Role of Prostaglandin E₂ and Indomethacin in the Febrile Response of Pigeons

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Abstract: Intravenous (I.V.) injection of 10 μ g/kg *Escherichia coli* lipopolysaccharide (LPS), applied at 13:00, evoked in pigeons a biphasic rise of core temperature (T_{core}), so that LPS induced with a latency of 30 min first a decrease of T_{core} , and 90 min after LPS, T_{core} increased, obtaining maximum values from 18:00 to 20:00. Prostaglandins have been considered to be importantly involved in fevers in mammals. To investigate an involvement of prostaglandins in the cyclic variations of T_{core} in birds, pigeons were injected I.V. with either 10 mg/kg indomethacin (INDO) or 100 mg/kg aspirin, or they were treated with intracerebroventricular (I.C.V.) injections of 100 μ g/kg INDO at various times before or after LPS. When INDO or aspirin was I.V. injected 30 or 15 min before LPS, it diminished the initial decrease of T_{core} by more than 50%,

whereas the I.V. injection of these drugs 2 and 4 h after LPS did not affect the febrile rise of T_{core} . I.C.V. injections of INDO given either before or after LPS neither influenced the initial drop of T_{core} nor the following febrile hyperthermia. Both the I.V. injection of 1 mg/kg prostaglandin E₂ (PGE₂) and the I.C.V. injection of 1 μ g/kg PGE₂ lowered T_{core} . Our observations suggest that prostaglandins are not involved in the febrile elevation of T_{core} in pigeons, but appear to participate in the decrease of T_{core} , which shortly follows the I.V. injection of LPS. This initial drop of T_{core} following LPS may be caused by a peripheral action of prostaglandins because it was not influenced by the I.C.V. injection of indomethacin. [The Japanese Journal of Physiology 53: 253–258, 2003]

Key words: lipopolysaccharide, fever, indomethacin, prostaglandin E₂, pigeon.

Birds, like mammals, develop a febrile response after an injection of bacterial endotoxin [1–9] or following bacterial infection [10, 11]. In most mammals, prostaglandin E₂ (PGE₂) has been found to be an important mediator of fever [12, 13], though some studies of avian fever concluded that the central mechanism causing the febrile rise of core temperature (T_{core}) in birds differs from that in mammals. Although it has been described that the inhibitors of prostaglandin synthesis such as INDO or aspirin lower the febrile response in chickens [1, 5] and pigeons [10], these findings cannot be generalized. Artunkal *et al.* found that the pyretic effect of intrahypothalamic injections of PGE₁ in chickens was intensified and prolonged after a blockade of prostaglandin synthesis

with INDO [14]. Recently, Fraifeld *et al.* reported that systemic injection LPS elicited fever in chicken, but without an elevation of hypothalamic PGE₂ production [15]. Because of these conflicting results, the aim of the present study was to investigate the role of PGE₂ and INDO in fever generation in pigeons.

MATERIALS AND METHODS

This study was approved by the Committee of Animal Care of Tokyo Metropolitan Institute of Gerontology. Twenty-four domestic pigeons (*Columba livia*) weighing 474.6 ± 44.3 g (mean $\pm$ SD) were used in this study. They were housed in individual cages (length: 30 cm; width: 20 cm; height: 20 cm) under control conditions

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and during the experiments in a climatic chamber kept at $26 \pm 1^\circ\text{C}$, with light on at 09:00 and off at 21:00. Food and tap water were provided ad libitum at all times. T_{core} were obtained by using a biotelemetry system (Dataquest® LabPRO™, Data Sciences International Inc., St. Paul, MN, USA), sampled in 1 min intervals, and averaged over 10 min. The battery-powered transmitter (PhysioTel® Implant, Model TA10TA-F20, Data Sciences International Inc.) was implanted intraperitoneally, and a polyethylene catheter (i.d.: 0.5 mm; o.d.: 0.8 mm) filled with physiological saline was placed into the jugular vein at least 10 d before the experiments under equithesin anaesthesia (2.5 ml/kg I.M.). A stainless steel cannula (Plastics ONE Inc., Roanoke, VA, USA, C313 System, i.d.: 0.39 mm; o.d.: 0.71 mm) was implanted into the third ventricle by stereotaxic techniques, using the coordinates of Karten and Hodós [16] under equithesin anesthesia at least 7 d before the experiments.

On the day of the experiment between 09:00–09:30, the intravenous (I.V.) catheter and the intracerebroventricular (I.C.V.) cannula were elongated with polyethylene tubing. This maneuver inevitably caused a rise of T_{core} , but its return to baseline occurred within 90 min. For the time of the experiments, the pigeons remained in their cages after its width was narrowed by 10 cm, allowing them to move only back and forth. Bacterial lipopolysaccharide (LPS, *Escherichia coli* Serotype 0111: B4, Sigma, St. Louis, MO, USA) was dissolved in sterile saline to a concentration of $10 \mu\text{g}/\text{ml}$. One mg PGE_2 (Sigma) was dissolved in $100 \mu\text{l}$ ethanol and stored at -20°C . Immediately before the injection, ethanol was evaporated under nitrogen, and PGE_2 was dissolved in sterile saline to a concentration of $1 \text{ mg}/\text{ml}$ for I.V. injection and to $1 \mu\text{g}/10 \mu\text{l}$ for I.C.V. injection. Twenty mg INDO were dissolved in $100 \mu\text{l}$ ethanol together with 80 mg sodium hydrogen carbonate. Thereafter, ethanol was evaporated and sterile saline was added to give a final concentration of $10 \text{ mg}/\text{ml}/\text{kg}$ injections. The antipyretic efficiency of the INDO solution was satisfactorily tested in febrile rabbits. As a rule, saline or $10 \mu\text{g}/\text{kg}$ LPS were I.V. injected at 13:00. INDO at a dose of $10 \text{ mg}/\text{kg}$ was I.V. injected either 30 or 15 min before LPS or 2 or 4 h after. The I.C.V. injection of $100 \mu\text{g}/10 \mu\text{l}/\text{kg}$ INDO was made 15 min before LPS or 2 h after. DL-Lysine-mono-acetylsalicylic acid (Bayer, Leverkusen, FRG) was dissolved in saline to a concentration of $100 \text{ mg}/\text{ml}$, and $100 \text{ mg}/\text{kg}$ were I.V. injected at 12:45. PGE_2 was I.V. or I.C.V. injected at a dose of $500 \mu\text{g}/500 \mu\text{l}/\text{pigeon}$ I.V., or $1 \mu\text{g}/10 \mu\text{l}/\text{kg}$ I.C.V., respectively, at 13:00. At least 7 d were allowed for recovery after each experiment.

All data are presented as means $\pm$ SEM. T_{core} values taken from the 2 d before each experiment served as controls. Statistical analysis was carried out by using standard two-way parametric ANOVA coupled with Bonferroni/Dunn fractal ANOVA for repeated comparisons. A value of $p < 0.05$ was taken to indicate a significant difference.

RESULTS

As illustrated in Figs. 1–4 and by the data given in Table 1, the T_{core} of afebrile and febrile pigeons showed a clear day-night rhythm with a maximum of T_{core} occurring from 18:00 to 20:00, and a minimum from 05:00 to 06:00. An I.V. injection of LPS evoked a biphasic fever response in pigeons. As shown in Fig. 1, the injection of LPS first induced, with a latency of 30 min, a decrease of T_{core} of $0.94 \pm 0.14^\circ\text{C}$ (first phase). T_{core} started to rise about 90 min after LPS, with a steeper slope in comparison with normal rise during the light phase, obtaining maximum values from 18:00 to 20:00 (second phase). T_{core} then decreased parallel to the decline of the dark phase, but with a flatter slope, approaching values that were $0.2 \pm 0.1^\circ\text{C}$ higher than control from 05:00 to 06:00. As shown in Fig. 2, I.V. injection of the prostaglandin synthesis inhibitor INDO given either 30 or 15 min before LPS significantly diminished the initial decrease of T_{core} to values of 0.32 ± 0.09 or $0.50 \pm 0.07^\circ\text{C}$, respectively (Fig. 2a, b). The pretreatment of pigeons with aspirin, injected 15 min before LPS, diminished the initial drop of T_{core} to values of $0.48 \pm 0.14^\circ\text{C}$, but thereafter it did not alter the febrile

Fig. 1. Time course of core temperature (T_{core}) of pigeons following I.V. injections of either saline (open circles, $n=8$) or LPS (solid circles, $n=11$) at 13:00. The rise of T_{core} around 10:00 is due to handling. Means $\pm$ SEM. Values under the brackets are statistically significant at $p < 0.05$.

Fig. 2. Time course of T_{core} of pigeons following i.v. injections of LPS at 13:00 (open circles, $n=11$) and LPS combined with i.v. injection of INDO (solid circles) at 12:30 (a) ($n=8$), 12:45 (b) ($n=8$), 15:00 (c) ($n=8$), or at 17:00 (d) ($n=8$). Means $\pm$ SEM. Values under the brackets are statistically significant at $p < 0.05$.

Table 1. Changes of T_{core} ($^{\circ}\text{C}$, means $\pm$ SEM) following i.v. or i.c.v. injection of saline, LPS, INDO, or PGE₂ at 13:00, or following injection with LPS at 13:00 and treatment with i.v. or i.c.v. injection of INDO or aspirin (ASA) at the times indicated.

	n	Time				
		13:00	15:00	18:00	20:00	06:00
Saline i.v. 13:00	8	41.28 $\pm$ 0.08	+0.15 $\pm$ 0.11	+0.54 $\pm$ 0.12 [§]	+0.47 $\pm$ 0.11 [§]	-1.60 $\pm$ 0.20 [§]
Saline i.c.v. 13:00	5	41.44 $\pm$ 0.24	-0.05 $\pm$ 0.21	+0.13 $\pm$ 0.13	+0.07 $\pm$ 0.12	-1.87 $\pm$ 0.16 [§]
LPS i.v. 13:00	11	41.62 $\pm$ 0.05*	-0.66 $\pm$ 0.11* [§]	+0.75 $\pm$ 0.07* [§]	+0.65 $\pm$ 0.10* [§]	-1.71 $\pm$ 0.08 [§]
INDO i.v. 13:00	8	41.50 $\pm$ 0.09	+0.08 $\pm$ 0.09	+0.51 $\pm$ 0.11 [§]	+0.56 $\pm$ 0.13 [§]	-1.25 $\pm$ 0.21* [§]
LPS/INDO i.v. 12:30	8	41.42 $\pm$ 0.07	-0.22 $\pm$ 0.12	+1.13 $\pm$ 0.14* [§]	+1.05 $\pm$ 0.15* [§]	-1.25 $\pm$ 0.08* [§]
LPS/INDO i.v. 12:45	8	41.43 $\pm$ 0.11	-0.23 $\pm$ 0.05	+1.00 $\pm$ 0.13* [§]	+0.94 $\pm$ 0.18* [§]	-1.23 $\pm$ 0.19* [§]
LPS/INDO i.v. 15:00	8	41.45 $\pm$ 0.13	-0.47 $\pm$ 0.20* [§]	+1.04 $\pm$ 0.11* [§]	+0.95 $\pm$ 0.12* [§]	-1.06 $\pm$ 0.17* [§]
LPS/INDO i.v. 17:00	8	41.52 $\pm$ 0.08	-0.72 $\pm$ 0.15* [§]	+0.72 $\pm$ 0.14* [§]	+0.82 $\pm$ 0.22* [§]	-1.42 $\pm$ 0.09* [§]
LPS/INDO i.c.v. 12:45	5	41.36 $\pm$ 0.10	-0.53 $\pm$ 0.11* [§]	+0.97 $\pm$ 0.09* [§]	+1.07 $\pm$ 0.24* [§]	-1.04 $\pm$ 0.09* [§]
LPS/INDO i.c.v. 15:00	4	41.13 $\pm$ 0.36	-0.19 $\pm$ 0.22*	+1.38 $\pm$ 0.25* [§]	+1.44 $\pm$ 0.10* [§]	-0.72 $\pm$ 0.16*
LPS/ASA i.v. 12:45	8	41.38 $\pm$ 0.14	-0.45 $\pm$ 0.16* [§]	+0.76 $\pm$ 0.16* [§]	+0.43 $\pm$ 0.13 [§]	-1.48 $\pm$ 0.17 [§]
PGE ₂ i.v. 13:00	8	41.63 $\pm$ 0.16*	-1.29 $\pm$ 0.20* [§]	-1.07 $\pm$ 0.13* [§]	-0.92 $\pm$ 0.13* [§]	-1.82 $\pm$ 0.10 [§]
PGE ₂ i.c.v. 13:00	4	41.17 $\pm$ 0.13	-0.24 $\pm$ 0.15*	-0.14 $\pm$ 0.20*	+0.35 $\pm$ 0.15	-1.65 $\pm$ 0.16 [§]

Ambient temperature: 26 $\pm$ 1 $^{\circ}\text{C}$. * $p < 0.05$ vs. saline i.v.; [§] $p < 0.05$ vs. values at 13:00.

response to LPS during the day and the night phases. The i.v. injections of INDO at 15:00 or 17:00 h did not significantly influence the febrile levels of T_{core} during the light phase (Fig. 2c, d); however, the levels of T_{core} during the dark phase remained significantly higher when INDO was injected 15 min before and 2 h after LPS (Fig. 2b, c). Figure 3 shows that the i.c.v. injection of INDO given either 15 min before or 2 h

after LPS induced no significant alteration of the fever profile in comparison with that of saline-treated febrile pigeons. Because neither the i.v. nor the i.c.v. application of INDO nor i.v. aspirin exhibited significant effects on LPS-induced hyperthermia, the effects of PGE₂ on T_{core} were investigated. As shown in Fig. 4, both the i.v. and i.c.v. injection of PGE₂ lowered T_{core} with short latency. This effect lasted until the end

Fig. 3. Time course of T_{core} of pigeons following I.V. injections of LPS combined with I.C.V. saline at 15:00 (a) ($n=6$), I.C.V. INDO at 12:45 (b) ($n=5$), or I.C.V. INDO at 15:00 (c) ($n=4$). Means $\pm$ SEM. Values under the bracket are statistically significant vs. saline I.C.V. at $p < 0.05$.

of the light phase. The usual decrease of T_{core} in the dark phase differed from control because after the I.C.V. injection of PGE_2 , T_{core} decreased to significantly lower values from 01:00 to 05:00.

Fig. 4. Time course of T_{core} of pigeons following I.V. injections of saline at 13:00 (open circles, $n=8$), I.V. PGE_2 at 13:00 (solid circles, $n=8$), or I.C.V. PGE_2 at 13:00 (open triangles, $n=4$). Means $\pm$ SEM. Values under or over the brackets are statistically significant at $p < 0.05$.

DISCUSSION

The present study shows that LPS injected in pigeons during the light phase evokes first a decrease of T_{core} , but then body temperature rises to values significantly higher than those of the normal diurnal rise. This additional elevation of T_{core} persists also during the dark phase. Thus pigeons respond to LPS with biphasic fevers, superimposed on their diurnal rise and fall of T_{core} . These fevers, starting with an initial or protracted decrease of T_{core} following I.V. LPS has been observed by Pittman *et al.* [17] and Jones *et al.* [3] in chickens and by Nomoto [7, 8] and D'Alecy and Kluger [10] in pigeons, the latter injecting *Pasteurella multocida* bacteria intraperitoneally. All other studies available on avian fever report a monophasic fever regardless of whether LPS was I.V. injected [5, 6, 11, 14] or intraperitoneally injected [15] into the hypothalamus [18] or I.C.V. [1, 2]. We have found that an I.V. injection of LPS at night produces a monophasic fever [7]. Ambient temperature and the dose and time at which LPS is injected appears to be important in producing the biphasic febrile response, especially in small animals with a pronounced diurnal rhythm. The present study shows that prostaglandins are involved in the initial drop of T_{core} but not in the febrile response of pigeons because the initial decrease of T_{core} was significantly reduced when INDO or aspirin was injected I.V. either 30 or 15 min before LPS, but INDO did not influence the hypothermia when applied 2 or 4 h after LPS (Table 2). The dose of INDO used in the present study in pigeons effectively blocked LPS fever in rabbits [19] and was well above the dose used by

Table 2. Mean maximum level of the initial decrease of T_{core} (°C) after I.V. injection of LPS at 13:00 and I.V. injection of INDO or ASA at the times indicated.

LPS I.V. injection	<i>n</i>	
At 13:00	11	-0.94 ± 0.14
LPS I.V. at 13:00/INDO I.V. injection		
At 12:30	8	$-0.32 \pm 0.09^{* \$}$
At 12:45	8	$-0.50 \pm 0.07^{* \$}$
At 15:00	8	-0.69 ± 0.17
At 17:00	8	-1.04 ± 0.20
LPS I.V. at 13:00/ASA I.V. injection		
At 12:45	8	$-0.48 \pm 0.14^{* \$}$

Ambient temperature: $26 \pm 1^{\circ}\text{C}$. * $p < 0.05$ vs. LPS I.V. at 13:00; § $p < 0.05$ vs. INDO I.V. at 17:00.

Clark to inhibit the pyrogenic effect of peripherally or centrally administered leukocytic pyrogen in the unanesthetized cat [20].

The lowering of T_{core} by I.V. or I.C.V. injections of PGE₂, as shown in the present study, contrasts with the observations of Pittman *et al.* [17], Nisticò and Marley [21], and Macari *et al.* [5], who described only a hyperthermia in chickens, fowls, and broilers following intrahypothalamic or I.C.V. injections of prostaglandins of the E series. Artunkal *et al.* found in chicken that intrahypothalamic or I.V. injections of PGE₁ or PGE₂ induced hyperthermia in warm ambient temperature, but hypothermia in cold ambient temperature [14, 18]. On the other hand, a dose-dependent hypothermic effect following I.C.V. or intrahypothalamic injections of PGF_{2 α} was observed in adult fowls by Nisticò and Marley [21]. These results suggest that not a single prostaglandin but the entire profile of the derivatives of arachidonic acid after the stimulation of phospholipase-A₂ by pyrogens may influence the febrile alterations of body temperature. There have been reports that in echidna, a monotreme, I.C.V. injections of PGE₁ or PGE₂ induced hypothermia in thermoneutral and cold ambient temperature [22]. The initial drop of T_{core} following a pyrogen, however, is not a species-specific effect seen only in some birds or monotreme. Initial hypothermias have been observed in the rat [23, 24], and certain strains of mice [25], greatly depending on ambient temperatures, and hypothermias may therefore be detectable only in animals having low body mass.

The absence of any effects of the prostaglandin synthesis inhibitors INDO and aspirin on fever, as shown in the present study, casts some doubts on whether the febrile elevation of T_{core} of pigeons was produced by prostaglandins. Fraifeld *et al.* [15] reported that LPS elicited an elevation of body temperature, but not of hypothalamic PGE₂ production. They concluded that

hypothalamic PGE₂ is not involved in the development of the febrile response in birds, and that the central mechanisms of avian fever differ from those in mammals. Our results showing that I.V.- but not I.C.V.-injected INDO diminished the initial drop of T_{core} may be taken as evidence that LPS stimulated prostaglandin synthesis only at peripheral sites, and that the initial decrease of T_{core} might be a consequence of that. Also because in some mammals a common direct correlation between LPS-induced changes of T_{core} and hypothalamic prostanoids could not be established, Fraifeld and Kaplanski [26] concluded that PGE₂ might even not be a common mediator of fever in homeotherms. The results of our study are in line with the concept that there exists a prostaglandin-independent mechanism for LPS fever generation in the pigeon, a phenomenon that has been discussed also by Veale and Cooper [27] and by Mitchell *et al.* [28] in regard to rabbit.

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