Recurrent Herpes Simplex in the Mouse: Inflammation in the Skin and Activation of Virus in the Ganglia Following Peripheral Stimulation

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SUMMARY

The originally infected ear of mice latently infected in the cervical ganglia with herpes simplex virus (HSV) was treated with one of five stimuli: stripping with cellophane tape, irradiation with u.v. light, or the application of xylene, dimethyl sulphonyxide (DMSO) or retinoic acid. Each of these stimuli induced the appearance of infectious virus in the ganglia 1 to 5 days later, most frequently after 1 to 3 days. Virus was also isolated from the treated ears, most frequently 3 to 5 days after stimulation. In a proportion of mice treated with cellophane tape stripping, xylene, retinoic acid or DMSO, clinical recurrent disease was observed, although in the case of DMSO this proportion was low. Some of the physiological changes induced in the skin by the five stimuli were studied. Treatment with DMSO, cellophane tape stripping or xylene induced almost immediate inflammation in the skin as judged by extravasation of Evans blue dye. Studies with inhibitors suggested that this was mediated by a neurogenic factor together with histamine or 5-hydroxytryptamine, or both of these. In addition, with the exception of mice treated with DMSO, the levels of prostaglandins of the E and F classes in the skin of the ear were elevated 1 to 3 days after treatment. These results are discussed with reference to the mechanisms by which recurrent herpetic disease develops.

INTRODUCTION

Following infection of the mouse ear, herpes simplex virus (HSV) becomes latent primarily in the cervical ganglia (Hill et al., 1975). Recurrence of infection can be induced in the skin of the originally infected ear by irradiating this ear with u.v. light (Blyth et al., 1976); recurrent clinical disease follows induction of mild trauma by stripping the skin with cellophane tape (Hill et al., 1978). We now report three chemical stimuli to the skin (xylene, retinoic acid and dimethyl sulphonyxide) which induce recurrent disease and show that each of the five stimuli also induce the reactivation of infectious virus in the ganglia. In addition, we report on some physiological changes which occur in the skin following each of the stimuli. The results are discussed with reference to possible mechanisms of the development of recurrent disease.

METHODS

Injection of the mouse ear. Four-week-old female, outbred Swiss white mice were inoculated subcutaneously in the right ear with \(3 \times 10^5\) p.f.u. of HSV-1 strain SC16 (Hill et al., 1975). Mice were used in experiments on reactivation of the virus only if they fulfilled certain criteria (Hill et al., 1978) of severity of clinical signs, i.e. if they showed erythema of at least + severity (on a scale 0 to +++) both 6 and 10 days after infection, or erythema of ++ severity or ear paralysis on one or both of these days.

Chemicals. Capsaicin (8-methyl-N-vanillyl-6-nonenamide), retinoic acid and silicic acid were purchased from Sigma. Xylene (sulphur free) and the 'Analar' grades of dimethyl sulphonxide (DMSO), chloroform and ethyl acetate were purchased from BDH. Antisera to goat and rabbit \(\gamma\)-globulins, and to prostaglandin \(E_2\) (PGE\(_2\)) and \(F_2\alpha\) (PGF\(_2\alpha\)) were purchased from Calbiochem. Acetylcholine and the neurogenic compounds histamine and 5-hydroxytryptamine were purchased from Sigma.
Tritiated prostaglandins were from Amersham International. Cyproheptadine was a gift from Merck, Sharp & Dohme Research Laboratories, mepyramine from May & Baker and methysergide from Sandoz.

Mepyramine and methysergide were dissolved in Dulbecco's PBSA for use. Cyproheptadine was dissolved in ethanol, then diluted in deionized water. Capsaicin was dissolved at the working concentration in an ethanol–Tween 80–physiological saline mixture (Jancsó, 1960).

Stimuli to the skin. All stimuli were applied to the right ear. For stripping with cellophane tape (Hill et al., 1978) and u.v. irradiation (Blyth et al., 1976) mice were anaesthetized by intraperitoneal injection of sodium pentobarbitone. Retinoic acid was applied as a 0.01% (w/v) solution in acetone, xylene as a 50% mixture with ethanol, and DMSO was undiluted. In each case 50 µl was dropped onto the ear taking care to avoid contact with the animals' eyes.

Definition of recurrent disease. After cellophane tape stripping, or application of DMSO or xylene, recurrent disease was recorded if erythema of at least + severity (Hill et al., 1982) continued for at least 4 days after the stimulus, or if, after a period without erythema, this reappeared to at least + severity for 2 or more consecutive days, or to at least ++ severity for at least 1 day. (For the definition of recurrent disease after application of retinoic acid, see Results.)

Isolation of virus from the ear and cervical ganglia. Mice were killed by intraperitoneal injection of sodium pentobarbitone. The skin was scraped from the upper surface of the ear, ground in 0.4 ml maintenance medium in a tissue grinder, and put on to Vero cell monolayers grown in Sterilin 25 cm² plastic flasks. Cultures were examined for cytopathic effects for 1 week (Hill et al., 1978). The 2nd and 3rd cervical ganglia were removed, ground together in 0.2 ml maintenance medium, then subjected to three cycles of freezing and thawing. The resulting homogenate was put on the Vero cell monolayers and examined as above.

Extraction and separation of prostaglandins. Prostaglandins were extracted from skin by a modification of the method described by Salmon & Karim (1976). The mice were killed by cervical dislocation and each ear was removed and placed in 4 ml ethanol chilled to about −23 °C in an ice–salt bath, and ground in a tissue grinder. After centrifugation at 1000 g for 5 min, the supernatant fluid was removed and the precipitate washed with a further 4 ml cold ethanol and discarded. The washings were combined with the supernatant fluid and the ethanol driven off under nitrogen or by lyophilization. The dried precipitate was dissolved in 2.5 ml phosphate-buffered saline and the pH adjusted to about 4.0 with 2 M-citric acid. The prostaglandins were extracted with 2 vol. ethyl acetate equal to each to the volume of the original solution. The pooled ethyl acetate extracts were dried under nitrogen and the prostaglandin preparations stored dehydrated at −35 °C before separation by chromatography.

Chromatography was performed on a column of SIL-LC silicic acid by the method of Hillier & Kasonde (1976) as modified by Salmon & Karim (1976). To test the efficiency of these procedures tritiated PGF2α and tritiated PGE2 (30000 d/min of each) were injected subcutaneously into the right ears of six mice about 5 min before the ears were transferred to chilled ethanol. Subsequent analysis showed that 98% of PGF2α and 68% of PGE2 were recovered.

Assay of prostaglandins. PGF was assayed by the radioimmunoassay method described by Cornette et al. (1972) except that the first equilibration period was 1 h instead of 15 min, and the second equilibration period was 18 h instead of 2 days. PGE was assayed by a similar procedure except that the buffer was pH 7-4 rather than pH 8.0. For both assays, the samples were counted in Dimilume 30 (Packard) or PCS (Amersham International) in a Packard Tri-Carb 3330 scintillation counter. The antisera to PGF2α cross-reacted with PGF1α by about 50% and the antisera to PGE2 cross-reacted with PGE1 by about 60%.

Measurement of extravasation of dye. The inflammatory response often involves release of mediators such as histamine and 5-hydroxytryptamine (5-HT). One effect of these mediators is to increase the permeability of smaller blood vessels. Hence, their presence, or inhibition of their action or release by drugs, can be detected by measuring changes in such permeability; the method used in these studies was extravasation of Evans blue dye. Nine-week-old male mice were injected into the lateral vein of the tail with 0.5 ml of 0.4% (w/v) Evans blue in physiological saline. After 30 min, a stimulus was applied to the right ear (mice were anaesthetized by intraperitoneal injection of sodium pentobarbitone before stripping with cellophane tape or irradiation with u.v. light). After a further 30 min, the mice were killed by cervical dislocation and the intensity and distribution of dye in the ear recorded on a scale from 0 to + + + + (+, No blue; +, scattered spots of pale blue; +, medium blue on half or less of the ear; + +, medium blue on more than half the area of the ear; + ++, medium blue to deep blue over the whole ear; + ++++, intense blue over the whole ear.) These scores were found to correlate well with absorbance values obtained following extraction of the dye by the method of Harada et al. (1971) and spectrophotometry at 620 nm. In experiments where inhibitory or antagonistic drugs were tested, these drugs were injected subcutaneously at an appropriate time before injection of the dye. For capsaicin, methysergide and cyproheptadine the period was 30 min.
Herpes simplex and inflammation in skin

Table 1. Isolation of HSV from ganglia* of mice after stimuli to the skin of the originally infected ear

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>None (anaesthetized)†</td>
<td>0/23‡</td>
</tr>
<tr>
<td>Stripped with xylene in ethanol (50%)</td>
<td>4/46 (9%)</td>
</tr>
<tr>
<td>Retinoic acid in acetone (0.01%)</td>
<td>1/28 (4%)</td>
</tr>
<tr>
<td>DMSO</td>
<td>4/24 (17%)</td>
</tr>
</tbody>
</table>

* From pooled 2nd and 3rd right cervical ganglia after grinding, freezing and thawing.
† Of a further 74 completely untreated mice, 2 (3%) yielded virus.
‡ Number with virus/number tested.
§ ND, Not done.

RESULTS

Effect of stimuli to the ear of uninfected and latently infected mice

The effects of stripping the skin of the ear of normal mice with cellophane tape have been described previously (Hill et al., 1978). In a series of experiments involving 520 latently infected mice, stripping induced recurrent disease, as judged by erythema (Hill et al., 1978), in 166 mice (32%; range 15 to 50%).

Virus was isolated from the ears of about 20% of mice 3 days after u.v. irradiation (Blyth et al., 1976). However, induction of erythema cannot be used as a criterion for recurrent disease in this case since the erythema due to the irradiation masks that which might result from recurrent disease.

Application of 50% xylene to the ear of 8-week-old uninfected male mice produced almost immediate erythema in the skin, and the mice responded as though in pain. The erythema had disappeared in 58 of 63 (92%) mice by the 3rd day after treatment and in all mice by the 4th day. When latently infected mice were tested, 21 of 57 (37%) had erythema of sufficient duration or intensity to be defined as recurrent disease. In addition, a group of 62 latently infected mice was treated with xylene, and tested to see whether virus could be isolated from the skin of the ear. Of these, 34 developed recurrent erythema; 17 (50%) yielded virus when the ear was sampled on the day new erythema appeared.

DMSO applied to the right ear of 17 uninfected 8-week-old male mice induced almost immediate intense erythema, without signs of pain. The erythema had disappeared by the next day. When 31 latently infected mice were treated similarly, 4 (13%) developed recurrent disease as defined by Hill et al. (1978).

Of 53 female uninfected mice treated with retinoic acid, none had erythema on the first day after treatment. Erythema was seen in some animals during the 2nd to 6th days after treatment, with a peak incidence of 30% on the 3rd day. However, no animal had erythema of + severity for more than 2 days, or of ++ severity for more than 1 day. Thus, to define recurrent disease by erythema after retinoic acid treatment, the following criteria were used. Erythema should be of at least ++ intensity for 2 or more days, or of + intensity for at least 3 days. Using these criteria, 17 of 57 (30%) mice treated with retinoic acid developed recurrent disease. Of 27 mice treated with retinoic acid to test for the presence of virus in the skin, 13 developed erythema, and of these, 4 yielded virus when the ears were sampled on the day erythema first developed.

Isolation of virus from the ears and ganglia of mice

The originally infected ears of latently infected mice were treated with one of the stimuli. At different times after treatment, groups of mice were killed by intraperitoneal injection of sodium
pentobarbitone, and the ear and ganglia tissues tested for the presence of infectious virus (Tables 1 and 2). In a further group of mice, only the ganglia were tested.

**Isolation from ganglia**

As controls, attempts were made to isolate virus from ganglia of mice whose ears had not been treated. Virus was isolated from the ganglia of 2 of 74 (3%) untreated mice, but from none of 163 mice anaesthetized 1 to 4 days before the ganglia were sampled. By contrast, up to 30% of ganglia yielded infectious virus 1 to 5 days after stimulation of the ear (Table 1), most frequently 1 to 3 days after stimulation. The mean number of p.f.u. per mouse that yielded virus was 7 (range 1 to 75) and there was no significant difference in this yield between mice receiving any of the stimuli.

**Isolation from skin**

Again, attempts were made to isolate virus from the ears of unstimulated animals. Some were never anaesthetized; others were anaesthetized 2 to 4 days before sampling. No viruses were isolated. Virus was isolated from the skin of mice whose ears had been treated most often (up to 44%) 3 to 5 days after treatment (Table 2).

**Extravasation of dye after stimulation of the skin**

Extravasation of Evans blue dye into the skin was tested after each stimulus. Treatment with u.v. irradiation or retinoic acid did not induce extravasation during 4 days following the

Table 2. **Isolation of HSV from the originally infected ears of mice after stimuli to the skin of this ear**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (anaesthetized)*</td>
<td>1/25 (4%) 0/13‡</td>
</tr>
<tr>
<td>Stripped with cellophane tape</td>
<td>0/10 4/11 (36%) 3/10 (30%)</td>
</tr>
<tr>
<td>Xylene in ethanol (50%)</td>
<td>0/25 0/21 3/25 (12%)</td>
</tr>
<tr>
<td>Retinoic acid in acetone (0.01%)</td>
<td>0/28 0/27 3/23 (13%)</td>
</tr>
<tr>
<td>DMSO</td>
<td>1/24 (4%) 3/24 (13%)</td>
</tr>
</tbody>
</table>

* Of a further 23 completely untreated mice, none yielded virus.
‡ ND, Not done.
† Number with virus/number tested.

Table 3. **Effects of drugs on extravasation of Evans blue dye induced by stimuli to the skin**

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Stripping with cellophane tape</th>
<th>50% Xylene</th>
<th>DMSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>+++++†</td>
<td>+++</td>
<td>+++++</td>
</tr>
<tr>
<td>Mepyramine</td>
<td>+</td>
<td>+</td>
<td>+++++</td>
</tr>
<tr>
<td>Methysergide</td>
<td>+++++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mepyramine + methysergide</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mepyramine + capsaicin</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Methysergide + capsaicin</td>
<td>+</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>Mepyramine + methysergide + capsaicin</td>
<td>ND†</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>Cyproheptadine + capsaicin</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

* See Methods for doses, etc.
† See Methods for code.
‡ ND, Not done.
Table 4. Prostaglandin levels in the skin of the ear of uninfected female mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days after treatment</th>
<th>Prostaglandin level (ng/g wet tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>PGE 16.1 ± 5.0*</td>
</tr>
<tr>
<td>Stripping with cellophane tape</td>
<td></td>
<td>PGF 5.1 ± 2.4*</td>
</tr>
<tr>
<td>Xylene in ethanol (50%)</td>
<td></td>
<td>PGE 596.2 ± 23.2 (37)^†</td>
</tr>
<tr>
<td>Ultraviolet irradiation (50 s)</td>
<td></td>
<td>PGF 0.3 ± 0.3 (0.06)</td>
</tr>
<tr>
<td>Retinoic acid in acetone (0.01%)</td>
<td></td>
<td>PGE 217.9 ± 20.1 (13.5)</td>
</tr>
<tr>
<td>DMSO</td>
<td></td>
<td>PGF 4.5 ± 3.0 (0.9)</td>
</tr>
<tr>
<td>Untreated skin.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Mean of left and right ears.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>† Ratio of amount in treated skin to amount in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>untreated skin.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each of the other stimuli increased both PGE and PGF levels, although the patterns of increases varied with the stimulus (Table 4). PGE levels were greatly increased 1 day after treatment with

stimulus, but stripping or the application of xylene or DMSO to skin was followed by increased vascular permeability which could be assayed by measuring the intensity and extent of dye leakage into the tissue. Thus, the action of the stimuli could in part be analysed by studying the effects on the extravasation of dye of drugs antagonistic to particular mediators of inflammation (Green et al., 1979). The drugs were mepyramine (antihistamine), methysergide (antiseratonin) and cyproheptadine (non-specific antiamine). Capsaicin (Jancsó, 1960) was used to diminish the neurogenic response (Table 3). Extravasation of dye following treatment with xylene was reduced by treatment with mepyramine, methysergide, cyproheptadine or capsaicin, and almost completely abolished by treatment with capsaicin together with any one of the antiamine drugs.

Leakage of dye following stripping was reduced by mepyramine, cyproheptadine or capsaicin but not by methysergide. Treatment with capsaicin together with mepyramine or cyproheptadine further decreased, but did not completely abolish the dye leakage.

Extravasation of dye after treatment with DMSO was reduced by methysergide, cyproheptadine or capsaicin but hardly at all by mepyramine. Furthermore, capsaicin together with methysergide or cyproheptadine reduced leakage to very low levels.

Prostaglandin levels in the skin

The mean levels of PGF in the ears of 14 normal 8-week-old female mice were 5.2 ± 2.4 ng/g wet tissue (left ears), and 4.9 ± 2.2 ng/g (right ears). The corresponding figures for PGE were 14.8 ± 4.9 ng/g (left) and 17.3 ± 5.3 ng/g (right). None of the stimuli altered prostaglandin levels 2 h after stimulation. The level of PGE was reduced 1 to 4 days after treatment with DMSO, although an increase in the level of PGF was found 1 day after treatment but not later. Each of the other stimuli increased both PGE and PGF levels, although the patterns of increases varied with the stimulus (Table 4). PGE levels were greatly increased 1 day after treatment with
xylene, u.v. light or stripping and, thereafter, declined, although there was a biphasic pattern with peaks 1 and 4 days after xylene. The level of PGE was reduced 1 day after treatment with retinoic acid but was increased 2 to 3 days after treatment.

One day after stimulation with retinoic acid the level of PGF was increased. However, 1 day after treatment with xylene, stripping or u.v. irradiation, levels of PGF were decreased and did not become increased until later times.

Treatment with acetone (the solvent for retinoic acid) or ethanol (the diluent for xylene) did not affect PG levels.

DISCUSSION

Since our early attempts to produce recurrent herpes simplex in the skin of mice by irradiation of the originally infected ear with u.v. light (Blyth et al., 1976) we have investigated several other stimuli. One of these, stripping the ear with cellophane tape, has proved of value in the study of recurrent clinical disease (Hill et al., 1978; Blyth et al., 1980; Harbour et al., 1981). In addition to these physical stimuli we have now studied three chemical stimuli to the skin (the application of DMSO, xylene or retinoic acid), which also induce recurrent erythema. Two of these stimuli, retinoic acid and xylene, induced an incidence of recurrent disease (defined solely by the development of erythema; Hill et al., 1978) similar to that after stripping with cellophane tape, i.e. 22 to 43% (Hill et al., 1978; Blyth et al., 1980; Harbour et al., 1981). In contrast, application of DMSO was followed by erythema characteristic of recurrent herpes in only 13% of animals. Despite this difference, infectious virus was isolated from the skin of similar proportions of animals after treatment with DMSO, stripping or xylene. Moreover, with both of these chemical treatments, as with stripping, virus is isolated most frequently at the time that clinical disease develops (i.e. 3 to 5 days after treatment).

An observation of particular interest was the appearance of infectious virus in the cervical ganglia as early as 1 or 2 days after stimulation of the skin of the ear. Numbers of plaques were low and after stripping or application of xylene, virus was isolated from only about 10% of animals. However, it is noteworthy that application of DMSO to the ear, which induced the lowest incidence of recurrent disease, produced the highest peak incidence of isolation from the ganglia (29% on day 2) and was the only one of the three stimuli after which the peak incidence of isolation from ganglia equalled that from skin. In the light of this it is somewhat ironic that DMSO is used as a vehicle for 5-iododeoxyuridine in treatment of herpes labialis. Others have shown that a variety of different stimuli will cause reactivation of virus in the latently infected ganglion (for review, see Hill, 1983). However, in these reports it is often impossible to decide which of a combination of treatments was the reactivating stimulus and it has not previously been possible to study the relationship between reactivation in the ganglion, appearance of virus in the peripheral tissue and induction of clinical disease.

Possible differences between the sensitivities of isolating virus from nervous tissue and skin must not be overlooked. However, discrepancies between the incidence of infectious virus in the ganglion and skin, and the development of clinical disease prompts a reappraisal of previous theories of the mechanisms underlying the recurrence of herpes simplex (Hill & Blyth, 1976). For instance, in the 'ganglion trigger' theory it is postulated that virus latent in the sensory ganglion is reactivated by a stimulus to the ganglion. This results in release of the virus to the skin where recurrent disease develops. However, it is obvious from our results that clinical disease does not develop in every mouse in which virus is reactivated. Equally, the 'skin trigger' theory states that virus is frequently shed from the ganglion to form microfoci of infection in the skin. These develop into clinically apparent lesions only if conditions in the skin are favourable for virus growth. However, this does not allow for reactivation of virus in the ganglion by stimuli to the skin.

The early appearance of infectious virus in the ganglia preceding its arrival in the skin and the fact that stimuli such as DMSO are efficient 'ganglion triggers' without inducing much clinical disease suggest that only some stimuli can provide both the 'ganglion trigger' and the 'skin trigger' that are needed together to induce clinical recrudescent herpes. By such a 'ganglion and skin trigger' mechanism (Hill, 1981), the virus would be reactivated in the ganglion by the
stimulus to the skin. It would then travel to the periphery by axonal flow. In the skin, developing microfoci of infection might be eliminated by defence mechanisms unless conditions there were made favourable for virus replication, again as a result of changes induced by the original stimulus.

Some of the physiological changes induced by the different stimuli were studied in an attempt to shed light on the mechanisms underlying the proposed ganglion and skin triggers. All five stimuli examined in the present study induced inflammation in the skin. The physiological changes which mediate this inflammation include the release of histamine and 5-HT, the synthesis of prostaglandins of the E and F classes, and a neurogenic component which is probably mediated through the release of substance P (Walker & Chahl, 1980). The pattern of these physiological changes differed with the stimulus. Thus, treatment with u.v. light or retinoic acid stimulated prostaglandin synthesis but did not induce the release of vasoactive amines or substance P (at least in the period immediately after treatment). Stripping with cellophane tape, or application of xylene or DMSO each induced the neurogenic component of the inflammatory response and release of one or both of the vasoactive amines. Xylene induced both histamine and 5-HT, whereas stripping induced mainly histamine, and DMSO mainly 5-HT.

The physiological changes which lead to reactivation of virus in the ganglion presumably occur soon after stimulation of the skin since infectious virus appears in the ganglion 1 to 2 days later. Such reactivation can be induced by stimuli such as retinoic acid (and, by extrapolation, u.v. light) which do not cause an immediate inflammatory response with rapid release of histamine, 5-HT or neurogenic factor. Hence, reactivation in the ganglion cannot readily be correlated with release of these factors in the peripheral tissue unless they are present in amounts below the sensitivity of detection of the indirect tests used here.

The nature of the message which induces new production of virus in the ganglia after stimulation in the skin is not known. However, this virus reactivation may be related to metabolic changes in neurons associated with repair of damage to nerves or nerve endings (Price & Schmitz, 1978). It is probable that the physical and chemical stimuli to the skin all produce alterations or damage in the membranes of nerve endings and thereby cause such metabolic changes in the ganglion.

In contrast to the relatively rapid effects of stimuli on the ganglion, changes induced by a skin trigger need to be present when virus begins to arrive in the skin, 2 to 3 days after stimulation. Unlike the vasoactive amines and substance P, which are transiently released during the immediate inflammatory response, prostaglandins are often produced over longer periods and during later stages of inflammation (Di Rosa et al., 1971).

Levels of prostaglandins were raised during the 3 day period following all the stimuli tested, except DMSO. PGE was increased most on the first day but the increase was present on the third day, at the time when PGF levels were also most consistently raised. However, in marked contrast to this, amounts of PGE were severely depressed after treatment with DMSO and those of PGF were little affected.

Hence, as we have previously suggested (Hill & Blyth, 1976) prostaglandins, particularly of the E series are likely candidates for mediating 'skin trigger' effects of those stimuli which induce recurrent clinical disease. Such effects might involve enhancement of virus growth (Harbour et al., 1978) or local suppression of immune mechanisms (Trofatter & Daniels, 1979), and might operate even if they remained active for only 1 or 2 days.

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REFERENCES


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