

## ELEVATED BLOOD HISTAMINE LEVELS AND MAST CELL DEGRANULATION IN SOLAR URTICARIA

J.L.M. HAWK, R.A.J. EADY, A.V.J. CHALLONER,  
A. KOBZA-BLACK, T.M. KEAHEY\* & M.W. GREAVES

Institute of Dermatology, Homerton Grove, London E9 6BX

- 1 Ultraviolet radiation (UVR)-induced wealing was studied in four patients with solar urticaria, whose measured action spectra were within the range 300 to 700 nm.
- 2 Elevated histamine levels were found in blood draining wealed skin in all four patients.
- 3 Histological and electron microscopical studies of the irradiated skin showed evidence of mast cell degranulation.
- 4 These findings demonstrate an association between histamine release from mast cells and wealing in solar urticaria, and should encourage evaluation of drugs which suppress histamine release in this disorder.

### Introduction

Direct evidence for histamine release in solar urticaria is lacking; attempts to recover histamine from perfusates of wealed skin have been unsuccessful, (Sams, Epstein & Winkelmann, 1969; Ramsay, Scrimenti & Cripps, 1970), although in a single patient we have previously found elevated histamine levels in wealed skin following ultraviolet irradiation, (Michell, Hawk, Shafir, Corbett & Magnus, 1979). Histamine is readily recovered from other types of physical urticaria, (Bentley-Phillips, Black & Greaves, 1976; Greaves & Søndergaard, 1970). We now report elevated histamine levels in venous blood draining ultraviolet-irradiated wealed skin in four patients with solar urticaria.

### Methods

The details of the four patients are given in Table 1. Informed consent was obtained. No patient had been taking anti-histamines or other drugs for at least the previous 7 days.

In this group solar urticaria was unassociated with any other photodermatosis. In particular, no patients had clinical or biochemical evidence suggestive of erythropoietic protoporphyria. All patients developed itching, erythema and wealing less than half an hour after sun exposure, fading within an hour of protection from sunlight. The action spectrum for wealing in each patient was determined

by irradiation of the skin with a high intensity water prism monochromator (Table 1). In each experiment, after collection of a control sample of blood, wealing was evoked using four parallel enclosed Philips TL 20W/12 UVB fluorescent lamps, placed symmetrically about the forearm. The UVR dosage was calculated at the skin surface using an established method, (Diffey & Challoner, 1978), and varied from 1.8 kJ/m<sup>2</sup> to 8.0 kJ/m<sup>2</sup> (irradiation times: 40–180 s). Immediately after withdrawal of the arm from irradiation, blood was taken from an indwelling antecubital vein catheter, 10 units of heparin being included in each 2 ml sample. Further samples were taken at 2 min, 5 min, 10 min and 40 min after withdrawal and in two patients were also taken from the opposite non-irradiated arm. Whole blood histamine was detected and measured by bioassay immediately after the blood was withdrawn, using the cascade superfusion technique (Gaddum, 1953), with modification (Vane, 1964). Thus, fresh venous blood was cascaded over two isolated guinea pig ileum smooth muscle preparations mounted in series in organ baths and superfused with Krebs' solution. All contractions were recorded using force-displacement transducers and a six-channel Devices recorder. Any contracting activity in blood samples due to acetylcholine, serotonin and catecholamines was excluded by the addition of the corresponding specific antagonists to the Krebs' solution. In order to ensure that the activity noted was in fact due to histamine, the specific anti-histamine mepyramine was added to the superfusate of one of the ileum preparations. Thus, any activity markedly greater in the

\*Present address: Tulane University, University Health Service, New Orleans, Louisiana, U.S.A.

**Table 1** Clinical characteristics of four patients with solar urticaria

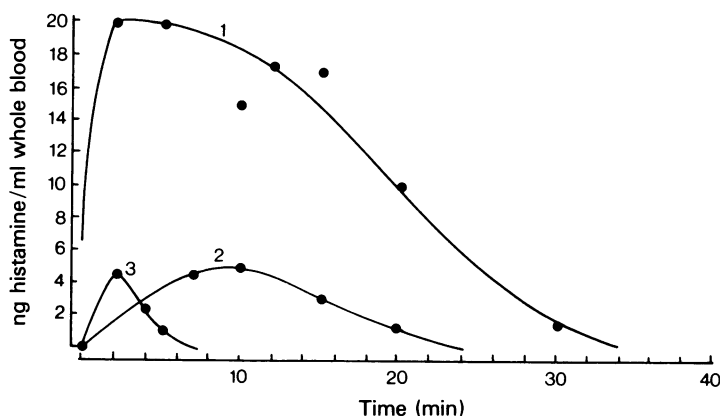
Patient	Age (years)	Sex	Duration of symptoms	Action spectrum (nm)
B.L.	19	F	4 years	300–360
W.F.	31	M	7 years	300–400
M.F.	36	M	3 years	300–400
S.B.	30	F	6 months	300–700

**Table 2** Elevated venous blood histamine levels in solar urticaria

Patient	Blood histamine concentration (ng/ml)				
	0 min	2 min	5 min	10 min	40 min
B.L.	<1	20	20	15	<1
*B.L.	<1	ND	2.5	5	<1
W.F.	<1	7	8.5	3	1**
M.F.	<1	3.5	<1	2.2	<1
S.B.	1.2	4.8	5	2.5	1

\* Values following a reduced dose of ultraviolet radiation evoking submaximal wealing.

\*\* Sample taken at 23 min.

**Figure 1** Venous blood histamine levels after ultraviolet irradiation in patient B.L.:

1. From wealed skin after UVR dose of  $5.4 \text{ kJ/m}^2$  (maximal wealing).
2. From wealed skin after UVR dose of  $1.8 \text{ kJ/m}^2$  (submaximal wealing).
3. From contralateral non-irradiated arm during 1. above.

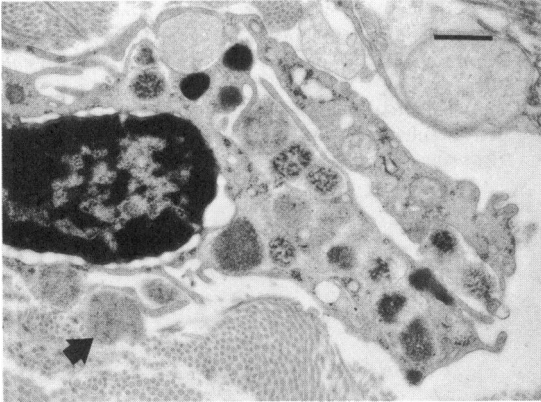
mepyramine-free preparation could be said to be due to histamine. The responses were quantified by comparison with the responses to authentic reference standards by the bracketing method of bioassay (Schild, 1942). The minimum concentration of histamine which could be reliably estimated using this method was 1 ng/ml.

## Results

The pharmacological results in the patients with solar urticaria are summarized in Table 2.

Patients B.L. and W.F. showed rises in blood

histamine to 20 and 8.5 ng/ml respectively at 2 and 5 min after irradiation, falling towards zero by 40 min. The other two patients showed smaller increases. In patient B.L., irradiation with a reduced dose of UVR, which produced sub-maximal wealing, resulted in a correspondingly smaller elevation of blood histamine levels (Figure 1). Pre-irradiation control samples contained no detectable histamine except for patient S.B., sensitive up to 700 nm, who had a low pre-irradiation value of 1.2 ng/ml, possibly as a result of persistent histamine release due to continuing visible light exposure. Samples from the contralateral (non-irradiated) arm in patients B.L. and M.F. contained maximum histamine



**Figure 2** Electron micrograph showing part of a degenerating dermal mast cell in the skin of patient B.L. which had become urticated following ultraviolet irradiation. Arrow indicates extruded granule. Bar = 1  $\mu$ m.

concentrations of 4.5 ng/ml (3.0 ng/ml during sub-maximal wealing) and 2.5 ng/ml respectively. These small rises are probably due to carry-over of histamine released from the ipsilateral (irradiated) arm into the general circulation. In control experiments, blood taken at the same times before and after irradiation with a UVR dose of 5.3 kJ/m<sup>2</sup> (irradiation time 120 s) from three normal subjects contained no detectable histamine. In the solar urticaria patients light microscopical examination showed that mast cells of normal shape and size were present around dermal blood vessels and nerves. In the electron microscope, numerous mast cells appeared to be undergoing exocytotic changes which are characteristically seen during histamine release (Rohlich, Anderson & Uvnas, 1971) (Figure 2). Some cells, however, showed no signs of degranulation.

## References

- BAART DE LA FAILLE, H., ROTTIER, P.B. & BAART DE LA FAILLE-KUYPER, E.H. (1975). Solar urticaria: a case with a possible increase in skin mast cells. *Br. J. Derm.*, **92**, 101–107.
- BENTLEY-PHILLIPS, C.B., BLACK, A.K. & GREAVES, M.W. (1976). Induced tolerance in cold urticaria caused by cold-evoked histamine release. *Lancet*, **ii**, 63–66.
- BENTLEY-PHILLIPS, C.B., EADY, R.A.J. & GREAVES, M.W. (1978). Cold urticaria: inhibition of cold-induced histamine release by doxantrazole. *J. invest. Derm.*, **71**, 266–268.
- DIFFEY, B.L. & CHALLONER, A.V.J. (1978). Absolute radiation dosimetry in photochemotherapy. *Phys. Med. Biol.*, **23**, 1124–1128.
- GADDUM, J.H. (1953). The technique of superfusion. *Br. J. Pharmac.*, **8**, 321–326.
- GREAVES, M.W. & SØNDERGAARD, J.S. (1970). Urticaria pigmentosa and factitious urticaria: direct evidence for release of histamine and other smooth muscle contracting agents in dermographic skin. *Arch. Derm.*, **101**, 418–425.
- HUBER, J.D., PARKER, F. & ODLAND, G.F. (1968). A basic fuchsin and alkalinised methylene blue stain for epoxy-embedded tissue. *Stain Technology*, **43**, 83–87.
- IVE, H., LLOYD, J. & MAGNUS, I.A. (1965). Action spectra in idiopathic solar urticaria. A study of 17 cases with a monochromator. *Br. J. Derm.*, **77**, 229–236.
- KEAHEY, T.M. & GREAVES, M.W. (1979). Cold urticaria: disassociation of cold-evoked histamine release and urticaria following cold challenge, (in preparation).
- MICHELL, P., HAWK, J.L.M., SHAFRIR, A., CORBETT, M.F. & MAGNUS, I.A. (1979). Assessing the treatment of solar

## Discussion

Like many other forms of physical urticaria, solar urticaria is generally considered to be due to histamine released from skin mast cells, the triggering factor in this disorder being ultraviolet or visible radiation. Although this belief is supported by the clinical features of the reaction, which resembles Lewis' triple response, firm direct evidence is lacking: anti-histamines are often given, but evidence of their effectiveness is unconvincing (Baart de la Faille, Rottier & Baart de la Faille-Kuyper, 1975). Furthermore, prior histamine depletion in skin by intradermal injection of the chemical histamine liberator compound 48/80 has not consistently inhibited wealing (Ive, Lloyd & Magnus, 1965). Our findings establish an association between histamine release and wealing in solar urticaria, since elevated histamine levels could be demonstrated in venous blood draining wealed skin in four patients with different action spectra. Furthermore, microscopical studies of the irradiated skin showed evidence of degranulation of mast cells, findings consistent with the view that the observed release of histamine derives from skin mast cells.

Conventional anti-histamine therapy is of only marginal benefit and addition of the H<sub>2</sub> anti-histamine cimetidine, has not been found advantageous (Michell *et al.*, 1979). Our findings should encourage evaluation of other drugs which suppress histamine release by skin mast cells, such as doxantrazole (Bentley-Phillips, Eady & Greaves, 1978), and combined salbutamol and aminophylline therapy (Keahey & Greaves, 1979).

This work was supported by grants from the Medical Research Council, Wellcome Trust and the Sir Herbert Dunhill Trust.

- urticaria, the dose response as a quantifying approach. *Dermatologica* (in press).
- RAMSAY, C.A., SCRIMENTI, R.J. & CRIPPS, D.J. (1970). Ultraviolet and visible action spectrum in a case of solar urticaria. *Arch. Derm.*, **101**, 520-523.
- ROHLICH, P., ANDERSON, P. & UVNAS, B. (1971). Electron microscope observations on compound 48/80 induced degranulation in rat mast cells. *J. Cell Biol.*, **51**, 465-482.
- SAMS, JR., W.M., EPSTEIN, J.H. & WINKELMANN, R.K. (1969). Solar urticaria: investigation of pathogenetic mechanisms. *Arch. Derm.*, **99**, 390-397.
- SCHILD, H.O. (1942). A method of conducting a biological assay on a preparation giving repeated graded responses illustrated by the estimation of histamine. *J. Physiol.*, **101**, 115-130.
- VANE, J.R. (1964). The use of isolated organs for detecting active substances in the circulating blood. *Br. J. Pharmac.*, **23**, 360-373.

(Received April 23, 1979)