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Short communication

Effect of the bradykinin B_2 receptor antagonist Hoe140 in experimental pneumococcal meningitis in the rat [1]

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Abstract

To elucidate the role of bradykinin in the complex pathophysiology of bacterial meningitis we investigated the effect of the bradykinin B_2 receptor antagonist Hoe140, icatibant (D-Arg[Hyp^3-Thi^5-D-Tic^7-Oic^8]-bradykinin), on pathophysiological alterations in experimental pneumococcal meningitis. Untreated rats injected intracisternally (i.c.) with heat-killed pneumococci developed an increase of regional cerebral blood flow (185.4 ± 27.4%, baseline 100%, mean ± S.D.), brain water content (79.16 ± 0.23%), intracranial pressure (21.4 ± 6.0 mm Hg), and white blood cell count in the cerebrospinal fluid (CSF) (4621 ± 1894 cells/μl) within 6 h after i.c. challenge. Treatment with Hoe140 (0.1 mg/kg i.v. at baseline and 0.05 mg/kg s.c. at 2 h after i.c. challenge) attenuated the increase of brain water content (78.53 ± 0.28%; $P < 0.05$), intracranial pressure (7.5 ± 2.2 mm Hg; $P < 0.05$), and regional cerebral blood flow (128.6 ± 23.1%; $P < 0.05$), and reduced CSF pleocytosis (2690 ± 1898 cells/μl, N.S.). When treatment was started 4 h after i.c. challenge Hoe140 reduced intracranial pressure ($P < 0.05$), but was no more capable to significantly influence the other pathophysiological parameters. Treatment with lower (0.01 mg/kg i.v. at baseline, followed by 0.005 mg/kg s.c. at 2 h) and higher (2 mg/kg i.v., followed by 1 mg/kg s.c. at 2 h) concentrations of Hoe140 was ineffective. Likewise, i.c. injection of Hoe140, at different dosages (4 nmol, 40 nmol, 400 nmol) did not significantly alter the pathophysiological parameters in pneumococci-induced meningitis, but caused changes in mean arterial blood pressure at dosages greater than 4 nmol. We conclude that bradykinin is involved as an inflammatory mediator of microvascular changes, brain edema, and increased intracranial pressure during the early phase of experimental pneumococcal meningitis.

Keywords: Bradykinin; Hoe140; Pneumococcal meningitis; Cerebral blood flow; Brain edema; Intracranial pressure

1. Introduction

Streptococcus pneumoniae is the most common pathogen causing bacterial meningitis in adults. Pneumococcal meningitis is still a serious disease with a fatality rate of 20–30% (Pfister et al., 1993). Major determinants of a poor prognosis are cerebral complications arising during bacterial meningitis, such as cerebrovascular involvement, brain edema, hydrocephalus, and increased intracranial pressure (Quagliarello and Scheld, 1992; Pfister et al., 1993). The pathophysiological mechanisms of these major intracranial complications are incompletely understood in detail. With a better understanding of their complexity new management strategies using anti-inflammatory agents combined with antibiotics, could be developed in the future to improve the outcome of the disease. Studies using rabbit and rat models of pneumococcal meningitis have identified several mediators, including cytokines, cyclooxygenase metabolites, platelet activating factor, excitatory amino acids, reactive oxygen species, nitric oxide, and peroxynitrite, which appear to play a role in the pathophysiological mechanisms of the disease (Quagliarello and Scheld, 1992; Guerra-Romero et al., 1993). In addition, there is increasing evidence that leukocyte-endothelial interaction is involved in central nervous system damage during bacterial meningitis (Tuomanen et al., 1989; Weber et al., 1995).

Bradykinin is a nonapeptide formed from kininogen by the serine protease kallikrein (Bhoola et al., 1992; Walker et al., 1995). The kallikreins are divided into two main groups: tissue kallikreins and plasma kallikreins (Bhoola et al., 1992). Bradykinin has been implicated to play a role in several pathophysiological conditions such as inflamma-

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tion, enhanced vascular permeability, and edema, pain induction, vasodilatation and increased blood flow (Wahl et al., 1988; Bhoola et al., 1992; Dray and Perkins, 1993). Bradykinin can mediate these pathophysiological processes by several modes of action: for example, it can induce the release of prostaglandins, free radicals, nitric oxide, cytokines, and neuropeptides including substance P, neurokinin A, and calcitonin gene-related peptide (Bhoola et al., 1992; Dray and Perkins, 1993; Walker et al., 1995). Some of these substances are known to play a role in the pathophysiology of bacterial meningitis (Quagliarello and Scheld, 1992; Pfister et al., 1995). The role of bradykinin in the complex network of mediators in the pathophysiology of this disease is completely unknown.

On the basis of the activity of selective agonists and antagonists, bradykinin receptors can be divided into the classic bradykinin receptors B_1 and B_2. However, there is increasing evidence for the existence of bradykinin receptor subtypes (Bhoola et al., 1992; Hall, 1992; Regoli et al., 1994). Most of the biological activity of bradykinin seems to be mediated by the B_2 receptor, including vasodilatation, pain, and increased vascular permeability (Bhoola et al., 1992; Dray and Perkins, 1993). A potent long-acting bradykinin B_2 receptor antagonist, Hoe140, icatibant (D-Arg[Hyp^3-Thi^5-D-Tic^7-Oic^8]-bradykinin) was recently developed (Lembeck et al., 1991; Wirth et al., 1991). In previous studies we showed in a rat model of pneumococcal meningitis that intracisternal (i.c.) injection of heat-killed pneumococci or pneumococcal cell wall components induced a rise in regional cerebral blood flow, intracranial pressure, brain water content, and CSF white blood cell count (Koedel et al., 1995). These pathophysiological changes were similar to that observed after i.c. challenge with live pneumococci in the same rat model (Pfister et al., 1990). In the current study we investigated the effect of systemic and intracisternal Hoe140 on these pathophysiological parameters in meningitis induced by heat-killed pneumococci.

2. Materials and methods

2.1. Animal model of pneumococcal meningitis

We used a well-characterized meningitis model that was previously described in detail (Pfister et al., 1990). The protocols used in this study were approved by the Government of Upper Bavaria. A total of 30 adult male Wistar rats (250–300 g) were used. The rats were anesthetized with thiopental (100 mg/kg) intraperitoneally (i.p.), tracheotomized, artificially ventilated (small animal ventilator, model 683; Harvard, South Natick, MA, USA), and kept under anesthesia throughout the experiment. Skeletal muscle relaxants were not used. The endexspiratory CO_2 was continuously monitored with an infrared CO_2 analyser (model 2200; Heyer, Bad Ems, Germany) and maintained at a level of about 30 mm Hg by adjusting the respirator. Mean arterial blood pressure was measured through a catheter placed in the left femoral artery using a Statham P23 pressure transducer. The left femoral vein was cannulated and used for drug administration. Arterial blood samples were taken hourly and analyzed for pCO_2, pO_2, pH, and hematocrit. Rectal body temperature was maintained at 38°C by a thermometer-controlled heating pad. CSF white blood cell count was determined at baseline and at 6 h. The rats were placed in a stereotaxic frame. A burr hole was made in the occipital bone in order to place the cisterna magna catheter as previously described (Pfister et al., 1990). A craniotomy with a diameter of 5 mm was performed over the right parietal cortex for placement of the laser-Doppler probe. The dura remained intact. A stainless steel cap was placed over the craniotomy site to keep the laser-Doppler probe in place (model BPM 403a; Vasamedics, St. Paul, MN, USA). Regional cerebral blood flow was continuously recorded by laser-Doppler flowmetry. Changes in regional cerebral blood flow were expressed as percent changes from the baseline value (= 100%). The following parameters were continuously monitored by a personal computer system after analog-digital conversion for signal processing: intracranial pressure (measured with a Statham P23 pressure transducer connected to the cisterna magna catheter), regional cerebral blood flow, mean arterial blood pressure and endexspiratory CO_2. The rats were killed by exsanguination 6 h after i.c. inoculation. The brain was removed, weighed, and dried in a stove for 16 h at 130°C to a stable weight. The brain water content was calculated by the formula (wet weight − dry weight)/wet weight × 100 as previously described (Pfister et al., 1990). When a stable baseline of regional cerebral blood flow and intracranial pressure was achieved for 30 min, 100 μl CSF was removed through the i.c. catheter. Meningitis was induced by i.c. inoculation of 100 μl of 10^7 CFU/ml heat-killed pneumococci, strain type 3. The preparation of pneumococci (strain type 3) used in this study has been described in detail (Pfister et al., 1990; Koedel et al., 1995). Heat-killed (60°C for 4 h) unencapsulated pneumococci stem from an isogenic mutant of the encapsulated strain *Streptococcus pneumoniae* type 3 (No. 17260) (Koedel et al., 1995).

2.2. Experimental protocol

Rats were divided into the following groups: untreated rats injected i.c. with heat-killed pneumococci ($n = 5$); rats injected i.c. with heat-killed pneumococci and treated systemically with Hoe140 at three different dosages: 2 mg/kg i.v. at baseline and 1 mg/kg s.c. at 2 h ($n = 5$); 0.1 mg/kg i.v. at baseline and 0.05 mg/kg s.c. at 2 h ($n = 5$); 0.01 mg/kg i.v. at baseline and 0.005 mg/kg s.c. at 2 h ($n = 3$); rats injected i.c. with heat-killed pneumococci and treated systemically with Hoe140 0.1 mg/kg i.v. at 4 h after i.c. challenge ($n = 5$) (Hoe140 was kindly provided

by Dr. K.J. Wirth, Hoechst, Frankfurt, Germany). Furthermore, we tested whether i.c. administration of Hoe140 would be effective. Hoe140 injected i.c. was given at three different dosages. The following groups were investigated: rats injected i.c. with heat-killed pneumococci and simultaneously treated with 4 nmol ($n = 3$), 40 nmol ($n = 2$) or 400 nmol ($n = 2$) of Hoe140.

2.3. Analysis of nitric oxide production and determination of interleukin-6 levels in the CSF

To study the possible influence of Hoe140 on IL-6 and nitric oxide production we determined CSF IL-6 and nitrite levels. Nitric oxide production was assessed by measuring nitrite, a stable metabolic product of nitric oxide, using the Griess reaction (Koedel et al., 1995). Interleukin-6 was assessed using the IL-6-dependent B-cell hybridoma 7TD1 as previously described (Frei et al., 1988).

CST nitrite and interleukin-6 levels were measured in five rats injected with heat-killed pneumococci; five rats injected with heat-killed pneumococci and treated with Hoe140 0.1 mg/kg (followed by 0.05 mg/kg); and four rats injected with heat-killed pneumococci and treated with Hoe140 2 mg/kg (followed by 1 mg/kg).

2.4. Statistical analysis

Groups were compared using ANOVA. Data of regional cerebral blood flow and intracranial pressure were compared at 3 and 6 h after starting the experiment; P values were corrected for repeated measurements using the Bonferroni-Holm procedure. Differences were considered significant when $P < 0.05$. Data are expressed as mean ± S.D.; N.S. in the text indicates the lack of a significant difference.

3. Results

3.1. Physiological parameters

Mean arterial blood pressure, pO_2, pCO_2, pH, and hematocrit were within normal ranges in rats injected with heat-killed pneumococci irrespective of whether they were untreated or systemically treated with Hoe140 (Table 1; for mean arterial blood pressure changes in rats injected i.c. with Hoe 140 see section 3.3.).

3.2. Effect of systemic Hoe140 on regional cerebral blood flow, intracranial pressure, brain water content, and CSF white blood cell count

There was a significant increase of regional cerebral blood flow, intracranial pressure, brain water content, and CSF white blood cell count in rats injected with heat-killed pneumococci within 6 h (Table 2). Treatment with Hoe140 at a dosage of 0.1 mg/kg i.v. (followed by 0.05 mg/kg s.c. at 2 h) significantly attenuated the increase in regional cerebral blood flow, intracranial pressure, and brain water content ($P < 0.05$, compared with untreated rats, injected with heat-killed pneumococci) and reduced CSF pleocytosis (N.S.) (Table 2). The lower and higher dosage of Hoe140 given systemically did not significantly affect regional cerebral blood flow, intracranial pressure, brain water content, and CSF pleocytosis in rats injected with heat-killed pneumococci (Table 2). Post-treatment with Hoe140 (0.1 mg/kg i.v. at 4 h) attenuated the increase of intracranial pressure ($P < 0.05$), but had no effect on regional cerebral blood flow, brain water content and CSF pleocytosis (Table 2).

3.3. Effect of i.c. administration of Hoe140 on regional cerebral blood flow, intracranial pressure, brain water content, CSF white blood cell count, and mean arterial blood pressure

I.c. injection of 4 nmol together with heat-killed pneumococci did not significantly modulate the increase of regional cerebral blood flow, intracranial pressure, brain water content and CSF white blood cell count at 6 h (Table 2). In addition, i.c. injection of 40 nmol and 400 nmol did not influence these pathophysiological parameters measured at 6 h in two rats investigated: regional cerebral blood flow was 168.8% and 164.7% in rats injected with 400 nmol and 178.8% and 209.5% in rats injected with 40 nmol i.c.; intracranial pressure was 12.6 mm Hg and 24.5 mm Hg in rats injected with 400 nmol i.c. and 20.8 mm Hg and 15.0 mm Hg in rats injected with 40 nmol i.c.; brain water content was 79.09% and 79.84% in rats injected with 400 nmol i.c. and 79.09% and 79.12% in rats injected with 40 nmol i.c.; CSF white blood cell count was 7296 cells/μl and 6460 cells/μl in rats injected with 400 nmol i.c. and 18800 cells/μl and 5487 cells/μl in rats injected with 40 nmol i.c.

I.c. administration of Hoe140 at dosages of 40 nmol and 400 nmol together with heat-killed pneumococci induced transient changes of mean arterial blood pressure, whereas the administration of 4 nmol did not alter mean arterial blood pressure. For example, in both rats given 400 nmol i.c. the following course of mean arterial blood pressure data was recorded: rat 1, 126 mm Hg at baseline, 165 mm Hg at 10 min after i.c. injection of Hoe140, 69 mm Hg at 20 min, 172 mm Hg at 40 min, 110 mm Hg at 70 min, 100 mm Hg at 180 min, 110 mm Hg at 360 min; rat 2, 114 mm Hg at baseline, 120 mm Hg at 10 min, 71 mm Hg at 20 min, 122 mm Hg at 55 min, 76 mm Hg at 70 min, 151 mm Hg at 180 min and 112 mm Hg at 360 min.

3.4. Effect of systemic Hoe140 on nitrite and interleukin-6 levels in the CSF

We did not find a significant effect of Hoe140 on CSF interleukin-6 concentrations; interleukin-6 levels were

Table 1
Physiological parameters in different experimental groups

Group	Mean arterial blood pressure (mm Hg)			$PaCO_2$ (mm Hg)			PaO_2 (mm Hg)			pH			Hematocrit (%)	
	Baseline	3 h	6 h	Baseline	3 h	6 h	Baseline	3 h	6 h	Baseline	3 h	6 h	Baseline	6 h
HKP-injected														
Untreated ($n = 5$)	114 ± 16	108 ± 14	102 ± 12	38 ± 3	37 ± 2	34 ± 3	137 ± 30	118 ± 24	129 ± 18	7.44 ± 0.03	7.42 ± 0.01	7.44 ± 0.03	48 ± 1	45 ± 0
Hoe140 2 mg/kg i.v. + 1 mg/kg s.c. ($n = 5$)	116 ± 11	101 ± 17	101 ± 16	38 ± 6	42 ± 5	36 ± 4	110 ± 16	91 ± 11	106 ± 11	7.41 ± 0.04	7.38 ± 0.02	7.41 ± 0.04	48 ± 1	46 ± 2
Hoe140 0.1 mg/kg i.v. + 0.05 mg/kg s.c. ($n = 5$)	101 ± 5	108 ± 7	97 ± 11	42 ± 3	42 ± 2	37 ± 1	116 ± 28	135 ± 11	123 ± 11	7.39 ± 0.03	7.38 ± 0.01	7.42 ± 0.02	48 ± 1	46 ± 1
Hoe140 0.01 mg/kg i.v. + 0.005 mg/kg s.c. ($n = 3$)	112 ± 23	109 ± 8	95 ± 7	43 ± 8	39 ± 4	36 ± 3	127 ± 23	142 ± 21	137 ± 3	7.40 ± 0.06	7.42 ± 0.01	7.42 ± 0.01	48 ± 1	46 ± 1
Hoe140 0.1 mg/kg i.v. at 4 h ($n = 5$)	116 ± 13	112 ± 5	102 ± 19	39 ± 6	36 ± 5	35 ± 1	121 ± 17	129 ± 20	124 ± 22	7.43 ± 0.06	7.42 ± 0.03	7.41 ± 0.03	48 ± 1	46 ± 1
Hoe140 4 nmol i.c. ($n = 3$)	98 ± 11	100 ± 6	94 ± 13	40 ± 4	37 ± 5	38 ± 6	92 ± 16	120 ± 32	106 ± 19	7.42 ± 0.05	7.42 ± 0.02	7.41 ± 0.05	48 ± 1	45 ± 1
PBS-injected ($n = 5$)	100 ± 10	95 ± 13	99 ± 8	36 ± 4	35 ± 5	37 ± 3	129 ± 35	120 ± 17	143 ± 35	7.42 ± 0.03	7.43 ± 0.05	7.40 ± 0.05	48 ± 1	46 ± 1

HKP, heat-killed pneumococci; i.v., intravenous; s.c., subcutaneous; i.c., intracisternal. Data are expressed as means ± S.D.V.

Table 2
Effect of the bradykinin B_2 receptor antagonist Hoe140 in experimental meningitis

Group	Regional cerebral blood flow (%)		Intracranial pressure (mm Hg)			Brain water content (%)	CSF white blood cells (cells/μl)
	3 h	6 h	Baseline	3 h	6 h	6 h	6 h
HKP-injected							
Untreated ($n = 5$)	147.2 ± 22.0 [a]	185.4 ± 27.4 [a]	2.7 ± 0.5	8.4 ± 3.6 [a]	21.4 ± 6.0 [a]	79.16 ± 0.23 [a]	4621 ± 1894 [a]
Hoe140 2 mg/kg i.v. + 1 mg/kg s.c. ($n = 5$)	145.0 ± 34.6	160.4 ± 28.0	3.8 ± 1.3	10.0 ± 4.0	19.3 ± 5.7	79.04 ± 5.7	9380 ± 7324
Hoe140 0.1 mg/kg i.v. + 0.05 mg/kg s.c. ($n = 5$)	147.0 ± 26.4 [a]	128.6 ± 23.1 [b]	4.2 ± 1.7	3.7 ± 2.8 [b]	7.5 ± 2.2 [a,b]	78.53 ± 0.28 [b]	2690 ± 1898 [a]
Hoe140 0.01 mg/kg i.v. + 0.005 mg/kg s.c. ($n = 3$)	152.4 ± 15.8	196.5 ± 14.32	4.5 ± 1.5	5.5 ± 1.8	16.0 ± 2.5	79.09 ± 0.06	7699 ± 948
Hoe140 0.01 mg/kg i.v. at 4 h ($n = 5$)	135.6 ± 6.4	181.9 ± 38.6	2.6 ± 1.1	6.5 ± 1.3	8.4 ± 2.0 [b]	78.86 ± 0.41	6615 ± 1080
Hoe140 4 nmol i.c. ($n = 3$)	151.6 ± 41.8	187.8 ± 31.6	2.6 ± 0.6	6.1 ± 1.8	16.2 ± 2.9	79.28 ± 0.23	6951 ± 2529
PBS-injected ($n = 5$)	103.9 ± 7.8	111.6 ± 15.5	3.4 ± 1.2	3.3 ± 0.7	2.8 ± 1.4	78.02 ± 0.23	49 ± 26

[a] $P < 0.05$ compared to PBS-injected rats (controls); [b] $P < 0.05$ compared to HKP-injected untreated rats.
HKP, heat-killed pneumococci; CSF, cerebrospinal fluid; i.v., intravenous; s.c., subcutaneous; i.c., intracisternal.
Data are expressed as means ± S.D.V. P values were corrected for repeated measurements using the Bonferroni Holm procedure.
Statistical analysis (one-way analysis of variance) was done to compare the following groups:
(1) HKP-injected untreated rats; HKP-injected rats treated with Hoe140 0.1 mg/kg i.v. + 0.05 mg/kg s.c.; and PBS-injected rats (controls).
(2) HKP-injected untreated rats; HKP-injected rats treated with Hoe140 2 mg/kg i.v. + 1 mg/kg s.c.; and HKP-injected rats treated with Hoe140 0.1 mg/kg i.v. + 0.05 mg/kg s.c.
(3) HKP-injected untreated rats; HKP-injected rats treated with Hoe140 0.1 mg/kg i.v. + 0.05 mg/kg s.c. at 4 h; and PBS-injected rats (controls).

857990 U/ml ± 891308 U/ml; 636140 U/ml ± 819701 U/ml, and 1194760 U/ml ± 912915 U/ml, respectively, in rats injected with heat-killed pneumococci; rats injected with heat-killed pneumococci and treated with Hoe140 0.1 mg/kg (followed by 0.05 mg/kg); and rats injected with heat-killed pneumococci and treated with Hoe140 2 mg/kg (followed by 1 mg/kg), respectively.

CSF nitrite concentrations in the CSF were lower in rats injected with heat-killed pneumococci and treated with Hoe140 0.1 mg/kg followed by 0.05 mg/kg (0.3 ± 0.5 μM) as compared to the corresponding data of untreated rats injected with heat-killed pneumococci (1.3 ± 1.2 μM; N.S.). The highest CSF nitrite concentrations were found in rats injected with heat-killed pneumococci and treated with Hoe140 2 mg/kg followed by 1 mg/kg (7.3 ± 6.8 μM; $P < 0.05$, compared to untreated rats injected with heat-killed pneumococci). The latter finding might be explained by a partial agonistic effect of Hoe140 in higher dosages.

4. Discussion

The major finding of this study was that the bradykinin B_2 receptor antagonist Hoe140 given systemically in a dosage of 0.1 mg/kg i.v. at baseline and 0.05 mg/kg s.c. at 2 h after i.c. pneumococcal challenge significantly attenuated the increase of brain water content, regional cerebral blood flow and intracranial pressure. The failure of Hoe140 to completely inhibit pathophysiological changes in our study might be explained by the fact that (a) mediators other than bradykinin are involved, (b) bradykinin receptor subtypes other than B_2, e.g. B_1, which are not influenced by Hoe140, may play a role. While the dosage of 0.1 mg/kg (followed by 0.05 mg/kg) of Hoe140 was effective, the higher and lower dosage of Hoe140 given systemically were ineffective. Likewise, in another study the effect of three different dosages of Hoe140 on brain edema formation after experimental cerebral ischemia in spontaneously hypertensive rats was investigated (K. Wirth, personal communication). The ranges of the dosages used in the latter study (0.01, 0.1 and 1 mg/kg) were comparable to that used in our study. Only the middle dosage of Hoe140 (0.1 mg/kg) significantly reduced brain edema formation. The observation that the highest dosage used in our study was not able to inhibit pathophysiological changes but even augmented CSF pleocytosis might be explained by a partially agonistic effect of Hoe140 when used in higher dosages as previously reported by Wirth et al. (1991) and Lembeck et al. (1991).

Another important finding of this study was that i.c. administration of Hoe140 (in three different dosages) was not able to significantly modulate pathophysiological parameters measured in early pneumococcal meningitis. The i.c. administration of Hoe140 in dosages of 40 nmol and 400 nmol produced side effects, namely blood pressure disturbances, whereas the dosage of 4 nmol Hoe140 given i.c. did not modulate blood pressure. This finding is in accordance with a previous study (Lopes et al., 1993) in which several bradykinin antagonists produced an increase in mean arterial blood pressure when administered intrathecally in higher dosages. Blood pressure increases

following i.c. administration of Hoe140 as seen in our study may be attributable to a direct action on B_2 receptors (agonistic effect). Recently, agonistic properties of Hoe140 have been reported (Feletou et al., 1994). When isolated blood vessels (sheep femoral artery without endothelium) were studied Hoe140 had a dramatic contractile effect exhibiting the same efficacy and very similar potency as bradykinin (Feletou et al., 1994).

The pathophysiological mechanisms of bacterial meningitis seem to be very complex in nature. Animal studies provide increasing evidence that nitric oxide (Brian et al., 1995; Boje, 1995; Koedel et al., 1995; Buster et al., 1995), reactive oxygen species (Pfister et al., 1990; McKnight et al., 1992; Berkowitz and Traystman, 1993), and cyclooxygenase metabolites (Pfister et al., 1990; Tureen et al., 1987) are involved in the pathophysiology of bacterial meningitis. Several reports indicate that bradykinin may interact with these mediators (Bhoola et al., 1992; Walker et al., 1995). Bradykinin stimulates the production of free radicals and lipid peroxidation (Kontos et al., 1984; Walker et al., 1995). In addition, bradykinin stimulates nitric oxide synthase and phospholipase A_2 in vascular endothelial cells to produce nitric oxide and prostaglandins (Bhoola et al., 1992; Walker et al., 1995). One possible explanation for the effect of Hoe140 given systemically in our study is that Hoe140 blocks bradykinin B_2 receptors on endothelial cells which in turn prevents nitric oxide release. Nevertheless, the source of endogeneous kinins as well as the definite site of action of Hoe140 during early bacterial meningitis are not known.

In conclusion, our data indicate that bradykinin is involved as a mediator in the early phase of pneumococcal meningitis in the rat and contributes to the increase in regional cerebral blood flow, intracranial pressure, and brain water content. The bradykinin B_2 receptor antagonist Hoe140 was effective when given systemically in a dosage of 0.1 mg/kg i.v. plus 0.05 mg/kg s.c. followed 2 h thereafter, whereas the higher and lower dosages used in this study were ineffective.

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