Yonago Acta medica 2003;46:83–90

*Special Contribution*

# Angiotensin II and Fever in Rodents

**Tatsuo Watanabe, Michio Miyoshi and Toshiaki Imoto**

*Division of Integrative Physiology, Department of Functional, Morphological and Regulatory Science, Tottori University Faculty of Medicine, Yonago 683-8503 Japan*

**Angiotensin II (ANG II), a bioactive peptide well known to play an important role in blood-pressure and body-fluid regulation, participates in inflammatory responses, too. Recently, we reported results suggesting that ANG II is involved in the development of the fever induced by intravenous (i.v.) injection of lipopolysaccharide (LPS, 2 μg/kg) in dehydrated rats (in which the secretion of ANG II is elevated). Furthermore, we verified the contributions made by ANG II and its type 1 receptor ($AT_1$ receptor) to the LPS-induced production of interleukin-1β (IL-1β) in those rats. It therefore seems likely that in rats, ANG II and its receptors contribute to the induction of this fever at its 1st step (namely, the LPS-induced production of pyrogenic cytokines such as IL-1β). Moreover, we have revealed that intrahypothalamic (i.h.) ANG II and $AT_2$ receptors are involved in the development of the fever induced by i.h. injection of prostaglandin $E_2$ ($PGE_2$), a final fever mediator. ANG II given i.h., which had no effect on the resting body temperature, facilitated $PGE_2$-nduced fever. These results suggest that in rats, ANG II and its receptors contribute to the induction of fever at its final step, too (namely, the action of $PGE_2$ to cause fever). Finally, a single i.p. injection of IL-1β results in a weaker IL-1β-induced fever in $AT_2$-receptor-deficient mice than in wild-type mice, suggesting that the brain $AT_2$ receptor is involved in the development of fever (possibly at its final step) in mice as well. Collectively, these results suggest that in rodents, ANG II and its receptors contribute to the development of fever, both at the 1st and final steps in the pathway for fever induction.**

**Key words:** $AT_1$ receptor; $AT_2$ receptor; interleukin-1; lipopolysaccharide; prostaglandin $E_2$

Angiotensin II (ANG II), a bioactive peptide well known to play an important role in blood-pressure and body-fluid regulation, seems to participate in inflammatory responses, too. For example, ANG II and ANG-II-type-1 ($AT_1$) receptors are involved in certain types of cardiovascular inflammation (Usui et al., 2000). Furthermore, angiotensin-converting-enzyme (ACE) inhibitors have an anti-inflammatory effect (Delfraissy et al., 1984; Martin et al., 1984; Rezkalla et al., 1990). We recently revealed that ANG II and its receptors are involved in the development of fever (another example of an inflammatory response) both in rats (Watanabe et al., 1997, 2000; Miyoshi et al., 2003) and in mice (Watanabe et al., 1999).

This review focuses on the role of ANG II and its receptors in the development of febrile responses in rodents.

Abbreviations: ACE, angiotensin-converting-enzyme; aCSF, artificial cerebrospinal fluid; ANG II, angiotensin II; $AT_1$, ANG II type 1; i.c.v., intracerebroventricular; i.h., intrahypothalamic; IL-1β, interleukin-1β; i.p., intraperitoneally; i.v., intravenous; LPS, lipopolysaccharide; $PGE_2$, prostaglandin $E_2$; PO/AH preoptic/anterior hypothalamic

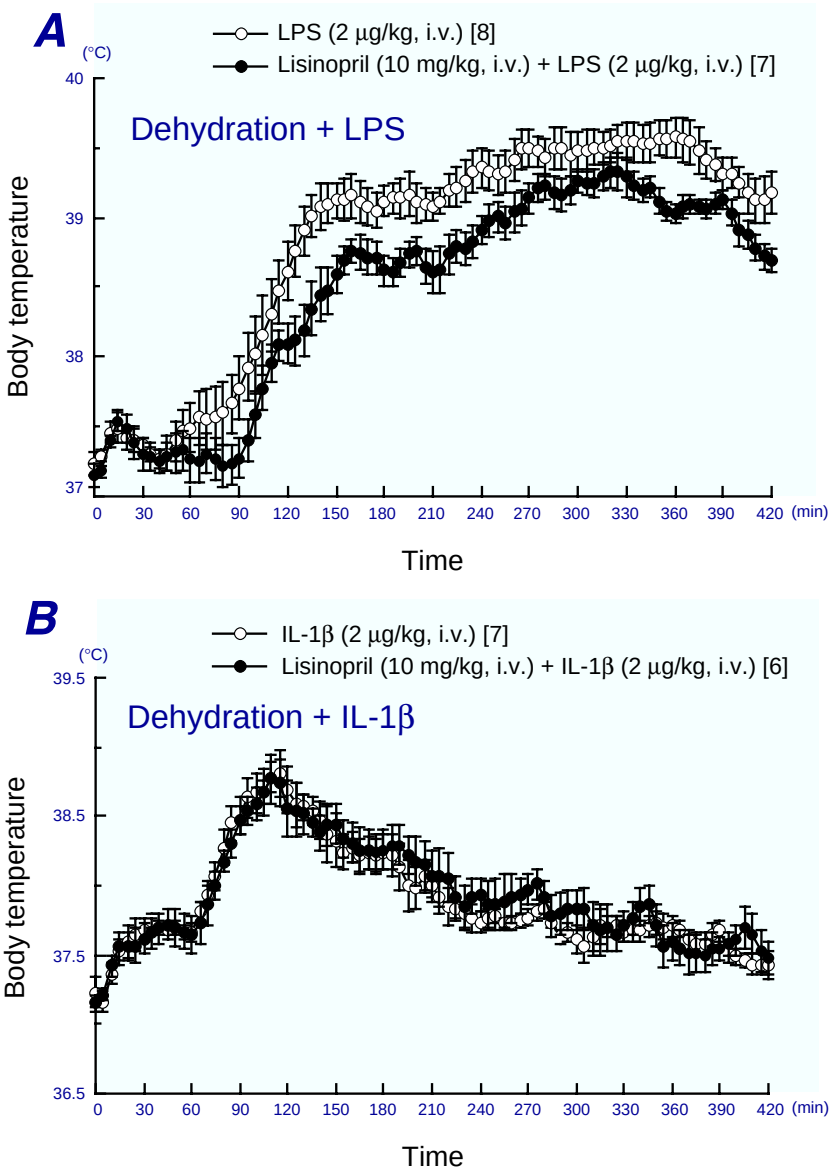


**Fig. 1.** Effect of intravenous (i.v.) injection of lisinopril on lipopolysaccharide (LPS)- or interleukin-1β (IL-1β)-induced fever in dehydrated rats. Changes (mean ± SEM) in body temperature (˚C) in dehydrated rats after i.v. injection at time 0 of LPS (**A:** 2 μg/kg) or IL-1β (**B:** 2 μg/kg). Lisinopril (10 mg/kg) was administered i.v. immediately before the injection of LPS or IL-1β. [ ], number of subjects. Data from Watanabe et al. (2000).

## ANG II and Fever in Rats

It is widely accepted that once in the body, bacterial endotoxin [or lipopolysaccharide (LPS)] stimulates leukocytes to produce pyrogenic cytokines, such as interleukin-1 (IL-1) or IL-6, leading to fever induction (Kluger, 1991; Dinarello, 1999). Furthermore, the febrile response to pyrogenic cytokines is believed to be mediated by prostaglandin E (PGE), acting within the brain as a final fever mediator (Blatteis and Sehic, 1997; Ushikubi et al., 2000). We have reported that in rats, ANG II and its receptors contribute to the induction of fever not only at its 1st step [namely, the LPS-induced production of pyrogenic cytokines (Watanabe et al., 2000;

Miyoshi et al., 2003)] but also at its final step [namely, the action of $PGE_2$ to cause fever (Watanabe et al., 1997)]. We should like to present our findings below.

### *ANG II is involved in fever production in rats at its 1st step, the LPS-induced production of IL-1*β

It is well known that a host develops a higher fever under dehydrated conditions than under euhydrated conditions. Indeed, in our hands, i.v. injection of a given dose of LPS induced a fever that was significantly greater in dehydrated rats than in euhydrated rats. However, dehydration had no effect on the fever induced by i.v. injection of IL-1β (Watanabe et al., 2000). These results suggested that the LPS-induced production of pyrogenic cytokines such as IL-1β might be enhanced by dehydration. Furthermore, since the secretion of ANG II increases under dehydrated conditions it seemed possible that ANG II might be involved in this enhanced production of pyrogenic cytokines, and ultimately in enhancing the fever seen in response to LPS. To test this possibility, we examined the effect of an angiotensin-converting-enzyme (ACE) inhibitor on febrile responses in dehydrated rats.

Figure 1 illustrates the effect of the ACE inhibitor lisinopril on the fever induced in dehydrated rats by an i.v. injection of LPS (2 μg/kg) (Watanabe et al., 2000). When lisinopril was given i.v. just before the LPS, the LPS-induced fever was significantly attenuated (Fig. 1A), indicating that ANG II is indeed involved in LPS-induced fever in dehydrated rats. In contrast, the same inhibitor had no effect on the fever induced by IL-1β itself (Fig. 1B), suggesting that ANG II may act by contributing to the LPS-induced production of pyrogenic cytokines, such as IL-1β.

To test the above possibility, we then examined the effect of lisinopril on the expression of IL-1β mRNA in the liver of dehydrated rats given an i.v. injection of LPS. Animals were sacrificed, the liver quickly removed and its IL-1β mRNA examined by Northern blot analysis. As shown in Fig. 2, LPS induced a significant increase in the expression of hepatic IL-1β mRNA at both 2 and 4 h after its injection, and this increase was reduced by treatment with lisinopril (Fig. 2A), an effect that, by quantitative analysis, was revealed to be statistically significant (Fig. 2B) (Miyoshi et al., 2003). This result suggested that ANG II contributes to the LPS-

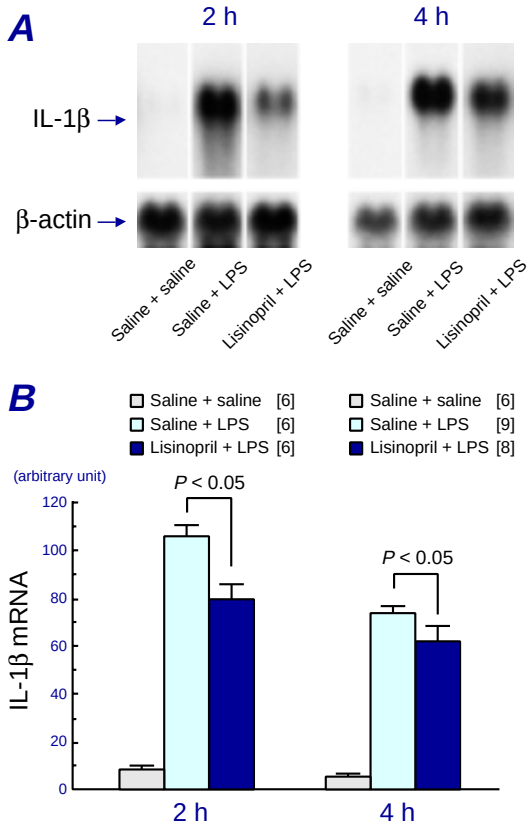


**Fig. 2.** Effect of i.v. injection of lisinopril on LPS-induced increase in IL-1β mRNA expression in the liver in dehydrated rats. IL-1β mRNA expression in the liver of "Saline + saline", "Saline + LPS" and "Lisinopril + LPS" groups. Lisinopril (20 mg/kg) or saline was administered i.v. 30 min before a single i.v. injection (at time 0) of LPS (2 μg/kg) or saline in dehydrated rats.

**A:** Autoradiograms showing IL-1β mRNA and β-actin mRNA bands in a representative animal from each group at 2h and 4h after "time 0".

**B:** Analysis of the density of the IL-1β mRNA bands in each group. Mean values (± SEM) obtained for IL-1β mRNA in the liver are expressed in arbitrary units. For each sample, the density of the IL-1β mRNA fraction was normalized with respect to the β-actin density. [ ], number of subjects. Data from Miyoshi et al. (2003).

induced induction of IL-1β at the mRNA level in dehydrated rats.

Next we investigated the effect of lisinopril on the production of IL-1β protein in the liver of dehydrated rats given an i.v. injection of LPS, the hepatic concentration of IL-1β being measured by enzyme-linked immunosorbent assay. The results are depicted in Fig. 3. The LPS-induced increase in the IL-1β protein concentration was significantly attenuated by lisinopril at both 2 and 4 h after the injection of LPS (Miyoshi et al., 2003). Furthermore, it should be mentioned that i.v. injection of ANG type 1 ($AT_1$) receptor antagonist reduced this LPS-induced IL-1β response in the liver as well (Miyoshi et al., 2003).

Taken together, the above results made it seem likely that ANG II and the $AT_1$ receptor are involved in the peripheral IL-1β production induced in dehydrated rats by LPS.

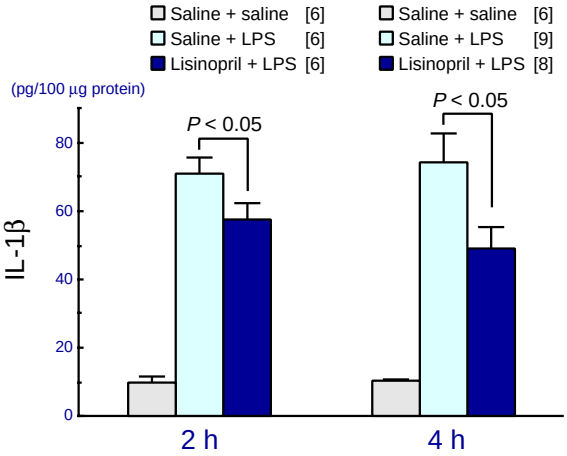


**Fig. 3.** Effect of i.v. injection of lisinopril on LPS-induced increase in liver concentration of IL-1β protein in dehydrated rats. Changes (mean ± SEM) in liver concentration of IL-1β in dehydrated rats 2 and 4 h after i.v. injection of LPS (2 μg/kg). Lisinopril (20 mg/kg) or saline was administered i.v. 30 min before a single i.v. injection (at time 0) of LPS (2 μg/kg) or saline. [ ], number of subjects. Data from Miyoshi et al. (2003).

### *ANG II is also involved in fever production in rats at its final step, the action of $PGE_2$ within the brain to induce fever*

Recently, we suggested that ANG II and its receptors within the brain participate in the development of one particular type of body-temperature increase, namely stress-induced hyperthermia (Saiki et al., 1997). Two types of ANG II receptors are present within the brain, $AT_1$ and $AT_2$ receptors (Saavedra, 1994; Wright and Harding, 1994; Aguilera et al., 1995; Watanabe et al., 1998) and we have shown that the brain $AT_1$ receptor is the one responsible for the induction of restraint-stress-induced hyperthermia in rats (Saiki et al., 1997). We therefore decided to investigate the effect of an intracerebroventricular (i.c.v.) injection of the $AT_1$-receptor antagonist losartan (60 μg) on the febrile responses induced in rats by an i.c.v. injection of $PGE_2$ (200 ng), a final fever mediator (Blatteis and Sehic, 1997; Ushikubi et al., 2000). We postulated that $AT_1$ receptors play an important role in this type of fever, too. Surprisingly, however, i.c.v. treatment with losartan (60 μg) had no effect on the febrile response induced by $PGE_2$. This dose of losartan (60 μg) is actually rather high, because less than 10 μg of the drug is sufficient to inhibit ANG II-induced responses such as increases in water intake (Rowland et al., 1992) and arterial blood pressure (Hogarty et al., 1992) in rats. Thus, since it seemed that $AT_1$ receptors are not involved in $PGE_2$-induced fever, even though they participate in stress-induced hyperthermia, we hypothesized that the other ANG receptor, the $AT_2$ receptor, might contribute to the development of $PGE_2$-induced fever. Indeed, we found that when an $AT_2$-receptor antagonist, CGP 42112A (20 μg), was administered i.c.v. just before i.c.v. $PGE_2$, the fever was significantly reduced (Watanabe et al., 1997). This result suggested that $AT_2$ receptors located somewhere in the brain contribute to the induction of fever by $PGE_2$.

To try to determine where in the brain these $AT_2$ receptors might be situated, we gave intrahypothalamic (i.h.) injections of CGP 42112A and observed their effects on fevers, because the rostral hypothalamus is thought to be the site at which $PGE_2$ acts to induce fever. For these i.h. injections, a stainless-steel cannula was implanted into the preoptic/anterior hypothalamic (PO/AH) region on one side at AP 1.8 mm, L 1.2 mm, and V 8.5 mm

[coordinates from the rat brain atlas of Pellegrino et al. (1979)] under sodium pentobarbitone anaesthesia (50 mg/kg, i.p.).

Figure 4 shows the effects of i.h. injections of CGP 42112A on the fever induced by $PGE_2$ (Watanabe et al., 1997). In artificial cerebrospinal fluid (aCSF)-treated controls, injection of $PGE_2$ (100 ng, i.h) resulted in a monophasic fever, the body temperature beginning to increase immediately and reaching peak at 25 min. This febrile response was attenuated by i.h. treatment with CGP42112A (2 and 5 μg) in a dose-related manner, the effect being significant at $P < 0.05$ [for CGP42112A (5 μg) + $PGE_2$, 0–40 min] (Fig. 4). CGP42112A (5 μg, i.h.) given alone had no effect on resting body temperature (Fig. 4).

These results suggest that $AT_2$ receptors in the rostral hypothalamus (PO/AH region) are involved in $PGE_2$-induced febrile responses in rats.

The question then arose as to whether ANG II mediates or, on the other hand, modulates febrile responses through its action on $AT_2$ receptors. To clarify this point, ANG II alone was administered into the rostral hypothalamus to observe its effect on resting body temperature. The results showed that ANG II, given i.h. at 25 ng or 5 μg, did not exert any significant effects on body temperature in rats (Watanabe et al., 1997). It therefore seems unlikely that ANG II mediates the induction of fever in rats; rather, ANG II is more likely to modulate the fevers induced by other agents. Having found that ANG II at a dose of 25 ng i.h. had no effect on resting body temperature, we used this dose to investigate whether ANG II modulates the fever induced by $PGE_2$. As shown in Fig. 5, this dose of ANG II, which had no effect on resting body temperature, enhanced the $PGE_2$-induced fever (Watanabe et al., 1997), suggesting that centrally acting ANG II modulates $PGE_2$-induced fever in rats.

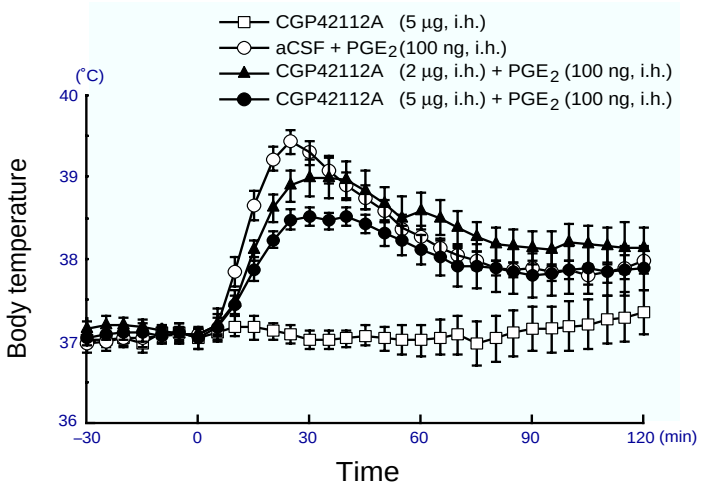


**Fig. 4.** Effect of intrahypothalamic (i.h.) injection of CGP 42112A on prostaglandin $E_2$ ($PGE_2$)-induced fever in rats. Changes (mean ± SEM) in body temperature (˚C) in rats after i.h. injection at time 0 of $PGE_2$ (100 ng). CGP 42112A (2 μg, $n = 11$; or 5 μg, $n = 8$) or aCSF ($n = 9$) was administered i.h. immediately before the injection of $PGE_2$. Also shown is the effect on resting body temperature produced by CGP 42112A (5 μg i.h., $n = 6$) given alone at time 0. Data from Watanabe et al. (1997).

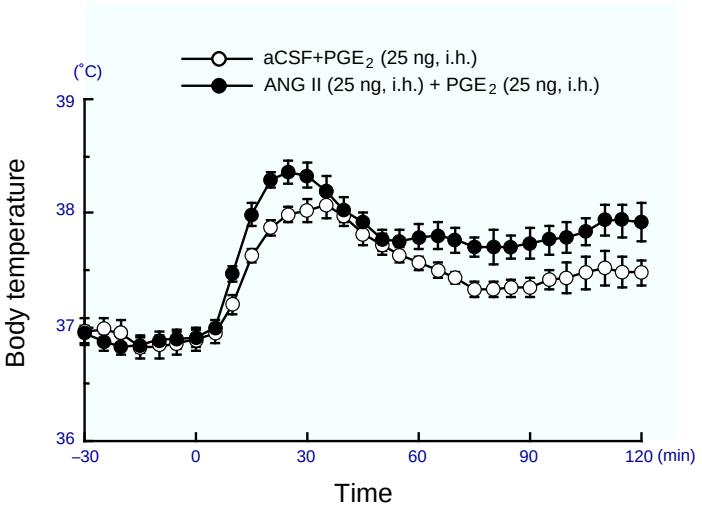


**Fig. 5.** Effect of i.h. injection of ANG II on $PGE_2$-induced fever in rats. Changes (mean ± SEM) in body temperature (˚C) in rats after i.h. injection at time 0 of $PGE_2$ (25 ng). ANG II (25 ng, $n = 8$) or aCSF ($n = 8$) was administered i.h. immediately before the injection of $PGE_2$. Data from Watanabe et al. (1997).

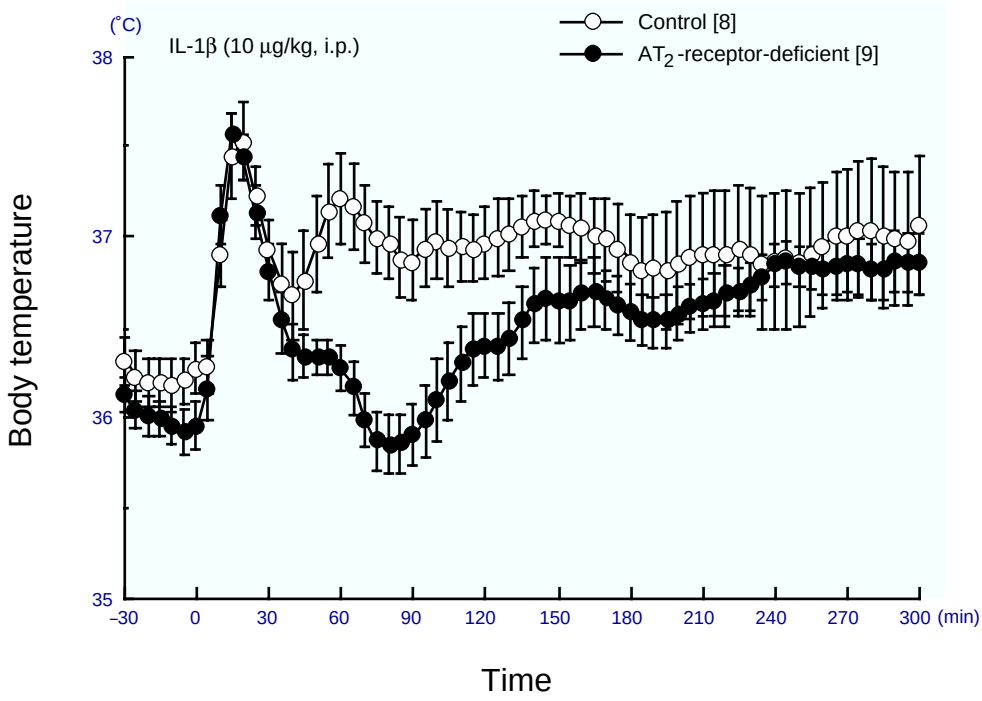


**Fig. 6.** Febrile responses induced in control and $AT_2$-receptor-deficient mice by intraperitoneal (i.p.) injection of IL-1β. Changes (mean ± SEM) in body temperature in control and $AT_2$-receptor-deficient mice after i.p. injection of IL-1β (10 μg/kg). [ ], number of subjects. Data from Watanabe et al. (1999).

Finally, we investigated the effects of an i.h. injection of an ACE inhibitor, lisinopril, on $PGE_2$-induced fever in rats. Lisinopril (5 or 10 μg, i.h.) or aCSF was given to rats 15 min before an injection of $PGE_2$ (100 ng, i.h.). The results showed that treatment with lisinopril reduced the $PGE_2$-induced fever in a dose-related fashion (Watanabe et al., 1997). Lisinopril (10 μg, i.h.) given alone had no marked effect on the resting body temperature. Thus, inhibition of ANG II synthesis within the rostral hypothalamus resulted in an attenuation of $PGE_2$-induced fever.

Taken together, our results suggest that in the rat, hypothalamic ANG II, which is synthesized and released in response to $PGE_2$, acts on $AT_2$ receptors located within the hypothalamus to facilitate $PGE_2$-induced fever. Interestingly, there are published reports indicating that $AT_2$ receptors are present in the rostral hypothalamus (Lenkei, et al., 1996; Lenkei, et al., 1997). Moreover, using microdialysis (perfusion flow rate = 2 μL/min and recovery rate = 14.2%) we recently found that i.h. perfusion with $PGE_2$ (2 μg/2 μL perfusate/min) resulted in ANG II release (on average, 0.17 pg/2 μL perfusate/min; $n$ = 3) within the rat's rostral hypothalamus (unpublished observations).

## ANG II and Fever in Mice

Recently, 2 laboratories developed mice deficient in $AT_2$ receptors that showed increased pressor responses to ANG II and a lower than normal body temperature (Hein et al., 1995; Ichiki et al., 1995). These mice also exhibit attenuated exploratory behavior and reduced spontaneous movements, suggesting that endogenous ANG II and $AT_2$ receptors regulate brain functions. We administered IL-1β intraperitoneally (i.p.) to $AT_2$-receptor-deficient mice to allow us to compare the febrile response in such mice with that in wild-type mice. As shown in Fig. 6, in the controls a single injection of IL-1β (10 μg/kg, i.p.) resulted in a biphasic fever which began after 5 min and reached its 1st peak at 15 to 20 min

(Watanabe et al., 1999). The 2nd peak occurred at around 60 min. The 1st phase involves an injection-stress-induced hyperthermia, while the 2nd phase is a true IL-1β fever. This IL-1β fever was suppressed in the $AT_2$-receptor-deficient mice, the effect being significant at $P < 0.05$ (25–180 min), while there was no difference in the 1st phase of the hyperthermia between the 2 groups of mice. The body temperature of the mutant mice was similar to that of the controls from 150 min onwards.

These results suggest that in mice, the pathway distal to the point at which IL-1β acts involves an action of ANG II on $AT_2$ receptors. Since in rats central injection of an $AT_2$-receptor antagonist attenuates $PGE_2$-induced fever [see above (Watanabe et al., 1997)], it is likely that the brain $AT_2$ receptor is important in the induction of $PGE_2$-induced fever in mice as well in rats. However, it should be noted in the above results that an attenuation of the IL-1β fever was observed only during the early stage of the hyperthermia (10–180 min). Therefore, it may be that the $AT_2$ receptor is just one of a number of factors contributing to IL-1β fever, and that its important role is performed mainly during the rising phase of this fever.

## Concluding Remarks

In this mini-review, we have focussed on the role of ANG II in the development of fever in rats and mice.

We have shown that an i.v. injection of LPS induces a fever that is significantly greater in "dehydrated" than in "euhydrated" rats (Morimoto et al., 1986; Watanabe et al., 1997). We have suggested i) that the LPS-induced production of pyrogenic cytokines such as IL-1β might be enhanced by dehydration and ii) that ANG II is involved in this enhanced production of pyrogenic cytokines, and ultimately in enhancing the fever seen in response to LPS. Indeed, an ACE inhibitor inhibited the LPS-induced production of hepatic IL-1β, as well as the fever, in dehydrated rats (Watanabe et al., 2000; Miyoshi et al., 2003).

It is widely accepted that $PGE_2$ acts within the rostral hypothalamus to induce fever, as a final mediator (Blatteis and Sehic, 1997; Ushikubi et al., 2000). We found that i.h. injection of either an $AT_2$-receptor antagonist or an ACE inhibitor inhibited the fever induced by an i.h. injection of $PGE_2$. Furthermore, ANG II given i.h., which had no effect on the resting body temperature, facilitated $PGE_2$-induced fever (Watanabe et al., 1997). These results suggest that hypothalamic ANG II, following its synthesis and release in response to $PGE_2$, acts on $AT_2$ receptors in the rat hypothalamus to facilitate $PGE_2$-induced fever.

Finally, when we gave a single i.p. injection of IL-1β to $AT_2$-receptor-deficient mice we found that the IL-1β-induced fever was significantly weaker than in the wild-type mice, suggesting that the brain $AT_2$ receptor is involved in the development of such fever in mice as well.

Taken together, the observations reviewed here make it seem likely that ANG II contributes to the development of fever by acting at both the 1st and final steps in the pathway for fever-induction in rodents.

*Acknowledgments:* The authors gratefully acknowledge 3 collaborators who contributed to the studies described here, Dr. Yukio Saiki, Dr. Yoshiyuki Sakata and Dr. Katsumi Nagata. We also thank Dr. R. Timms for his critical reading of the English manuscript. We are grateful to Otsuka Pharmaceutical and Dupon Merk Co. Ltd. for the supply of human recombinant IL-1β and losartan, respectively.

These studies were partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan.

## References

1 Aguilera G, Kiss A, Luo X, Akbasak BS. The renin angiotensin system and the stress response. Ann N Y Acad Sci 1995;771:173–186.

2 Blatteis CM, Sehic E. Prostaglandin E2: a putative fever mediator. In: Mackowiak PA, ed. Fever: basic mechanisms and management. Philadelphia: Lippincott-Raven; 1997. p. 117–146.

3 Delfraissy JF, Galanaud P, Balavoine JF, Wallon C, Dormont J. Captopril and immune regulation. Kidney Int 1984;25:925–929.
4 Dinarello CA. Cytokines as endogenous pyrogens. J Infect Dis 1999;179 Suppl 2:S294–S304.
5 Hein L, Barsh G S, Pratt RE, Dzau VJ, Kobilka BK. Behavioural and cardiovascular effects of disrupting the angiotensin II type-2 receptor gene in mice. Nature 1995;377:744–747.
6 Hogarty DC, Speakman EA, Puig V, Phillips MI. The role of angiotensin, $AT_1$ and $AT_2$ receptors in the pressor, drinking and vasopressin responses to central angiotensin. Brain Res 1992;586:289–294.
7 Ichiki T, Labosky PA, Shiota C, Okuyama S, Imagawa Y, Fogo A, et al. Effects on blood pressure and exploratory behaviour of mice lacking angiotensin II type-2 receptor. Nature 1995;377:748–750.
8 Kluger MJ. Fever: role of pyrogens and cryogens. Physiol Rev 1991;71:93–127.
9 Lenkei Z, Palkovits M, Corvol P, Llorens-Cortes C. Distribution of angiotensin II type-2 receptor ($AT_2$) mRNA expression in the adult rat brain. J Comp Neurol 1996;373:322–339.
10 Lenkei Z, Palkovits M, Corvol P, Llorens-Cortes C. Expression of angiotensin type-1 ($AT_1$) and type-2 ($AT_2$) receptor mRNAs in the adult rat brain: a functionalneuroanatomical review. Front Neuroendocrinol 1997;18:383–439.
11 Martin MFR, Surrall KE, McKenna F, Dixon JS, Bird HA, Wright V. Captopril: a new treatment for rheumatoid arthritis? Lancet 1984;i:1325–1327.
12 Miyoshi M, Nagata K, Imoto T, Goto O, Ishida A, Watanabe T. ANG II is involved in the LPS-induced production of proinflammatory cytokines in dehydrated rats. Am J Physiol 2003;284:R1092–R1097.
13 Morimoto A, Ono T, Watanabe T, Murakami N. Fever in rats during normal and dehydrated conditions. J Appl Physiol 1986;61:2060–2066.
14 Pellegrino LJ, Pellegrino AS, Cushman AJ. A stereotaxic atlas of the rat brain. 2nd ed. New York: Plenum; 1979.
15 Rezkalla S, Kloner RA, Khatib G, Khatib R. Beneficial effects of captopril in acute coxsackievirus B3 murine myocarditis. Circulation 1990;81: 1039–1046.
16 Rowland NE, Rozelle A, Riley PJ, Fregly MJ. Effect of nonpeptide angiotensin receptor antagonists on water intake and salt appetite in rats. Brain Res Bull 1992;29:389–393.
17 Saavedra JM. Brain angiotensin II receptor subtypes. In: Saavedra JM, Timmermans PBMWM, eds. Angiotensin receptors. New York: Plenum; 1994. p. 151–175.
18 Saiki Y, Watanabe T, Tan N, Matsuzaki M, Nakamura S. Role of central ANGII-receptors in stress-induced cardiovascular and hyperthermic responses in rats. Am J Physiol 1997;272:R26–R33.
19 Ushikubi F, Sugimoto Y, Ichikawa A, Narumiya S. Roles of prostanoids revealed from studies using mice lacking specific prostanoid receptors. Jpn J Pharmacol 2000;83:279–285.
20 Usui M, Egashira K, Tomita H, Koyanagi M, Katoh M, Shimokawa H, et al. Important role of local angiotensin II activity mediated via type 1 receptor in the pathogenesis of cardiovascular inflammatory changes induced by chronic blockade of nitric oxide synthesis in rats. Circulation 2000;101:305–310.
21 Watanabe T, Fujioka T, Hashimoto M, Nakamura S. Stress and brain angiotensin II receptors. Crit Rev Neurobiol 1998;12:305–317.
22 Watanabe T, Hashimoto M, Okuyama S, Inagami T, Nakamura S. Effects of targeted disruption of the mouse angiotensin II type 2 receptor gene on stress-induced hyperthermia. J Physiol 1999;515.3:881–885.
23 Watanabe T, Hashimoto M, Wada M, Imoto T, Miyoshi M, Sadamitsu D, et al. Angiotensin-converting-enzyme inhibitor inhibits dehydration-enhanced fever induced by endotoxin in rats. Am J Physiol 2000;279:R1512–R1516.
24 Watanabe T, Saiki Y, Sakata Y. The effect of central angiotensin II receptor blockade on interleukin-1β- and prostaglandin E-induced fever in rats: possible involvement of brain angiotensin II receptor in fever induction. J Pharmacol Exp Ther 1997;282:873–881.
25 Wright JW, Harding JW. Brain angiotensin receptor subtypes in the control of physiological and behavioral responses. Neurosci Biobehav Rev 1994;18: 21–53.

*Received and accepted September 19, 2003*

*Corresponding author: Tatsuo Watanabe, MD, PhD*