

Food, food additives and urticaria

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Urticaria represents a common reaction pattern in the skin, which affects some 15-20 per cent of the population at least once in their lifetime (Barnetson 1987)¹. In a few cases there is a clear association with a specific food or drug trigger and with evidence of a specific immunoglobulin E (IgE) antibody response to the food or drug concerned. Since H1 anti-histamines can often abolish the reaction, the release of histamine must play a substantial part, and it can reasonably be assumed that this type of case involves mast cell activation.

When other forms of urticaria are considered, the mechanism is less clear. Roughly 75 per cent of people who present to a doctor with this symptom have chronic idiopathic urticaria and develop repeated episodes of urticaria or even continuous urticaria without any evidence of an IgE reaction or of a precipitating cause (Warin 1976)². While an IgE mechanism leading to mast cell activation can thus lead to urticaria, it is also clear that there must be other means of mast cell activation leading to urticaria or other mechanisms which are not directly dependant on mast cell activity at all.

Histamine may not be the only mediator which can produce this type of skin response and antihistamines are not always effective in treatment. The type of wheal produced by injecting histamine into the skin can also be produced by injecting kinins, prostaglandins, serotonin, complement products, or leukotrienes. Angiotensin converting enzyme inhibitors given for hypertension can provoke angioedema by a non-immunological mechanism, possibly by interfering with the metabolism of kinins (Slater et al 1988)³ and a failure to inhibit the activity of C1 esterase can provoke a reaction which is not dissimilar to urticaria, in cases of hereditary angioedema.

The non-immunological forms of urticaria are thus more important than those with an allergic trigger and provide a model for the study of pseudo-allergic disease. There remain the alternative possibilities that non-immunological mechanisms may lead to mast cell activation or that the reaction may be triggered by an increased absorption or failure to metabolise mediators such as histamine.

Release of Histamine

In studying blood and urine levels of histamine and the release of other inflammatory mediators or metabolites in urticarial subjects, it is not necessary to make any prior assumptions about the mechanisms involved. Murdoch and Pollock (1987)⁴ studied the blood and urine levels of histamine and the urine level of prostanoid metabolites in 2 patients who had been shown to develop urticarial reactions after a tartrazine challenge but had no evidence of an immunological abnormality. They were able to demonstrate rises in histamine blood level and urinary excretion in both cases and a simultaneous rise in prostanoid metabolites in one, coinciding with the onset of symptoms. The clinical appearance of a rash appeared to provide a less sensitive indicator than the histamine level since, in the second case, a clearcut rise in blood and urine histamine levels was accompanied by intense itching of the skin, but the urticarial rash did not appear until several hours later.

There was no evidence of an immunological abnormality in Murdoch's cases, and it seemed possible that tartrazine had directly triggered the release of histamine and prostanoid. When ten healthy volunteers consumed tartrazine in quantities rising from 5 mg to 50 mg and then 150 mg, 9 of the 10 had a very significant rise in urinary histamine excretion after the 150 mg dose which, however, exceeded the normal daily intake by at least a factor of 2. Since an increased urinary excretion of histamine and its metabolites can follow 1-3 hours after normal food intake (Imamura et al 1984)⁵, the significance of this finding remains uncertain. A second possibility remained - that affected individuals were unable to metabolize amounts of histamine which would not cause illness in normal subjects. A further study was carried out to test this point.

Metabolism of Histamine

After obtaining permission from Guy's Hospital Ethical Committee, Pollock and Murdoch infused histamine intravenously into three groups of volunteer subjects. The protocol involved an intravenous infusion for periods of 30 minutes at increasing infusion rates of 0.05 µg/kg/minute and then 0.1, 0.15, 0.2, 0.25, 0.3 and 0.35 µg/kg/minute. The end point for the experiment was the development of a rise in skin temperature exceeding 1°C or extensive skin flushing, an increase in pulse rate of over 20% of the baseline rate, widening of the pulse pressure of more than 25%, or severe headache. Recovery from these effects was rapid when the infusion was stopped.

The three groups who were studied each consisted of 5 people. The first were non-atopic volunteers, the second were atopic subjects who had no urticaria but had positive skin tests, and the third had chronic urticaria with negative skin tests and no atopic history. The detailed findings are published elsewhere (Pollock et al 1990)⁶. Whereas the plasma histamine levels in atopic subjects showed the same rate of rise as in the normal

subjects, they did not tolerate high plasma levels and reached the limit of tolerance more quickly. The urticarial subjects had a significantly more rapid rise in plasma histamine levels at the same rate of intravenous infusion but tolerated plasma levels equivalent to those seen in the healthy volunteers. These levels were achieved, however, after a significantly smaller total quantity had been infused (1.12 ± 0.33 mg) than in the control subjects (2.2 ± 0.51 mg, $p < 0.01$). Furthermore, there was a relatively slow decline in plasma histamine levels when the infusion was stopped.

Although these results suggest a defect in histamine metabolism, they do not exclude the possibility that a slight but continuous endogenous release of histamine might modify the result of histamine infusion and so explain the results seen in urticaria subjects. Further studies were therefore carried out to assess diamine oxidase (E9.4.3.6; histaminase) activity. Histamine is metabolized by two pathways, oxidation and methylation. N-methyl transferase methylates histamine in the skin and is active in other sites, notably the liver. Diamine oxidase (DAO) normally degrades histamine, methyl histamine and diamines such as putrescine. It is largely confined to the small bowel mucosa, especially in the ileum but also in the more easily studied jejunum and in the fasting state is barely detectable in the plasma. It can however be displaced from the intestinal mucosa into the peripheral circulation by intravenous heparin (D'Agostino et al 1987;⁷ Luk et al 1980)⁸ and this has become the basis of a test in which plasma DAO levels are measured before and after intravenous injections of heparin. Out of 9 cases of chronic urticaria challenged with 5,000u heparin (Lessof et al 1990)⁹ two had an almost flat DAO response in the ensuing two hours and three others had levels at the lower end of the normal range. Since a linear relationship has been claimed between the post-heparin DAO profile and jejunal mucosal activity (Rokkas et al 1988)¹⁰ jejunal mucosal biopsies were taken at separate times in the five subjects who were willing to have this investigation carried out (see Table 1). There was a significant difference ($p < 0.02$, Mann-Whitney twotailed test) between the jejunal mucosal activity levels and those found in 10 control subjects who proved to have no organic disease. There was a good correlation between the post-heparin plasma response and jejunal mucosal biopsy levels in all but one subject.

Although the group of subjects in this study did not prove to be homogeneous in terms of their DAO activity, our evidence points to defective enzyme activity in some but not all urticaria subjects. This was also the case in three subjects (cases 4, 8 and 9) who had had simultaneous urticaria and abdominal colic, one of whom also had evidence of small bowel mucosal thickening during an attack, similar to that noted by Robertson and Wright in a recent case report (1987)¹¹. Further evidence is however needed before firm conclusions can be drawn about the relationship of this finding to the aetiology of urticaria. Low levels could represent a secondary effect since, at least in the rat (D'Agostino et al 1989)¹² the depletion of intestinal DAO which

Table 1

Post-heparin diamine oxidase activity (area under 2h curve) and jejunal mucosal DAO activity in same subjects

Case number, age and sex	Associated abdominal colic	Post-heparin "area under curve"	Jejunal mucosal DAO*
3. 29 F	0	12.4	16.1
4. 46 F	++	2.3	1.2
5. 25 F	0	1.0	0.7
8. 34 F	+	14.6	0.9
9. 22 M	+	5.1	0.7
Normal range (mean $\pm$ sem) in control subjects		5.6-31.7 (16.0 $\pm$ 2.3;n=11)	8.4-58.6 (19.0 $\pm$ 2.37;n=10)

* mU/g mucosal protein

occurs after intensive stimulation can take some days to recover. It is also possible that transient DAO blocking could result from the effects of alcohol, spoiled food, or drugs. In any event, the loss of the protective role of mucosal DAO, whether primary or secondary, might allow an increased absorption of biological amines, while a lack of DAO in the circulation could delay their elimination.

These investigations suggest that pseudo-allergic manifestations are not only the result of mast cell activation. Further studies are needed of the potential effects of enzyme depletion and inhibition on the metabolism of inflammatory mediators. Conditions which lead to an increase in food-derived biogenic amines or in their absorption also need to be better understood.

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