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Solanidine and tomatidine trigger scar pruritus

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ABSTRACT

Scar pruritus is frequently encountered in clinical practice (particularly in burn patients) owing to its poorly known pathogenesis and difficult treatment. In previous work, we demonstrated the usefulness of a diet excluding edible solanaceae (*viz.*, potatoes, tomatoes, peppers and aubergines) in patients with antihistamine-resistant scar pruritus. We hypothesized that alkaloids in solanaceae (particularly their secondary metabolites or aglycones) might be the actual pruritogens. In order to test this hypothesis, we conducted a single-blind prospective study on patients responding favourably to a solanaceae-free diet whose scar pruritus could be ascribed to one of the four foods. The study involved applying the aglycones solanidine and tomatidine to each scar and checking whether, and which, had a pruritogenic effect. A total of 18 patients (90%) responded by developing pruritus; also, the triggering aglycone coincided with that prevailing in the pruritogenic food. We concluded that solanaceae aglycones are directly involved in the pathogenesis of scar pruritus.

1. Introduction

Scar pruritus is frequently encountered in clinical practice, particularly in burn patients. If strong enough, pruritus can decrease alertness, cause psychic and sleep alterations, and scratch injuries, all of which can hamper successful recovery [1]. In fact, some recent studies have shown pruritus to be a major determiner of multifunctional rehabilitation [2] or quality of life [3] in burn patients. Possibly, this led to pruritus being included among the top three priorities in research on such patients [4]. This has largely been the result of (a) the lack of sound knowledge about the pathogenesis of scar pruritus, which has led to its being virtually equalled to chronic pruritus [5]; and (b) the little effectiveness of conventional, antihistamine-based treatments in many cases [6], which has fostered a search for alternative treatments [7] that have never reached level I clinical effectiveness [8].

We recently reported a study demonstrating the effectiveness of a diet excluding edible solanaceae (*viz.*, potatoes, tomatoes, peppers and aubergines) in patients with antihistamine-resistant scar pruritus [9]. Interestingly, a systemic challenge test involving intake of the suspect foods allowed the specific culprit to be identified and the need to avoid all other solanaceae to be dispensed with. We hypothesized that the molecular effectors (*i.e.*, the actual pruritogens) might be specific alkaloids or, particularly, their corresponding aglycones (*viz.*, secondary metabolites resulting from gastric or hepatic deglycosylation) [10], which bear a close structural similarity (Table 1). We tested our starting hypothesis *via* a prospective clinical trial on antihistamine-resistant patients with scar pruritus in whom treatment with an exclusion diet had been successful and the specific food causing the pruritus identified. The aim was to determine whether pruritus was triggered by direct application of the aglycones concerned on the scars of those patients.

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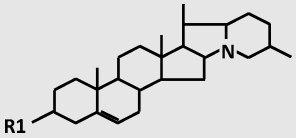
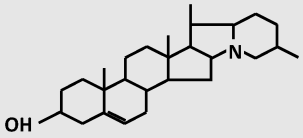
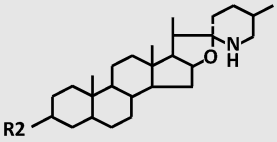
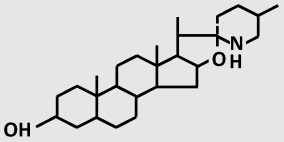
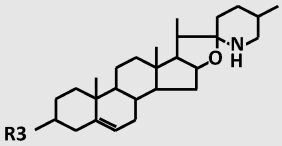
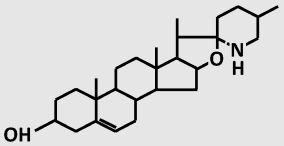
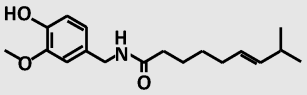
Table 1 – Glycoalkaloids and alkaloids (aglycones) present in edible solanaceae. Pepper contains no glycoalkaloids or alkaloids other than capsaicin [11]; this alkaloid is responsible for the typical urent feeling caused by hot peppers but differs markedly from all others in structural terms.

Solanacea	Glycoalkaloid	Alkaloid
Potato	Solanine	Solanidine
Solanum tuberosum		
Tomato	Tomatine	Tomatidine
Solanum lycopersicum		
Aubergine	Solamargine	Solasodine
Solanum melongena		
Pepper	Not identified	Capsaicin
Capsicum annuum		

R1: galactose + glucose + rhamnose. R2: galactose + glucose (2) + xylose. R3: rhamnose (2) + glucose.

2. Patients and methods

2.1. Patients

Participants in the study were selected from the patient base of the Plastic Surgery Office of Reina Sofía University Hospital (Córdoba, Spain). The criteria for inclusion were the presence of pruritogenic scars unsuccessfully treated with antihistamines (*i.e.*, refractory pruritus) in patients who had responded to a solanaceae-free diet (SFD) and in whom the specific culprit for the pruritus had been identified. Exclusion criteria included refusal to participate in the study or being <18 years old. Also, a group of patients with healthy skin (no history of allergic or dermatological processes and irrelevant skin examination) was collected as control. All patients volunteered for the study and signed an informed consent. The clinical protocol complied with the principles of the Declaration of Helsinki and was approved by the hospital's Ethics Committee.

2.2. Preparation of alkaloid-containing creams

Absorption of alkaloids by the skin is facilitated by their lipophilic nature [12], for which the corneal stratum is thus no insurmountable barrier. These principles were used to obtain creams in the form of O/W emulsions containing the target alkaloids in 0.1% proportions. The lack of commercially available for all solanaceae alkaloids only allowed two different creams containing solanidine and tomatidine, respectively, to be prepared. Both chemicals were supplied by Sigma-Aldrich. Although using a wider variety of alkaloids would have been desirable, the availability of only two posed no problem since, based on previous experience, most of the patients were sensitive to either potatoes or tomatoes.

2.3. Single-blind trial

The subjective nature of pruritus led us to strengthen the power of the trial by using a single-blind approach. To this end, both creams were applied to the scars without the patients knowing their composition. This allowed us to check whether pruritus was actually triggered and whether the pruritogen coincided with that in the culprit food—which was known by the patient.

2.4. Application of alkaloid-containing creams (topical challenge test)

Each scar was treated with a dose (*ca.* 0.5 mL) of solanidine cream and another of tomatidine cream (avoiding contact between them), after which the treated area was covered with