ANTI-UVEITIS AND INHIBITION OF FIBROBLAST-LIKE CORNEAL AND CONJUNCTIVAL CELLS BY INTERLEUKIN-1 BLOCKERS

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ABSTRACT


Effects of interleukin-1 (IL-1) blockers, CK130 and CK131, on IL-1-induced uveitis and proliferation of fibroblast-like corneal and conjunctival cells were investigated in this study. It was found that CK130 and CK131 inhibited IL-1-induced uveitis in rat eyes effectively at 3 mg/kg and 10 mg/kg, respectively. Further, CK130 and CK131 inhibited fibroblast-like corneal and conjunctival cell growth effectively at 10–300 μg/ml and 30–300 μg/ml, respectively. It was also found that DNA synthesis was markedly reduced by CK130 and CK131 at 30–100 μg/ml. RNA synthesis was also inhibited by these CK compounds but protein synthesis was little affected or enhanced.

Keywords: interleukin-1 blockers, anti-uveitis, fibroblast-like corneal cell, conjunctival cells, DNA synthesis inhibition

INTRODUCTION

The number of patients with ocular inflammation has increased drastically in recent years due to cataract operations, laser treatment of secondary cataract and retinal diseases, trabeculectomy in glaucoma, improper use of contact lenses, etc. [1]. Although a few non-steroidal anti-inflammatory drugs (NSAIDs) are available, most of them are not suitable for eyedrops because they induce eye irritation. Further, their potencies are much lower than those of corticosteroids [2]. Consequently, steroidal eyedrops and systemic steroids are still the mainstay for the preventive/treatment of ocular inflammation [3]. Unfortunately, it is known that steroid drugs produce numerous serious side-effects when large doses are used for long periods of time. These require discontinuation of drug administration and result in a recurrence of the ocular inflammation [3].

Major efforts have been made for decades without success to find ideal NSAIDs to replace steroidal drugs. The majority of these efforts have centred on preventing the production of arachidonate metabolites, such as prostaglandins and leukotrienes. Since prostaglandins and leukotrienes are not potent inflammatory agents, the prevention of their production does not affect anti-inflammatory actions [3]. Recently,
it has been found that interleukin-1 (IL-1) is a major cytokine producing broad-spectrum inflammation [1]. Thus, IL-1 blockers could become strong NSAIDs, much more so than arachidonate-related NSAIDs to prevent/treat ocular inflammation [1,4–8]. In this study, two potent IL-1 blockers, CK130 and CK131, have been identified which block effectively IL-1-induced uveitis in rat eyes.

Because of their anti-inflammatory actions, IL-1 blockers can also be used as inhibitors of fibroblast-like corneal and conjunctival cell proliferation [7–12]. If effective, these compounds could also be used to improve the success rate and functional period of cannula created after filtration surgery (trabeculectomy) in close-angle and low-tension glaucoma treatments [13,14]. Thus, the inhibitory actions of CK130 and CK131 on fibroblast-like corneal and conjunctival cells have also been studied.

MATERIALS AND METHODS

Materials

1,2,3,3a,4,6a-Hexahydro-5-(2-hydroxyphenyl)-3a-methyl-2-oxopyrrole[2,3-b]pyrrole (CK130) and 1,2,3,3a,4,5,6,7,8,8a-decahydro-1,8-dibenzyl-3a,6,6d-trimethyl-2,4-dioxopyrrolo[2,3-b]indole (CK131)* were synthesized by published methods [15] and their chemical structures are presented in Figure 1. Hyamine hydroxide (a cell solubilizer), CytoScint scintillation cocktail, [3H]leucine (121 Ci/mmol), [3H]uridine (44 Ci/mmol), and [3H]thymidine (64 Ci/mmol) were purchased from ICN Radiochemicals (Irvine, CA). Eagle's minimum essential medium (MEM), Medium 199, and antibiotic–antimycotic (penicillin G, 10 000 IU/ml; streptomycin sulphate, 10 000 µg/ml; amphotericin B, 25 µg/ml) were obtained from Grand Island Biological Co. (Grand Island, NY). Dimethyl sulphoxide (DMSO) and fetal bovine serum were purchased from Sigma Chemical Company (St. Louis, MO). All solutions of the CK compounds were prepared in pure DMSO and then diluted to the desired concentration in the culture medium. Equal amounts of DMSO were used as a control vehicle in the experiments. The final concentration of DMSO in the cell culture was 1%.

Sprague–Dawley rats, weighing 250–350 g, were anaesthetized with 35 mg/kg ketamine and 5 mg/kg xylazine, intramuscularly. Ten µl of 1 ng IL-1 were injected intravenously, and the animals were allowed to recover from the anaesthesia. Drug doses of 3 mg/kg and 10 mg/kg were injected intraperitoneally at times 0, 4 and 10 h after the IL-1 injection. The uveitis was measured with a fluorophotometer at 12 h after the IL-1 injection.