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Lipopolysaccharide-induced fever in Pekin ducks is mediated by prostaglandins and nitric oxide and modulated by adrenocortical hormones

David A. Gray,1 Shane K. Maloney,1,2 and Peter R. Kamerman1

1School of Physiology, University of the Witwatersrand, Johannesburg, South Africa; and 2Physiology, School of Biomedical and Chemical Sciences, University of Western Australia, Perth, Australia

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To understand the phylogeny of the febrile response, it is clearly necessary to know as much as possible about fever in phyla other than mammals. In particular, a great deal could be learned from studies in the other homeothermic phylum, birds. To date, there is very little information available about fever in birds, although there is some evidence to suggest that the functional characteristics of avian fever are similar to those found in mammals. For example, as in mammals, bacterial infection (8) or administration of exogenous pyrogen such as LPS (30, 35) causes the development of fever in birds. However, unlike the situation for mammals, very little is known about the mechanisms underlying avian fever, and in particular, our understanding of the factors that mediate and modulate the febrile response in birds is not at all clear.

In mammals, there is clear evidence that prostaglandins (PGs) are key mediators of fever. For example, PG levels in the plasma, cerebrospinal fluid, and the preoptic/anterior hypothalamus, rise during fever, and this rise in PG levels correlates with the rise in febrile temperature. Also, injection of PG into the cerebral ventricles stimulates fever, while inhibition of prostaglandin synthesis blocks or attenuates fever (for a review, see Refs. 5, 50, 52). Nitric oxide (NO) has also been postulated to play a role in fever genesis, but its role is equivocal depending on whether the nitric oxide signaling is disrupted or augmented centrally or peripherally (48). In the periphery, NO is thought to be involved in maintaining thermogenic scope during fever genesis, rather than being involved in afferent pyrogenic signaling (22, 34, 49). As far as modulation of mammalian fever is concerned, it is generally accepted that glucocorticoids play a pivotal role, as their plasma concentrations rise during fever (37, 43). The febrile response is attenuated by dexamethasone (7), a synthetic glucocorticoid, and adrenalectomized animals are significantly more sensitive to the effects of endotoxin (6).

For birds, there is currently limited available information about the mediators and modulators of the febrile response and what is available is equivocal. For example, a role for PGs has not consistently been demonstrated, as some studies in birds have shown that inhibition of PG synthesis produces an attenuation of the febrile response to pyrogens (1, 8, 19, 29), whereas others have not shown such an effect (36, 38). In addition, a potential concern in studies is the effect of the drugs on normal body temperature. Indeed, in one study sodium salicylate lowered core temperature of both febrile and afebrile animals (8). It is therefore not clear whether the drug was truly antipyretic or induced hypothermic effects. Because most other studies also have not tested whether the drugs, at doses used, influence afebrile core temperatures, doubt has to be cast upon the interpretation that PG inhibition was actually antipyretic.

In view of the general paucity of our understanding of the mediation and modulation of fever in birds, the present study attempts to clarify the picture. Specifically, we have investigated the role in avian fever of PGs, important mediators of afferent pyrogenic signaling pathways in mammals, and NO, a putative efferent pyrogenic signaling molecule, by examining the effects of inhibiting PG and NO synthesis on LPS-induced...

Address for reprint requests and other correspondence: D. A. Gray, School of Physiology, Univ. of the Witwatersrand, Medical School, 7 York Rd., Parktown 2193, Johannesburg, South Africa (e-mail: grayd@physiology.wits.ac.za)
fever in Pekin ducks, a commonly used representative of the avian class, using doses of the relevant inhibitors that do not affect normal body temperature. In addition, the possible modulatory role of adrenocortical steroids has been assessed, first of all by measuring plasma concentrations of corticosterone, the primary glucocorticoid in birds (16, 17), during fever and, secondly, by determining the effects of exogenous dexamethasone and corticosterone upon the febrile response to LPS.

METHODS

Animals The studies were carried out with a group of 10 (4 male, 6 female) adult Pekin ducks (Anas platyrhynchos) within a body weight range of 2.4–3.5 kg, housed in flocks at a room temperature of 22°C and with a natural day-night cycle. They were fed dry chicken food enriched with minerals and vitamins, and drank tap water ad libitum. The study was approved by the Animal Ethics Screening Committee of the University of the Witwatersrand (clearance numbers ETH/1/90 and 01/16).

Body temperature measurement. Core temperatures of the ducks were recorded at 10-min intervals using wax-coated miniature temperature data loggers (Tidbit, Onset Computer, Bourne, MA) implanted into the abdominal cavity. Data logger implantation was done under ketamine and xylazine anesthesia at least 10 days before experimentation. Before implantation, data loggers were calibrated over a range of temperatures (34 to 44°C at 2°C intervals) against a certified precision quartz-crystal thermometer (Quat 100, Heraeus, Germany) such that abdominal temperatures could be measured to an accuracy of 0.04°C.

Pyrogens and drugs. Stock solutions of LPS (Salmonella typhosa, Sigma, St. Louis, MO) and N-nitro-l-arginine methyl ester (l-NAMe), a NO synthase inhibitor (Sigma), were prepared in sterile, pyrogen-free isotonic saline, such that appropriate doses of each could be administered in an injected volume of 1 ml/kg. Stock solutions of dexamethasone (Sigma) and corticosterone (Sigma) were prepared in ethanol and then diluted with sterile, pyrogen-free saline, such that appropriate doses could be given in an injected volume of 1 ml/kg. The cyclooxygenase inhibitor diclofenac was obtained as a commercial preparation in sterile ampules containing 75 mg diclofenac sodium in 3 ml sterile saline with a small amount of alcohol as solvent/preservative (Merck, RSA, New York). Because the drug solutions contained a small proportion (2%) of alcohol as solvent, the solutions of saline that were used as the controls were spiked with the same amount.

LPS was given intramuscularly at a dose of 100 μg/kg, a dose which when given intravenously produces a marked rise in body temperature of Pekin ducks (15, 30). The chosen doses of drugs used were based on reports from similar experiments in mammals (6, 9, 20, 21, 43). l-NAMe was given intraperitoneally at a dose of 200 mg/kg. Diclofenac, a cyclooxygenase inhibitor, was given intraperitoneally at the same amount. LPS, and body temperature was analyzed for 7 h postinjection.

Series 1. The effect of PG synthase inhibition upon LPS-induced febrile response was evaluated by comparing the body temperature responses to the endotoxin with and without a simultaneous injection of l-NAMe. We also tested for an effect of this dose of l-NAMe on normal body temperature by injecting l-NAMe alone. In random order, birds received either l-NAMe intraperitoneally, LPS intramuscularly with saline intraperitoneally, or LPS intramuscularly with l-NAMe intraperitoneally, and body temperature was analyzed for 7 h postinjection.

Series 2. The effect of NO synthase inhibition upon the LPS-induced febrile response was evaluated by comparing the body temperature responses to the endotoxin with and without a simultaneous injection of l-NAMe. We also tested for an effect of this dose of l-NAMe on normal body temperature by injecting l-NAMe alone. In random order, birds received either l-NAMe intraperitoneally, LPS intramuscularly with saline intraperitoneally, or LPS intramuscularly with l-NAMe intraperitoneally, and body temperature was analyzed for 7 h postinjection.

Series 3. The effect of adrenocortical hormones upon LPS-induced fever was evaluated by comparing the body temperature responses to the endotoxin with and without the administration of dexamethasone or corticosterone. We also tested for an effect of these doses of dexamethasone or corticosterone on normal body temperature by injecting dexamethasone or corticosterone alone. In random order, the birds received either dexamethasone or corticosterone alone, LPS intramuscularly with saline subcutaneously or LPS intramuscularly with either dexamethasone or corticosterone subcutaneously. The administration of the corticoids (or saline) was done 1 h before the LPS, and body temperature was analyzed for 7 h post-LPS injection.

For the above three series, the birds were removed from their holding stalls to be given the various treatments and then returned to the holding stalls for the remainder of the experiment. The injections were given at about 10:00 AM, and LPS injections were given at 14-day intervals to avoid tolerance developing to the pyrogen (8, 45).

Series 4. The plasma corticosterone concentration changes during fever were evaluated by comparing the hormone concentrations at 0, 1, 2, and 4 h after birds had received either saline or LPS. For this series, the birds were placed in restraining stands in a laboratory, and an indwelling cannula (Braunula 18G, Braun, Germany) was inserted into a leg vein and kept patent by the infusion of isotonic saline containing heparin (5 U/ml) at a rate of 0.1 ml/min. In random order, the birds received either LPS or saline intramuscularly, and blood samples (2 ml) were collected via the indwelling cannula. The blood was centrifuged at 3,000 rpm for 10 min, and the decanted plasma was stored at −20°C for subsequent measurement of corticosterone by radioimmunoassay (see later).

At the end of the series of experiments, the birds were killed by an overdose of pentobarbital sodium (Eutha-Naze, Centaur Laboratories, RSA, Chapel Hill, NC) administered intravenously according to Animal Ethics Screening Committee guidelines, and the data loggers were retrieved, and the data were downloaded.

Corticosterone assay. The plasma levels of corticosterone were measured using a commercially available radioimmunoassay (MP Biomedicals, Irvine, CA) following the extraction of the steroid by dichloromethane as previously described (14). The recovery of corticosterone averaged 76.7 ± 3.3%, and the results were corrected for this recovery. The inter- and intra-assay coefficients of variation were 7.2% and 10.4%, respectively.

Data analysis. All temperature data are shown as means ± SD. Body temperature figures are plotted as 10-min averages. For clarity, standard deviations on the body temperature figures are shown only at 1-h intervals and have been offset from each other. Body temperature data were analyzed using two-way ANOVA with treatment and time as main effects. To reduce the size of the model, hourly averages were calculated for each animal; from 1 h (series 1 and 2) or 2 h (series 3) before each intervention, until 7 h after each intervention. A Newman-Keuls post hoc test was used to compare hourly means when significant main effects or interactions were detected by the ANOVA. In all analyses, changes in body temperature after each intervention were compared with body temperature data that were recorded on the day before each intervention. Corticosterone data are shown as median (interquartile range). Plasma corticosterone concentrations after saline overdoses of pentobarbital sodium (Eutha-Naze, Centaur Laboratories, RSA, Chapel Hill, NC) administered intravenously according to Animal Ethics Screening Committee guidelines, and the data loggers were retrieved, and the data were downloaded.
or LPS injections were compared at each of the four sampling intervals using Wilcoxon matched-pairs sign-ranked test. A Bonferroni correction for multiple comparisons was made.

RESULTS

Series 1. Figure 1 shows the effects of administering two different doses of diclofenac on normal daytime body temperature (A) and LPS-induced fever (B). The administration of diclofenac at the doses of 5 mg/kg and 15 mg/kg had no significant effect on the normal daytime body temperature of the ducks (Fig. 1A) [5 mg/kg—Treatment effect: $F(1,6) = 0.003$, $P = 0.954$; 15 mg/kg—Treatment effect: $F(1,6) = 0.182$, $P = 0.684$], except for the occurrence of small, stress-induced hyperthermias at the time of injection (Fig. 1A) [5 mg/kg Time effect: $F(7,42) = 6.683$, $P < 0.001$, Interaction: $F(7,42) = 4.069$, $P = 0.002$; 15 mg/kg—Time effect: $F(7,42) = 2.376$, $P < 0.039$, Interaction: $F(7,42) = 2.785$, $P = 0.018$]. All animals administered with LPS, including those coinjected with diclofenac, developed fevers that had not resolved within 7 h of the pyrogen injection (Fig. 1B) [Treatment effect: $F(3,8) = 36.57$, $P < 0.001$, Time effect: $F(7,42) = 85.91$, $P < 0.001$, Interaction: $F(21,126) = 21.53$, $P < 0.001$]. However, both doses of diclofenac attenuated the magnitude of the fever from 180 to 320 min postinjection of LPS. This period of fever attenuation coincided with the time when the fever induced by LPS (with saline) was at its peak. Thereafter, the magnitude of the LPS with saline fever subsided with time, whereas the fevers produced when diclofenac was coadministered with LPS remained relatively constant. Consequently, from 380 min after the pyrogen was given, there were no significant differences in the size of the febrile response between drug- and saline-injected animal. Both doses of diclofenac had similar degrees of antipyretic actions, presumably indicating maximal effects.

Series 2. Figure 1 also shows the effects of injecting 200 mg/kg of L-NAME on normal daytime body temperature (C) and LPS-induced fever (D). Injection of L-NAME had no effect on normal daytime body temperature (Fig. 1C) [Treatment effect: $F(1,6) = 0.453$, $P = 0.526$]. However, the main effect of time was significant [$F(7,42) = 2.497$, $P = 0.031$], which probably was related to a general trend for body temperature to decrease over the course of the day; post hoc analysis, however, did not detect where differences detected by the ANOVA lay. No significant interaction between the main effects was detected [$F(7,42) = 1.519$, $P = 0.187$]. Injection of LPS, either with saline or L-NAME, induced a brief stress-induced handling hyperthermia, which after a short period of eutermia, was followed by a fever that had not resolved after 7 h (Fig. 1D) [Treatment effect: $F(2,12) = 28.04$, $P < 0.001$; Time effect: $F(7,42) = 25.61$, $P < 0.001$; Interaction: $F(14,84) = 17.50$, $P < 0.001$]. Although coinjection of LPS and L-NAME produced a fever, the magnitude of the febrile response was markedly reduced, being on average 0.8°C lower than the fever produced when LPS was administered with saline. Hence, inhibition of NO production caused a significant attenuation of the fever response to LPS.

Series 3. Figure 2 shows the effects of injecting dexamethasone or corticosterone on normal daytime body temperature (A) and LPS-induced fever (B). Injection of the steroids had no effect on normal daytime body temperature (Fig. 2A) [dexamethasone—Treatment effect: $F(1,11) = 3.631$, $P = 0.083$; corticosterone—Treatment effect: $F(1,11) = 2.558$, $P = 0.138$], except for the periods of stress-induced hyperthermia at the time of drug and saline administration (Fig. 2A) [dexamethasone—Time effect: $F(8,88) = 9.689$, $P < 0.001$, Interaction: $F(8,88) = 5.487$, $P < 0.001$; corticosterone—Time effect: $F(8,88) = 7.921$, $P < 0.001$, Interaction: $F(8,88) = 3.091$, $P < 0.001$]. All animals responded to LPS by developing a fever (Fig. 2B) [Treatment effect: $F(3,21) = 5.839$, $P < 0.001$; Time effect: $F(8,126) = 53.789$, $P < 0.001$; Interaction: $F(24,168) = 11.878$, $P < 0.001$]. However, although neither steroid affected the initial rise in body temperature, starting at about 240 min after LPS injection, both adrenocortical hormones blunted the continued development and maintenance of the fever. For example, after the divergence in temperature responses at 240 min, the average febrile temperature main-
The main objective of the present study was to evaluate the roles of prostaglandins and nitric oxide in the mediation of fever in birds and to determine whether or not the febrile response is modulated by adrenocortical steroids. Although there is some evidence suggesting that PGs, as in mammalian fevers (5, 31), play a role in the generation of fever in birds, the evidence is equivocal. For example, the febrile response in chickens is not associated with an increase in hypothalamic PGE2 production (10), nor have the body temperature responses to endotoxin been consistently affected by the inhibition of PG synthesis (29, 35, 36, 38). Moreover, studies that have apparently implicated PGs in the mediation of the febrile response of birds by demonstrating an attenuation of the response by cyclooxygenase inhibition, used doses of PG inhibitors that themselves are hypothemeric (8) and therefore invalidate the interpretation that PG inhibition is antipyretic. Currently, nothing is known about the role, if any, of NO in avian fever, and our selection of this particular candidate is based on the substantial evidence that supports a role for NO in the generation of fever in mammals (11). The same is true for adrenocortical hormones in so much that these steroids have been shown to modulate the febrile response in mammals (6, 7, 24). In this study, we chose to use dexamethasone, a synthetic steroid that has been shown to attenuate mammalian fever in several different animal models (6, 7, 24, 33), and we also investigated the effect of corticosterone, which is the main endogenous glucocorticoid of birds (16, 17).

Because of the limitations of previous avian studies involving cyclooxygenase inhibitors, it was very important to demonstrate that the doses of the specific enzyme inhibitors and steroid hormone that we used did not themselves affect normal body temperature. On the basis of this criterion, it is valid to assume that any reduction in the febrile response to LPS in the presence of PG and NO synthesis inhibitors, as well as the steroids, represents a true antipyresis.

Our results showed a marked reduction in the febrile response to LPS when PG synthesis was blocked by diclofenac and therefore agree with the growing body of evidence from studies in chickens (1, 8, 19, 29), which support a role for PGs in the development of fever in some birds. Interestingly, findings in pigeons seem to exclude applying the latter statement to birds in general, because at least one study with that species concluded that PGs are not involved in the LPS-induced elevation of body temperature (36). However, the findings in pigeons, which support the idea of a PG-independent mechanism, at least for LPS-induced fever, might explain why in our study there was no difference in the degree of inhibition produced by the two doses of diclofenac used, suggesting a maximum achievable inhibition. It may well be that two pyrogenic mechanisms exist in birds and that the relative importance varies in different avian species. This could also explain why the attenuation produced by PG inhibition ceased after about 5 h, perhaps because other mediators were responsible for maintaining the fever. Taken together with the

DISCUSSION

The main objective of the present study was to evaluate the roles of prostaglandins and nitric oxide in the mediation of fever in birds and to determine whether or not the febrile response is modulated by adrenocortical steroids. Although there is some evidence suggesting that PGs, as in mammalian fevers (5, 31), play a role in the generation of fever in birds, the evidence is equivocal. For example, the febrile response in chickens is not associated with an increase in hypothalamic PGE2 production (10), nor have the body temperature responses to endotoxin been consistently affected by the inhibition of PG synthesis (29, 35, 36, 38). Moreover, studies that have apparently implicated PGs in the mediation of the febrile response of birds by demonstrating an attenuation of the response by cyclooxygenase inhibition, used doses of PG inhibitors that themselves are hypothemeric (8) and therefore invalidate the interpretation that PG inhibition is antipyretic. Currently, nothing is known about the role, if any, of NO in avian fever, and our selection of this particular candidate is based on the substantial evidence that supports a role for NO in the generation of fever in mammals (11). The same is true for adrenocortical hormones in so much that these steroids have been shown to modulate the febrile response in mammals (6, 7, 24). In this study, we chose to use dexamethasone, a synthetic steroid that has been shown to attenuate mammalian fever in several different animal models (6, 7, 24, 33), and we also investigated the effect of corticosterone, which is the main endogenous glucocorticoid of birds (16, 17).

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fact that chickens respond to intracerebroventricular PG with fever (29, 38), there seems little doubt that at least some fevers in birds are ultimately PG-mediated and that the final, centrally acting mechanism in birds shows the same functional characteristics as mammals. In mammals, it is PGE2 that is thought to be the major central mediator of fever (23); however, there is no change in hypothalamic PGE2 production in chickens made febrile with LPS (10), perhaps excluding the likelihood that there is a common final mediator of fever in homeotherms. By inhibiting the prostaglandin synthesis pathway before the differentiation of the different classes of prostaglandin (46), we do not know which series of the prostaglandins is responsible for driving, at least partially, the fever in our birds, especially since there is evidence to indicate that multiple PG systems are activated during the acute phase response in birds (19). Like mammals, birds also express constitutive (39) and inducible (25) isoforms of cyclooxygenase; however, our use of diclofenac sodium, a relatively unspecific cyclooxygenase inhibitor (51), does not allow us to speculate whether the source of prostaglandins in our study is from inducible or constitutive isoforms of the enzyme. In fact, even in mammals the role(s) of inducible and constitutive isoforms of the cyclooxygenase enzyme is not clear (52). Our study also does not reveal the signaling pathways that lead to prostaglandin synthesis during avian fever. However, although largely speculative, a role for cytokines, especially interleukin-1, has been suggested (29).

The fact that L-NAME produced a marked attenuation of the LPS-induced fever is consistent with the concept that NO is a component of the mediatory mechanism of avian fever. It is unlikely that L-NAME produced its effects via NO-independent effects, such as via an action at muscarinic receptors (2). We say this because, unlike the inhibition of NO synthase by L-NAME, the blockade of muscarinic receptors by L-NAME is not reversed by L-arginine (11). Although we did not inject our animals with L-arginine, substantial evidence exists from mammalian studies that the thermoregulatory effects of NO synthase inhibition are reversed by L-arginine (11). In addition, LPS-induced fever was unaffected by muscarinic blockade by scopolamine in rats (44). Nevertheless, whether the role of NO in avian fever is the same as in mammalian fever is equivocal. Unfortunately, even in mammals, the mechanisms by which NO influences fever is a matter for speculation. For example, inhibiting NO synthesis may attenuate fever development by disrupting afferent fever signaling pathways, central processing of pyrogenic signals, effenter output to thermoeffector organs, or the functioning of those thermoeffectors. Within the central nervous system, NO has consistently been shown to promote thermolysis in mammals (12, 13, 32, 47). Thus, if the gas has similar actions in birds, the attenuation of fever in our ducks is unlikely to have been caused by central inhibition of NO synthesis because this would have resulted in heat storage and higher body temperatures. Also, extrapolating from mammalian studies, it is improbable that inhibiting NO synthesis reduced fever magnitude by attenuating pyrogen-induced cytokine production (40, 41, 42). Recent evidence from rats indicates that NO is not important in pyrogenic signaling over the blood-brain barrier (49), but even within the mammalian phylum, there may be some species variation in this role of NO, with NO being important for transduction of pyrogenic signals over the blood-brain barrier in rabbits (18, 26, 27, 28). Thus L-NAME may influence avian fever by disrupting pyrogenic signaling over the blood-brain barrier. Alternatively, L-NAME may have decreased activation of thermoeffector or decreased the capacity of thermoeffector to increase heat storage (22, 34, 44). Consequently, our current findings that L-NAME had no effect on normal body temperature control but did affect fever development can be explained by blockade of the pyrogenic signal transduction mechanism or by the thermogenic scope being reduced.

It is well established that in mammals, fever can be modulated by both endogenous and exogenous glucocorticoids (6, 24), an action that is attributed to the inhibition of production of pyrogenic cytokines and PGs (7, 33). In the present study, the elevation of circulating concentrations of corticosterone during fever, which has also been demonstrated in chickens (1, 19), and the attenuation of the LPS-induced fever by dexamethasone and corticosterone, indicate a similar role for glucocorticoids in avian fever. However, the precise role that glucocorticoids play in avian fever is difficult to assess because plasma levels of the autocoid were elevated during the early part of the fever, whereas exogenously administered steroid only affected the later phase of the temperature response. It could well be that if two pyrogenic mechanisms are in fact involved that glucocorticoids have differential effects and/or interactions with the two mechanisms. However, this is extremely speculative and unlikely to be resolved until our understanding of the identity and physiological actions of regulatory mediators (especially cytokines) in birds is enhanced.

In addition to clarifying some of the mechanisms behind the mediation and modulation of fever in birds, this study also illustrated some other points of interest. The first concerns the sensitivity of the ducks to LPS given via different routes. In the present study, the Pekin ducks responded to intramuscularly injected LPS at a dose of 100 μg/kg with a marked increase in body temperature within 2 h of administration and a peak of temperature elevation after 3–4 h. The magnitude of the response was almost identical to that observed in previous studies with Pekin ducks, in which the same dose of LPS was given intravenously (15, 30), indicating a similar degree of sensitivity to LPS for the two routes of administration. In addition, the profile of the febrile response was the same for both routes, in that the temperature elevation was monophasic. This itself raises another point of interest, as it is unclear whether it is the monophasic profile seen in our ducks that is the “typical” avian febrile response or the biphasic response seen in pigeons (8, 35, 36) and chickens (38), under certain circumstances. It is highly likely that, as in mammals (23), the specific avian febrile response is dependent on several factors including type, route, and dose of pyrogen, as well as species. The final point of interest concerns the stress-induced hyperthermia associated with the handling of the birds. In mammals this elevation of body temperature has been categorized as a fever by some researchers (4) and for birds too, it has been suggested that the elevation in body temperature due to handling (15, 30, 35, 36) can be regarded as a fever (3). However, in the present study, the fact that the handling-induced rise in body temperature was not at all changed by any of the inhibitors of the LPS-induced rise in body temperature suggests that the stress-induced hyperthermia is not a fever, at least not one that works via the same mechanism as LPS.
MEDIATORS AND MODULATORS OF FEVER IN DUCKS

Perspectives

The implication of this study is that the list of similarities between avian and mammalian fevers can be extended and provides important information about the evolution of fever. The apparent involvement of NO and PGs as mediators of fever in both birds and mammals, together with the analogous modulatory role for glucocorticoids in both groups of animals, is evidence in support of the idea that the febrile mechanism has a common origin, even if the relative roles of mediators such as PGE2 may differ. Future experiments will need to examine the precise roles of PGs, NO, and adrenocorticoids, especially in view of the indication of our study that other, as yet unidentified, modulators of avian fever may be important at different stages of the fever profile in birds. In addition, if the physiology of avian cytokines can be characterized, then our understanding of the similarities and differences between mammalian and avian fever will be markedly enhanced.

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