Synovitis reduced by inhibition of leukotriene B_4

Carragheenan-induced gonarthritis studied in dogs

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The pathophysiologic significance of leukotriene B_4 (LTB_4) in arthritis was studied in dogs by unilateral intraarticular deposition of 15-hydroxy-eicosatetraenoic acid (15-HETE), an endogenous inhibitor of the formation and the effects of LTB_4, in bilateral carragheenan-induced gonarthritis. LTB_4 in synovial fluid was selectively inhibited in 15-HETE treated joints, the formation of prostaglandin E_2 (PGE_2) being largely unaffected. The clinical symptoms, intraarticular pressure, and extractable synovial fluid volume were reduced in treated joints. No effect could be discerned regarding blood flow in the synovial membrane, capsule, or juxtaarticular bone as measured by tracer microspheres; and no effect on bone metabolism was found as judged by ^{99m}Tc-diphosphonate uptake. Thus, inhibition of LTB_4 reduces joint exudation, but does not seem to interfere with changes in juxtaarticular hemodynamics or bone metabolism following synovial inflammation.

Prostaglandins and leukotrienes are inflammatory mediators generated by polymorphonuclear leukocytes and monocytes/macrophages by enzymatic transformation of arachidonic acid via the cyclooxygenase and lipoxygenase pathways, respectively. Leukotriene B_4 (LTB_4), a product of 5-lipoxygenase, is a potent leukocyte chemotactic and chemokinetic agent (1–3), with the capacity to enhance vascular permeability, particularly in the presence of prostaglandin E_2 (PGE_2) (4). LTB_4 has been detected in synovial fluid from patients with rheumatoid arthritis, spondylarthritis, and gout (5–7), and we have previously demonstrated LTB_4 in synovial fluid from canine carragheenan-induced arthritis (8). The significance of these findings still is uncertain.

We studied the pathophysiologic role of LTB_4 in arthritis by unilateral inhibition of LTB_4 formation in bilateral acute carragheenan-induced arthritis. The inhibition was achieved by local intraarticular administration of 15-hydroxy-eicosatetraenoic acid (15-HETE), a 15-lipoxygenase product of arachidonic acid with the capacity to inhibit LTB_4 formation (9, 10) and LTB_4-induced neutrophil chemotaxis (11).

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Materials and methods

Nine young labrador dogs, weighing 9–14 kg, comprised the material. Bilateral arthritis of the knee was induced by carragheenan injections every third day for 14 days. 15–HETE was administered to the right knee by continuous intraarticular infusion using implanted miniosmotic pumps, as well as by discontinuous injection with each provocation. The left knee received infusion and instillation of isotonic saline via the same two routes and served as the arthritic reference joint. The joint content of LTB_4 and PGE_2 was determined bilaterally at 3-day intervals, and the pathophysiology of arthritis was assessed by volume of effusate, joint pressure, ^{99m}Tc-DPD scintimetry, and juxtaarticular blood flow measured with radioactive microspheres.

Catheter and osmotic pump implantation was performed 2 weeks prior to arthritis induction. Un-

der general anesthesia with Immobilon® vet. (etorphine 0.125 mg + acepromazine 0.4 mg/mL) preceded by s.c. premedication with 1.0 mL Combelen® vet. (propionylpromazine 10 mg/mL), a fine-bore polyvinyl catheter (BB317-85 V/3, Alza Corp., Palo Alto, CA, USA) connected to a beaded metal cannula was implanted into each knee joint. Insertion was made through a small medial parapatellar arthrotomy. A mechanically neutral point was identified on femur in the intercondylar notch, just behind the articular cartilage at the origin of the posterior cruciate ligament. From there, an oblique 1.2-mm hole was drilled across the lateral femoral condyle to the posterolateral condylar corner. The catheter was pulled through the canal guided by an introducing needle piercing the lateral joint capsule posterior to the lateral recess of the suprapatellar pouch. The metal cannula was firmly impacted into the drilled canal leaving the bead flush with bone. A miniosmotic pump (Alzet® 2ML4, rate 2.5 µL/h for 28 days), bilaterally loaded with 2 percent ethanol in isotonic saline, was then connected to the proximal catheter end and implanted in a subcutaneous pocket proximally on femur through a 2-cm lateral skin incision. The dogs ambulated freely for 14 days until all the incisions had healed. The dogs tolerated the catheter and Alzet® osmotic pump implantation well. No adverse joint reactions to the implanted material were seen, and limb function prior to arthritis induction was completely unlimited. Two dogs had to be excluded from the study because of leakage of one of the catheters, and the following results are based on 7 dogs.

Induction of arthritis. 15-HETE was synthesized, extracted, and purified as described elsewhere (12, 13). Two solutions were prepared: A 250 µM solution of 15-HETE in isotonic saline with 1 percent ethanol for treatment of the experimental right joints, and a control solution of isotonic saline with 1 percent ethanol for the left reference joints. Initially, the subcutaneous pocket on the right femur was incised and the osmotic pump exchanged with an Alzet® 2ML2 osmotic pump (rate 5 µL/h for 14 days) filled with 2 mL 15-HETE solution. Acute synovial inflammation was then induced bilaterally by intraarticular instillation of 2.0 mL 1 percent carrageenan plus either 0.4 mL 15-HETE (right) or control solution (left) every third day for 14 days (five provocations). Immediately before each carrageenan injection, synovial fluid samples for determination of eicosanoids were obtained by extraction of fluid (if possible) and lavage with 7 mL isotonic saline injected in the intercondylar area through an inferomedial joint puncture. The needle was withdrawn after injection of lavage fluid and the joint was moved passively for 1–2 minutes through several flexion/extension cycles in order to secure adequate intraarticular mixing. The lavage fluid was evacuated immediately thereafter by lateral puncture of the suprapatellar recess followed by injection of the carrageenan solution through the same needle. All the inductions were performed under a short i.v. general anesthesia with Brietal® sodium (methohexital sodium, 7 mg/kg) after premedication.

^{99m}Tc-diphosphonate joint scintigraphy. Bone metabolism was investigated by ^{99m}Tc-diphosphonate scintimetry (14, 15) 8 hours after the fourth carrageenan injection and was expressed as the count ratio between the right 15-HETE treated and the left arthritic reference knee.

Regional blood flow, synovial effusion, and intraarticular pressure were measured 8–10 hours after the final carrageenan induction under general anesthesia (premedication s.c. 1.0 mL Combelen® vet. [propionylpromazine 10 mg/mL], induction Brietal® sodium 7 mg/kg [methohexital sodium], maintenance Immobilon® vet [etorphine-acepromazine] and Pavulon® [pancuronium bromide]) on constant volume ventilation. The dogs were positioned supine with the knees in 45° flexion and the hips in slight abduction and neutral rotation. Cardiopulmonary steady state was controlled with continuous recording of the mean arterial blood pressure, heart rate, central venous pressure, and repeated analyses of arterial gases, pH, and base excess. The microsphere method, described in detail elsewhere (16, 17), was used to measure the regional blood flow. The intraarticular pressure was measured bilaterally in the intercondylar compartment immediately after microsphere injection by a fluid filled electromanometric pressure recording system. Atmospheric pressure outside the joint served as the reference pressure level. Synovial fluid was then extracted for eicosanoid analysis. The dogs were killed by intracardial methohexital and absolute alcohol. The osmotic pumps were removed, and patency and function of the joint catheters were controlled by arthrography through the free catheter end. Regional blood flow rates (mL/min/100 g) were calculated in standardized biopsies according to Hales (17).

LTB_4 and *PGE_2* were determined in joint fluid or lavage fluid by reversed-phase, high-performance liquid chromatography and a radioimmunoassay (18) and expressed as total joint content. The detection limits were 15 pg/joint LTB_4 and 0.05 ng/joint PGE_2.

Statistics. Wilcoxon's analysis was used for paired comparison of values from 15-HETE treated

Table 1. Leukotriene B_4 (LTB_4, pg/joint) and prostaglandin E_2 (PGE_2, ng/joint) determined in synovial fluid from dogs with bilateral carrageenan-induced arthritis. The experimental knee (E) was treated with 15-HETE intraarticularly, the contralateral knee served as the arthritic control (C) and received saline treatment

Dog	Day 0		Day 4[a]		Day 7[a]		Day 10[a]		Day 14[a]		Day 14[b]	
	E	C	E	C	E	C	E	C	E	C	E	C
Leukotriene B_4												
1	< 15	< 15	–	< 15	32	164	50	214	68	154	19	20
2	< 15	< 15	47	50	129	136	< 15	60	59	132	34	–
3	< 15	< 15	< 15	45	163	129	120	143	27	214	51	77
4	< 15	< 15	< 15	858	290	366	268	1807	250	182	98	107
5	< 15	< 15	< 15	73	52	1250	313	1786	643	669	< 15	188
6	< 15	< 15	< 15	847	121	304	113	1562	< 15	175	< 15	262
7	< 15	< 15	68	68	109	145	288	250	< 15	723	54	69
Median	< 15	< 15	< 15*	68	128*	164	118*	250	59*	182	40*	92
Prostaglandin E_2												
1	0.07	0.16	7.20	6.40	2.10	2.00	0.34	0.71	0.62	1.17	6.16	7.20
2	< 0.05	0.08	< 0.05	< 0.05	0.29	1.44	< 0.05	0.33	0.11	1.84	1.55	4.10
3	< 0.05	< 0.05	1.65	2.80	0.25	1.22	7.07	1.36	1.93	4.93	0.45	2.86
4	< 0.05	< 0.05	0.70	0.70	2.32	3.34	1.84	2.14	6.00	1.03	2.15	3.70
5	0.60	0.50	1.03	0.98	0.61	3.50	1.85	3.00	2.38	10.5	5.90	15.8
6	< 0.05	0.08	0.08	4.40	1.61	0.85	0.33	0.60	1.37	< 0.05	2.85	28.9
7	< 0.05	0.05	0.60	< 0.05	3.09	1.67	0.50	1.21	< 0.05	1.61	0.80	0.35
Median	< 0.05	0.08	0.70	0.98	1.61	1.67	0.50	1.21	1.37	1.61	2.15*	4.10

* $P < 0.05$ compared with simultaneous control knee value.
[a] Sample taken in quiescent stage of arthritis before new provocation.
[b] Sample taken 8 hours after carrageenan provocation.

joints with those of arthritic reference joints. The relationship between parameters was explored with Kendall's rank correlation analysis.

Results

All the knee joints showed increasing clinical signs of acute synovial inflammation throughout the study period. An arthritic flare occurred within the first 6–24 hours after each induction. An overall tendency of fewer symptoms and more rapid recovery of the right 15-HETE treated joints was noticed.

Synovial fluid eicosanoids (Table 1). Before arthritis induction, no LTB_4 could be detected. In the left arthritic reference joints, increasing amounts of LTB_4 were retrieved by joint lavage in the quiescent stage of arthritis just prior to carrageenan provocation, beginning already after the first injection and peaking on Day 10. The LTB_4 generation in the right 15-HETE treated joints was inhibited throughout the study. PGE_2 was undetectable before arthritis induction. Substantial amounts of PGE_2 were retrieved by joint lavage before carrageenan injections, but no differences were found between 15-HETE treated and reference joints.

Joint pathophysiology. The volume of synovial fluid and intraarticular pressure of 15-HETE treated joints were reduced (Table 2). No blood flow differences between 15-HETE and reference joints could be discerned (Table 3). Profound hyperemia was present bilaterally in the synovial membrane, menisci, and the joint capsule. A marked blood flow gradient was found bilaterally within the distal femoral epiphysis with the highest flow rates at the periphery ($P < 10^{-4}$). The scintimetric count ratio between 15-HETE treated knee and control knee was 0.96 (0.85–1.14) in the distal femoral epiphysis, 1.01 (0.89–1.16) in the femoral metaphysis, and 0.99 (0.94–1.13) in the proximal tibial metaphysis.

The basal LTB_4 content of joints correlated positively with the effusion volume generated after the final provocation ($\tau = 0.38$, $P = 0.05$), but not with intraarticular pressure. A trend was observed for correlation between basal LTB_4 content and

Table 2. Effusion volume (mL) and intraarticular pressure (mmHg) in the arthritic flare 8–10 hours after the final carrageenan provocation. The experimental knee (E) was treated with 15-HETE intraarticularly; the contralateral knee served as an arthritic control (C) and received saline treatment

Dog	Effusion volume		Intraarticular pres.	
	E	C	E	C
1	4.3	5.7	5	11
2	4.0	6.6	7	23
3	5.7	15.4	9	24
4	7.9	10.0	4	10
5	9.8	26.3	19	19
6	12.0	10.1	12	17
7	7.7	10.1	22	42
Median	7.7*	10.1	9*	19

* $P < 0.05$, experimental knee compared with control knee.

Table 3. Regional juxtaarticular blood flow rates (mL/min/100 g). Median (range)

	15-HETE	Saline
Synovial membrane	57 (35–114)	52 (29–114)
Meniscus	30 (7–44)	25 (10–99)
Capsule	14 (9–24)	27 (6–35)
Patella	12 (7–19)	12 (6–24)
Femoral epiphysis	14 (9–32)	15 (9–27)
center	8 (5–29)	13 (6–32)
periphery	18 (11–32)	17 (10–32)
Femoral metaphysis	12 (7–20)	13 (6–19)
growth zone	9 (7–18)	9 (6–16)
proximal part	11 (3–27)	11 (4–29)

blood flow measured in the arthritic flare in the following juxtaarticular structures: Synovial membrane ($\tau = 0.34$, $P = 0.08$), medial meniscus ($\tau = 0.40$, $P = 0.05$), central epiphyseal bone ($\tau = 0.35$, $P = 0.08$), subchondral bone ($\tau = 0.33$, $P = 0.10$), patella ($\tau = 0.38$, $P = 0.06$), and metaphyseal growth zone ($\tau = 0.37$, $P = 0.06$), but not in proximal metaphyseal bone at some distance from the inflammatory process. No correlation was found between PGE_2 and any of the physiologic parameters nor between intraarticular pressure and blood flow in any location.

Discussion

The carrageenan arthritis model is well characterized and reproducible with respect to juxtaarticular hemodynamics (19, 20, 21) and bone metabolism (14, 15). The inflammatory activity of carrageenan is initiated by macrophage ingestion followed by release of lysosomal enzymes, accumulation of polymorphonuclear leukocytes, release of prostaglandins and leukotrienes, and formation of an inflammatory exudate (22–24). We found PGE_2 and LTB_4 accumulation in untreated arthritic joints already after the first provocation, although the amounts retrieved varied greatly between individual dogs. 15-HETE treatment consistently depressed the LTB_4 accumulation, whereas PGE_2 values generally were unaffected, which indicates that 15-HETE selectively inhibited the lipoxygenase pathway as intended. The intermittent percutaneous 15-HETE administration aimed at an immediate synovial fluid concentration of at least 25 μM, which offers an almost 100 percent in vitro inhibition of LTB_4 formation (9, 10). However, pilot studies on the fate of injected ^{3}H-15-HETE failed to detect activity in synovial fluid after 2 hours, and activity persisted in periarticular soft tissue for less than 6 hours. Hence, injected 15-HETE seems to be cleared from joints too rapidly to secure adequate inhibitor coverage between injections. We therefore developed the method for continuous intraarticular drug delivery with implantable pumps. The 15-HETE infusion rate was selected so that a tissue concentration of 6 μM (corresponding to IC_{50} of 5-lipoxygenase in vitro [9, 10]) could be maintained in a distribution volume of 1 mL assuming a tissue half-life of 2 hours. Because the actual distribution space of 15-HETE in tissues is unknown, it remains uncertain whether these calculations actually were relevant. And because LTB_4 was low in 15-HETE treated joints both before and during the arthritic flare after provocations, both routes of administration presumably contributed to the enzyme inhibition. All the joints were initially equipped with 2ML4 pumps with a secretion rate of 2.5 μL/h for 4 weeks, which was sufficient for the length of the study. The pumps in the experimental limbs were exchanged with a 2ML2 with the double secretion rate for half the duration. The ethanol con-

centrations were adjusted so that the ethanol delivery rate was identical in both experimental and control joints. The extra delivery of 2.5 microliters isotonic saline per hour to experimental joints evidently represents a flaw in the study design, but was judged to be without physiologic significance in view of the rapid disappearance of even large volumes of isotonic saline after instillation in joints.

15-HETE has no known direct effect on the synthesis of prostaglandins (25), and the decreased PGE_2 content in 15-HETE treated joints in the final synovial fluid analysis probably was an indirect effect of a less severe inflammation in treated joints with fewer cells to stimulate. This view seems supported by the observation that the proliferation of synovial cell cultures derived from carragheenan-induced arthritis is stimulated by LTB_4 and inhibited by addition of 15-HETE alone as well as in combination with LTB_4 (26).

The inhibited LTB_4 synthesis was accompanied by reduced synovial infiltration of leukocytes (18), clinical improvement, reduced joint effusion, and lower intraarticular pressure. Presumably, LTB_4 acts as a chemoattractant to polymorphonuclear leukocytes in the early cellular recruitment during joint inflammation (2, 3) with an enhancing effect on synovial vascular permeability in synergism with PGE_2 (4).

Although we observed a weak trend for correlation between basal LTB_4 content and blood flow in juxtaarticular structures, no differences were found between 15–HETE treated and reference joints. Hence, it seems that inhibition of LTB_4 formation does not have any direct effect on synovial or bone blood flow. Although it may be argued that the relatively greater intraarticular pressure in control joints could compromise the synovial and epiphyseal circulation (16) and thereby conceal part of the inflammatory hyperemia in these reference joints, the treatment effect of 15-HETE on synovial effusion clearly was insufficient to influence the juxtaarticular hemodynamic pattern convincingly. In contrast, selective inhibition of prostaglandin synthesis had a dramatic effect on the hyperemia of juxtaarticular soft tissue and bone associated with carragheenan-induced arthritis (27). These results corroborate earlier findings of Bray (4), who reported that intradermal injection of PGE_2 elicited a vasodilatory response, which was not observed after injection of LTB_4.

We conclude that inhibition of LTB_4 formation reduces the exudative aspects of arthritis, but does not prevent major derangements in the hemodynamics of juxtaarticular soft tissue and bone.

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