Br. J. exp. Path. (1988) 69, 577–588

Fever and acute phase reactants in the rat

H. van Vugt, J. van Gool and N.E.P. Deutz
Department of Experimental Internal Medicine, Academic Medical Centre, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands

Received for publication 12 March 1987
Accepted for publication 17 March 1988

Summary. In rats synthesis of some acute phase reactants can be induced by a combination of corticosteroids and adrenaline. During fever both hormones show high plasma levels. We studied the effect of fever induced by intra-cerebroventricular (i.c.v.) injection of PGE_2 on the acute phase response. Fever was continuously recorded and 24 h after induction acute phase reactant (APR) response was measured as indicated by the rise of α-macrofetoprotein (α_M FP, α_2 macroglobulin of the rat). Controls received 0.9% saline i.c.v. Controls did not develop fever (dTmax $\leqslant$ 1°C) nor did they show significant APR response. The maximal rise in body temperature after PGE_2 (2.6 ± 0.7°C) correlated significantly with the rise in α_M FP concentration 24 h later. Adrenalectomy prevented the APR response completely but the magnitude of the fever reaction remained the same (2.1 ± 0.3°C). α-Blockade gave a smaller fever response but had no effect on the APR response. In α- and β-blockade, fever response was normal but no APR response was obtained. Destroying the sympathetic nerve supply to the liver with 6-OH dopamine retarded the fever response but again APR response was not impeded. In order to differentiate between the role of fever as such and the effect of PGE_2 on APR synthesis, we used heat exposure to induce hyperthermia in normal rats who showed an APR response comparable with that after i.c.v. PGE_2. Pretreatment with sodium salicylate before inducing hyperthermia led to a variable rise in α_M FP. Fever as such, without tissue injury, induces an APR response. The pathway to this effect probably involves circulating corticosterone and adrenaline, possibly via a β-receptor mediated stimulation.

Keywords: fever, acute phase reaction, PGE_2, rat α_2 macroglobulin

Inflammatory processes and many other forms of tissue injury are often accompanied by an elevation of the so-called acute phase proteins, also designated acute phase reactants (APR). Many authors consider endogenous pyrogen or interleukin-1 as the common determinant inducing the liver to enhanced synthesis of APR (Baily *et al.* 1976; Turchik & Bornstein 1980; Blatteis *et al.* 1984; Ahokas *et al.* 1985). However, many conditions exist where APR is elevated but a relation with fever is either not obvious or totally absent. After surgical intervention or a myocardial infarction strongly elevated APR can be observed without fever. The reverse is also true: in some diseases with fever an APR reaction is minimal or absent. The clinical significance of this phenomenon

Correspondence: Dr H. van Vugt, Department of Experimental Internal Medicine, G.2-130, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam.

is intriguing but not yet understood, and more insight into the effect of fever on the production of APR is needed.

It is well known that fever is often accompanied by prolonged elevation of plasma catecholamine and glucocorticoid levels (Jones *et al.* 1958; Chowers *et al.* 1966). Experiments in rabbits show that endogenous pyrogen, administered intra-cerebroventricularly, induces fever and production of APR (Turchik & Bornstein 1980). In the rat some APRs can be induced by administration of glucocorticoids, particularly in combination with adrenaline (Van Gool *et al.* 1984). In this situation α_2 macrofetoprotein (α_2-macroglobulin of the rat, α_M-FP), a typical APR of the rat shows a sharp rise after 24 h. It is thus possible that fever induces high levels of stress hormones which, in turn, enhance APR synthesis.

To analyse this hypothesis we induced fever in rats by intra-cerebroventricular (i.c.v.) administration of PGE_2, thus avoiding peripheral tissue lesion and systemic macrophage activation, in order to minimize endogenous pyrogen activity. Acute phase proteins were monitored by measurement of α_M-FP levels before and 24 h after induction of fever. Corticosteroids and catecholamines were studied in relation to the fever. Other experiments and various blocking procedures were carried out to analyse the observed phenomena in more detail. For this we used adrenalectomy, α- and β-blockade and sympathetic denervation of the liver by 6-OH dopamine. In order to differentiate between the role of fever as such and the effect of PGE_2 on APR synthesis we used heat exposure to induce hyperthermia in normal rats and rats pretreated with sodium salicylate, a blocker of prostaglandin synthesis (Vane 1971).

Materials and methods

Experimental procedure

Male Wistar rats, weighing between 250 and 300 g (TNO-Zeist, The Netherlands) were used throughout the experiments. For i.c.v. injections a polyethylene cannula was implanted in the right lateral cerebral ventricle under pentobarbital (4.8 mg/100 g bodyweight i.p.) anaesthesia. Coordinates were 2 mm lateral and 1 mm caudal from the bregma. The cannula was kept patent by inserting a stilette and keeping it inserted after implantation. The injections were given to the unanaesthetisized rat at least one week after implantation. Colonic temperature was measured with a thermistor probe inserted about 6 cm into the rectum and taped to the base of the tail. Temperature was recorded every 5 min for at least three hours. Rats were housed in individual cages and moved freely during the experiments after the injection in the cerebral ventricle. Room temperature was 21–23°C.

To give injections the stilette was removed and a polyethylene tube was passed through the cannula. This tube was connected to a Hamilton microlitre syringe and injections were made slowly over one minute in a volume of 5 μl. Adrenalectomy was performed bilaterally under pentobarbital anaesthesia using a paravertebral dorsal approach. After adrenalectomy the rats received a 0.9% NaCl solution instead of normal drinking water and were allowed to eat *ad libitum*.

Corticosterone was determined using a fluorimetric method (Silber *et al.* 1958) with slight modifications involving methylene chloride for the extraction of plasma. Adrenaline and noradrenaline were determined by a radioenzymatic liquid chromatographic determination as described by Endert & Punt (1982). α_2-macrofetoprotein was measured by the Mancini method with monospecific rabbit antiserum. PGE_2 was obtained from Serva Feinbiochemica, Heidelberg, Germany, and kept as a stock solution at −20°C. Solutions were prepared from stock with sterile and pyrogen-free 0.9% NaCl (2 μg PGE_2 in 5 μl) and used immediately.

α-Blockade was performed with Dibenyline (phenoxybenzamine HCl BP) (Smith Kline and French, Hertfordshire, UK). Rats

received 2.5 mg Dibenyline/kg i.p during four days. Experiments were performed on the fourth day. β-Blockade was performed with Tenormin (atenolol 5 mg/10 ml) (ICI-Farma, Rotterdam, The Netherlands) used at a dosage of 3 × 2 mg/kg/i.p. daily for four days. Experiments were performed on the fourth day. 6-OH dopamine (β-(2,4,5-trihydroxyphenyl)ethanylamin-HCl, rein) was obtained from Serva Feinbiochemica, Heidelberg, Germany. Rats received 50 mg/kg injected in the portal vein. The drug was dissolved in saline containing ascorbic acid (0.1%) and used immediately after preparation. Experiments were performed one week later.

Heat exposure

Rats were placed in individual cages in which the temperaure was maintained between 34 and 36°C by means of a heating lamp, such that the magnitude of the colonic temperature rises were similar to that of the PGE_2-treated animals. When colonic temperature reached 41°C the exposure was ended. In other experiments, rats received sodium salicylate in 0.9% NaCl (200 mg/kg i.p.) one hour before heat exposure. Statistical analyses used Student's *t*-test for paired and unpaired data.

Results

Effect of PGE_2 and 0.9% NaCl in normal rats

Table 1 summarizes the data obtained in the control group receiving 0.9% NaCl i.c.v. and the group receiving PE_2 i.c.v. In controls little or no elevation of temperature was observed, maximum 1°C. This could be due to handling the animals, which were unrestrained and not under anaesthesia. There was a slight, variable rise of α_M-FP. The difference before and after the experiment was not significant. PGE_2 induced fever in high frequency in most cases accompanied by a rise in APR. Maximal rise of temperature was reached in 20–25 min. The difference in α_M-FP before and after fever was significant ($P<0.001$). In two animals no rise of temperature was observed (11% of the experiments). On the other hand, two animals showed no increase in α_M-FP despite a rise in temperature of 2–2.5°C (Fig. 1). In the group treated with PGE_2 a correlation was found between the maximal rise in temperature (dT max) and the level of α_M-FP after 24 h ($n=17$, $r=0.5897$, $P<0.05$) (Fig. 1). The same relation was found using the area under the temperature curve till dT max and the α_M-FP levels after 24 h ($n=17$, $r=0.650$, $P<0.01$) (Fig. 2).

Table 1. Maximal rise in body temperature (dT max) after PGE_2 i.c.v. and 0.9% NaCl i.c.v. α_M-FP levels at the time of the experiment and 24 h later. Values, mean ± SE. Student's *t*-test for paired data

Experimental group	dT max °C	α_M-FP μg/ml	
		Before fever	24 h after fever
Controls (0.9% NaCl) ($n=13$)	0.34 ± 0.09	58 ± 13	173 ± 55
PGE_2 ($n=17$)	2.61 ± 0.70	89 ± 36	572 ± 124*

* $P<0.001$ *vs* α_MFP before PGE_2. $P<0.05$ *vs* α_MFP 24 h after NaCl.

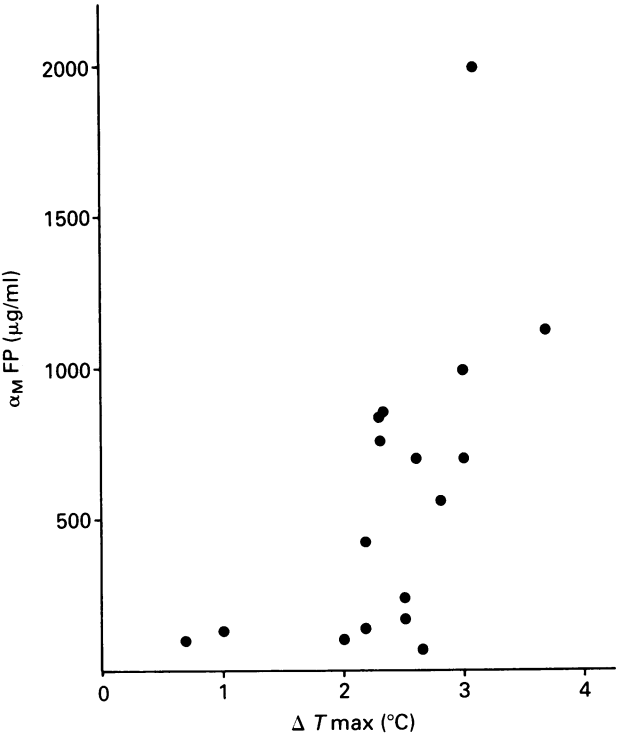

Fig. 1. Relation between the maximal rise in body temperature (dT max) and α_MFP levels 24 h later ($n=17$, $r=0.5897$, $P<0.05$).

We concluded that in most cases centrally induced fever led to an APR reaction, at least of α_M-FP, but that exceptions exist in both directions. Figure 1 suggests that a maximal rise of at least 2°C is needed to enhance α_M-FP level significantly, indicating some kind of threshold value.

Fever and APR in adrenalectomized rats

Adrenalectomy was performed 10 days before induction of fever. This procedure was adopted because laparotomy, necessary to perform adrenalectomy, itself induces a transient acute phase reaction (Van Gool *et al.* 1984).

From Table 2 it is obvious that adrenalectomized animals developed fever after PGE_2 administration but that none had elevated α_M-FP. Thus after adrenalectomy, fever and APR response are clearly uncoupled suggesting that adrenal activity is necessary for elevation of APR but not for centrally induced fever.

Catecholamine and corticosterone levels during fever

In a series of experiments serum corticosterone and catecholamine levels were measured at the point of maximal rise of body temperature after PGE_2 administration, and 20 min after injection of 0.9% NaCl. The results are summarized in Table 3. It can be seen there was no significant ($P>0.05$) difference in the rise of corticosterone between animals receiving either 0.9% NaCl or PGE_2 i.c.v. Adrenalectomized rats had no rise of corticosterone after challenge with PGE_2 despite a normal rise in temperature.

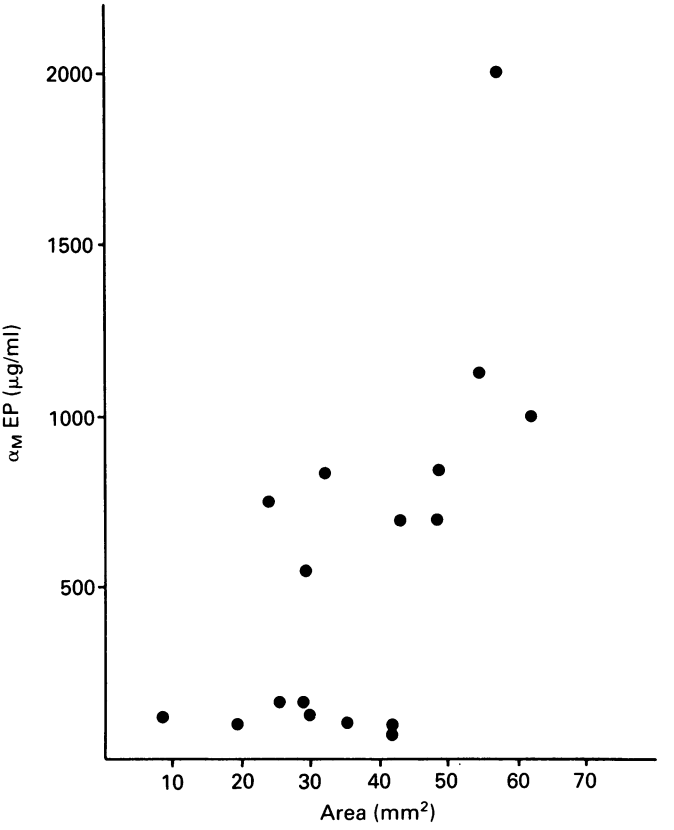

Fig. 2. Relation between the area under the fever curve till the maximum rise in body temperatures (dT max) and α_MFP levels 24 h later ($n=17$, $r=0.650$, $P<0.01$).

Table 2. Maximal rise in body temperature after PGE_2 i.c.v. and α_M-Fp levels at the time of the experiment and 24 h later. Values mean ± SE

		α_M-FP μg/ml	
Experimental group	dT max °C	Before fever	24 h after fever
Adrenalectomy ($n=8$)	2.10±0.32	111±10	108±11

On the contrary, the corticosterone levels remained very low (10 ng/ml). Adrenaline levels rose significantly after PGE_2 i.c.v. to three times that of the control value. Noradrenaline was slightly elevated in animals receiving PGE_2. Adrenalectomized rats had low adrenaline levels (50 ng/l) that rose slightly to 150 ng/l after PGE_2, but noradrenaline response was very high, significantly more than after PGE_2 in normal rats.

Thus the most important effects of fever in normal rats after PGE_2 appear to be elevation

Table 3. Adrenaline, noradrenaline and corticosterone levels in rats at the time of maximal rise in body temperature (dT max) after PGE_2 i.c.v. of 25 min after 0.9% NaCl i.c.v. Normal rats received no i.c.v. injection. Values, mean ± SE

Experimental group	Adrenaline (ng/l)	Noradrenaline (ng/l)	Corticosterone (ng/ml)
Normal rats ($n=6$)	262±14	427±12	129±10
0.9% NaCl ($n=5$)	356±38	496±74	560±40*
PGE_2 ($n=6$)	1076±212†	717±87	730±56‡
Adrenalectomy and PGE_2 ($n=4$)	151±2	1344±112§	10±1

* $P<0.002$ *vs* normal rats. $P<0.001$ *vs* adrenalectomy.
† $P<0.05$ *vs* normal rats and 0.9% NaCl. $P<0.01$ *vs* adrenalectomy.
‡ $P<0.001$ *vs* normal rats and adrenalectomy.
§ $P<0.001$ *vs* normal rats and 0.9% NaCl. $P<0.005$ *vs* PGE_2.

of circulating adrenaline and corticosterone levels. By contrast, in adrenalectomized animals only noradrenaline levels rise significantly, and adrenaline and corticosterone levels remain normal.

Adrenergic blocking

We used Dibenyline as an α-blocker (2.5 mg/kg i.p.) and atenolol as a β-blocker (2 mg/kg i.p. three times a day). As can be seen in Fig. 3, α-blockade delayed the rise in temperatures significantly, whereas α- and β-blockade had no effect on the time to reach dT max (not shown in Fig. 3). The data from α- and β-blockade are summarized in Table 4; dT max was reduced after α-blockade but not significantly and α_M-FP synthesis remained normal, even high. Combined blockade had virtually no effect on dT max, but abolished α_M-FP synthesis.

6-OH dopamine

Sympathetic denervation of the liver was obtained by injection of 50 mg/kg 6-OH dopamine in the portal vein via laparotomy 10 days before the experiments. After administration of 6-OH dopamine α_M-FP did not completely return to basal values. Sympathetic denervation of the liver led to a smaller rise of body temperature after PGE_2 i.c.v. comparable to the effect of α-blockade. The levels of α_M-FP 24 h after stimulation with PGE_2 reached the same level as in normal rats and after α-blockade (Table 5).

Heat exposure

In these experiments we used normal rats and rats pretreated with sodium salicylate one hour before heat exposure. Salicylate treatment had no effect on basal colonic temperature. Figure 4 shows the rise in temperature obtained with heat exposure. Compared with rats receiving PGE_2 i.c.v. dTmax was reached a little later and lowering of temperature more slowly. As expected, salicylate had no effect on the rise of temperature caused by heat exposure. Table 6 shows that hyperthermia led to a rise in α_M-FP after 24 h comparable with the rise after PGE_2 i.c.v.

Hyperthermia and salicylate combined led

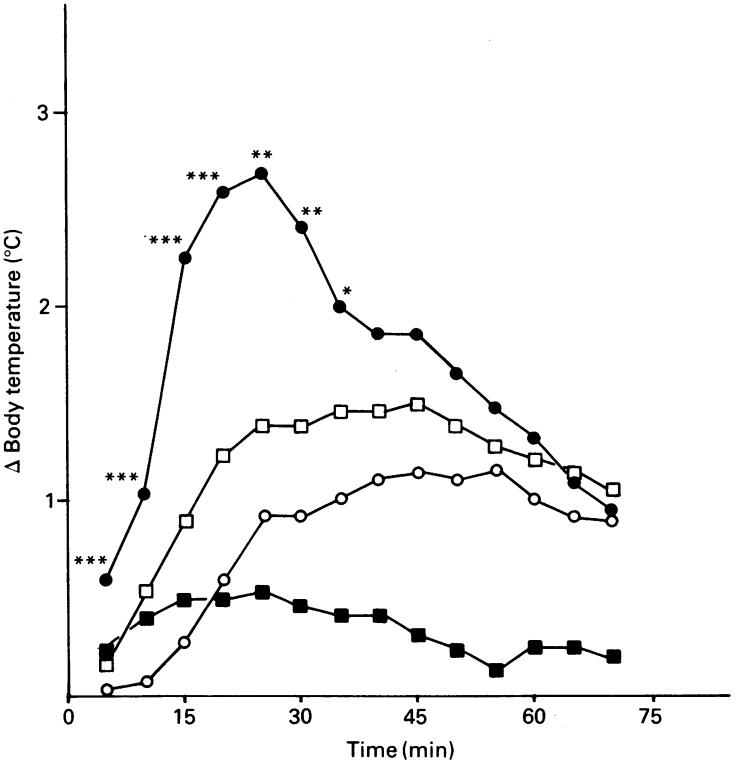

Fig. 3. The effect of the course of PGE_2 induced fever of α-blockade and liver denervation with 6-OH dopamine. ●, PGE_2 ($n=5$); □, PE_2 and 6-OH dopamine ($n=9$); ○, PGE_2 and α-blockade ($n=7$); ■, saline controls ($n=13$). Differences between these values and the maxima in Tables 1, 4 and 5 are due to the fact that in these tables means of dT max are represented irrespective of the time of their occurrence, while those in the figures are calculated as the difference between body temperatures at the time plotted and those at time 0. * $P<0.05$ *vs.* ○. ** $P<0.02$ *vs* ○, $P<0.05$ *vs.* □. *** $P<0.002$ *vs* ○, $P<0.01$ *vs.* □.

Table 4. Effect of α- and β-blockade on the maximal rise of body temperature (dTmax) after PGE_2 i.c.v. and α_M-FP levels during the experiment and 24 h later. Values, mean ± SE. Student's *t*-test for paired data

		α_M-FP μg/ml	
Experimental group	dT max °C	Before fever	24 h after fever
α-blockade ($n=7$)	1.60±0.61	75±8	1019±312*
α- and β-blockade ($n=6$)	2.36±0.59	67±35	92±30

* $P<0.005$ *vs* α_MFP before PGE_2.

Table 5. Effect of liver denervation with 6-OH dopamine on the maximal rise of body temperature (dT max) after PGE_2 i.c.v. and α_M-FP levels during the experiment and 24 h later. Values, mean ± SE. Student's *t*-test for paired data

Experimental group	dT max °C	α_M-FP μg/ml	
		Before fever	24 h after fever
6-OH dopamine ($n=9$)	1.90±0.38	357±53	884±199*

* $P<0.05$ *vs* α_MFP before PGE_2.

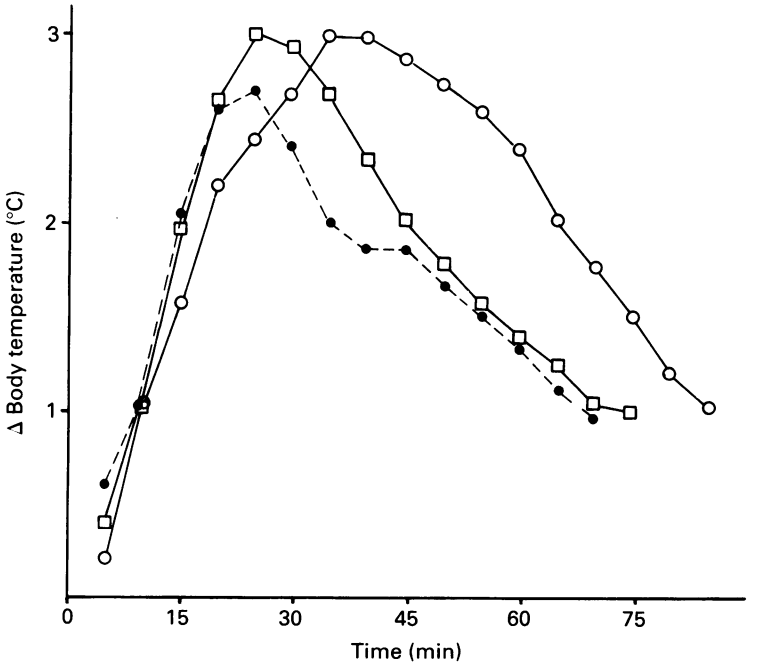

Fig. 4. Hyperthermia induced by heat exposure compared with PGE_2 induced fever. ○, Hyperthermia ($n=5$); □, hyperthermia after pretreatment with sodium salicylate ($n=5$); ●, PGE_2 ($n=15$).

to a high mortality. Of the group of five rats who tolerated hyperthermia alone very well only two survived the combination of hyperthermia and salicylate for 24 h. These animals reached α_M-FP values comparable with those after hyperthermia alone (mean 1133 *vs* 1020 μg/ml). After this we removed the rats quickly from the heat as soon as a temperature of 41°C was reached and let them cool passively at 23°C instead of removing the heating lamp. Under these circumstances α_M-FP production was erratic as can be seen in Table 6. Levels at 24 h did not differ significantly from those at the beginning of the experiment due to the high variability.

Table 6. Effect of hyperthermia and hyperthermia after pretreatment with sodium salycilate on the maximal rise of body temperature (dT max) and α_M-FP levels during the experiment and 24 h later. Values, mean ± SE. Student's *t*-test for paired data

Experimental group	dT max °C	α_M-FP μg/ml	
		Before fever	24 h after fever
Hyperthermia ($n=5$)	3.4±0.19	140±6	798±163*
Hyperthermia + sodium-salycilate ($n=5$)	3.1±0.24	67±3	630±358

* $P<0.025$ *vs* α_MFP before heat exposure.

Discussion

Many clinicians believe that induction of acute phase proteins (APR) is mainly due to infection and/or sepsis. As fever is an essential feature of these processes, interleukin-1 (IL-1), or related proteins, are thought to be important triggers for both phenomena (Bornstein 1982; Kushner 1982; Dinarello 1984).

However, many non-infectious conditions exist, e.g. myocardial infarction, in which high plasma APR levels also develop, related to the mass of infarcted tissue (Smith 1977). In all these acute lesions high levels of so-called stress hormones are found, especially of corticosteroids and catecholamines (Logan & Murdoch 1966; Opie 1975; Pinardy *et al.* 1979; Young *et al.* 1983). We have reported previously that in rats, corticosteroids and catecholamines in the absence of tissue injury can provoke a strong APR elevation in which corticosteroids play a permissive role (Van Gool *et al.* 1984). In view of these observations, it has to be asked whether fever alone can induce an APR response. To answer this question we induced fever by i.c.v. application of PGE_2, which is the natural transmitter for fever (Feldberg & Saxena 1971, 1975), thus avoiding peripheral tissue injury leading to Il-1 production. We used α_M-FP, also known as α_2 macroglobulin of the rat, as a parameter for response.

Our results show that in this model, fever rapidly develops together with a significant rise of α_M-FP (Table 1). In the same animals, which act as their own controls, 0.9% NaCl i.c.v. induces only a very small reaction of APR (Table 1). Fig. 1 shows that a threshold value of around 2°C fever is necessary to induce a rise of α_M-FP, which has a linear relation with the degree of fever. By calculating the relation between α_M-FP and the area under the temperature curve till dTmax, the same relationship is obtained ($r=0.650$, $n=17$, $P<0.01$) (Fig. 2). Fever, as induced in our model, is accompanied by high levels of catecholamines and corticosterone (Table 3). Adrenaline in particular rises considerably. Plasma noradrenaline and corticosterone levels are also elevated but do not differ significantly from controls treated with 0.9% NaCl.

Thus the most important difference between PGE_2 and the controls is the high plasma adrenaline level. In adrenalectomized rats with i.c.v. PGE_2, plasma noradrenaline rises significantly (Table 3) but corticosterone and adrenaline remain very

low. However, fever response in adrenalectomized rats is quite normal. Notwithstanding this normal fever response, no APR induction occurs (Table 2). APR induction, at least α_M-FP, only occurs when corticosteroids are present as permissive substances (Tables 2 and 3). These findings are fully in accordance with our earlier experiments (Van Gool *et al.* 1984). Although we could not measure IL-1 levels the results strongly argue against IL-1 as the only factor inducing the APR, at least of α_M-FP.

To clarify the role of catecholamines during fever in the production of APR, we destroyed the sympathetic innervation of the liver by 6-OH dopamine injections in the portal vein (Lautt & Côté 1977). Fever in this situation was significantly retarded and lower (Fig. 3). 6-OH dopamine, in the dose we used, does not penetrate the blood–brain barrier (Laverty *et al.* 1965) and systemic sympathetic denervation is thus unlikely (Lautt & Côté 1977). Our results suggest that liver energy metabolism activated by the sympathetic system is involved in the rise of body temperature, additional to the effects of peripheral vasoconstriction and shivering (Splawinsky *et al.* 1978). However, after 6-OH dopamine, APR production, as measured by α_MFP, is unimpaired (Table 4) indicating that free circulating catecholamines are more important. α-Blockade by means of Dibenyline, reduced PGE_2-induced fever but the APR response was undisturbed (Fig. 3 and Table 4) and comparable to 6-OH dopamine. The lower fever after α-blockade (Fig. 3) may be explained by the antagonistic effect on peripheral vasoconstriction and/or shivering (Splawinski *et al.* 1978).

When β-blockade by means of atenolol is added to α-blockade, fever response after PGE_2 is restored (Table 4) but no APR induction occurs. As in adrenalectomized animals, fever and APR induction are uncoupled. We conclude that synthesis of α_M-FP is under control of β-receptor-mediated stimulation, provided sufficient corticoid levels are present. We could not differentiate between β_1 or β_2 stimulation.

Our results accord partially with those of Brady & Helvig (1984) concerning liver zinc metallothionein, which could be stimulated by glucocorticoids, adrenaline and noradrenaline. But here synthesis of this protein was suppressed by α-blockade and to a lesser degree by α- and β-blockade. Hepatic zinc metallothionein, however, is not an export protein and is an entirely different protein.

An explanation for our finding that α- and β-blockade does not impair PGE_2-induced fever (Table 4) could be that the vasodilatatory effects of α-blockade are overruled by more peripheral vasoconstriction, due to the dose of atenolol we used. A central effect of β-blockade is unlikely (Street *et al.* 1979). Others also found no significant effect of peripheral α- or β-blockade on PGE_2-induced fever (Hoffman & Valigura 1979; Hofman *et al.* 1984).

As a model to elevate body temperature without direct intervention at the cerebrocortical level we used hyperthermia induced by heat exposure. After hyperthermia α_M-FP levels rose in 24 h to values comparable to those after PGE_2-induced fever. In animals with environmentally induced hyperthermia no rise of PGE occurs in the cerebrospinal fluid (Bernheim *et al.* 1980). When we pretreated the rats with sodium salicylate they tolerated heat exposure less well. The results of these experiments are therefore variable, but all who survived during 24 h showed a distinct or moderate increase of α_M-FP. These findings argue against a direct role of PGE on α_M-FP synthesis.

Several other data argue against this hypothesis. Earlier in our laboratory we could not induce fever, nor α_M-FP synthesis by systemic injections of prostaglandins, including PGE_2, up to doses of 1 mg/kg i.v. Neither could we induce synthesis of α_M-FP in primary livercell cultures (unpublished results). These negative findings accord to those of Shultz *et al.* (1982). Another argument against a direct effect of PGE_2 on APR synthesis is our observation that during combined α- and β-blockade, fever persists but no APR response follows (Table 4). It is

not understood how an eventual effect of systemic prostaglandins could be abolished in these cases. Summarizing, we do not believe that prostaglandins, adminstered by the i.c.v. route, play a direct role in α_MFP synthesis.

In our study on the relation between fever and APR synthesis the experiments of Blatteis *et al.* (1984) must be mentioned; they could not demonstrate stimulation of APR after PGE_2-induced fever. However, these authors studied plasma Zn, Fe, Cu and N-acetyl neuraminic acid as indicators of acute phase response, being clearly other components of the generalized acute phase response than α_MFP, which is a very active and rapidly reacting acute phase protein of hepatic origin.

Finally, the problem remains whether fever, induced by PGE_2, does release Il-1 or one of the other interleukins, thus inducing an APR response. Studies are in progress to investigate this intriguing probem, but if this occurs it only proves that, in this *in vivo* situation, acute fever is the primary factor which induces α_MFP response. Catecholamines and corticoids here are the mediators, with corticoids playing a permissive role, whereas interleukins, if liberated, represent a secondary phenomenon which possibly enhances APR synthesis.

References

Ahokas R.A., Seydoux J., Llanos Q.J., Mashburn T.A. Jr, & Blatteis C.M. (1985) Hypothalamic opioids and the acute phase glycoprotein response in guinea pigs. *Brain Res. Bull.* **15**, 603–608.

Bailey P.T., Abeles F.B., Hauer E.C. & Mapes C.A. (1976) Intracerebrovcentricular administration of leucocytic endogenous mediators (LEM) in the rat. *Proc. Soc. Exp. Biol. Med.* **153**, 419–423.

Bernhaim H.A., Gilbert T.M. & Stitt J.T. (1980) Prostaglandin E levels in third ventricular cerebrospinal fluid of rabbits during fever and changes in body temperature. *J. Physiol.* **301**, 69–78.

Blatteis C.M., Hunter W.S., Llanos-Q.J., Ahokas R.A. & Mashburn T.A. Jr, (1984) Activation of acute-phase responses by intrapreoptic injections of endogenous pyrogen in guinea pigs. *Brain Res. Bull.* **12**, 689–695.

Bornstein D.L. (1982) Leucocytic pyrogen: a major mediator of the acute phase reaction. *Ann. N.Y. Acad. Science* **389**, 323–337.

Brady F.O. & Helvig B. (1984) Effect of epinephrine and norepinephrine on zincthionein levels and induction in rat liver. *Am. J. Physiol.* **247**, E318–E322.

Chowers I., Hammel H.T., Eisenman J., Abrams R.M. & McCann S.M. (1966) Comparison of effect on environmental and preoptic heating and pyrogen on plasma cortisol. *Am. J. Physiol.* **210**, 606–610.

Dinarello C.A. (1984) Interleukin-1. *Rev. Infect. Dis.* **6**, 51–95.

Endert E. & Punt R. (1982) A readioenzymatic liquid chromatographic determination of plasma noradrenaline, adrenaline and dopamine. In *Biological/biomedical applications of liquid chromatography IV* Ed. G.L. Hawk. New York & Basel: Marcel Dekker.

Feldberg W. & Saxena P.N. (1971) Fever produced by prostaglandin E_1. *J. Physiol.* **217**, 547–556.

Feldberg W. & Saxena P.N. (1975) Prostaglandins endotoxin and lipid A on body temperature in rats. *J. Physiol.* **249**, 601–615.

Hoffman W.E. & Valigura T.J. (1979) Independence of cardiovascular and hyperthermic effects of prostaglandin E_2. *Brain Research* **173**, 160–165.

Hoffman W.E., Albrecht R.F. & Miletich D.J. (1986) Effect of sympathetic blockade on central prostaglandin E_2-induced hyperthermia. *Brain Research* **367**, 73–76.

Jones R.S., Mayne Y.C. & Eik-Nes K. (1958) C_{14} Labeled bacterial polysaccharide and adrenal cortical function in the guinea pig. *Endocrinology* **62**, 843–852.

Kushner I. (1983) The phenomenon of the acute phase response. *Ann. N.Y. Acad. Science* **389**, 39–48.

Laverty R., Sharman D.E. & Vogt M. (1965) Action of 2, 4, 5, -trihydroxy phenyl ethylamine on the storage and release of noradrenaline. *Brit. J. Pharmacol.* **24**, 549–560.

Lautt W.W. & Côté M.G. (1977) The effect of 6-OH dopamine induced hepatic sympathectomy on the early hyperglycemia response to surgical trauma under anaesthesia. *J. Trauma* **17**, 270–272.

Logan R.W. & Murdoch W.R. (1966) Blood levels of hydrocortisone, transaminases and cholesterol after myocardial infarction. *Lancet* **2**, 521–524.

OPIE L.H. (1975) Metabolism of free fatty acids, glucose and catecholamines in acute myocardial infarction: Relation to myocardial isccheмia and infarct. *Am. J. Cardiol.* **36**, 938–953.

PINARDI G., TALMACIK R.K., SANTIAGO E. & CUBBEDEK L.X. (1979) Contribution of adrenal medulla, spleen and lymph to the plasma levels of dopamine, b-hydroxylase and catecholamines induced by hemorrhagic hypotension in dogs. *J. Pharmacol. Exp. Ther.* **209**, 176–184.

SCHULTZ D., MACINTYRE S., CHELLADURAI M. & KUSHNER I. (1982) The role of prostaglandins in the C-reactive protein response. *Ann. N.Y. Acad. Sci.* **389**, 465–471.

SILBER R.H., BUSCH R.D. & OSLAPAS R. (1958) Practical procedure for estimation of corticosterone or hydrocortisone. *Clin. Chem.* **4**, 278–285.

SMITH S.J. (1977) Acute phase proteins from the liver and enzymes from myocardial infarction: a quantitative relationship. *Clin. Chim. Ata* **81**, 75–85.

SPLAWINSKI J.A., GORKA Z., ZACNY E. & WOJTASZEK B. (1978) Hyperthermic effects of arachidonic acid, prostaglandins E_2 and F_{2a} in rats. *Pflügers Arch.* **374**, 15–21.

STREET J.A., HEMSWORTH B.A., ROACH A.G. & DAY M.D. (1979) Tissue levels of several labelled beta-adrenoceptor antagonists after intravenous administration in rats. *Arch. Int. Pharmacodyn.* **237**, 180–190.

TURCHIK J.B. & BORNSTEIN D.L. (1980) Role of the central nervous system in acute-phase responses to leucocytic pyrogen. *Inf. Imm.* **30**, 439–444.

VANE J.R. (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature, New Biol.* **231**, 232–235.

VAN GOOL J., BOERS W., SALA M. & LADIGES N.C.J.J. (1984) Glucocorticoids and catecholamines as mediators of acute-phase proteins, especially rat-macrofoetoprotein. *Biochem. J.* **220**, 125–132.

YOUNG J.B., FISH S. & LANDSBERG L. (1983) Sympathetic nervous systems and adrenal medullary response in ischemic injury in mice. *Am. J. Physiol.*, **245**, E67–E73.