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Influence of adrenalectomy on protective effects of urocortin I, a corticotropin-releasing factor (CRF)-related peptide, against indomethacin-induced enteropathy in rats

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Abstract. The influence of adrenalectomy on indomethacin-induced enteropathy in rats was examined and the possible involvement of adrenal glucocorticoids in protective effects of urocortin I, a CRF agonist, was investigated. Male SD rats were administered indomethacin (10 mg/kg) s.c., killed 24 h later, and small intestines were examined for hemorrhagic lesions. Urocortin I (20 μg/kg) was given i.v. 10 min before indomethacin. Bilateral adrenalectomy was performed a week before the experiment. Indomethacin caused hemorrhagic lesions in small intestines, accompanied by intestinal hypermotility, enterobacterial invasion and iNOS expression. Adrenalectomy markedly increased ulcerogenic and motility responses caused by indomethacin, with further enhanced bacterial invasion and iNOS expression. This worsening effect was reproduced by pretreatment with mifepristone. Urocortin I prevented indomethacin-induced enteropathy; this effect was abrogated by astressin 2B, a CRF2 receptor antagonist, but was not affected by either adrenalectomy or mifepristone pretreatment. These results suggest that adrenalectomy aggravates indomethacin-induced enteropathy, and intestinal hypermotility response may be the key element in the mechanism underlying this aggravation, while endogenous glucocorticoids play a role in intestinal mucosal defense against these lesions but do not account for protective effects of urocortin I, which are mediated by peripheral CRF2 receptors.

Keywords: corticotropin-releasing factor (CRF), urocortin I, indomethacin-induced enteropathy, CRF2 receptor, adrenalectomy, endogenous glucocorticoids.

Introduction & Aim

Corticotropin-releasing factor (CRF), a hypothalamic neuropeptide, is the principal regulator of hypothalamus-pituitary-adrenal (HPA) axis as it triggers the release of adrenocorticotropic hormone from the anterior pituitary gland (Martinez et al. 2004). Indomethacin-induced small intestinal lesions were prevented by urocortin I, a non-selective CRF receptor (CRFR) agonist, and aggravated by astressin, a non-selective CRFR antagonist. Both these effects, in turn, were mediated by CRF2R but not CRF1R (Kubo et al. 2010). It is assumed that CRF plays a role in intestinal mucosal defense against nonsteroidal anti-inflammatory drugs (NSAIDs) through activation of CRF2R. However, since dexamethasone inhibits indomethacin-induced enteropathy (Takeuchi, Satoh 2015), it is possible that protective effects of urocortin may be, at least in part, mediated by endogenous glucocorticoids released from the adrenal gland through activation of peripheral CRF receptors. The present study examines the influences of bilateral adrenalectomy and mifepristone, a glucocorticoid receptor antagonist, on indomethacin-induced enteropathy in rats in order to investigate possible involvement of adrenal glucocorticoids in the protective effects of urocortin I (Takeuchi et al. 2016).

Methods

Male Sprague-Dawley rats (220–260 g) were administered indomethacin s.c. and killed 24 h later in order to examine hemorrhagic lesions that

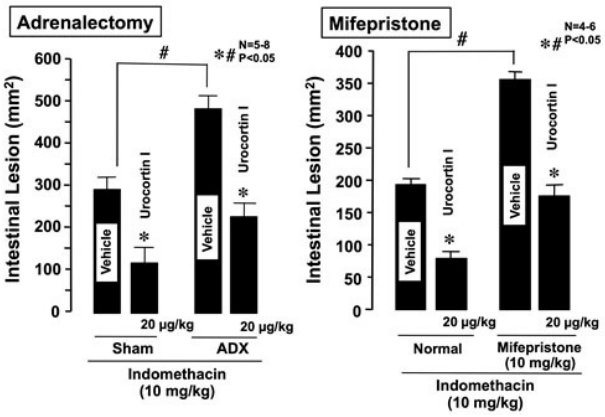

Fig. 1. The effects of urocortin I on indomethacin-induced enteropathy in rats with or without adrenalectomy (ADX) or mifepristone pretreatment. Animals were administered indomethacin (10 mg/kg) s. c. and killed 24 h later. Urocortin I (20 μg/kg) was given i. v. 10 min before the administration of indomethacin. A sham operation (Sham) or bilateral adrenalectomy (ADX) was performed one week before the experiment. Mifepristone (10 mg/kg) was given twice 30 min before and 6 h after the administration of indomethacin. Data are presented as the means ± SE of 4–8 rats. Significant difference at $P < 0.05$; * from vehicle in Sham or ADX or Normal; # from vehicle in Sham or Normal

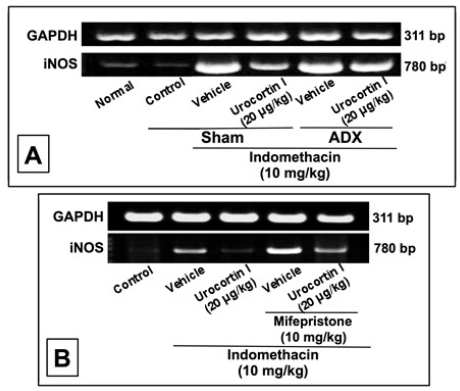

Fig. 2. Effects of urocortin I on the expression of iNOS mRNA in the small intestine of adrenalectomized rats (A) or mifepristone-treated rats (B). A sham operation (Sham) or bilateral adrenalectomy (ADX) was performed one week before the experiment. Animals were administered indomethacin (10 mg/kg) s. c. and killed 6 h later to examine the expression of iNOS mRNA by RT-PCR. Mifepristine (10 mg/kg) was administered p. o. 30 min before the administration of indomethacin. Urocortin I (20 μg/kg) was given i. v. 10 min before indomethacin. Note that indomethacin up-regulated the expression of iNOS in the small intestine of sham-operated, adrenalectomized and mifepristine-treated rats, whereas all these responses appeared to be mitigated by the prior administration of urocortin I

developed in their small intestines. Urocortin I (20 μg/kg) was given i.v. 10 min before the administration of indomethacin. Bilateral adrenalectomy was performed a week before the experiment.

Results

Indomethacin (10 mg/kg) caused multiple hemorrhagic lesions in the small intestine, which were accompanied by a decrease in mucus secretion and increases in intestinal motility, enterobacterial invasion and iNOS expression (fig. 1, 2).

Adrenalectomy markedly increased ulcerogenic and motility responses caused by indomethacin, with further enhanced bacterial invasion and iNOS expression; severe lesions occurred at 3 mg/kg, a dose that did not induce any damage in sham-operated rats. This worsening effect was also observed after pretreatment with mifepristone (a glucocorticoid receptor antagonist). Urocortin I prevented indomethacin-induced enteropathy, and this effect was completely abrogated by the pretreatment with astressin 2B, a CRF2R antagonist, but was not affected by either adrenalectomy or mifepristone pretreatment.

Conclusion

The results of the present study confirmed that urocortin I, a CRF-related peptide, produced a protective influence on the development of indomethacin-induced enteropathy, and this effect may be mediated by activation of peripheral CRF2R and functionally associated with suppression of intestinal hypermotility caused by indomethacin. The intestinal

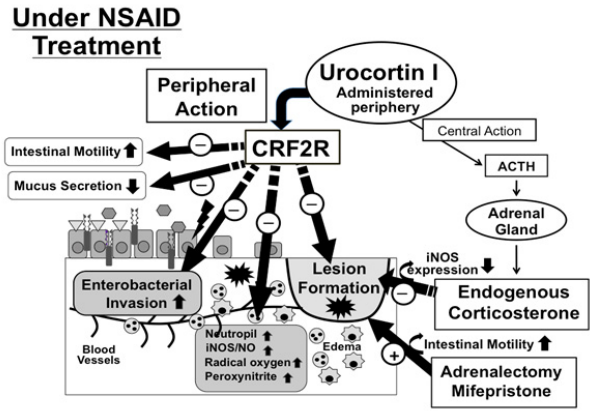

Fig. 3. Urocortin I demonstrates protective effects against NSAID (indomethacin)-induced enteropathy through activation of CRF2R. Adrenalectomy aggravates the intestinal ulcerogenic response to indomethacin, and the intestinal hypermotility response is a key element for this aggravation. Endogenous glucocorticoids play a role in intestinal mucosal defense against indomethacin-induced enteropathy but do not account for the protective effects caused by peripheral administration of urocortin I against these lesions

ulcerogenic response was worsened by adrenalectomy or pretreatment with mifepristone, suggesting that endogenous glucocorticoids play a role in the maintenance of intestinal mucosal integrity under adverse conditions such as NSAID treatment. Since urocortin I prevented NSAID-induced enteropathy in glucocorticoid-deficient rats, similar in normal animals, it may have exhibited such protective effects without involvement of endogenous glucocorticoids released from the adrenal glands (fig. 3).

Furthermore, the present study strongly suggests that glucocorticoid deficiency enhanced the intestinal hypermotility response to indomethacin, which is an important functional event underlying aggravation of intestinal damage by adrenalectomy.

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