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Cyclooxygenase inhibitors acetylsalicylic acid and indomethacin do not affect capsaicin-induced neurogenic inflammation in human skin

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Abstract

Neurogenic inflammation is evoked by neuropeptides released from primary afferent terminals and, presumably, by other secondarily released inflammatory mediators. This study examines whether prostaglandins might participate in the development of neurogenic inflammation in humans and whether cyclooxygenase inhibitors have any anti-inflammatory effect on this type of inflammation. In healthy volunteers, neurogenic inflammation was elicited by epicutaneously applied capsaicin (1%), after systemic pretreatment with acetylsalicylic acid, or topically applied indomethacin compared to pretreatment with saline or vehicle, respectively. The extent of neurogenic inflammation was quantified by planimetry of visible flare size and recording the increase of superficial cutaneous blood flow (SCBF) with a laser Doppler flowmeter. Capsaicin-induced flare sizes and outside SCBF (both representing neurogenically evoked inflammation) were unaffected by acetylsalicylic acid or indomethacin. Only the capsaicin-induced increase of inside SCBF was attenuated by local pretreatment with indomethacin, reflecting the participation of prostaglandins in the inflammatory response of those areas which were in direct contact with capsaicin.

Introduction

Neurogenic inflammation may be involved in a variety of diseases including e.g. arthritis, skin inflammation, and asthma (cf. [1, 2]). The mediators of this inflammation include neuropeptides such as substance P and CGRP released from afferent nerve terminals, and putative secondarily released or synthetized inflammatory mediators. Histamine seems to play no primary role in the development of capsaicin-induced inflammation in human skin [3].

This double-blind, randomized, placebo-controlled study examines whether prostaglandins might be involved in the development of neurogenic inflammation, and whether cyclooxygenase inhibitors such as acetylsalicylic acid (ASA) and indomethacin have any anti-inflammatory effect on acutely induced neurogenic inflammation in humans.

Materials and methods

Subjects

Twelve healthy volunteers, 6 women and 6 men, aged 22–28 years, with no history of pain, skin

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disease, or dysfunction of the upper extremities took part in this study and gave informed consent to the double-blind, placebo-controlled design. The study was approved by the Ethics Committee of Würzburg University.

All experiments were performed in a quiet room maintained at 22–25 °C after subjects had acclimatised to room temperature for at least 30 min. To ensure drug washout and skin recovery, experiments were separated by 1–2 weeks.

Induction of neurogenic inflammation

Neurogenic inflammation was induced with capsaicin (1%) using a modified patch technique. The 13 $\times 18\,mm^2$ area of commercially available plasters were soaked with 0.1 ml capsaicin (1%) and applied on volar forearm skin for 25 min.

Quantification of neurogenic inflammation

After the plaster had been removed and a 5 min period for drying had elapsed, the inflammatory response was quantified by planimetry of visible flare size and by recording the superficial cutaneous blood flow (SCBF) underlying (inside SCBF) and surrounding (outside SCBF) the application site of capsaicin with laser Doppler flowmetry (Periflux PF3, Perimed, Stockholm, Sweden). Representative inside SCBF was calculated as the mean of values at four measuring points inside the plaster application side and representative outside SCBF as the mean of eight measuring points each 8 mm outside the plaster application side. The results expressed as mean $\pm$SD were tested for significance ($p<0.05$) using the two-tailed Wilcoxon-test.

Drug application

A. Acetylsalicylic acid (ASA). Prior to any drug application the assigned skin areas were pretreated with 10% DMSO for 1 h under occlusive tapes to improve and standardize cutaneous capsaicin absorption.

A control inflammatory response was induced on one forearm, and on the contralateral side the same procedure was repeated after ASA (10 mg/kg body weight, Aspisol, Bayer, Leverkusen) or the same volume of saline (0.9%) had been injected intravenously.

B. Indomethacin. Prior to capsaicin testing, the assigned skin area was pretreated with topically applied indomethacin or vehicle (Elmetacin, Luitpold-Werk, München, Germany) for 4 h. The plasters ($60 \times 40\,mm^2$) soaked with either 4 ml indomethacin (32 mg) or 4 ml vehicle were applied in randomized order under occlusive tapes to either forearm skin.

Results

Following systemic saline injection, flare sizes ($1753.0 \pm 471.9\,mm^2$) and capsaicin-induced increase of inside SCBF (96.3 ± 25.3 perfusion units (p.u.)) and outside SCBF (65.8 ± 27.7 p.u.) were not different from those seen on the control forearm ($1755.0 \pm 471.9\,mm^2$, 108.4 ± 19.3 p.u., 71.5 ± 36.1 p.u.). Intravenously injected ASA had no effect on inside SCBF (98.6 ± 15.9 p.u.), outside SCBF (65.0 ± 27.7 p.u.), and flare sizes ($1607.7 \pm 872.4\,mm^2$) compared to controls and placebo (saline).

Capsaicin-induced outside SCBF (78.1 ± 31.3 p.u.) and flare size ($1959.3 \pm 687.1\,mm^2$) were unaffected after local pretreatment with indomethacin (81.3 ± 25.0 p.u., $2166.8 \pm 559.1\,mm^2$, respectively) but increase of inside SCBF (105.3 ± 27.5 p.u.) was significantly ($p<0.05$) lower compared to pretreatment with vehicle (120.9 ± 23.1 p.u.).

Discussion

The results indicate that potent cyclooxygenase inhibitors, such as intravenously administered acetylsalicylic acid in an anti-inflammatory dose, or indomethacin in high local concentrations have no influence on capsaicin-induced neurogenic inflammation. We propose, therefore, that prostaglandins are not major inflammatory mediators in neurogenic inflammation in human skin; consequently, cyclooxygenase inhibitors cannot be expected to reduce neurogenically evoked inflammation.

The reduction in the extent of the inner SCBF increase following local indomethacin pretreatment confirms the assumption that the inflammatory response underlying the contact area of capsaicin to skin is of more complex origin, presumably including the participation of prostaglandins. It also supports the contention that this inflamed area should be distinguished from the neurogenic inflammation proper represented by outside SCBF and flare.

References

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