yet no safe and effective anti-obesity therapeutics are currently available that stimulate RMR
- Increasing evidence demonstrates a role for the renin-angiotensin (RAS) within the arcuate nucleus of the hypothalamus (ARC) in the control of RMR
- The angiotensin Agtr1a receptor is expressed in one (“SST3”) subset of neurons within the ARC that express the leptin receptor (LepR) and Agouti-related peptide (Agrp), but Agtr1a is absent from the other subset of Lepr- / Agrp-expressing cells of the ARC (“GABA14” subset)
- The activation of Agtr1a in the SST3 subset of Agrp neurons is absolutely required for thermogenic autonomic and RMR responses to an array of stimuli including leptin, high fat diet, and deoxycorticosterone (DOCA)-salt, but dispensable for appetite and blood pressure responses
- Because of opposing actions of the brain RAS (*stimulates RMR*) and circulating/adipose RAS (*suppresses RMR*), therapeutically targeting Agtr1a signaling in SST3 neurons to stimulate RMR will require increased understanding of the unique second-messenger pathways activated by Agtr1a within, and the anatomical projections and neurotransmitter utilization of, the SST3 cell

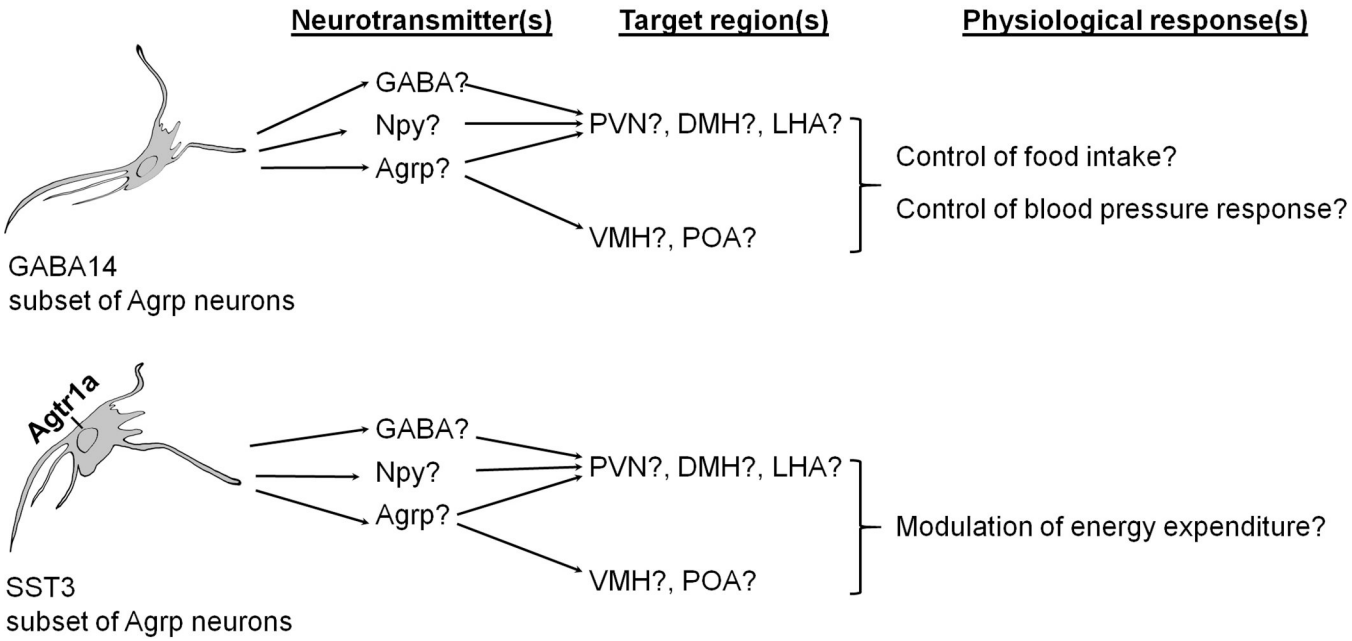

Figure 1. Localization of Agtr1a and hypothesized role(s) for distinct subtypes of Agrp neurons within the arcuate nucleus.

Agtr1a is expressed in the SST3, but not GABA14, subset of Agrp neurons. Clarification of the neurotransmitter(s) and efferent projections utilized by the GABA14 and SST3 subsets of AgRP neurons will provide critical insight into the integrative control of energy expenditure, versus blood pressure and food intake. Agouti-related peptide (Agrp), dorsomedial hypothalamus (DMH), γ-aminobutyric acid (GABA), lateral hypothalamic area (LHA), neuropeptide Y (Npy), paraventricular nucleus of hypothalamus (PVN), preoptic area (POA), ventromedial hypothalamus (VMH).

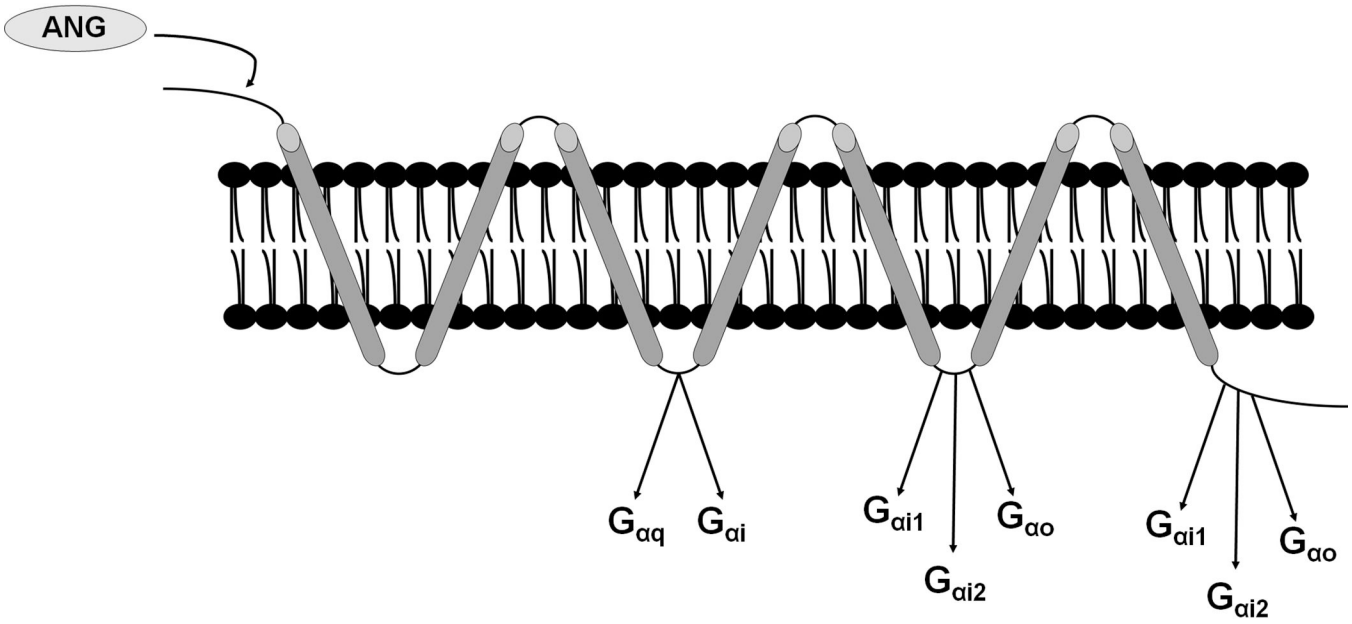

Figure 2. Structure of the AGTR1 with documented sites of interaction with Gα subunits highlighted.

Structural mapping studies performed by Shibata et al (47) and Shirai et al (48) identified critical regions within the human AGTR1 and rodent Agtr1a essential for association and activation of $G_{\alpha q}$, $G_{\alpha i}$ and $G_{\alpha o}$.

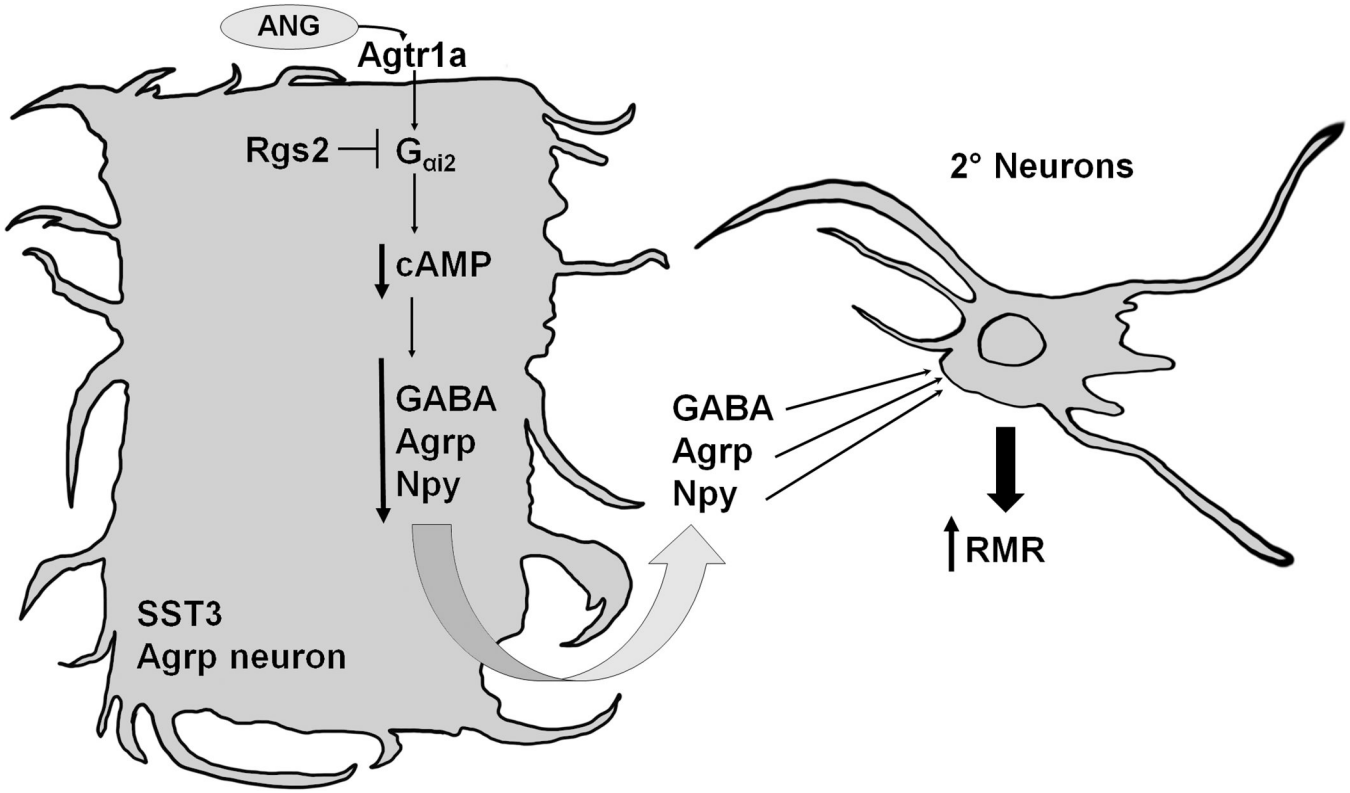

Figure 3. Hypothesized second-messenger signaling cascade of Agtr1a within the SST3 subtype of Agrp neurons.

Agtr1a within SST3 Agrp neurons may couple to a $G_{\alpha i2}$ cascade that is sensitive to inhibition by the regulator of G protein signaling-2 (Rgs2), resulting in decreased intracellular cyclic adenosine monophosphate (cAMP) concentrations and repression of genes encoding the neurotransmitters Agouti-related peptide (Agrp), γ-aminobutyric acid (GABA), neuropeptide Y (Npy). This would disinhibit second-order neurons in the paraventricular nucleus, dorsomedial hypothalamus, lateral hypothalamic area, ventromedial hypothalamus and/or preoptic area, ultimately leading to the stimulation of resting metabolic rate (RMR).