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EVIDENCE FOR THE INVOLVEMENT OF THE ORGANUM VASCULOSUM LAMINAE TERMINALIS IN THE FEBRILE RESPONSE OF RABBITS AND RATS

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SUMMARY

1. Control febrile responses to intravenous injections of endogenous pyrogen were determined in groups of rabbits and rats, exposed to their respective thermoneutral ambient temperatures.

2. Discrete electrolytic lesions were placed within the confines of the organum vasculosum laminae terminalis (o.v.l.t.) of each species. The fever responses of the animals were remeasured 3 days later, and in every case there was a marked enhancement of the fevers produced, using the same doses of endogenous pyrogen that were used earlier.

3. Similar lesions that were placed unilaterally within the preoptic anterior hypothalamic area in groups of control animals, were not effective in enhancing the febrile responses of these animals.

4. The course of this lesion-induced fever enhancement in rabbits was studied during the succeeding 3 week period, when it was found to return gradually towards the control levels.

5. It is postulated that the o.v.l.t. is involved in some manner in the process whereby circulating pyrogen is translated into a febrile stimulus. Lesions posited within this region are thought to either increase the amount of pyrogen entering the o.v.l.t., or to increase the sensitivity of pyrogen receptor sites within the o.v.l.t.

INTRODUCTION

It is now widely accepted that fever is produced by the interaction of various pathogens with bone-marrow-derived macrophages to elicit the release of an endogenous pyrogen, which in turn travels via the circulation to the brain. Here it is thought to act upon the preoptic anterior hypothalamic (p.o.a.h.) area, possibly by stimulating the production of prostaglandin E, to cause alterations in the thermoregulatory controller that result in the febrile response (Dinarello, 1984). However, there are some difficulties with such a hypothesis. For example, it has yet to be demonstrated that endogenous pyrogen, a polypeptide of molecular weight at least 15000 daltons, even enters the brain neuropile from the cerebral circulation (Dinarello, Weiner & Wolff, 1978). Indeed, fevers that result from the direct introduction of

endogenous pyrogen into the cerebral ventricles of rabbits have very different characteristics from those of the fevers that are produced by the intravenous injection of that pyrogen into the same animal (Stitt & Bernheim, 1985). For these reasons it might be supposed that the site of action of endogenous pyrogen is much closer to the circulation than has been supposed previously, perhaps in a specific region within the cerebral circulation possessing atypical 'blood–brain barrier' characteristics, that might allow the pyrogen molecules limited access to the cells or neural elements that act as receptor sites in the febrile mechanism.

An obvious candidate is the organum vasculosum laminae terminalis (o.v.l.t.). This mid-line circumventricular organ is located within the rostral wall of the third ventricle, immediately dorsal to the optic chiasma, above the supraoptic recess, and it is bounded on either side by the medial septal and preoptic areas (Behnsen, 1927; Wislocki & Leduc, 1952; Weindl, 1965). It has a copious vasculature of distinctive architecture, which originates from the preoptic arteries and veins (Weindl, Schwink & Wetzstein, 1967). It is also devoid of typical tight-junctioned vascular epithelial cells that are characteristic of the cerebral vasculature (Weindl & Joynt, 1972). It has been demonstrated that proteins of molecular weight of as large as 45000 daltons, such as horseradish peroxidase, can leave the cerebral circulation and enter the perivascular spaces within the o.v.l.t. (Weindl, 1969; Weindl & Joynt, 1969). This area also contains several neural elements that are in direct contact with the brain neuropile proper (Brizzee, 1955; Weindl, Schwink & Wetzstein, 1968; Moore, 1977; Camacho & Phillips, 1981). More recently, in their review of the mechanisms of fever, Hellon & Townsend (1983) suggested that pyrogens might gain entry into the brain from the circulation via the o.v.l.t., and Blatteis, Bealer, Hunter, Llanos-Q, Ahokas & Mashburn (1983) reported that lesions within the anteroventral portion of the third ventricle, adjacent to the o.v.l.t., resulted in the suppression of fevers produced by the intraperitoneal injection of endotoxin in guinea-pigs. It seemed reasonable, therefore, that if endogenous pyrogen were to gain access into the o.v.l.t., then discrete lesions placed within this region should alter or even abolish the febrile responses produced by intravenous injections of endogenous pyrogen. A preliminary report of these findings was delivered at the twenty-ninth I.U.P.S. Congress in Sydney, Australia (Stitt & Shimada, 1983).

METHODS

The experiments were conducted on both male New Zealand white rabbits weighing 3·0–3·5 kg and male Sprague–Dawley rats weighing 250–300 g. They were conditioned to accept restraint in conventional neck stocks. In the case of the rats, 5 days prior to the start of the experiments, a polyvinyl catheter was implanted in the femoral vein of each animal under general anaesthesia. The catheter was passed subcutaneously to the dorsal thoracic region, and exteriorized at the mid-scapular level, behind the neck. The catheter was kept patent by flushing it twice a week with a dilute solution of heparinized 0·9% (w/v) saline (100 u./ml) and all intravenous injections of endogenous pyrogen were made by this route. In the case of rabbits, prior to the start of each experiment, a 25 gauge butterfly needle attached to a polyvinyl catheter was inserted into the marginal ear vein and taped to the ear. All injections of endogenous pyrogen into these animals were administered via this cannula.

The control febrile responses of a group of ten rabbits and twelve rats to intravenous injections of endogenous pyrogen were determined at their respective thermoneutral ambient temperatures (T_a) using partitional calorimetry, prior to the placement of lesions. The rabbits were placed in the

calorimeter at $T_a = 20$ °C and allowed to reach a thermal steady state before they were injected with a standard dose of endogenous pyrogen of 0·5 ml/kg, while the rats were studied at $T_a = 26$ °C and were injected with a standard dose of endogenous pyrogen of 2·0 ml/kg after they had attained a thermal steady state. All experiments were carried out on the conscious animals, minimally restrained in the indirect partitional calorimeter that we have described previously (Stitt, 1976; Stitt, Hardy & Stolwijk, 1974). Rectal and skin extremity (tail or ear) temperatures, metabolic rate, respiratory evaporative heat loss and extremity vasomotor tone were measured continuously and recorded once per minute by an on-line data acquisition system.

The endogenous pyrogen used in this study was produced from human monocytes derived from freshly banked blood. The cells were stimulated to produce endogenous pyrogen by heat-killed staphylococci, using techniques for preparation and purification that have been reported previously (Dinarello & Bernheim, 1981). Each millilitre of the semi-purified pyrogen contained the supernatant product of 2×10^6 stimulated monocytes and polymyxin B sulphate (10 μg/ml) was added to remove any traces of endotoxin contamination. The pyrogen was stored in the refrigerator at 4 °C and all aliquots were dispensed using rigidly sterile techniques.

After a control febrile response was obtained in each animal, small discrete electrolytic lesions were placed in the mid line within the body of the o.v.l.t. in half of the animals of each species, using a Kopf stereotaxic apparatus. The coordinates for the o.v.l.t. lesions in the rabbits were: $A = 4·5$ mm, $L = 0·0$ mm, $V = -2·0$ to $-3·0$ mm, using the stereotaxic atlas and coordinates of Sawyer, Everett and Green (1954), while those of the rat were: $A = 8·0$ mm, $L = 0·0$ mm, $V = -1·0$ to 2·0 mm, using the stereotaxic atlas and coordinates of de Groot (1967). Under general anaesthesia a medial incision was made in the skin of the scalp and the overlying muscles and periosteum were scraped off the calvaria to expose the skull and a small hole was trephined in the medial sagittal suture. The dura was punctured with a sharp needle and the lesioning electrode was introduced into the brain and lowered to the required coordinates. The lesions were made with stainless-steel electrodes (0·4 mm in diameter) insulated to less than 0·5 mm from their etched tips. These electrodes had tip diameters of 75–100 μm in order to allow the lesions to be positioned within the narrow strip of tissue in the roof of the supraoptic recess and within the lamina terminalis that comprised the o.v.l.t. The lesions were made in rats by passing 2 mA of anodal d.c. current for 10 s, and in rabbits by passing currents of 3 mA for 10–15 s. Control lesions of similar magnitude were placed, unilaterally, within the adjacent p.o.a.h. area in the other half of the animals in each group. The electrode craniotomy holes in the calvaria were filled with acrylic dental cement and the animals were permitted a minimum of 3 days to recover from the surgery. During this time body temperatures were normal and there were no obvious disturbances in either food or water intake, although most animals did lose some weight ($< 3\%$), which they subsequently regained. All lesions were verified by standard histological techniques at the end of the experiments, when the brains were perfused *in situ* and then fixed with 10% (w/v) formalin solution. The brains were cut routinely at 50 μm, on a Histofreeze microtome and the coronal sections containing the lesions were mounted serially and stained with Cresyl Violet. The size and extent of the lesions were reconstructed from these sections.

RESULTS

Fig. 1*A* illustrates a typical control febrile response of the rabbit to an intravenous injection of endogenous pyrogen in a thermoneutral environment. The increase in metabolic rate, although present, was slight and rectal temperature peaked at about 50 min after the injection at 0·7 °C and began to decline thereafter. However, when the same animal was retested using the same dose of pyrogen three days after the placement of a lesion in the o.v.l.t., as shown in Fig. 1*B*, there was a more intense and sustained increase in the metabolic rate that resulted in the elevation of rectal temperature by more than 1·4 °C. However, it will be noted that the peak increase in temperature was still attained at 50 min after the injection of the pyrogen. By contrast, those rabbits that had received lesions outside the o.v.l.t., but within the adjacent p.o.a.h. area, showed no significant differences in their responses to

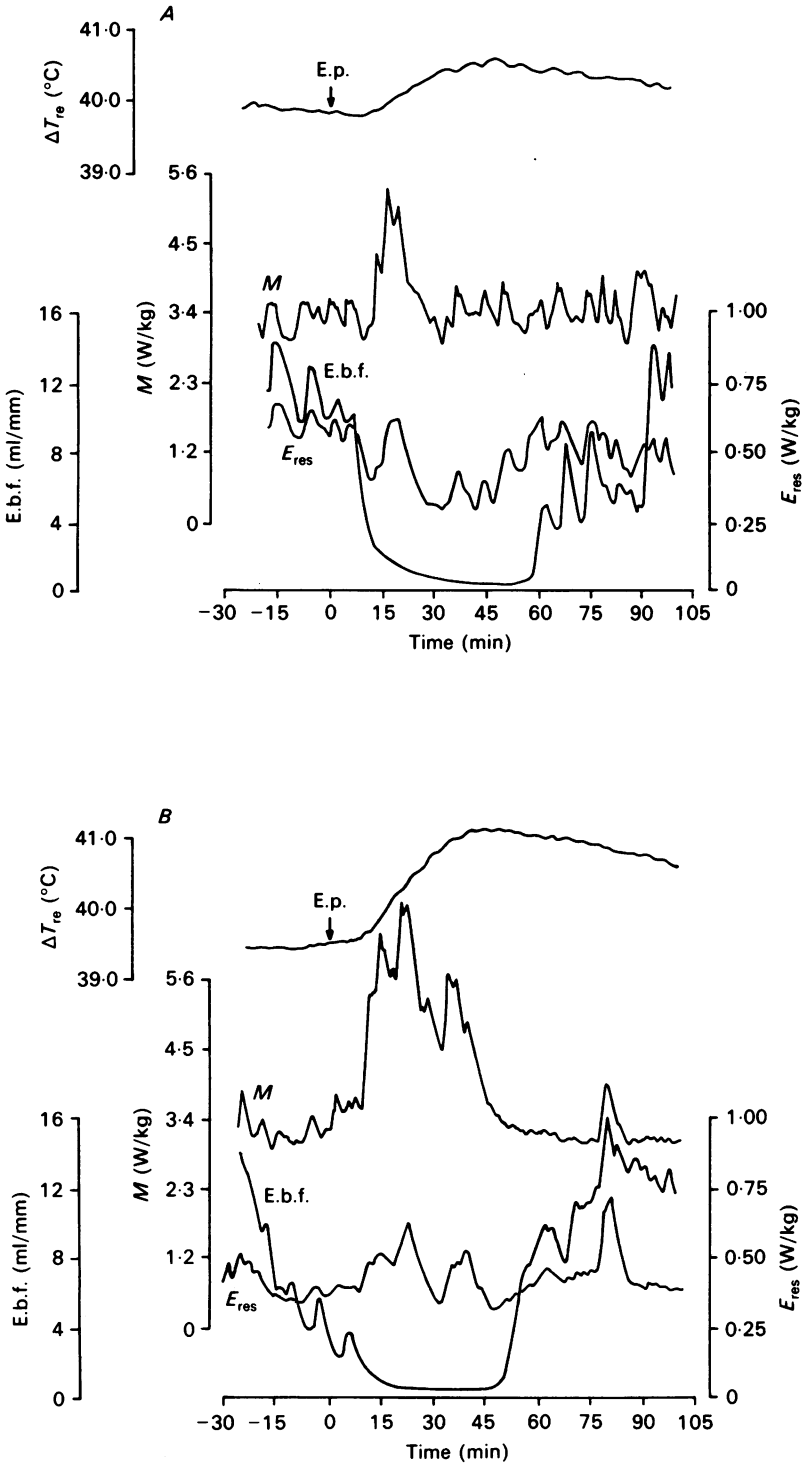

Fig. 1. For caption see opposite.

endogenous pyrogen when these were compared to their pre-lesion control febrile responses. The febrile responses of both groups of rabbits, both before and after the placement of their lesions, are compared in Fig. 2. Fig. 2*A* shows the mean changes in rectal temperature of the o.v.l.t.-lesioned rabbits in response to the standard dose of pyrogen, compared to the changes obtained in these animals prior to the placement of the lesions. The febrile responses were more than doubled, yet there was no change in the shape of the fever curves; they were still monophasic, attaining their peak value around 50 min and declining toward pre-injection levels during the second hour. Fig. 2*B* shows that the increases in rectal temperature obtained in response to the pyrogen, after the placement of lesions within the p.o.a.h. area, were not significantly different from those obtained prior to the placement of the lesions. Similar results were obtained using rats, and these are summarized in Fig. 3. It can be seen that the typical febrile responses of rats, while comparable to those displayed by rabbits, were somewhat shorter lived, in that the peak increase in rectal temperature was attained at 20–30 min after injection, and by 60 min body temperature had almost returned to pre-injection levels. All rats that received lesions within the o.v.l.t. showed a comparable enhancement of their febrile responses to endogenous pyrogen, yet there was no change in the characteristics of their febrile responses.

Since lesions placed within the o.v.l.t. produced large and consistent fever-enhancing effects, it seemed of interest to study the temporal duration of this enhancement. Consequently, the o.v.l.t.-lesioned rabbits were retested with the same dose of endogenous pyrogen on days 6, 11 and 19 after the lesions were made. The results of this study are shown in Fig. 4, were it can be seen that by day 19 the initially enhanced febrile responses had gradually diminished toward their pre-lesion control values.

In general the lesions produced in this study were small and in no way encompassed the entirety of the o.v.l.t., so that they are more correctly to be regarded as irritative rather than ablationary in nature. This can be seen in Pl. 1, where photomicrographs of coronal sections of the rabbit brain at the level of the rostral optic chiasma are shown. Pl. 1 *A* shows a normal, intact o.v.l.t., forming the roof of the supraoptic recess. Plate 1 *B* illustrates a lesioned o.v.l.t., where damage (indicated by the arrows) is confined to the body of the o.v.l.t. at this level. The parts of the o.v.l.t. dorsocaudal to this area, within the lamina terminalis reaching up toward the anterior commissure were unscathed. Pl. 1 *C* shows a comparable control lesion placed within the confines of the adjacent, but caudal, medial p.o.a.h. area of another rabbit. These lesions generally appeared more uniformly prescribed than those made in the o.v.l.t. This may be due to the fact that when o.v.l.t. lesions were being made, some part of the electrode tip was usually in contact with the cerebrospinal fluid contained in the supraoptic recess or the prechiasmatic cistern. Thus, the lower resistance offered by

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Fig. 1. Example of the thermoregulatory responses of a rabbit during fever, *A*, control response to a dose of endogenous pyrogen (0·5 ml/kg I.V.). *B*, enhanced response from the same animal to the same dose of pyrogen, 3 days after a lesion was placed in the o.v.l.t. M = metabolic rate, e.b.f. = ear blood flow, E_{res} = respiratory evaporative heat loss, T_{re} = rectal temperature, e.p. = injection of endogenous pyrogen.

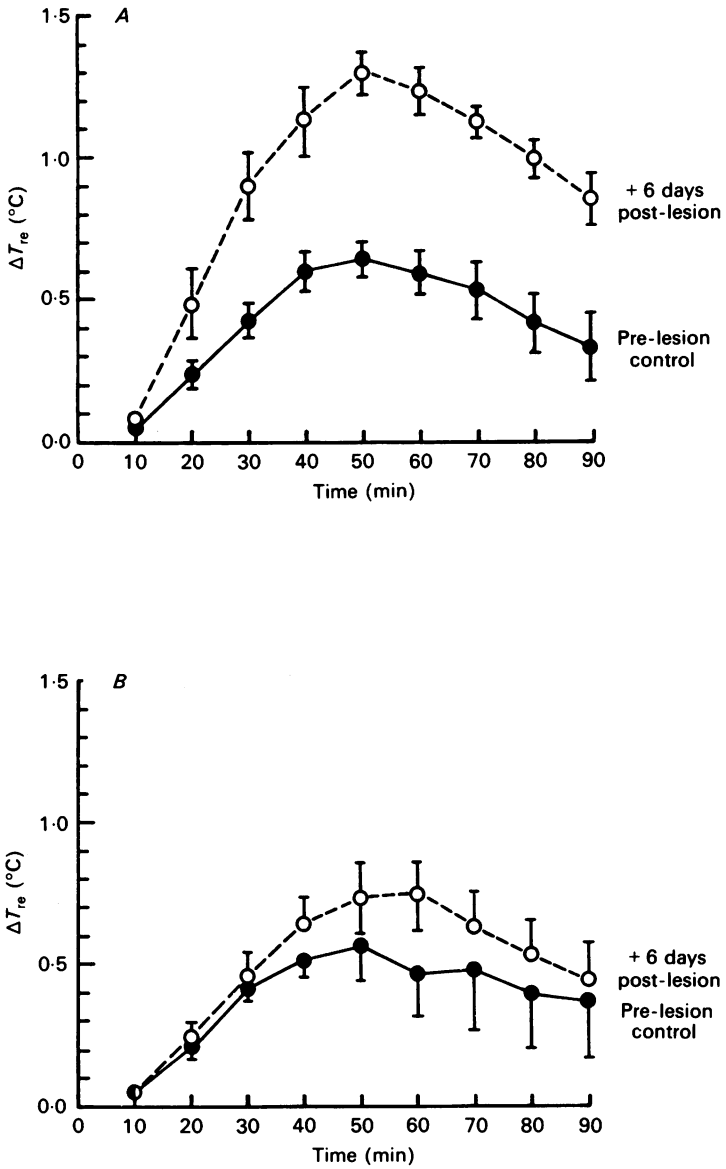

Fig. 2. *A*, comparison of the rectal temperature (T_{re}) changes in rabbits induced by a standard dose of endogenous pyrogen (0·5 ml/kg I.V.) both before and 6 days after the placement of a lesion within the o.v.l.t. ($n = 6$). *B*, comparison of the rectal temperature changes in rabbits both before and 6 days after the placement of a lesion unilaterally in the medial p.o.a.h. area ($n = 4$).

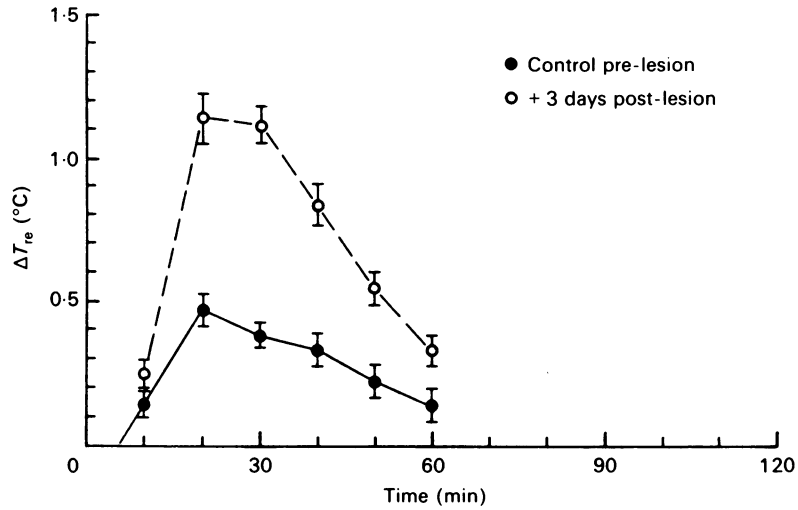

Fig. 3. A comparison of the rectal temperature (T_{re}) changes in rats induced by a standard dose of endogenous pyrogen (2·0 ml/kg I.V.), both before and after the placement of a lesion within the o.v.l.t. ($n = 6$).

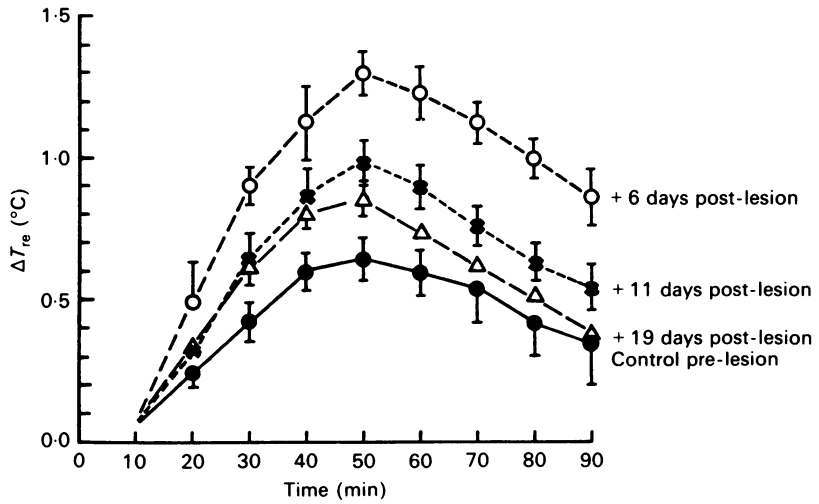

Fig. 4. The progressive diminution of the enhanced febrile response to endogenous pyrogen produced by o.v.l.t. lesions in rabbits, over a period of 19 days. The same standard dose of pyrogen (0·5 ml/kg) was administered on days 6, 11 and 19 after placement of the lesion ($n = 6$).

this fluid and the subsequent gas-bubble formation occurring within the fluid during current passage, reduced the size and altered the uniformity of these lesions. Pl 1 *D* and *E* illustrate comparable control and lesioned o.v.l.t. tissues in the rat at the level of the rostral supraoptic recess.

DISCUSSION

Contrary to what might have been expected, lesions that were placed within the confines of the o.v.l.t. produced an enhancement of the febrile responses of both rabbits and rats. This enhancement of fever was not produced by a prolongation of the duration of the febrile episode; rather it appeared to be due to an intensification of the fever. This is clearly illustrated in Fig. 1, where it can be seen that the duration of the fever after the lesion was identical to that of the control fever. There was no decrease in the latency of the onset of the fever, and in both instances it took about 50 min to attain the peak increase in the body temperature. Defervescence, as indicated by the rapid increase in ear blood flow, began in both cases in less than 60 min after the injection of the pyrogen. Thus, the major difference between the two febrile responses illustrated in Fig. 1, apart from the difference in the magnitude of the increases in body temperature, was the intensity and duration of the increase in metabolic rate exhibited by the o.v.l.t.-lesioned animal. It should be noted that the same dose of endogenous pyrogen (0·5 ml/kg, obtained from the same batch) was injected in both cases. Therefore, it may be concluded that o.v.l.t.-lesioned animals became more sensitive to endogenous pyrogen. This increased sensitivity appeared to last for several weeks, and it extinguished in a gradual manner. The effective lesions that were placed in the o.v.l.t. to produce this fever enhancement phenomenon, were small and discrete. Each lesion was the result of a single penetration of the electrode and invariably the damage was confined to the body of the rostral portion of the o.v.l.t. that protruded into the supraoptic recess, close to the prechiasmatic cistern that rostrally abuts the lamina terminalis (see Pl. 1 *B* and *E*).

The results of this study indicate that the o.v.l.t. is, in some manner, concerned with the febrile response to circulating endogenous pyrogen. However, the exact nature of this involvement is not clearly discernible from the experiments described. It could be that the o.v.l.t., due to the peculiar absence of typical tight-junctioned capillary epithelial cells within this circumventricular organ, acts as a portal by which circulating endogenous pyrogen enters the brain neuropile. Lesions such as those that were placed within the o.v.l.t. in the current study might increase the capillary permeability of this region to the large endogenous pyrogen molecule, and thereby increase the amount of pyrogen that gains access to the thermoregulatory centre. This, in turn, could account for the state of enhanced febrile sensitivity that appears to exist for several weeks after the placement of the lesions in the o.v.l.t. It has been shown that physical damage to the brain, to the cerebral cortex for example, causes a temporary increase in the local permeability of the cortical vasculature at the site of the injury, so that labelled serum albumin proteins can gain local access to the neuropile below the injury (Klatzo, Piraux & Laskowski, 1958; Klatzo, Miguel & Otanasek, 1962). This state of increased vascular permeability lasted several weeks before returning to normal. Such a time course is consistent with the observed duration of the enhancement of the febrile responses produced by lesions placed in the o.v.l.t. in this study.

However, if the action of the lesion were merely to increase the cerebral vascular permeability to endogenous pyrogen at the site of the lesion, then one would expect that those animals that had received lesions in the p.o.a.h. area also would have displayed enhanced febrile responses to endogenous pyrogen. This would be expected because several investigators have shown that when endogenous pyrogen is injected directly into the tissue of the p.o.a.h. region, fever results (Cooper, Cranston & Honour, 1967; Jackson, 1967). Thus, any action that would increase the entry of pyrogen into the p.a.o.h. area should also increase the febrile response. As can be seen in Fig. 2*B*, this was clearly not the case since fever was not enhanced after p.o.a.h. lesions. Therefore, one may conclude that the action of the lesion was not merely to increase vascular permeability in a non-specific fashion, but that the actual site of the effective lesions, the o.v.l.t., had a specific role in the mediation of the febrile response to circulating endogenous pyrogen. Furthermore, there is good evidence to support the idea that circulating proteins that have gained entry to the perivascular space within the o.v.l.t. cannot travel beyond the immediate confines of the o.v.l.t. into the brain neuropile proper (Weindl, 1969; Weindl & Joynt, 1969).

Thus, it seems possible that the actual site of action of endogenous pyrogen in producing fever could be confined to within the o.v.l.t. itself, a plausible hypothesis since it is known that at least two types of neuronal elements exist within the body of the o.v.l.t. (Brizzee, 1955; Weindl *et al.* 1968; Moore, 1977; Camacho & Philips, 1981). In that case the action of the lesion within the o.v.l.t. might be to increase its local vascular permeability, allowing more endogenous pyrogen to enter the o.v.l.t. to act upon the local pyrogen receptor sites and thereby create larger fevers. Alternatively, it may be that the small lesions within the o.v.l.t. create a localized irritative or inflammatory reaction that sensitizes the pyrogen receptor mechanisms that reside in the o.v.l.t., so that the pyrogenic stimulus becomes more effective than it was prior to the placement of the lesion. In either case it now has been demonstrated that the o.v.l.t. plays some role in mediating the febrile responses of rabbits and rats to circulating endogenous pyrogen.

The idea that the receptors for endogenous pyrogen are confined to the o.v.l.t. is an attractive one for several reasons. First, it could explain why endogenous pyrogen has never been found within the confines of the blood–brain barrier (Dinarello *et al.* 1978), since the o.v.l.t. is 'outside' the brain neuropile proper. Secondly, it could account for the fact that the latency of fevers produced by the intravenous injection of endogenous pyrogen, is much shorter than the latency of the fevers produced by the intracerebroventricular injection of the same endogenous pyrogen (Stitt & Bernheim, 1985). Finally, it could be the site at which the putative mediator of the febrile response, prostaglandin E, is produced by specific cells that possess receptors for endogenous pyrogen. Since prostaglandin E is a lipophilic molecule, the blood–brain barrier would present little resistance to its diffusion into the brain neuropile of the adjacent p.o.a.h. area.

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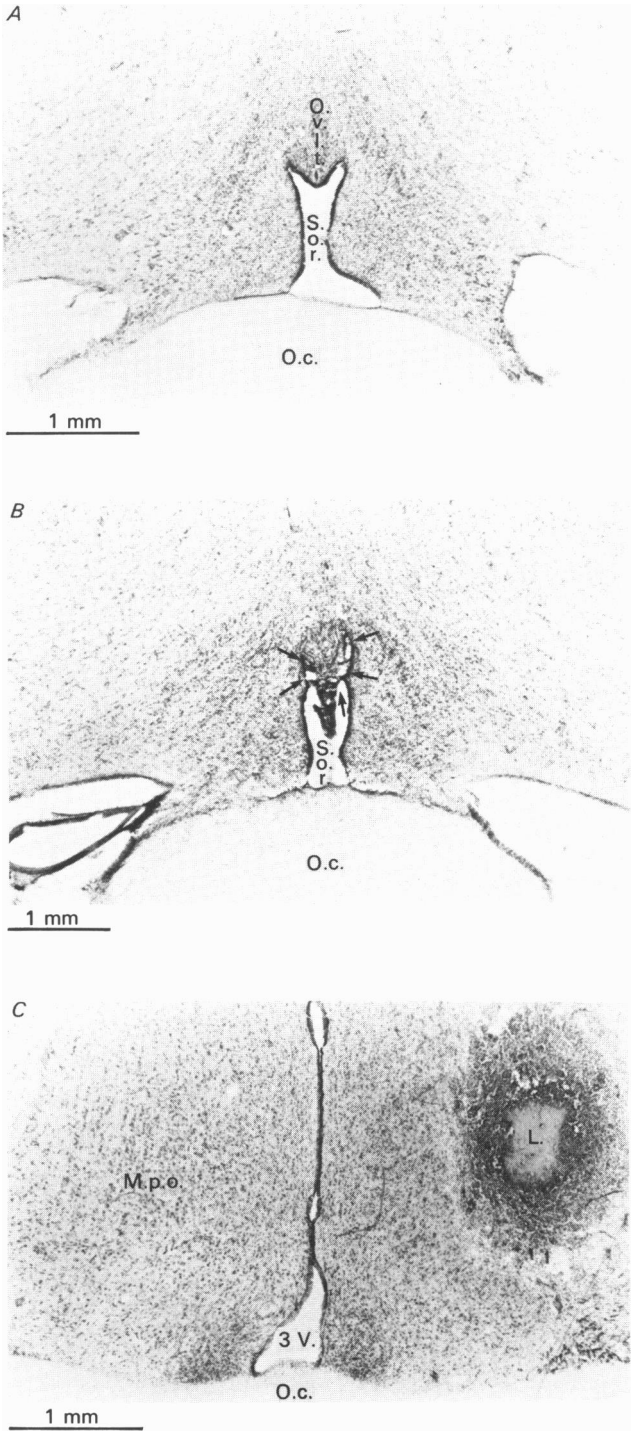
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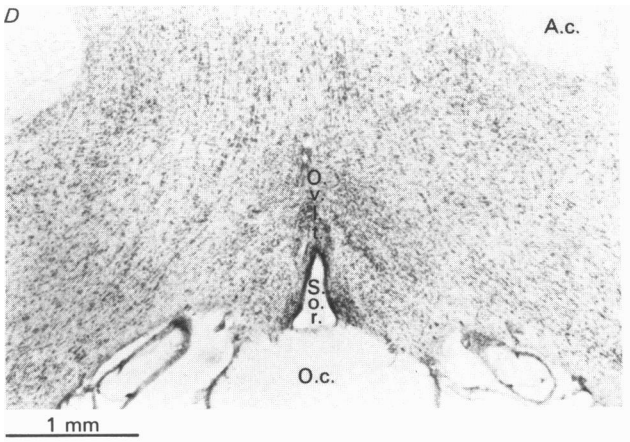
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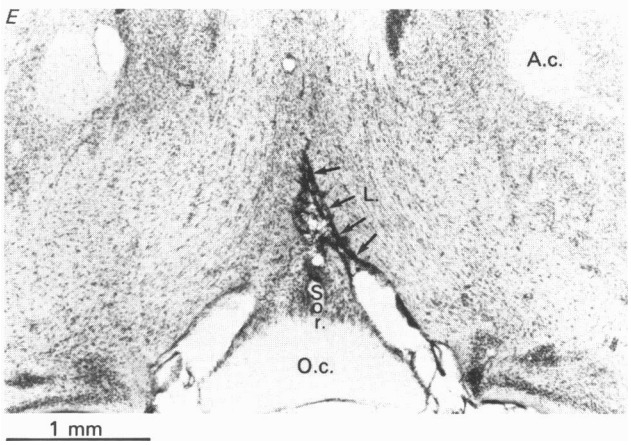
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EXPLANATION OF PLATE

A, a coronal section of a normal rabbit brain at the level of the rostral optic chiasma (O.c.) showing the intact o.v.l.t., part of which is protruding into the supraoptic recess (S.o.r). *B*, a comparable coronal section from a lesioned rabbit, showing that the damage is confined to the o.v.l.t. (indicated by the arrows). *C*, a coronal section of a rabbit brain at the level of the medial preoptic area (M.p.o.), showing the unilateral control lesion (L.) in the p.o.a.h area (3V. = third ventricle). *D*. a coronal section of a control rat brain showing the intact o.v.l.t. above the supraoptic recess (A.c. = anterior commissure). *E*, a comparable coronal section from the brain of a rat which received a lesion in the o.v.l.t. Damage is discrete and indicated by the arrows.