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Effect of angiotensin II infusion on rhythmic clock gene expression and local renin-angiotensin system in the aorta of Wistar rats

Herichova I, Zsoldosova K, Vesela A, Zeman M

Department of Animal Physiology and Ethology, Faculty of Natural Sciences, Comenius University Bratislava
E-mail: herichova@fns.uniba.sk

Objective. Endogenous daily rhythms in physiology are regulated by the circadian system consisting of the central and peripheral components. The renin-angiotensin system, involved predominantly in water balance and blood pressure control, exerts 24 h rhythmicity in many of its parameters. The present study is aimed to study possible interactions between these two control systems. We analyzed effects induced by angiotensin II administration on clock gene expression in the aorta of rat and an ability of angiotensin II to influence the local tissue renin-angiotensin system.

Methods. Angiotensin II was infused in a dose of 100 ng/kg/min by subcutaneously implanted osmotic minipumps for 28 days to male Wistar rats. Gene expression was measured by real time PCR.

Results. Angiotensin II administration resulted in an increase in blood pressure, heart weight/body weight index, and water intake in comparison with controls. We observed a significant phase advance in *per2* and *npas2* mRNA rhythms and decreased mesor of *npas2* rhythmic expression in the aorta of angiotensin II-treated rats compared to control. Angiotensin II administration did not influence daily pattern and level of *at1* mRNA expression. The ratio *ace*/*ace2* showed a rhythmic pattern in the aorta of control rats with peak levels in the dark period.

Conclusions. Angiotensin II infusion influenced clock gene expression and diminished a daily rhythm in *ace*/*ace2* mRNA ratio indicating modulatory effect of angiotensin II on tissue renin-angiotensin system in the aorta.

Key words: clock, circadian, hypertension, *ace*, *ace2*, rhythm

The renin-angiotensin system (RAS) is a hormonal system with an essential role in the control of blood pressure, electrolyte, and water homeostasis. Deregulated RAS is implicated in the pathophysiology of hypertension, cardiovascular, and renal diseases (Cohn 2011; De Mello and Frohlich 2011; Takahashi et al. 2011). Angiotensin II (angII), as the final product of RAS, is a multifunctional molecule with vasoconstrictive and proliferative effects in the cardiovascular system (Bader and Ganten 2008). AngII concentrations in the organism are regulated at multiple levels. Among them the conversion of angI to angII by angiotensin converting enzyme (ACE) and degradation of angII by angiotensin converting enzyme 2 (ACE2) play a crucial role. In addition to the circulating RAS and angII that act via blood circulation, a tissue RAS is acquiring still more attention (Bader and Ganten 2008).

A substantial experimental support exists for the presence of all components of RAS and their receptors (except of renin synthesis) in vessels (Bader and Ganten 2008). Expression of renin mRNA is low or hardly detectable in the vasculature and its uptake via specific (pro)renin receptor is a more likely source of active enzyme in this tissue (Nguyen Dinh Cat and Touyz 2011). ACE and ACE2 are both expressed in the vasculature similarly as in most of other tissues. Imbalance in *ace*/

Corresponding author: Iveta Herichova, Department of Animal Physiology and Ethology, Faculty of Natural Sciences, Comenius University Bratislava, Mlynska dolina B-2, 842 15 Bratislava, Slovak Republic, e-mail: herichova@fns.uniba.sk.

ace2 expression ratio has been linked to the heart and kidney pathology (Hanafy et al. 2011; Bernardi et al. 2012; Yang et al. 2012; Ma et al. 2014).

Many parameters of circulating and tissue RAS show distinct daily rhythms. It has been shown that there are daily rhythms in plasma renin activity, angII, and aldosterone levels with higher levels at the beginning of the active phase, while in the ACE pattern during the second part of the active phase (Gordon et al. 1966; Kala et al. 1973; Portaluppi et al. 1990; Cugini and Lucia 2004). Except of the circulating RAS, tissue RAS also shows daily rhythms in expression of its components (Naito et al. 2002; Herichova et al. 2013).

In spite of extensive evidence of rhythms in several components of RAS, it is not clear how the daily pattern is generated. In this respect a possible role of the circadian system is implicated. The circadian system consists of the central part localized in the hypothalamic suprachiasmatic nuclei (SCN) and peripheral oscillators localized in all other tissues (Stratmann and Schibler 2006). Lesion of the SCN causes a loss of daily rhythms in many humoral parameters and locomotor activity (Kalsbeek et al. 2006). The role of the circadian system in the RAS rhythmicity is supported by finding that the SCN lesion diminishes the daily rhythm of plasma renin activity in the rat (Stoynev et al. 1980) and indirect evidence implicates that the SCN is involved in the control of body fluid volume (Nagai et al. 1994).

The circadian rhythm generation in mammals is based on rhythmic clock gene expression when protein product turns off its own mRNA expression. Three homologues of *per* gene (*per1*, *per2*, *per3*) and two homologues of *cry* genes (*cry1*, *cry2*) represent the negative component of the feedback loop. PER and CRY proteins are cumulated in the cell cytoplasm and after achieving of critical concentration they create heterodimers that are translocated into the nucleus. Transcription of *per* and *cry* genes is induced via E-box in their regulatory regions by transcriptional factors BMAL:CLOCK that represent positive component of feedback loop. Once heterodimer PER:CRY is translocated in to the nucleus it interacts with heterodimer BMAL:CLOCK (or their functional homologues). In this way *per* and *cry* transcription is inhibited and consequently their concentration in cytoplasm decreases and inhibition of BMAL:CLOCK is released. In this way the loop is closed and transcription of *per* and *cry* genes starts again. Whole process proceeds with a period close to 24 h and that defines the circadian oscillator period (Ko and Takahashi 2006). The above described loop is influenced by additional transcriptional factors (Guillaumond et al. 2005; Gachon 2007) and postranslational modifications (Reischl and Kramer 2011).

Evidence is rising that the RAS and circadian system reciprocally influence each other. Under physiological circumstances RAS shows 24 h rhythmicity (Naito et al. 2009). On the other hand, angII is able to induce expression of *per2* under *in vitro* conditions in the thoracic aorta (Nonaka et al. 2001) and clock gene expression in rat heart (Herichova et al. 2013). AngII infusion changes acrophase of daily rhythm in blood pressure in rats (Baltatu et al. 2001) which is usually under control of the SCN (Scheer et al. 2001). In TGR rats with genetically up-regulated RAS significant changes in clock gene expression in brain tissues regulating blood pressure and water balance have been described (Herichova et al. 2007; Monosikova et al. 2007).

Therefore, the aim of our study was to investigate effects of angII infusion on *per2* expression in the aorta under *in vivo* conditions. In parallel, we analyzed effect of angII administration on some components of local RAS in the rat aorta.

Methods and methods

Animals. Male Wistar rats (breeding station Dobra Voda, Institute of Experimental Pharmacology and Toxicology of Slovak Academy of Sciences, SR) were obtained at the age of 11 weeks with the initial body weight 149 ± 0.5 g. Animals were housed in temperature controlled rooms (21 ± 2°C) with the light (L) : dark (D) cycle 12:12. Food and water were available *ad libitum*. Body weight and water consumption were monitored during the experiment. AngII (Calbiochem, USA) was infused by osmotic minipumps (Alzet 2004 USA) implanted subcutaneously in the intrascapular area. AngII was released during 28 days in a dose 100 ng/kg/min. Sham operated control rats were implanted with an inert material of the same size and weight as the minipumps. At the end of the experiment minipumps were checked for complete release of angII. During experiment blood pressure and heart frequency were measured by the tail-cuff plethysmography method (AD Instruments, Germany). Sampling was performed at the end of the experiment in 4 h intervals during 24 h cycle. Samples were stored under -80°C until used for the RNA isolation. The experimental protocol was approved by the Ethical Committee for the Care and Use of Laboratory

Animals at Comenius University Bratislava and State Veterinary Authority of Slovak Republic.

RNA isolation and real time PCR. Total RNA from tissues was isolated with the use of Tri reagent (MRC, USA). The synthesis of cDNA was carried out with the use of ImProm-IITM (Promega, USA) according manufacturer instructions. The quantification of cDNA was performed by real time PCR using the QuantiTect SYBR Green PCR kit (Qiagen, Germany) and the StepOne™ Real-Time PCR System (Applied Biosystems, USA). The primers used for the amplification were: *per2* (AB016532) sense 5'-GAG GTT CAG GGA AGT GAG CA-3', antisense 5'-TTG ACA CGC TTG GAC TTC AG-3'; *npas2* (NM_001108214) sense 5'-CGG GAC CAG TTC AAT GTT CT-3', antisense 5'-CCA TCT AAC GCC TCC AAC AT-3'; *clock* (NM_021856) sense 5'-CCA ACT CCT TCT GCC TCC TC-3', antisense 5'-ACC TCC GCT GTG TCA TCT TC-3'; *ace* (NM_012544) sense 5′-AGGGTCTTTGACCGGAAGCA-3', antisense 5′-TCGTGGAACTGGAACTGGA-3'; *ace2* (NM_001012006.1) sense 5′-GACCAAAAAGTGGTGGGAGA-3', antisense 5′-AGTGGGCCATCATGTTTAGC-3'; *at1* (NM_030985) sense: 5'-AAT-TAT-GGC-GAT-TGT-GCT-TTT-C-3', antisense: 5'-GCT-ATG-CAG-ATG-GTG-ATG-G-3'; *rplp1* (NM_00107604) sense 5'-TCCACAACATGGCT-TCTGTC-3', antisense 5'-ATTGCAGATGAGGCT-TCCAA-3'. Real time PCR conditions were: hot start 95°C for 15 min followed by 50 cycles of 94°C for 15 s; 49-55°C for 30 s and 72°C for 30 s. The specificity of PCR reaction was validated by melting curve analysis. The fluorescence dye ROX was used as a passive internal reference in the reaction. Samples to be compared were run with the same mastermix. Gene expression was normalized to *rplp1* expression.

Statistical analysis. Comparison between two groups was calculated by the unpaired t-test. The differences were considered to be significant when $p<0.05$. Daily profiles of gene expression were evaluated by cosinor analysis (Klemfuss and Clopton 1993). Data were fitted into a cosinor curve with 24 h period and when experimental data significantly matched the cosinor curve its parameters were calculated with 95% confidence limits: mesor (the time series mean), amplitude (one half of the peak-trough difference expressed herein relative to the mesor), and acrophase (peak time referenced to the time of lights on in the animal facility). Time is expressed in relative units - Zeitgeber time (ZT), when ZT0 is defined as beginning of the light phase of day.

Results

As a result of 28-day angII infusion (100 ng/kg/min) we detected a significant increase in the blood pressure (158 ± 6 vs. 116 ± 4 mmHg; $p<0.001$, t-test), in water intake (59.5 ± 2.6 vs. 47.1 ± 2.1 ml/rat/24 h; $p<0.001$, t-test) and heart weight/body weight index (3.1 ± 0.1 vs. 3.6 ± 0.1; $p<0.001$, t-test) in comparison with the control.

We observed a distinct daily rhythm in *per2* expression in the aorta of control rats with peak levels at the beginning of the dark time ($p<0.001$, cosinor). *per2* expression showed a significant daily rhythm also in aorta of angII-treated rats with peak level at the transition from L to D part of 24 h regimen ($p<0.001$, cosinor). AngII infusion caused significant phase advance in rhythmic *per2* expression in the aorta (1 h 18 min, cosinor) (Fig. 1A).

Expression of *npas2* showed a distinct daily rhythm with peak levels at the beginning of the light phase of 24 h cycle in both, control and angII treated group ($p<0.001$, cosinor, Fig. 1B). Administration of angII caused significant phase advance (1 h, cosinor) and decrease in mean value (mesor) of rhythmic *npas2* mRNA expression in compared to control (by 25% of control level, cosinor).

Analysis of *clock* mRNA during 24 h cycle revealed a distinct daily rhythm with maximum levels at the beginning of light part of 24 h cycle ($p<0.01$, cosinor; Fig. 1C). We did not observe a significant difference between control and angII-treated groups (cosinor).

To analyze changes in the aorta tissue RAS, we measured expression of *ace*, *ace2* and *at1* mRNA. Expression of *ace* mRNA in the aorta was arrhythmic in both groups (cosinor). We observed significantly increased expression of *ace* mRNA during the dark time in angII-treated group compared to control ($p<0.05$, t-test, Fig. 2A). Expression of *ace2* mRNA was rhythmic in aorta of control group ($p<0.05$, cosinor). The marked trend to increased levels of *ace2* mRNA during the light part of 24 h cycle in angII-treated group as compared to controls did not reach level of significance in cosinor analysis ($p<0.08$) because of increased variability (Fig. 2B). Ratio *ace/ace2* showed a rhythmic daily profile with maximum during the dark part of 24 h cycle in the control group ($p<0.05$, cosinor) and was arrhythmic in experimental group ($p=0.11$, cosinor) mainly because of increased variability (Fig. 2C). We did not observe a daily rhythm in *at1* mRNA expression in the aorta of control and angII-treated rats. AngII treatment did not significantly influenced *at1* mRNA levels compared to control (Fig. 2D).

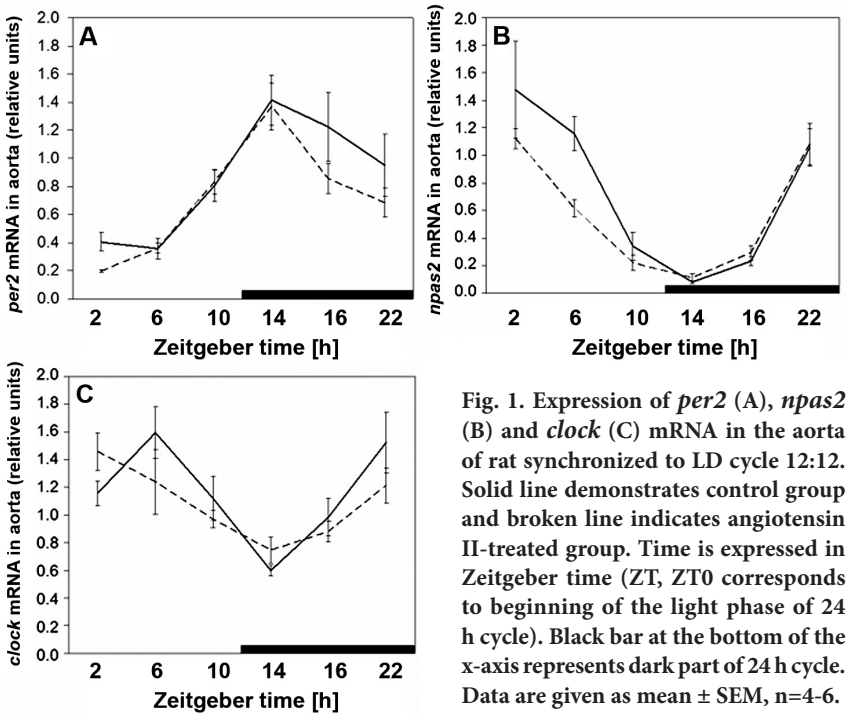

Fig. 1. Expression of *per2* (A), *npas2* (B) and *clock* (C) mRNA in the aorta of rat synchronized to LD cycle 12:12. Solid line demonstrates control group and broken line indicates angiotensin II-treated group. Time is expressed in Zeitgeber time (ZT, ZT0 corresponds to beginning of the light phase of 24 h cycle). Black bar at the bottom of the x-axis represents dark part of 24 h cycle. Data are given as mean ± SEM, n=4-6.

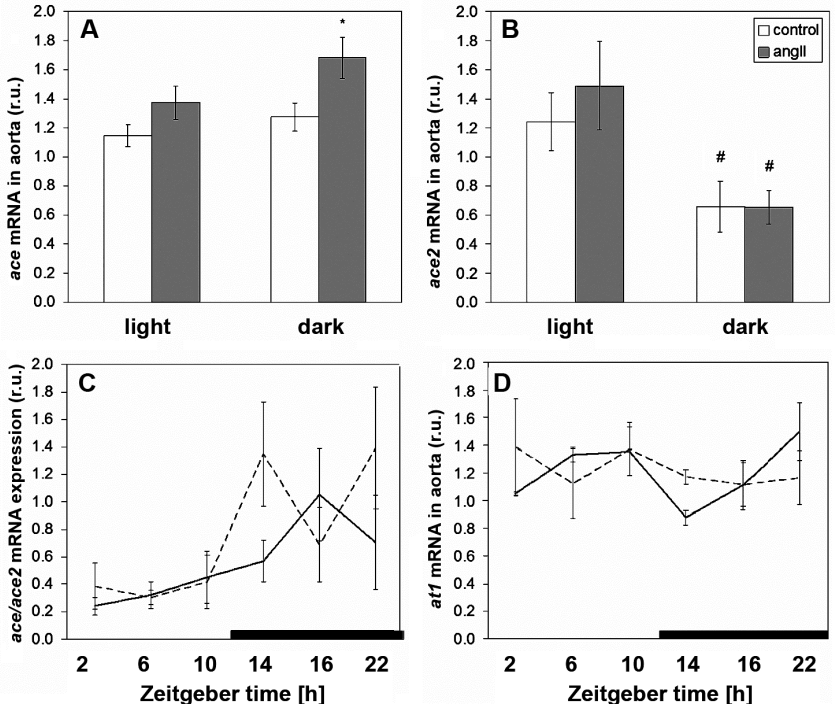

Fig. 2. Expression of *ace* (A), *ace2* (B), ratio *ace/ace2* (C) and *at1* (D) mRNA in the aorta of rat synchronized to LD cycle 12:12. White columns and solid line demonstrate control group, gray columns and broken line indicate angiotensin II-treated group. Time is expressed in Zeitgeber time (ZT, ZT0 corresponds to beginning of the light phase of 24 h cycle). Black bar at the bottom of the x-axis represents dark part of 24 h cycle. Data are given as mean ± SEM, n=4-6. *p<0.05 (control vs. angiotensin II-treated group, t-test), #p<0.05 (light vs. dark within control and angiotensin II-treated group, t-test). r.u. – relative units

Discussion

Our current study confirms effects of angII administration on clock gene expression in the cardiovascular system. In our previous study we have demonstrated that angII administered in the dose 100 ng/kg/min causes significant changes in *per2*, *rev-erbα* and *dbp* expression in the heart of rat after 28 days of infusion (Herichova et al. 2013). Here, we further extend our finding and refer that angII influences clock gene expression in the aorta under the same experimental conditions. In the recent study expression of clock core components *per2* and *npas2* was measured. Infusion of angII lasting 28 days caused phase advance in *per2* and *npas2* rhythmic expression and decrease in *npas2* mean value.

It was previously reported that angII is able to influence *per2* expression in cultured vascular smooth muscle cells isolated from the rat thoracic aorta under *in vitro* conditions (Nonaka et al. 2001). We found that effect of angII under *in vivo* conditions (in the presence of the LD cycle) is much less pronounced in comparison to the effect observed in *in vitro* study, but we can confirm its effect on peripheral oscillators in the aorta.

Clock genes *per1*, *per2*, *cry1*, *mop4,* and *bmal1* expression persists under constant conditions in mice aorta under *in vivo* conditions with *bmal1* expression in antiphase to *per* genes (McNamara et al. 2001; Reilly et al. 2008). Here, we report similar phase relationships between core clock genes. In our study, *clock* mRNA shows a significant daily rhythm with peak levels in the first half of passive part of LD cycle. We suppose that clock gene expression in the aorta and the heart show similar acrophases under synchronized conditions (Young et al. 2001; Herichova et al. 2007; Herichova et al. 2013).

So far, it is not clear if observed effect of angII is direct or mediated via the central oscillator. In our previous study we have reported effects of angII infusion on a way how locomotor activity is generated during the passive phase of LD cycle and decreased *per2* responsiveness to light pulse in the SCN (Herichova et al. 2013). AngII has been shown to stimulate activity of SCN neurons under *in vitro* conditions (Brown et al. 2008) but physiological interpretation of this finding is unclear so far. In this case, direct effect of angII is more likely since aorta express AT1 as well as AT2 receptors (Viswanathan et al. 1991) and effect of angII on aorta peripheral oscillator mediated via AT1 receptors under *in vitro* conditions has been reported (Nonaka et al. 2001). On the other hand, the angII effect mediated via AT1A receptor is not indispensable for the clock gene expression since under *in vivo* conditions AT1A-deficient mice exhibit rhythmic expression of *per2*, *bmal1* and *dbp* in the peripheral tissues (Masuda et al. 2009).

Because of extensive capacity of angII to regulate intracellular processes (Dinh et al. 2001), it is not surprising that the RAS can influence the generation and manifestation of the circadian rhythms. In the very first genetic model of the hypertension TGR(mREN-2)27 (Mullins et al. 1990) with an additional mouse renin gene in rat genome, unexpected circadian phenotype has been observed (Lemmer et al. 2003). TGR(mREN-2)27 rats showed inverted blood pressure profile with normal pattern of locomotor activity. The SCN lesion caused flattening of blood pressure pattern in TGR(mREN-2)27 rats (Witte et al. 1998). Inhibition of RAS activity in TGR(mREN-2)27 rats decreases blood pressure and normalizes the daily profile in a dose dependent manner (Schnecko et al. 1995). We have previously reported distinct changes in clock gene expression in the hypothalamic dorsomedial nucleus, nucleus abmiguus, nucleus tractus solitarii, rostral ventrolateral medulla, dorsal vagal motor nucleus, anteroventral third ventricle, area postrema, and kidney in TGR(mREN-2)27 in comparison with control Sprague-Dawley rats (Herichova et al. 2007; Monosikova et al. 2007) indicating changes in the circadian system induced by mouse renin 2 gene inserted into rat genome and thus induced consequent events.

Administration of angII leads to remodeling of the RAS. AngII inhibits renin release from the renal juxtaglomerulal cells (Kurtz and Penner 1990) by mechanism involving AT1 receptors (Kurtz and Wagner 1999) and decreases plasma renin activity (Sechi et al. 1996; Harrison-Bernard et al. 1999; Baltatu et al. 2000). Although antagonists of AT1 receptors (probably because of a removal of negative feedback on renin secretion) increases circulating angII levels (Bermann et al. 2007), the opposite direction of regulation is not evident. Effects of angII administration on AT1 expression has been reported in several studies but results are not conclusive and possible dose and tissue specific effects must be taken into consideration. AngII infusion (200 ng/kg per minute for 7 days) did not influence *at1* mRNA expression but was able to decrease angII binding in rat kidney (Sechi et al. 1996). Infusion of angII (350 ng/kg/min) lasting 13 days also did not significantly change the expression of *at1* mRNA in the kidney and liver of rat (Harrison-Bernard et al. 1999). AngII infused in dose 250 ng/kg/min during two weeks suppressed *at1*

mRNA expression in the aorta and mesenteric resistance arteries (Wang and Du 1998). In our study, angII administered in the dose 100 ng/kg/min during 28 days did not significantly influence *at1* mRNA expression in the rat aorta. We did not observe a significant daily rhythm in *at1* mRNA expression either in the control or angII-treated group. This implicates tissue specific influence of angII on remodeling of tissue RAS, since *at1* mRNA shows a low amplitude rhythm in the heart that was lost after angII administration (Herichova et al. 2013).

Effects of angII on *ace* and *ace2* mRNA expression in the aorta were studied mostly via pharmacological manipulation of AT1 receptors. It has been demonstrated that AT1 antagonist olmesartan increases *ace2* mRNA expression in the aorta (but not carotid) of SHR rats as well as plasma angII and angiotensin 1-7 levels in plasma and aorta (Igase et al. 2005). The original finding of present study is that the ratio *ace/ace2* in the aorta exhibits a significant daily rhythm with increased levels during the active phase of 24 h period. Administration of angII suppressed a daily rhythm mainly because of increased variability. Ratio *ace/ace2* has been used to describe changed dynamic of RAS in some tissues previously (Hanafy et al. 2011; Bernardi et al. 2012; Yang et al. 2012; Ma et al. 2014) in a tissue specific way (Riviere et al. 2005). We observed a similar daily pattern of *ace/ace2* ratio in the aorta as it has been previously observed in the heart (Herichova et al. 2013). On the other hand, the response of the heart and the aorta to angII was slightly different. Levels of *ace/ace2* decreased during the active phase of 24 h rhythm in the heart while we observed rather an increased variability than decreased levels in the aorta during dark phase. As a result a daily rhythm in *ace/ace2* ratio was suppressed or lost in both tissues. Our data are in accordance with previous knowledge about presence of daily rhythms in circulating and tissue RAS (Gordon et al. 1966; Portaluppi et al. 1990; Cugini and Lucia 2004; Herichova et al. 2013) and enzymes controlling angII synthesis and degradation probably contribute to this pattern. On the basis of recent knowledge it is possible to assume that modulation of *ace/ace2* daily profile by angII contributes to plasticity of RAS under physiological as well as pathological conditions.

To conclude, subcutaneous infusion of angII is able to modulate *per2* and *npas2* expression in the aorta of rat and influence *ace/ace2* ratio with possible impact on the turnover of angII in this tissue.

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