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The plasma corticosterone level in rat 6-sulfanilamidoindazole arthritis and influence of RU 486

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Abstract

The inflammatory reaction of the hindpaws inducible in rats by systemic administration of the sulfonamide 6-sulfanilamidoindazole (6-SAI) is characterized by a special tolerance reaction, i.e. the paw inflammation decreases despite a continued medication of 6-SAI. We found no change of the plasma corticosterone level in 6-SAI-dosed animals, neither at the beginning of 6-SAI administration nor when the inflammation reached maximal values nor during the remission of paw swelling.
Thus, a presumed regulatory increase of the endogenous glucocorticoid concentration cannot be the reason for the spontaneous remission of this special inflammatory process. Administration of the receptor antagonist RU 486 caused an increased corticosterone plasma level by about 40% but had no significant influence on paw swelling.

Introduction

The inflammatory reaction is said to be regulated either systemically and/or locally, with the endogenous glucocorticoids as important factors of regulation [1–3].
Inflammation in elderly rats induced by systemic administration of the sulfonamide 6-sulfanilamidoindazole (6-SAI) is characterized by a spontaneous remission despite a continued dosing of the 6-SAI [4]. According to our previous investigations, there is no evidence for mediator depletion [5], acute-phase reaction [6] or changes in pharmacokinetics/biotransformation [7] as a reason for this tolerance reaction.
In the present work we assessed the possible role of endogenous glucocorticoids in regulation and in spontaneous remission of 6-SAI inflammation.

Methods

Male rats (Wistar, Sulzfeld), body weight 300–400 g, were used. Arthritis was induced by oral administration of 125 mg/kg 6-sulfanilamidoindazole (10% suspension of 6-SAI in 1% aqueous gum tragacanth), once daily, over a period of 14 days.
The swelling of both hindpaws was determined by a sliding calliper. Blood was drawn from the orbital vein plexus under slight ether anaesthesia, at the same time of each day; 10.00 a.m..
Rat corticosterone plasma levels were determined by a HPLC technique (Merck-Hitachi; UV detection: 242 nm). The HPLC mobile phase was methyl alcohol–water (60/40% by volume). A C18 reversed phase column (5 µm, 125 × 4 mm; Merck) was used. For further details see [8].

Results and discussion

As shown in Table 1 there was no change in corticosterone plasma level upon administration of 6-SAI. The plasma concentration remained constant in all phases of the experiment: at the beginning, when no inflammation could yet be measured; at days 10/11 of 6-SAI administration, when the paw swelling reached maximal values; and the corticosterone level also remained unchanged during spontaneous decrease of the macroscopic signs of inflammation. The data were confirmed in a second experiment.

In contrast, the corticosterone plasma level increased significantly in primary adjuvant arthritis (Table 2).

Thus, the present data confirm that the 6-SAI-induced inflammation represents a special type of tissue irritation. The often pronounced macroscopic signs of this inflammation, mainly paw swelling and redness during a couple of days, provoke only negligible systemic regulatory events, such as a weak acute phase reaction [6] and no changes in glucocorticoid plasma level (Table 1). This is in contrast to other acute inflammatory processes such as primary adjuvant arthritis, where a strong acute-phase reaction [9] and significantly increased corticosterone plasma levels (Table 2, [10]) can be measured.

The tissue irritation during 6-SAI administration appears to be an unimportant challenge to the organism which can overcome the irritation without noteworthy systemic regulation. An increased endogenous glucocorticoid production is not responsible for the spontaneous remission of 6-SAI inflammation as might be expected (see above).

The increase in plasma corticosterone level after administration of the glucocorticoid receptor antagonist RU 486 in rats with adjuvant arthritis is likely to be due to the blockade of hypothalamus/hypophysis glucocorticoid receptors. Despite the increased corticosterone plasma level, no anti-inflammatory effect could be measured.

Thus, the regulation of 6-SAI inflammation might occur predominantly at the local level [1].

Table 1
Paw swelling and corticosterone plasma level during treatment with RU 486 (10 mg/kg, p.o.) from day 8 to day 10, once daily; $n = 6$.

Group	Paw swelling (mm) Mean ± SD			Corticosterone (ng/ml) Mean ± SD		
	8 d	10 d	11 d	8 d	10 d	11 d
Control h.	—	—	—	60 ± 18	62 ± 17	65 ± 21
6-SAI control	3.8 ± 0.8	5.2 ± 1.1	4.8 ± 0.9	62 ± 22	61 ± 22	65 ± 19
6-SAI + RU 486	3.7 ± 0.9	4.8 ± 1.4	4.7 ± 1.0	63 ± 14	87 ± 21	90 ± 25

h. = healthy.

Table 2
Paw swelling and corticosterone plasma level in primary adjuvant arthritis during treatment with RU 486 (10 mg/kg, p.o) from day 1 to day 3, once daily; $n = 5$.

Group	Paw swelling (ml) Mean ± SD			Corticosterone (ng/ml) Mean ± SD		
	3 d	4 d	7 d	3 d	4 d	7 d
Control h.	—	—	—	100 ± 37	94 ± 27	133 ± 47
Control a.	0.4 ± 0.1	0.4 ± 0.1	0.6 ± 0.1	179 ± 61	232 ± 77*	231 ± 62*
RU 486 a.	0.4 ± 0.02	0.3 ± 0.1**	0.6 ± 0.1	219 ± 35*	245 ± 48*	247 ± 64*

h. = healthy.
a. = arthritic.
* Significantly different ($p < 0.05$: analysis of variance) from non-arthritic rats.
** Significantly different ($p < 0.01$: Student's t-test) from arthritic rats.
Adjuvant arthritis was induced with Freund's complete adjuvant and quantified according to Hirschelmann et al. [9].

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