Fever is thought to be initiated by pyrogenic cytokines inducing the production of prostaglandin E2 (PGE2) in the preoptic area (POA). Specifically, these cytokines are thought to induce the production of prostaglandin E2 (PGE2) in the POA, which then stimulates the neural pathways that raise body temperature (Tb) (for review, see Kluger, 1991; Saper and Breder, 1994).

This essential role for prostaglandins in fever first was proposed 25 years ago, but the specific preoptic cell groups at which PGE2 acts and the pathways through which fever is produced remain poorly understood. To better define the role of preoptic PGE2 in fever, we developed a new method for combining acute brain injections with Fos immunohistochemistry. We microinjected a threshold dose of PGE2 to construct an anatomically detailed map of fever-producing preoptic sites. The most pyrogenic preoptic sites were clustered along the ventromedial aspect of the POA, surrounding and just anterior to the organum vasculosum of the lamina terminalis. We then used Fos immunohistochemistry to identify the pattern of neural activation induced by fever-producing preoptic injections of PGE2 and compared it with the Fos pattern seen after systemic immune stimulation. PGE2 fever was accompanied by Fos induction in the ventromedial POA and the parvicellular subnuclei of the paraventricular nucleus of the hypothalamus (PVH). In contrast to the Fos pattern seen after intravenous lipopolysaccharide administration, PGE2 injection did not induce Fos in the circumventricular organs or the magnocellular subnuclei of the PVH. These observations establish a potential site of PGE2 action during fever and help define candidate pathways through which fever occurs.

Key words: fever; prostaglandin E2; body temperature; thermoregulation; autonomic system; Fos; preoptic area; hypothalamus

MATERIALS AND METHODS

Animals. Pathogen-free, male Sprague Dawley rats (Taconic, Germantown, NY) weighing 280–350 gm were used in this study. Rats were housed individually in a pathogen-free barrier facility with unrestricted access to food and water in a room maintained at 21.5–22.5°C. Lights turned on at 7 A.M. and off at 7 P.M. All protocols were approved by the Institutional Animal Care and Use Committees of Beth Israel Hospital and Harvard Medical School. Each rat was used only once. Sixty-two rats were used in these experiments, and 15 others were excluded from the study because of occluded or missing catheters (14 rats) or temperature transmitter failure (1 rat).

Procedures and analysis. In experiment 1, we acutely injected 1–100 ng of PGE2 into the POA of briefly anesthetized rats to determine the minimum fever-producing dose of PGE2 in our model.

In experiment 2, we injected the threshold pyrogenic dose of PGE2 (1 ng) into the POA to determine the anatomic distribution of PGE2-sensitive sites. Tb was recorded for 2 hr, and febrile responses to PGE2 injections in different preoptic regions were compared.
In experiment 3, we studied the pattern of Fos expression in brain induced by fever-producing POA injections of PGE2. Vehicle or a high (100 ng) or low (1 ng) dose of PGE2 was acutely injected into the ventromedial region of the POA. Tb was recorded for 2 hr, and the brains were then processed for immunohistochemistry. To determine quantitatively the effects of PGE2 injection, Fos-immunoreactive nuclei were counted within three key autonomic sites that are activated during the fever produced by systemic immune stimulation: the ventromedial preoptic (VMPO) area, the paraventricular nucleus of the hypothalamus (PVH), and the nucleus of the solitary tract (NTS) (Sagar, 1994; Elmquist et al., 1996).

Placement of intravenous catheters and telemetry devices. Telemetry was used for monitoring Tb, and chronic intravenous catheters were used for injection of the general anesthetic just before brain injection. All temperature transmitters (type VM-FH, Mini Mitter, Sun River, OR) were calibrated in a warm water bath at temperatures between 35 and 39°C as detailed in the manufacturer's instructions. Five to seven days before the experiment, rats were anesthetized with chloral hydrate (350 mg/kg, i.p.), and SILASTIC® catheters were inserted into the femoral vein up to the level of the right atrium. The free end of the catheter was exteriorized at the interscapular area, flushed with 0.1 ml of heparinized (10 U/ml) pyrogen-free 0.9% saline (Sigma, St. Louis, MO), and plugged with a sterile wire stylet. Catheters were flushed again 2 d before the experiment to ensure patency. After insertion of the catheter, a temperature transmitter was placed into the peritoneal cavity. Transmitters were received by an antenna below the rat's cage and relayed to a signal processor connected to a Compaq 486 PC. Monitoring of Tb began at least 12 hr before drug injection to assess baseline Tb. Average baseline Tb was 37.1°C, and baseline Tb did not differ significantly among groups. Tb data are presented as the change in temperature from the average baseline over the hour preceding the brain injection. Tb data are presented as the mean ± SEM change in temperature in each 10 min interval relative to baseline (average temperature over the hour preceding injection). To determine quantitatively whether febrile responses differed among preoptic regions in experiment 2 (the 1 ng PGE2-mapping experiment), injection sites were categorized into one of seven possible regions (see Fig. 6): (1) the peri-OVLT region (three areas, OVLT, VMPO, and anteroventral periventricular nucleus, within 500 μm of the core of the OVLT) (n = 6); (2) the meningeal strand, which supports the optic chiasm just rostral to the OVLT or the cell-sparse parenchyma immediately above the strand (n = 6); (3) the median preoptic (mPO) nucleus (n = 6); (4) the vertical limb and the horizontal nucleus of the diagonal band (n = 5); (5) the medial or lateral POA (n = 7); (6) the subarachnoid space or third ventricle (n = 5); and (7) other sites >1 mm from the OVLT not listed above (n = 13) (these included the periventricular preoptic nucleus, perifornical region, medial septum, and other sites). The mPO was traditionally considered part of the peri-OVLT region, but we have separated it in our analysis to determine whether it might differ functionally. Preliminary experiments had indicated that the largest fevers were evident 30 min after the PGE2 injection, and, therefore, we chose to compare groups at this time point. To determine the effects of PGE2 treatment, each group was compared with the vehicle-injected group (n = 13). To establish anatomic specificity, each group of injection sites also was compared with the group of injection sites >1 mm from the OVLT. Groups were compared using a one-way ANOVA (SYSTAT, SPSS, Chicago, IL) with a Bonferroni correction; p was considered significant if <0.025, because two ANOVAs were performed.

In experiment 3, counts of Fos-immunoreactive nuclei in the 100 ng PGE2 group were compared with the 100 nl vehicle-injected group using t tests with a Bonferroni correction; p was considered significant if <0.017, because three regions were studied. In the 1 ng PGE2 experiment, Fos-IR in the VMPO was analyzed using a two-way ANOVA to determine the relative contributions of drug treatment (PGE2 vs vehicle) and injection location (inside or outside the ventromedial pyrogenic zone). Counts of Fos-immunoreactive nuclei were not corrected for double-counting errors (Konigsmark, 1970), because there was no change in sizes of labeled structures among groups and only relative, not absolute, values were sought.
RESULTS

PGE2 dose–response relationship
We first determined the minimum amount of PGE2 required to produce fever in our model. Injections of 1–100 nl of a 1 ng/ml PGE2 solution targeted at the peri-OVLT region produced dose- and volume-dependent fevers (Fig. 1). Injections of 100 ng of PGE2 produced very large fevers 30 min after injection, whereas 1 ng of PGE2 produced small, statistically insignificant increases in Tb except for one injection near the meningeal strand supporting the optic chiasm. Therefore, 1 ng of PGE2 was determined to be the threshold dose for producing fever, and a more dilute solution of PGE2 (1 ng/10 nl) was used in subsequent experiments to improve the reproducibility of these small injections.

Preoptic sites responsive to PGE2
We then mapped the sites at which 1 ng of PGE2 produced fever. Because we used fine (~30 μm tip) glass micropipettes, tissue injury was rarely visible within the diencephalon, and injection sites were identified by a tiny cluster of fluorescent latex microspheres (Fig. 2). PGE2 fever was maximal about 30 min after injection, and this time point was chosen for analysis. Injection of vehicle produced a small, insignificant drop in Tb (0.15 ± 0.31°C below baseline), and, therefore, fever was defined as a Tb increase of at least 0.5°C above baseline (±2 SDs above the vehicle response). PGE2 was administered to 48 rats, and 19 developed fever. The 10 largest fevers occurred after PGE2 injection into three areas: the peri-OVLT region, the mnPO nucleus, or the meningeal strand that supports the optic chiasm and the parenchyma immediately above the strand (Fig. 3). The febrile response among these three regions was indistinguishable but clearly greater than the Tb response to vehicle (p < 0.001 for each of the three groups). These three regions also differed significantly from the group of PGE2 injections >1 mm away from the OVLT (p < 0.001). The only other injections that produced a slight increase in Tb were those into the third ventricle or subarachnoid space, but these were not statistically different from vehicle injections.

Injections were categorized as producing no fever (<0.5°C), small fever (0.5–1.0°C), or large fever (>1.0°C) and mapped onto a series of POA drawings (Fig. 4). Injections into the diagonal band nucleus or the subarachnoid space >500 μm rostral to the OVLT had no significant effect on Tb. However, injections 200–
cleus consistently produced fevers that often were >1°C. PGE2 injections at the edge of this region often produced small fevers, and injections >300–400 μm dorsal or lateral to these regions produced little or no change in Tb. Overall, the most effective PGE2 injections were into the most ventromedial parts of the POA, surrounding the optic recess of the third ventricle. Vehicle injection, even into this “pyrogenic zone,” never produced fever.

**Sites of PGE2-induced Fos expression**

In our third experiment, we determined the brain regions activated by preoptic injection of a high (100 ng) or low (1 ng) dose of PGE2. The 100 ng injections were scattered throughout the POA and produced large fevers (2.3–3.3°C above baseline) that lasted 1.5 hr, with ventromedial preoptic injections tending to produce the largest fevers. The 1 ng injections were selected from among the animals described in the previous experiment. Injection of control volumes of vehicle (100 or 10 nl) had no significant effect on Tb.

**General Fos observations**

Fos-IR was seen as a blue-black reaction product that localized to neuronal nuclei. No change in the size or shape of nuclei was evident among groups. Preadsorption of the primary antiserum with Fos peptide or omission of the primary antiserum resulted in no specific staining.

Brains of animals that received 100 nl of vehicle contained a pattern of Fos-IR in many brain regions. Prominent among these was the cerebral cortex (especially the piriform area) ipsilateral to the burr hole. Moderate numbers of immunoreactive cells were seen in the ipsilateral caudate and putamen and in the lateral and central amygdaloid nuclei. A moderate number of immunoreactive cells also were seen bilaterally in and around the suprachias-
Injections of 100 ng of PGE2 induces Fos-IR in key thermoregulatory regions of rat brain. Bright-field photomicrographs of the VMPO (VMPO, roughly bounded by the bracket) demonstrate little Fos-IR 2 hr after preoptic injection of vehicle (A), but Fos-immunoreactive nuclei are numerous after PGE2 injection (B). Little Fos-IR is seen in the paraventricular nucleus of the hypothalamus after vehicle injection (C), but PGE2 injection stronglyinducesFos-IRwithinthe paraventricular, but not the magnocellular, subnuclei (D). After vehicle injection, almost no Fos-IR is visible within the nucleus of the solitary tract (E), but after PGE2 injection, the dorsomedial (dm) and medial (m) subnuclei contain moderate numbers of Fos-immunoreactive nuclei. pm, Posterior magnocellular subnucleus; dp, dorsal parvocellular subnucleus; mp, medial parvocellular subnucleus; vp, ventral parvocellular subnucleus; fx, fornix; sol, solitary tract; 10, dorsal motor nucleus of the vagus; AP, area postrema; cc, central canal. Scale bar, 500 μm.
matic nucleus and in the anterior hypothalamic nucleus, the inferior colliculus, the periaqueductal gray matter, the dorsal cochlear nucleus, and the principal sensory and spinal trigeminal nuclei. Moderate numbers of cells were found in the superior lateral, dorsal lateral, and central lateral parabrachial subnuclei and in the ventrolateral medulla (especially the A1/C1 and A1 regions). Immunoreactive cells were rarely observed in the VMPO. Moderate numbers of immunoreactive cells were consistently found in the PVH, especially in the medial parvicellular subdivision. Although no histological injury was evident, a thin, 100-μm-wide column of Fos-immunoreactive neurons extended along the pipette tract in vehicle- and PGE2-injected brains.

**PGE2 (100 ng)**

Microinjections of 100 ng of PGE2 into ventromedial preoptic sites produced a striking pattern of Fos-IR superimposed on the pattern attributable to the surgical procedures (Fig. 5). Large numbers of immunoreactive cells were observed bilaterally in the VMPO extending from the level of the OVLT caudally along the ventrolateral aspect of the third ventricle. In one animal that received PGE2 into the cell-sparse zone just below the diagonal band, Fos-IR was found in non-neuronal cells throughout the meninges just below the injection site. A prominent distribution of Fos-IR also was found within the PVH, particularly in the medial parvicellular subdivision, which contains many CRH-producing neurons, and within the dorsal, ventral, and lateral parvicellular subdivisions, which innervate central autonomic structures (Swanson and Sawchenko, 1983; Saper, 1995). The posterior magnocellular subdivision and the supraoptic nuclei contained few immunoreactive cells, except in one animal in which the PGE2 injection was centered on the VMPO, and moderate levels of Fos-IR were seen in the supraoptic nucleus. In the pons, many immunoreactive cells were seen in the lateral parabrachial nucleus, especially in the dorsal and central lateral subnuclei in a pattern similar to controls. In the nucleus of the solitary tract, many cells contained Fos-IR in the medial, dorsomedial, and ventrolateral subnuclei. The lateral edges of the area postrema also contained immunoreactive cells. Fos-IR was bilaterally symmetric in all these affected regions.

To verify these observations more rigorously, we counted the relative number of Fos-immunoreactive neurons in the VMPO, PVH, and NTS of rats that received 100 ng of PGE2 or 100 nl of vehicle (Fig. 6). Rats that received PGE2 had significantly greater numbers of Fos-immunoreactive neurons in the VMPO (t = −3.8, p = 0.009) and PVH (t = −6.03, p = 0.001) compared with rats that received vehicle. Due times as many Fos-immunoreactive neurons were seen in the NTS of PGE2-treated rats as compared with vehicle-injected rats, but the groups did not differ statistically (t = −2.87, p = 0.053).

**PGE2 (1 ng)**

We then sought to determine the minimal set of brain regions activated during fever by coupling the threshold dose of PGE2 with Fos histochemistry. Injection of 10 nl of vehicle induced Fos-IR in a pattern indistinguishable from that described above for 100 nl of vehicle (three of these injections were within the pyrogenic zone, four were scattered elsewhere in the POA). Three microinjections of 1 ng of PGE2 outside the pyrogenic zone did not produce fever or induce a distribution of Fos-IR that was notably different from vehicle injections. However, four injections of PGE2 within the pyrogenic zone produced fever and Fos-IR bilaterally in the VMPO; immunoreactive neurons were observed consistently throughout the rostro-caudal extent of the VMPO, although the number of cells was considerably fewer than the number seen after 100 ng of PGE2 (Fig. 7). Additionally, increased but variable numbers of Fos-immunoreactive neurons were seen in the dorsal and ventral parvicellular subnuclei of the PVH. No consistent Fos-IR was seen in the NTS or any other autonomic nuclear groups. Because the VMPO is close to many of the effective fever-producing injection sites, we performed a two-way ANOVA to determine the relative influences of PGE2 and injection sites. Neither drug treatment (PGE2 vs vehicle) nor injection site (inside vs outside the pyrogenic zone) in itself correlated with the induction of Fos-IR in the VMPO. Only PGE2 injections into the pyrogenic zone significantly increased the number of Fos-immunoreactive neurons in the VMPO (p = 0.03) (Fig. 8).

**DISCUSSION**

We found that microinjections of a threshold dose of PGE2 into the POA rapidly induces fever, and the most pyrogenic preoptic sites are clustered along the ventromedial aspect of the POA, surrounding and anterior to the OVLT. This PGE2 fever is accompanied by Fos induction in the VMPO and the autonomic regulatory and CRH-producing subdivisions of the PVH. These results suggest that during the acute-phase reaction, PGE2 may activate the VMPO, which, in turn, stimulates the PVH to produce fever.

**Methodological considerations**

Our injection technique has allowed us to construct a detailed map of pyrogenic sites in the POA. Compared with previous studies, we used very low doses and volumes of PGE2 to stimulate the smallest possible regions and obtain maximal anatomical precision. Previous investigations all used chronic injection cannulae or studied PGE2 fever in anesthetized animals. During sustained general anesthesia, animals often require considerably more PGE2 to develop fever, possibly because of anesthesia-
induced thermoregulatory dysfunction (Feldberg and Saxena, 1971). In contrast, the 10–15 min period of anesthesia in our preparation had little effect on thermoregulation. Furthermore, chronic cannulae may induce local PGE2 production (Yergey and Heyes, 1990) such that large amounts of PGE2 are subsequently required for physiological effects. These technical concerns may be why most previous studies of PGE2-induced fever required 50–100 ng of PGE2 to produce reliable fevers. Additionally, high doses of PGE2 may have been required in some studies, because the injections were too far from the pyrogenic ventromedial preoptic region. Stitt found that 1 ng of PGE2 injected close to the OVLT reliably produced 0.8°C fevers (Stitt, 1991), but the large volume injected (1 μl) and the trauma produced by the chronic cannulae preclude a detailed anatomic interpretation. Our technique of acute injections under brief anesthesia followed by careful injection-site identification allowed us to use small volumes of PGE2 to obtain high anatomic resolution; highly effective fever-producing sites were separated from ineffective sites by only 200–300 μm.

The coupling of brain injections with Fos immunohistochemistry allows us to identify candidate circuits involved in the production of fever but also raises several concerns. First, the stereotaxic surgical technique itself induces Fos-IR in a number of brain regions. We and others have noted that the injection procedure itself induces Fos-IR throughout much of the ipsilateral cortex, sensory trigeminal nuclei, and cochlear nuclei (Sharp et al., 1990; Krukoff et al., 1992; Amir et al., 1994). Fos induction in the cerebral cortex may be caused by glutamate-mediated spreading depression (Sharp et al., 1990), whereas Fos in sensory nuclei is more likely caused by meningeal and middle ear trauma secondary to the stereotaxic surgical technique itself. We commonly observed a thin column of Fos-immunoreactive neurons along the pipette tract that hinders interpretation of the Fos pattern in the immediate vicinity of the injection site, but as shown in the final experiment, functionally meaningful Fos expression can be studied in structures a few hundred microns away. Second, general anesthesia can induce Fos in autonomic regulatory regions; several authors have described Fos-IR in the medial POA, PVH.

Figure 7. Injection of 1 ng of PGE2 induces Fos-IR in the VMPO and PVH. Rare Fos-immunoreactive nuclei are evident in the VMPO after vehicle injection (A), but a moderate number of nuclei are seen after PGE2 injection (B). The PVH typically has few Fos-immunoreactive nuclei after vehicle injection (C), but occasional Fos-IR is seen in the dorsal (dp), medial (mp), and ventral parvicellular (vp) subnuclei after PGE2 injection (D).
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the VMPO may play a central role in fever, we suspect that
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wouldinduceFosinseveralbrainregionsessentialforfever,

fectedbyanesthesiaandtheregionalanesthesiausedin
manyautonomicregulatorystructuresareactivatedduringPGE2

(primarilytheparvocellularregions),ventromedialhypothalamus,
lateralparabrachialnucleus,NTS,andventrolateralmedulla
(VLM)afteranesthesiawithlong-actingagents(Millhorn,1991;
moderateFos-IRintheparabrachialnucleusandVLM,
butFos-immunoreactiveneuronswereuncommonintheNTS,
PVH,andPOA.Wesuspectthatpropofolanesthesiais-toolow
andtheautonomicchangesotoomildtoinduceFosintheselatter
regions.Afteranesthesiawithpropofol,Fos-IRneedsbeto
viewedcritically, but in areas little affected by anesthesia and
the injection technique, Fos is a useful indicator of which neuronal
groupsmaycontributetotheproductionoffever.

Conversely, the absence of Fos-IR cannot be used to exclude
functional participation of a nuclear group. Even excitatory re-
sponsesleadingto neuronalactivationmayhavedifferentthresh-
holdsforinducingFosin different brain regions (Ericsson et al.,
1994). Wewhadhypothesizedthata1ngthresholddoseofPGE2
wouldinduceFosinseveralbrainregionsessentialforfever,
but a notable effect was evident only in the VMPO and, to a lesser
degree, in autonomic regulatory regions of the PVH. Although
the VMPO may play a central role in fever, we suspect that
additional autonomic control regions must contribute to the pro-
ductionoffever;athresholddoseofPGE2maytobeweak
stimulusto reliablyinduceFosindistantlyactivatedregions.

The “pyrogeniczone”

PGE2injectionsintothemostventromedialregionsofthePOA
were most effective at producing fever. This ventromedial pyro-
genzone surrounds the OVLT, a highly vascular structure that
hasbeen hypothesized to be the site at which circulatingcytokines
inducePGE2productiontoinitiatefever(Stitt,1991). The
prostaglandin-synthesizingenzyme cyclooxygenase-2 isinduced
inmicroglialcellsalongbloodvesselsintheOVLTandadjacent
meninges after systemic (intravenous) immune stimulation with
the bacterial cell wall component lipopolysaccharide (LPS) (C.
BrederandC.Saper,unpublishedobservations). Theadjacent
pyrogeniczonecorrelateswellwiththehighconcentration
ofPGE2bindingitessthatsurroundtheOVLTandextenddorsally
intothemPO nucleusandlaterallyintotheVMPO(Matsumura
et al.,1990). Usinginisuthybridization,Ericssonrecently
described a similar pattern in the distribution of the EP3 type of
PGE2 receptor that may be important in fever (Ericsson et al.,
1995). Although PGE2 may be synthesized within the OVLT, our
observations, combined with the PGE2 binding studies and early
receptor localization work, suggest that PGE2 produces fever by
actingin preopticregions surroundingtheOVLT.

Fos pattern

Many autonomic regulatory structures are activated during PGE2
feverinapatternsimilartothatseenduringthefeverproducedby
systemic administration of LPS. Both intravenous LPS (Elmquist
et al., 1996) and 100 ng of intrapreoptic PGE2 induce Fos in the
VMPO, mnPO nucleus, parvicellular areas of the PVH, and NTS.
The most robust response among these regions is within the
VMPOwhereFosisinducedatthresholdpyrogenicdosesof
either LPS or PGE2.

The Fos pattern induced by intrapreoptic PGE2 differs from
that seen with LPS in several notable respects. In contrast to LPS,
PGE2 does not induce Fos within magnocellular PVH neurons or
within the core regions of three circumventricular organs (OVLT,
subfornical organ, and area postrema). These differences most
likelyareattributabletothedifferentrouteofactionandeffects
of LPS. First, intravenous LPS may act at circumventricular organs
toproduce many of the brain-mediated aspectsof the acute-phase
response (Saper and Breder, 1994; Elmquist et al., 1996). Second,
highdosesofLPSinducehypotensionandsubsequentreleaseof
vasopressinandoxytocin(Aiuraaletal.,1995);mostlikely, the
markedinductionofFosin magnocellular neuronsoccursduring
theincreasedfiringthatcausespeptidesecretion.

We hypothesize that the VMPO may be an essential link in the
production offever; PGE2 (either produced near the OVLT after
LPS or directly injected) may stimulate neurons in the VMPO
that alter the thermoregulatory setpoint by means of projections
tothePVH and other autonomic regulatory regions. Westressed
the potential role of the VMPO, because unlike other
PVH-projecting regionsofthepyrogeniczonethan the antero-
ventral periventricular nucleus and the mnPO nucleus (Saper
and Levisohn, 1983; Simler and Swanson, 1988; Standaert and Saper,
1988), the VMPO reliably produces Fos during LPS- and PGE2-
induced fever. VMPO neurons directly project to the dorsal and
ventravagalenterminalsofthePVH,areaswhichregulateauto-
nomic function, and these PVH-projecting VMPO neurons are
activatedduringfever(ElmquistandSaper,1996).Inaddition, we
arestudyingotherinputsfromtheVMPOtothePVHthatmaybe
relayed via the anterior perifornical region (Elmquist et al., 1995).

The PVH is well positioned to coordinate the neuroendocrine
and autonomic activity required for the production of fever. The
PVH projects directly to preganglionic sympathetic and parasym-
pathetic neurons as well as to sympathetic premotor sites in the
parabrachialnucleus,VLM,andNTS(SwansonandSawchenko,
1983; Saper, 1995). Thus, through its connections with the PVH,
the VMPO may contribute to the increased sympathetic activity
and redistributed blood flow required for the production of fever
(for detailed discussion, see Elmquist et al., 1996).

Figure 8. Injection of 1 ng of PGE2 into the pyrogenic zone induces
Fos-IRinthe VMPO. Injection of PGE2 outside the pyrogenic zone or
injection of vehicle even into the pyrogenic zone fails to induce much
Fos-IR (n = 3–4 in each group; *p = 0.03).

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and autonomic activity required for the production of fever. The
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1983; Saper, 1995). Thus, through its connections with the PVH,
the VMPO may contribute to the increased sympathetic activity
and redistributed blood flow required for the production of fever
(for detailed discussion, see Elmquist et al., 1996).
Perspective

We have demonstrated that threshold doses of PGE2 produce fever when injected into the ventromedial pyrogenic zone of the POA. These PGE2 fevers are accompanied by activation of neurons in the VMPO and other key autonomic regulatory areas in a pattern similar to that seen during the fever produced by intravenous LPS. These observations establish a potential site of PGE2 action during fever and help define the central pathways through which fever is mediated. However, it remains to be established whether PGE2 is necessary for fever and, if so, through which specific PGE2 receptors. Future experiments to block PGE2 production or selectively antagonize its action will greatly aid in clarifying the neural mechanisms of fever and the broader role of the brain in the acute-phase reaction.

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