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Cytokine enhancement of endothelin ET_B receptor-mediated contraction in human temporal artery

Linda R. White [a,*], Roar Juul [b], Karl O. Skaanes [b], Jan Aasly [a]

[a] *Department of Neurology, Trondheim University Hospital, N-7006 Trondheim, Norway*
[b] *Department of Neurosurgery, Trondheim University Hospital, N-7006 Trondheim, Norway*

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Abstract

Segments of human temporal artery were incubated in organ culture for 2 days in the absence or presence of cytokines. Thereafter, contractions were induced by the selective endothelin ET_B receptor agonist sarafotoxin S6c, a peptide that does not induce contraction in fresh human temporal artery. Interleukin-1β was most potent in increasing the sarafotoxin-induced contraction in cultured segments. Tumour necrosis factor (TNF)-α increased the magnitude of contraction to a similar degree, but at a higher dose. A significant increase was also induced by interferon-γ, but not by interleukin-6 at the concentrations used. The results suggest that endothelin ET_B receptor-mediated contraction can be enhanced by pro-inflammatory cytokines in a concentration-dependent manner, and this may have relevance for pathophysiological conditions where inflammation and vasoactivity are important.

Keywords: Cytokine; Endothelin ET_B receptor; Interleukin-1β; Interleukin-6; Interferon-γ; TNF-α (tumour necrosis factor-α); Sarafotoxin S6c; Vasoactivity

1. Introduction

Cytokines are recognised as potential mediators of brain damage following ischaemia (Kim, 1996) and both endothelin and cytokines are among the array of factors involved in local and systemic inflammation (Sharma et al., 2000). A number of reports suggest that an increase in endothelin-1 can lead to increased production of cytokines and vice-versa. Interleukin-1β enhances production of endothelin-1 in endothelial cell cultures (Yoshizumi et al., 1990), and a similar effect is induced in vascular smooth muscle cells by a combination of tumour necrosis factor (TNF)-α and interferon-γ (Woods et al., 1999). Endothelin-1 enhances transcription of TNF-α in macrophages (Ruetten and Thiemermann, 1997), and both are released in rats treated with endotoxin (Hohlfeld et al., 1995). Patients with sepsis have marked increases in pro-inflammatory factors (Van Deuren et al., 1995), and raised levels of endothelin-1 compared to controls have been found (Pittet et al., 1991).

In animal models, an interleukin-1 receptor antagonist (Garcia et al., 1995) or endothelin receptor antagonists (Patel et al., 1996a,b) ameliorate the effect of focal ischaemic damage after middle cerebral artery occlusion. Similarly, antagonists to factors involved in inflammatory responses attenuate the vasospasm of experimental subarachnoid haemorrhage (Bavbek et al., 1998). Most studies using animal models of experimental subarachnoid haemorrhage to test the effects of various endothelin receptor antagonists support the association of elevated endothelin and vasospasm (for reviews see Wanebo et al., 1998; Zimmermann and Seifert, 1998; Zuccarello et al., 1998). However, some studies in the monkey are not in agreement (Hino et al., 1996; Pluta et al., 1997) and there is clearly a need for human data.

Contraction of human pial vessels has been shown to be mediated by endothelin ET_A receptors (Pierre and Davenport, 1995, 1998) and no endothelin ET_B receptor-mediated contraction or dilatation can usually be detected. However, it appears that these vessels possess endothelin ET_B receptor-mediated contractile ability that is not readily observed in the experimental models employed (Touzani et al., 1997). While both endothelin ET_A and ET_B receptors have been implicated in the vasospasm that follows experi-

* Corresponding author. Tel.: +47-73-86-84-12; fax: +47-73-86-75-81.
E-mail address: linda.white@medisin.ntnu.no (L.R. White).

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mental subarachnoid haemorrhage (Zuccarello et al., 1994), there is evidence for a shift towards increased expression of mRNA for endothelin ET_B receptors (Roux et al., 1995; Hino et al., 1996). More recent work shows that experimental subarachnoid haemorrhage can be partially relieved with the aid of an endothelin ET_B receptor antagonist (Zuccarello et al., 1998).

It is now established that incubation of isolated segments of animal and human arteries induces contractile endothelin ET_B receptor-mediated activity that cannot be demonstrated in fresh arteries (Adner et al., 1996, 1998; Möller et al., 1997; White et al., 1998). Moreover, incubation of rat arteries together with the pro-inflammatory cytokines interleukin-1β or TNF-α augments this endothelin ET_B receptor-mediated contractile activity (Leseth et al., 1999; Uddman et al., 1999). In cultured isolated segments of human temporal artery, interleukin-1β potentiates endothelin ET_B receptor-mediated contraction, a reaction antagonised by interleukin-1 receptor antagonist. The reaction appears not to involve further transcription of endothelin ET_B receptor mRNA, but improved translation of existing mRNA (White et al., 1999). In the present work, the activities of interleukin-1β, interleukin-6, TNF-α, and interferon-γ have been compared in this model.

2. Materials and methods

2.1. Organ culture and vasomotor responses in vitro

Branches of human superficial temporal artery were obtained during excisions of brain tumours under conditions approved by the University Hospital Ethics Committee. After removal, arteries were immediately placed in ice-cold buffer (composition given below). Segments approximately 1.5 mm long were either tested at once, or placed in serum-free Dulbecco's minimal essential medium (Gibco BRL Life Technologies, Roskilde, Denmark) supplemented with 6 mM glucose, 2.5 mM glutamine, 40 mg l^{-1} gentamycin (Gibco), and 1 mg ml^{-1} human serum albumin, in 24 well plates (Nunc Products, Denmark) containing 1 ml medium per well. Where appropriate, cytokines were added at concentrations of 2, 10, or 50 ng ml^{-1}. No more than one segment was incubated per well. Incubation was carried out at 37°C and pH 7.4 for up to 4 days.

For experiments, segments were mounted on two L-shaped tungsten prongs, diameter 0.1 mm, in small reaction baths with 5 ml buffer solution containing (in mM): NaCl 119, KCl 4.6, $CaCl_2$ 1.5, $MgCl_2$ 1.2, $NaHCO_3$ 12, NaH_2PO_4 1.2, glucose 5.5. The baths were kept at a temperature of 37°C and continuously bubbled with a mixture of 95% O_2 and 5% CO_2 to maintain physiological pH (Högestätt et al., 1983). The holders were connected to Grass FT03C force-displacement transducers, linked to a MacLab analog-digital convertor (AD Instruments, London, UK), through a preamplifier (Transbridge TBM4, World Precision Instruments, New Haven, CT, USA). The digitalized tension was continuously monitored and stored in an Apple Macintosh computer. Artery segments were equilibrated for 1 h (passive tension 5–6 mN) during which time, the buffer was changed every 10 min to achieve a stable tension.

Table 1
Comparison of maximal contractions induced by 60 mM KCl, 10 μM prostaglandin $F_{2\alpha}$ and 0.1 μM endothelin-1, in fresh and cultured human temporal artery

Agonist	Day 0 ($n=9$)	Day 2 ($n=12$)	Day 4 ($n=10$)
KCl	15.3±5.6	–	15.2±4.5
Prostaglandin $F_{2\alpha}$	18.8±5.4	18.2±5.9	16.6±4.3
Endothelin-1	18.6±5.6	18.8±5.1	19.3±5.3

Values represent the mean±S.D. and are given in mN.
There is no significant difference for each agonist between fresh arteries (day 0) and up to 4 days in culture.

Preliminary experiments to examine the contractile capacity of the segments were carried out using 60 mM KCl (by exchanging 60 mM NaCl in the buffer solution for KCl), 10 μM prostaglandin $F_{2\alpha}$, and 0.1 μM endothelin-1. Comparisons were made between fresh arteries and segments cultured for up to 4 days (Table 1). Culture did not appear to significantly alter these reactions. Subsequently, all experiments were carried out on segments after 2 days of organ culture and started with pre-contraction of arteries by 10 μM prostaglandin $F_{2\alpha}$. After a washout period to remove this pre-contraction, the selective endothelin ET_B receptor agonist sarafotoxin S6c (Williams et al., 1991) was added in logarithmically increasing concentrations. At the end of this reaction, 0.1 μM endothelin-1 was added. Maximal contraction with sarafotoxin S6c (E_{max}) was calculated as a percentage of the endothelin-1 induced contraction, and contraction at the level of EC_{50} (the concentration inducing 50% response) was expressed as pEC_{50} (the negative logarithm of the concentration of agonist eliciting half-maximal response). All reagents were added in 50-μl aliquots. The number of experiments (n) denotes results obtained with artery preparations with n patients. No experiment was carried out more than once on the artery preparation from any patient.

2.2. Drugs

Sarafotoxin S6c and endothelin-1 were purchased from Novabiochem, Läufelfingen, Switzerland. Recombinant human interleukin-1β, interleukin-6 and TNF-α were from R&D Systems Europe, Abingdon, England. Human synthetic interferon-γ-1b, 0.2 mg ml^{-1}, was a gift from Boehringer Ingelheim International, Ingelheim, Germany. Human serum albumin was from Sigma, St. Louis, MO, USA. All other chemicals used were of analytical grade.

Table 2
Contractions induced by 0.1 μM endothelin-1 or 0.1 μM sarafotoxin S6c compared to those induced by 10 μM prostaglandin $F_{2\alpha}$, in fresh artery segments (day 0) and segments incubated for 2 days in organ culture

Agonist	Day	% prostaglandin $F_{2\alpha}$	*n*
Endothelin-1	0	100.7 ± 5.0	6
	2	100.0 ± 2.8	11
Sarafotoxin S6c	0	0.1 ± 0.1	6
	2	28.9 ± 5.6	11

Results are given as the mean ± S.E.M.

2.3. Statistics

Unless otherwise stated, results are expressed as the mean ± S.E.M. Statistical analysis was carried out using analysis of variance (ANOVA) with Student–Newman–Keul's test for multiple comparisons. Values of $P < 0.05$ were considered significant.

3. Results

As shown in Table 2, 0.1 μM endothelin-1 induced strong contractions in both fresh and cultured artery segments that were similar in magnitude to those induced by 10 μM prostaglandin $F_{2\alpha}$. Sarafotoxin S6c induced no contraction in fresh segments but a marked contraction following organ culture (Table 2). None of the cytokines added to the culture medium significantly affected either prostaglandin $F_{2\alpha}$ pre-contractions or contractions induced by 0.1 μM endothelin-1 in any test group (data not shown).

Concentration–response curves for contractions induced by sarafotoxin S6c in the absence or presence of cytokines are shown in Fig. 1a–d. Values of E_{max} and pEC_{50} are presented in Table 3. Increases in maximum contraction were induced by 2 and 10 ng ml^{-1} interleukin-1β, by 50 ng ml^{-1} TNF-α, and by 10 and 50 ng ml^{-1} interferon-γ (Table 2). Interleukin-1β (2 ng ml^{-1}) significantly increased sarafotoxin-mediated contraction at concentrations

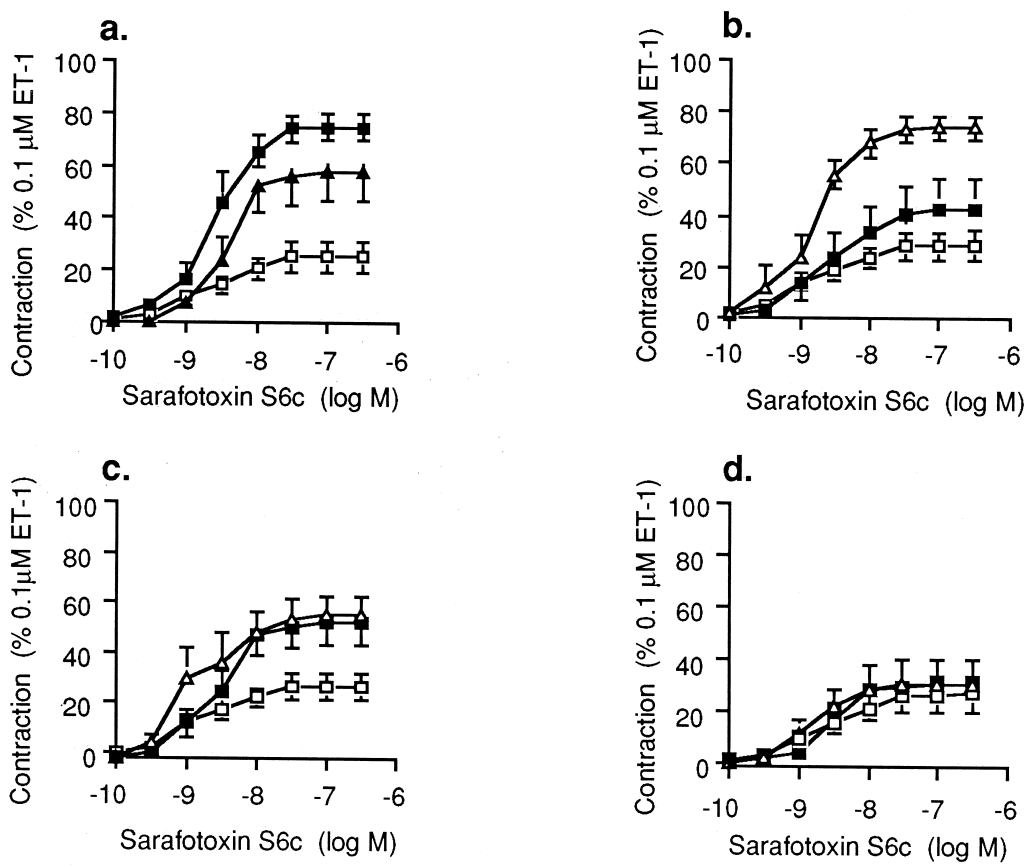

Fig. 1. Concentration–response curves for contractions induced by sarafotoxin S6c in human temporal artery after 2 days in organ culture: (a) □ control segments ($n = 9$) and segments incubated with ▲ 2 ng ml^{-1} ($n = 6$) or ■ 10 ng ml^{-1} ($n = 7$) interleukin-1β; (b) □ control segments ($n = 11$) and segments incubated with ■ 10 ng ml^{-1} ($n = 6$) or △ 50 ng ml^{-1} ($n = 6$) TNF-α; (c) □ control segments ($n = 12$) and segments incubated with ■ 10 ng ml^{-1} ($n = 7$) or △ 50 ng ml^{-1} ($n = 6$) interferon-γ; (d) □ control segments ($n = 9$) and segments incubated with ■ 10 ng ml^{-1} ($n = 6$) or △ 50 ng ml^{-1} ($n = 6$) interleukin-6. Contraction induced by sarafotoxin S6c was calculated as a percentage of the contraction induced by 0.1 μM endothelin-1 in each segment. Points represent the mean ± S.E.M. Some bars have been removed for clarity.

Table 3
Maximal contraction (E_{max}) induced by sarafotoxin S6c, and sensitivity expressed as pEC_{50} (negative logarithm of peptide concentration inducing half-maximal response) in segments of human temporal artery incubated in organ culture for 2 days in the absence or presence of cytokines (mean ± S.E.M.)

Cytokine	Concentration (ng ml^{-1})	E_{max} (% 0.1 μM endothelin-1)	pEC_{50}	n
Interleukin-1β	0	25.5 ± 6.0	8.70 ± 0.15	9
	2	58.1 ± 11.0[a]	8.43 ± 0.08	6
	10	74.7 ± 4.8[a]	8.70 ± 0.11	7
TNF-α	0	28.7 ± 5.5	8.93 ± 0.13	11
	10	42.5 ± 12.4	8.64 ± 0.18	6
	50	74.1 ± 4.6[a]	8.77 ± 0.24	6
Interferon-γ	0	28.9 ± 5.0	8.85 ± 0.14	12
	10	53.8 ± 9.0[a]	8.60 ± 0.13	7
	50	57.1 ± 6.9[a]	8.74 ± 0.20	6
Interleukin-6	0	27.9 ± 6.8	8.72 ± 0.17	9
	10	31.4 ± 10.1	8.59 ± 0.10	6
	50	32.1 ± 8.9	8.85 ± 0.11	6

[a] Significantly different from corresponding control group, $P < 0.05$ (ANOVA + Student–Newman–Keul). None of the cytokines significantly affected sensitivity to sarafotoxin S6c. There were no significant differences between the control groups.

of 10 nM and above, while the 10 ng ml^{-1} dose significantly increased contractions from a concentration of 3 nM (Fig. 1a) in comparison to the control. TNF-α (50 ng ml^{-1}) also significantly increased sarafotoxin-mediated contraction at concentrations of 3 nM and above, but 10 ng ml^{-1} TNF-α did not alter the contraction relative to the control (Fig. 1b). Interferon-γ (10 and 50 ng ml^{-1}) significantly increased the magnitude of contractions induced by sarafotoxin S6c at concentrations of 10 nM and above (Fig. 1c). Conversely, no changes were induced by interleukin-6 at either concentration used (Fig. 1d). There were no significant changes in the sensitivity to sarafotoxin S6c in any of the test groups (Table 3).

4. Discussion

The lack of contraction with sarafotoxin S6c in fresh arteries and induction of contraction after organ culture is consistent with previous results in human temporal artery (White et al., 1998). This reaction is unaffected by the selective endothelin ET_A receptor antagonist FR 139317 {(*R*)2-[(*R*)-2-[(*S*)-2-[[1-(hexahydro-1*H*-azepinyl)]carbonyl]amino-4-methyl-pentanoyl]amino-3-[3-(1-methyl-1*H*-indoyl)]propionyl]amino-3-[2-pyridyl)propionic acid}, but is abolished by the selective endothelin ET_B receptor antagonist BQ 788 (*N-cis*-2,6-dimethylpiperidinocarbonyl-β-tBu-Ala-D-Trp[1-methoxycarbonyl]-D-Nle-OH) and thereby shown to be mediated by endothelin ET_B receptors (White et al., 1998). A similar reaction occurs in other vascular beds (Adner et al., 1996, 1998; Möller et al., 1997). In human temporal artery, the augmentation of the reaction by interleukin-1β has been reported (White et al., 1999), but no comparison was made with other pro-inflammatory cytokines.

In the current study, the results clearly show that other cytokines besides interleukin-1β will enhance the endothelin ET_B receptor-mediated contraction that develops after organ culture of human temporal artery. There seems to be variation in the ability of cytokines to effect this increase and interleukin-1β was the most potent of those tested here. TNF-α enhanced the sarafotoxin-induced reaction at the higher, but not lower dose used, suggesting that the reaction is concentration-dependent. Interferon-γ enhanced the reaction at both concentrations tested, but increasing the concentration did not increase the level of reaction further. Conversely, interleukin-6 did not trigger any increase at all, so there is variation in cytokine reactivity and the influence on the sarafotoxin S6c-induced contraction is not a general response to any cytokine. Interleukin-1β and TNF-α are cytokines implicated in a wide array of pro-inflammatory reactions and disease states (Sharma et al., 2000). Interferon-γ is usually pro-inflammatory (Heremans et al., 1989), whereas interleukin-6 is a cytokine exerting both pro- and anti-inflammatory effects (Kim, 1996). Indeed, experimental studies suggest that interleukin-6 may have a neuroprotective role in ischaemia (Loddick et al., 1998). In the present study, interleukin-6 had no effect on the sarafotoxin S6c-induced reaction, whereas interferon-γ increased the reaction significantly. Since the mechanisms leading to the upregulation and enhancement of endothelin ET_B receptor-mediated contractile activity remain unknown, the reactions that may be triggered by particular cytokines remain unclear.

Previous results have suggested that interleukin-1β potentiates the sarafotoxin S6c-induced contraction (White et al., 1999). This was not found to be the case in the present study where only a marked augmentation was evident. Although it is still not clear why the endothelin ET_B receptor-mediated contraction should develop during organ culture, it seems likely that endogenous factors released from the artery segments (such as pro-inflammatory cytokines) could play a role, and subtle differences in culture conditions may be sufficient to change this basic reaction.

No endothelin ET_B receptor-mediated contractile activity is demonstrable in fresh human temporal artery in this assay, but evidence from endothelium-intact and denuded arteries suggests that endothelin ET_B receptor mRNA is nevertheless present in the smooth muscle (Lucas et al., 1996). It is interesting in this respect to consider the surprising results found in cerebral vessels by Touzani et al. (1997). As in human temporal artery, there is little evidence of endothelin ET_B receptor activity in pial arterioles under normal circumstances (Pierre and Davenport, 1995, 1998). However, both endothelial dilatatory and smooth muscle contractile endothelin ET_B receptors must be present as repeated application of the selective endothelin ET_B receptor agonist BQ 3020 (*N*-Ac,Ala^{11,15}-endothelin-1, 6-21) in vivo induced dilatation on the first

application, no reaction on the second application (tachyphylaxis only of endothelin ET_B receptor-mediated dilatation), and then a significant constriction on subsequent applications. Since both the BQ 3020-induced dilatation and constriction were antagonised by BQ 788, the authors concluded that their treatment of the vessels unmasked endothelin ET_B receptor-mediated contractile potential. It may well be that mechanisms exist in vivo to enable the rapid expression of endothelin ET_B receptors on smooth muscle when necessary.

Previous results with human temporal artery have indicated that interleukin-1β does not lead to increased transcription of endothelin ET_B receptor mRNA, but appears to enable increased translation of existing mRNA (White et al., 1999). This ability may be a general phenomenon for inflammatory states where pro-inflammatory cytokines are increased. Although many factors contribute to the pathological consequences of diseases like stroke, experimental models of ischaemia and subarachnoid haemorrhage suggest that these include both cytokines (Garcia et al., 1995; Bavbek et al., 1998) and endothelin ET_B receptor activity (Patel et al., 1996b; Zuccarello et al., 1998). Although it was previously held that increased release of endothelin-1 itself might lead to the vasospasm of subarachnoid haemorrhage, the results of Pluta et al. (1997) suggest that production of endothelin-1 is the result of cerebral ischaemia rather than the cause of vasospasm. It is also possible that the involvement of endothelin in such conditions may not depend so much on increased production of endothelin-1 as on the availability of endothelin receptors to agonists, and the role played by cytokines. Interleukin-1β and TNF-α act at different receptors, but exert biologically similar effects because both trigger intracellular cascades that ultimately activate the same set of transcription factors (Eder, 1997). Such reactions could in turn affect latent endothelin ET_B receptor-mediated contractile activity and thereby contribute to certain pathological situations.

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