Development and inhibition of mouse ear oedema induced with capsaicin

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Abstract

Oedema was induced in one ear of male mice of the CFLP strain with capsaicin solution (10 μl/40 μg/ear). The development in time and the extent of the oedema were determined by the oedema-disk gravimetric technique. The maximum oedema was attained in less than 1 h, and there was, subsequently, a gradual decrease. The extent of the mouse ear oedema induced in this way and measured after 60 min was inhibited to a statistically significant degree and in a dose-dependent manner by the antihistamine chloropyramine, the antihistamine-antiserotonin cyproheptadine, the non-steroidal anti-inflammatory agent piroxicam, the prostaglandin antagonist di-4-phloretin phosphate, and the lipoxygenase inhibitor nordihydroguairetic acid. The method proved suitable for the detection of oedema and for the biologically quantitative determination of the state of desensitization induced with capsaicin.

Introduction

Capsaicin is the active substance responsible for the irritating and pungent effects of hot peppers (paprika, Hungarian red pepper, Capsicum annuum L.). The pharmacological study of capsaicin dates back more than a century [1]. From the late 1940s, Jancsö and colleagues reported that topical application of capsaicin produced an inflammatory reaction in rats, after which there was a specific insensitivity to different chemical irritants [2, 3, 4]. We earlier investigated the oedema-inducing effects of some skin irritants (dithranol, croton oil) on mouse ear, and the possibility of influencing this [5, 6]. The aims of the present work were: (1) a study of the development in time and the extent of capsaicin oedema in mouse ear with a biological quantitative method, (2) investigation of the effects of selected drugs on mouse ear oedema induced with capsaicin, and (3) the detection and biologically quantitative determination of the state of desensitization induced with capsaicin in mice.

Materials and methods

The experiments were performed with the oedema-disk technique [5, 6]. Capsaicin (Fluka AG, Buchs) dissolved in 90% alcohol (10 μl/40 μg) was applied with a Hamilton syringe to the inner surface of the right ear of male mice of the CFLP strain, weighing 28–32 g. A similar volume of alcohol (10 μl) was applied to the inner surface of the other ear. After 60 min, the mice were killed under ether anaesthesia and the ears were cut off. Disks were cut out of the ears with a punch 6 mm in diameter, and the weights of these disks were measured on a torsion
balance. The extent of oedema can be expressed in terms of the weight difference between the inflamed and the control ear.

The experiments were always carried out at the same time of the day, in the late morning hours. Each experimental group of animals consisted of 6 mice. The control group, that is the untreated group, included 8–10 animals. Statistical evaluation was done by means of the two-tailed Student's t-test.

The following agents were employed: chloropyramine (EGIS, Pharmaceutical Works, Budapest), cyproheptadine (Peritol, Gedeon Richter Pharmaceutical Works, Budapest), piroxicam (Hotemin, EGIS Pharmaceutical Works, Budapest), di-4-phloretin phosphate (Leo Research, Fack, Helsingborg) and nordihydroguaiaretic acid (Fluka AG, Buchs).

The drugs were administered intraperitoneally in isotonic saline solution or (in the case of piroxicam) orally in a suspension in 1% methylcellulose, 30 min before treatment with capsaicin.

**Results**

*The development of mouse ear oedema induced with capsaicin*

In the various groups of mice, a dose of 30, 40 or 50 μg capsaicin was applied to one ear. The animals were killed after 1, 2, 4, 6 or 24 h, and the weights of the oedema disks were measured. The results are shown in Fig. 1. The maximum degree of oedema had already been achieved by 1 h, after which there was a continuous decrease. Similar degrees of oedema were observed following the different doses of capsaicin, the curves being practically identical. In subsequent experiments, therefore, a dose of 40 μg capsaicin was applied and the animals were killed after 1 h.

**Influence of selected agents on mouse ear inflammation induced with capsaicin**

The mouse ear oedema induced with capsaicin was found to be reduced by the H₁-receptor antagonist chloropyramine, the antihistamine-antiserotonin cyproheptadine, the non-steroidal anti-inflammatory agent piroxicam, the prostaglandin antagonist di-4-phloretin phosphate, and the lipoxygenase inhibitor nordihydroguaiaretic acid to statistically significant extents, in a dose-dependent manner (Table 1).

**The quantitative determination of capsaicin desensitization with the mouse ear oedema-disk technique**

In the various groups of experimental animals, 40 μg doses of capsaicin were applied to the inner surface of one ear of the mice as follows: in Group 1 on one occasion; in Group 2 on five occasions at 2-hour intervals; and in Group 3 on five occasions at 2-hour intervals, followed by a sixth dose 24 h later. In each group, the mice were killed 60 min after the final capsaicin application (Table 2). The extent of oedema was observed to decrease to a statistically significant extent in response to the desensitization.

**Discussion**

Capsaicin is known to be the prototype of neurogenic irritants. Its repeated local or general application desensitizes the chemosensitive pain receptors in the skin and mucous membranes [2, 3]. The oedema-producing potencies of different irritants in the ears of normal and capsaicin-desensitized rats were compared by Jancső [2]. The irritant was painted on the ear, 30 min later the ear was amputated and its weight was compared with that of the untreated ear. Jancső [2] concluded that: "Since one cannot amputate the ears exactly symmetrically, the quantitative date will be only approximate. The difference, however, is so marked that the inexactness is negligible. These experi-