Urticaria—current concepts

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Summary

The mechanisms, clinical features and management of the various forms of urticaria are discussed. The importance of histamine receptors, complement and the kinin cascade are reviewed.

Introduction

The urticarial weal is the product of different forces acting on the skin. As the histological appearances of the weal are non-specific, attention has focused on the urticarial response to physical agents, the chemical mediators and the therapeutic effects of pharmacological preparations. There is growing interest in the significance of *Candida* hypersensitivity.

Mediators and mechanisms

The principal mediators are histamine, kinins, complement, acetylcholine, prostaglandins and, probably, serotonin. Neither the mechanisms of weal formation nor the interactions of the various mediators are fully understood. Further research is needed, however, before the urticarias can be accurately defined and selectively treated by specific agents.

Histamine

This is concentrated in granular depots within both mast cells and circulating basophils. The Type I mast cells found close to the arterioles and venules seem more important in this regard than the larger, regularly shaped, Type II cells scattered in the perivascular supporting tissues (Beaven, 1976a). Histamine release is accompanied by degranulation of the mast cells and basophils and is induced through the influence of tissue trauma, antigen-antibody, immediate hypersensitivity reactions, burns and drugs. The release, which is often in phases, may differ with the provoking agent. Compound 48/80 is a polypeptide histamine liberator used in most research studies. The intracellular levels of adenosine-5-monophosphate (cAMP) and guanosine monophosphate (GMP) control the rate of histamine release. Exchange of calcium ion with extra cellular ions is also important.

While adrenaline increases the cellular reserve of cAMP and retards histamine release, carbachol and acetylcholine increase the level of GMP and its release. Otherwise the effects of drug action on the mast cells are unknown. Disodium cromoglycate has proved beneficial in allergic asthma but not in urticaria. Its action cannot be attributed to inhibition of antigen antibody reaction on the cell membrane, interference with cAMP or histamine antagonism (Beaven, 1976b).

Reduced basophil counts occur in attacks of acute physical urticaria, and particularly during episodes of hereditary angio-oedema (Robinson and Pennington, 1966). In predominantly basophilic leukaemias, high urinary and circulating histamine levels are found (Beaven, 1976b). However, in chronic urticaria, histamine release by IgE adherence to basophils is probably insignificant. Histamine is metabolized through two pathways, each capable of removing the entire histamine load. One pathway can be blocked by an aspirin inhibition of ribose conjugation (Beaven, 1976a).

Histamine dilates the peripheral capillaries. It increases the permeability of the venule, perhaps through longitudinal contraction of structures within the endothelial cell (Warin and Champion, 1974a). The fibrin constituents of the basement membrane may also be disturbed (Lennart and Michaëlsson, 1970). There may be a constant cycle of changing vascular tone governed by histamine and utilizing histidine from depots throughout the body (Beaven, 1976a).

The kinins

These are released during tissue damage and consist of three major groups, bradykinins (kinin 9), kallidins (kinin 10), and methonyl-bradykinin (kinin 11) which share three basic properties. They increase permeability of vessels, stimulate leukocyte response and apparently promote oedema formation (Berova, Petkov and Andreev, 1974). Bradykinin is the most potent of all vasodilators (Colman, 1974). Factor XII of the intrinsic clotting system, and from which the polypeptide pre-kallikrein activators are derived, is the parent substance in the kinin cascade.

The vigour of the kinin reaction is restrained by α -2-macroglobulin, anti-thrombin III and α -2-globulin which is also the inactivator of C1 and is functionally deficient in hereditary angio-oedema (Colman, 1974).

Bradykinin degeneration occurs in the endothelial lining of the pulmonary vessels or in the plasma where deactivation is achieved by a kinase which can also facilitate the conversion of angiotensin 1 to angiotensin 11.

Complement

The complement cascade and its side reaction are apparently directed towards the destruction of the antigen transporting cells. The extent of a complement reaction is influenced by events within the other cascade systems. The nine major components of the complement chain each have a distinctive role. They increase vessel permeability and enhance phagocytosis. Phagocytosis is enhanced by the adhesion of complement particles to formed elements in the blood, and their interference with cell membranes permits lysis to occur. An invading agent, such as the *Herpes simplex* virus, becomes coated with C1, C4 and perhaps C2 and C3, and is then bound to polymorphonuclear leukocytes, red cells and platelets. Once phagocytosis is facilitated, side reactions of C5, C6 and C7 allow for lysis in the presence of C8 and C9 (Ruddy, Gigli and Austen, 1972a).

Complement is essential for the Arthus and Type III allergic reactions and C3 is important in provoking histamine release (Warin and Champion, 1974a). The complement proteins are mainly β -globulins and are probably synthesized in the liver and spleen, both of which have high concentrations of macrophages. The C3 and C4 fractions are the most abundant, but the total complement comprises about 10% of all the plasma proteins (Ruddy *et al.*, 1972b).

The Hageman factor (factor XII)

This is the common activator of the complement, fibrinogen and kininogen cascades, which are each closely interrelated. When activated it allows the formation of plasmin, which itself partially dissolves Factor XII thereby activating the kallikrein, kininogen, bradykinin cascade. Products of kinin generation enhance the elements of the complement cascade which at an earlier stage began from activation by Factor XII (Ruddy *et al.*, 1972a).

Prostaglandins

The derivation, properties and catabolism of these substances await precise definition. Although some of their functions seem mutually antagonistic, their importance in urticaria lies in their vasodilatory properties and their functional resemblance to

acetylcholine (Editorial, 1970). Acetylcholine and serotonin also mediate in the urticarial response.

The clinical forms of urticaria

The weals of acute urticaria are of rapid onset and brief duration, while those of chronic urticaria persist for many hours. Differentiation between the two forms may be difficult, nonetheless. Acute urticaria is more common in atopics (Warin and Champion, 1974b). The chronic form however, is neither more common in, nor influenced by, the atopic state (Champion *et al.*, 1969). Chronic urticaria is commonest in women in their third or fourth decade. The weals vary greatly, being sometimes bullous and often involving the lips or eyelids asymmetrically.

Diagnosis

An exhaustive history is essential, and the following should be considered.

1. Urticaria may follow several years of exposure to the antigen.
2. The causative agent may not always provoke the anticipated response and its premature exclusion from the enquiry must be avoided.
3. A thorough interview will confirm the clinician's belief in an organic basis for the disorder.

Drug history

Drugs containing aspirin are widely used for alcoholic dyspepsia, tension headaches and premenstrual tension. Aspirin ingestion was noted in 21% in a series of 554 patients (Champion *et al.*, 1969) and in 41% in another series of 96 patients (James and Warin, 1970). This form develops within 4 hr, and usually involves the face.

Aspirin degradation products or a contaminant, aspirin anhydride, may react with proteins, provoking the allergic response (Warin and Champion, 1976b). Stimulation of prostaglandins could explain the increased gastric secretion, acute bronchospasm and disruption of normal coagulation mechanisms (Settipane *et al.*, 1976).

Indomethacin, tartrazine and benzoic acid may also cross-react with aspirin, Fisherman and Cohen (1976), and even salicylamide in teething powders has provoked urticaria (Bentley-Phillips, 1968).

Penicillins

The penicilloyl radicle is probably the active principle in most penicillin reactions although there may be other, unidentified agents (Warin and Champion, 1974a). Urticarial reactions developing soon after exposure to penicillin may be particularly severe, indeed anaphylaxis may occur before urticaria develops. Penicillin may be present as a contaminant in food products or blood transfusions,

provoking a vigorous IgE response to tissue-fixed antigens.

Tartrazine

This is an additive used in food and drugs which can provoke reactions similar to those produced by aspirin. It can provoke a reaction in up to 20% of aspirin-intolerant patients (Settipane *et al.*, 1976). The mechanism of the reaction is unexplained as it is not related to dosage. Moreover both substances differ in their molecular composition (Glovsky *et al.*, 1976).

Physical examination

This is often unrewarding. Dentures must be removed to exclude oral candidiasis and the presence of any vaginal discharge should be noted, as an allergic reaction to *Candida* may provoke urticaria. This is usually a delayed hypersensitivity response, although the immediate type also occurs (Holti, 1969). Some cases are incorrectly attributed to antibiotic hypersensitivity where the onset of the urticaria coincides with their administration (Holti, Winner and Hurley, 1966). Occasionally urticaria may be provoked by systemic lupus erythematosus (Walker and Church, 1966) or even rarities such as strongyloidiasis (Cunliffe and Garcia e Silva, 1968).

The physical urticarias

Spontaneous acquired cold urticaria begins in adult life subsiding within a few years. The urticarias of cryoglobulinaemia, paroxysmal cold haemoglobinaemia and cold haemagglutination may precede the serological diagnosis by 2 years (Warin and Champion, 1974c). Mediation by histamine is suggested by: (1) degranulation of the mast cells; (2) elevation of histamine levels in the immersed limbs, but not their control; (3) demonstration of an eosinophilic chemotactic factor of anaphylaxis (Soter, Wasserman and Austen, 1976).

However, others have demonstrated elevated histamine levels in the control limbs and antihistamines have been ineffective (Editorial, 1975). Local infusion of kinins can reproduce the reaction, suggesting that there is an IgE response to cold-induced tissue injury which activates a kinin cascade. Reaction to cold exposure may take some hours to develop (Matthews and Warin, 1970), and some reactions occur only at temperatures which are above the freezing point of water (Sarkany and Gaylarde, 1971). These forms, however, are not exacerbated by aspirin (Warin and Champion, 1974c).

Familial cold urticaria

This form is characterized by wealing of exposed surfaces in less than an hour. Lesions may persist for days. The mucous membranes are not involved and

there is no passive transfer. The inheritance is autosomal dominant (Warin and Champion, 1974c).

Solar urticaria

This is characterized by an inconstant eruption appearing on surfaces exposed to light. The onset is rapid and it subsides within the hour. The patient is in the third decade and the porphyria cutanea tarda, erythropoietic protoporphyria and sulphonamide sensitivity must be excluded (Warin and Champion, 1976c). The light elevates the local temperature and sweat is produced. The sweat droplets acting as lenses concentrate the ultra violet light on the mast cells. Histamine is released and there is a refractory period during mast cell regranulation (Shelley and Heaton, 1976).

Cholinergic urticaria

This self-limiting disorder is provoked by spiced foods, vigorous exercise or hot baths. Excessive salivation and abdominal pains accompany the weals which are usually perifollicular (Moore-Robinson and Warin, 1968). There is no abnormality of the sweat or the sweat glands, although an immune reaction to acetylcholine or a histamine liberator in the sweat may exist. Passive transfer occurs (Warin and Champion, 1974c).

Delayed pressure urticaria

This often disabling disorder develops some hours after prolonged pressure on an area of skin from, for example, standing on a ladder or carrying sacks of coal. It may be an Arthus-type reaction to tissues altered by pressure, although local deposition of complement has not been found (Ryan, Shim-Young and Turk, 1968).

Symptomatic dermatographism

This is common, occurs mainly in young people, and seldom lasts for more than 3 years. The weals follow vigorous towelling or any minor skin trauma and they subside within the hour. An IgE or IgA response to traumatized skin is postulated. Penicillin but not aspirin exacerbates the symptoms and passive transfer is positive (Warin and Champion, 1974c).

The treatment of urticaria

The antihistamines

These are more successful in the physical than in the chronic forms and are only of benefit for familial cold urticaria when high doses are used (Warin and Champion, 1974c). They alter the severity and timing of the reactions in delayed pressure urticaria (Ryan *et al.*, 1974). In general, they have been disappointing, possibly because they blockade H₁- and not H₂-receptors. The specific H₂ antagonist

cimetidine offers prospects for better treatment in the future. Hydroxyzine pamoate is useful in the treatment of cholinergic urticaria, for which, paradoxically, anti-cholinergics are disappointing. It has anti-serotonin, anti-acetylcholine and anti-histamine actions and white tablets free of tartrazine additives are available (Moore-Robinson and Warin, 1968).

Attacks of hereditary angio-oedema must be treated promptly and usually an oral antihistamine is sufficient. In life-threatening situations intramuscular adrenaline or even tracheostomy may be required. Adrenaline retards the release of histamine even beyond the time of its own clearance. It blocks the effects of histamine already released and prolongs the refractive period of the mast cell (Beaven, 1976c). Replacement therapy has the disadvantage of introducing excessive C2 and C4 although this may yet be surmounted (Ruddy *et al.*, 1972c).

Hereditary angio-oedema

In this autosomal dominant disorder, trivial trauma provokes severe oedema of the pharynx, larynx, urethra or small bowel. Alpha-neuraminoglycoprotein, an inhibitor of C1 formed early in the complement cascade is either absent or deficient. There is an overall mortality rate of 40% although the attacks are usually self limiting. New mutations, with a negative family history are rare (Warin and Champion, 1974d).

There is no known antagonist to the inhibitor and its catabolic pathways seem intact. Thirty per cent of the inhibitor's molecule is carbohydrate and an error in the synthesis of this moiety could result in its functioning defectively. The levels of bradykinin and C1 are elevated during an attack. The C2 and C4 levels are depressed, however, as they are formed after the block. Normally the inhibitor retards the formation of kallikrein, precursor plasminin, thromboplastins and plasmins (Ruddy *et al.*, 1972c). In its absence, the excess of these products is dispersed by ancillary catabolic pathways or other inhibitory systems (Colman, 1974).

Kallikrein inhibitors

These are derived from ox salivary glands. They suppress the release of kininogens from vessel walls and of proteolytic enzymes from the plasma. They also inhibit plasmin. They are used widely in pancreatitis and success has been reported in 81% of fifty-two patients with various forms of urticaris (Berova, Petkov and Andreev, 1974), but not in hereditary angio-oedema (Ruddy *et al.*, 1972c; Warin and Champion, 1974c).

Epsilon amino-caproic acid which is useful in cold urticaria without cryoglobulins is disappointing in hereditary angio-oedema (Ruddy *et al.*, 1972c).

This substance inhibits kininogenase as well as plasminogen/plasmin conversion, but prolonged use carries a risk of chronic fibrinolysis and teratogenicity has been described in animals (Reiss, 1971).

Solar urticaria and erythropoietic protoporphyria share the same sensitivity ranges to ultra violet and visible light. The value of β -carotene therapy is difficult to assess. The natural history of solar urticaria varies, and constant recalibration of the artificial light sources is required to prevent errors of distribution or intensity. The protective functions of carotenoids in man are uncertain, but they protect bacterial cells through retardation of photo-oxidation by chlorophyll (Kobza, Ramsay and Magnus, 1973). Other therapeutic possibilities are stabilization of mast cell lysosomes by chloroquine (Shelley and Heaton, 1976), psoralen-stimulated pigmentation or topical sunscreens corrected for wave length (Warin and Champion, 1974c).

Conclusion

Urticaria still offers more questions than answers. but a comprehensive understanding is evolving through simultaneous research in different disciplines. In practice, the best chances for successful management of chronic urticaria lie in abstinence from aspirin, elimination of *Candida*, and the administration of antihistamines.

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