

Substance P Is Not Involved in Primary and Secondary Erythralgia

Sir,

Erythralgia is a syndrome of bilateral symmetric burning and redness of, mainly, the lower extremities. Symptoms can be initiated by exercise or exposure to heat, while rest and cold bring relief (1). Primary erythralgia usually arises in childhood as an incurable variant of painful red extremities in the absence of thrombocytopenia or any other underlying disorder (2). Secondary erythralgia usually develops at adult age in association with or without an apparent underlying disorder. In some cases treatment of the underlying disorder is difficult and therefore symptoms may persist throughout life (3). Secondary erythralgia can arise as a side-effect of drugs. In those cases relief can be obtained by withdrawal of the causative drug. The pathogenesis of primary and secondary erythralgia remains to be elucidated. A neurogenic aetiology or vasomotoric dysregulation has been suggested as a potential cause of erythralgia.

Vasoactive neuropeptides, such as substance P (SP), are released from peripheral terminals from sensory nerve endings in human skin and are involved in (neurogenic) inflammatory cutaneous reactions (4). SP, when injected intradermally, elicits a triple response with local erythema, a rapidly spreading flare and a slowly developing wheal (5). The fact that erythralgic attacks are precipitated by an increase in skin temperature has given rise to speculations that temperature triggers release of inflammatory and pain mediating substances in sensitive areas of predisposed patients (6). In this respect SP might have a role in the pathogenesis of erythralgia. Further, hope is fuelled by the fact that symptoms of secondary erythralgia in one patient responded to topical application of capsaicin cream (7). Repeated application of capsaicin depletes the sensory neurons of SP and suppresses the flare response to SP (8). Consequently, we investigated the immunoreactivity of SP in fluid from artificial blisters from healthy and pathological skin in patients with primary and secondary erythralgia.

PATIENTS AND METHODS

Patients

Six women and one man (age 28–76 years), suffering from erythralgia, were invited to take part in the study. A 28-year-old patient suffered from primary erythralgia and 6 had secondary erythralgia. The associated conditions were autoimmune disorder of undetermined significance (1); hypertension (1); Sjögren's syndrome (2); unknown (2). Prior to the procedure all patients provoked their symptoms by putting their feet in warm water or by strenuous exercise.

Artificial blisters

Suction blisters were induced on the volar aspect of the erythralgic forefoot of every patient (9). Control blisters were evoked on apparent healthy skin on the upper legs. The blister devices were connected to the central suction unit of the hospital, and after application the pressure within the cup was slowly increased to 200 mmHg below the atmospheric pressure. Blisters of 8–10 mm developed 3–4 h after suction. Blister fluid was collected by aspiration with a thin needle and syringe. Samples were immediately frozen to -70°C .

Radioimmunoassay for SP

The concentration of SP was determined by a commercially available radioimmunoassay (Eurodiagnostica AB, Malmö, Sweden).

Polyclonal antibody against synthetic SP was raised in rabbits. Synthetic SP was radiolabelled with ^{125}I , and SP in blister fluid was measured in duplicate by nonequilibrium radioimmunoassay (10). For measurement of SP, 100 μl blister fluid was used. The lower detection limit of this method is 10 pg/ml (7 pmol/l).

The study protocol was approved by the Medical Ethical Committee of the University Hospital Dijkzigt in Rotterdam, The Netherlands. Written informed consent was obtained from all patients.

RESULTS

The SP concentration in blister fluid extracted from healthy skin in primary erythralgia was 316 pg/ml and <10 pg/ml in erythralgic skin. In one patient with secondary erythralgia the SP content in blister fluid from both erythralgic and healthy skin was elevated to 111 pg/ml and 120 pg/ml, respectively. In all other patients with secondary erythralgia the SP concentration in the samples was below the limit of detection.

DISCUSSION

The low concentration of SP in the blister fluid might suggest that SP present in sensory nerve endings in the skin does not diffuse in measurable amounts into the blister fluid. Other investigators using a similar design with a similar sensitive radioimmunoassay have detected increased SP in suction-induced blisters in lesional and control skin of patients with bullous pemphigoid and urticaria (10, 11). Our suction time of 3–4 h was considerably longer than that used in this study (75–90 min), which suggests that inadequate diffusion of cutaneous SP into blister fluid does not explain the low concentrations. On the other hand, it is also possible that a suction time of 3–4 h is too long, allowing proteolytic enzymes to degrade SP. We provoked blisters on the volar aspect of the forefoot, since it was known that the SP concentration is the highest in fingers and toes, opposed to axilla and thigh (12).

It also remains possible that SP is of minor importance as an inflammatory mediator in the pathogenesis of erythralgia. The concept of neurologic inflammation as a cause of erythralgia nevertheless remains an attractive hypothesis. An increased local production of other vasoactive neuropeptides, such as neurokinin A and calcitonin-G-related-peptide (CGRP), could be responsible for symptoms in erythralgia. Intradermal injection of CGRP leads to a prolonged increase in cutaneous blood flow and erythema, as seen in erythralgia. Although SP is chemotactic for human T-lymphocytes, CGRP is more potent (13). We have shown earlier that biopsy specimens from erythralgic skin are characterized by a mild mononuclear infiltrate, which suggests involvement of these vasoactive molecules (19). The contribution of these peptides to the pathogenesis of erythralgia thus requires further investigation, and in this respect immunoreactive staining of biopsy specimens might be helpful.

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