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Effects of the 5-HT_1 receptor agonists, sumatriptan and CP 93,129, on dural arterial flow in the rat

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Abstract

The blood flow in and around the medial meningeal artery (dural arterial flow) was recorded in the exposed parietal dura mater encephali of the anesthetized rat using laser Doppler flowmetry. Local electrical stimulation of the dura mater (pulses of 0.5 ms delivered at 7.5–17.5 V and 5 or 10 Hz for 30 s) caused temporary increases in dural arterial flow. The effects of the 5-HT_1 receptor agonists sumatriptan and CP 93,129 on the basal flow and the electrically evoked increases in flow were examined. Topical administration of undiluted sumatriptan (12 mg/ml) lowered the basal and the evoked flow by 20% on average. Systemic (i.v.) administration of sumatriptan (0.24, 0.72 and 3.6 μmol/kg) caused a short-lasting reduction of the evoked flow increases only at the higher doses while the basal flow was not significantly altered. Systemic administration of CP 93,129 (0.46 and 4.6 μmol/kg) caused no significant changes of the basal and the evoked flow. At a dose of 23 μmol/kg CP 93,129 lowered the basal flow by 20% and the evoked flow by 30% for 20 min. The systemic arterial pressure was not significantly altered by sumatriptan and CP 93,129 within the whole range of doses. It is suggested that sumatriptan and CP 93,129 at high doses exert inhibitory effects on those fine afferent nerve fibers which release the calcitonin gene-related peptide, since this neuropeptide mediates the evoked increases in dural arterial flow. © 1997 Elsevier Science B.V.

Keywords: Dura mater encephali; (Rat); Arterial blood flow; Neurogenic inflammation; 5-HT_1 receptor agonist; Migraine; Headache

1. Introduction

Stimulation of the trigeminal ganglion in the rat causes increased blood flow (Escott et al., 1995), plasma extravasation (Markowitz et al., 1987), aggregation and adhesion of platelets and activation of mast cells (Dimitriadou et al., 1991, 1992) in parts of the facial skin, mucous membranes and the dura mater encephali. These responses, which represent elements of a neurogenic inflammation, are most likely mediated by neuropeptides, in particular substance P and calcitonin gene-related peptide (CGRP), released from fine afferent fibres. These neuropeptides have first been demonstrated in cerebral arteries and the dura mater encephali of different species including rodents by Edvinsson et al. (1983, 1987) who used using immunocytochemistry and radioimmunoassay. An extended network of CGRP and substance P immunoreactive nerve fibres has been found in the dura mater of the rat (Von Düring et al., 1990; Keller and Marfurt, 1991; Messlinger et al., 1993). Some of the neurogenic inflammatory responses in the dura mater of rodents have been shown to be inhibited by 5-HT_1 receptor agonists (Buzzi and Moskowitz, 1990; Matsubara et al., 1991; Buzzi et al., 1991b, 1992). In man, the neurogenic inflammation of the meninges has been suggested to be involved in nociceptive mechanisms that cause migraine pain and other severe headaches (Hardebo, 1990; Moskowitz, 1993). Accordingly, 5-HT analogs such as dihydroergotamine and the specific 5-HT_1 receptor agonist sumatriptan are effectively used in the therapy of migraine attacks and cluster headache (Friberg et al., 1991; Ferrari, 1993; Saxena and Tfelt-Hansen, 1993; Goadsby and Edvinsson, 1994b; Wilkinson et al., 1995).

Using laser Doppler flowmetry, we have recently shown that local electrical stimulation of the rat dura mater causes increases in blood flow in and around the medial meningeal artery (Kurosawa et al., 1995), an effect that seems to require the excitation of primary afferents, since it could be blocked by local anesthetics and tetrodotoxin (unpub-

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lished results). The increases in blood flow could be inhibited also by local application of the CGRP receptor antagonist, human CGRP-(8-37), suggesting that they are mediated by CGRP released from stimulated perivascular afferents. The same type of stimulation was able to modify the shape of CGRP immunoreactive nerve fibers and to deplete immunoreactivity in the rat dura mater after stimulation periods of more than 20 min (Messlinger et al., 1995a). This type of stimulation has also been shown to activate trigeminal brainstem neurons with afferent input from the dura mater (Messlinger et al., 1995b).

The present investigation was undertaken in view of the long debate about a possible vascular origin of migraine attacks (Drummond and Lance, 1983; Friberg et al., 1991; Saxena and Tfelt-Hansen, 1993; Humphrey and Goadsby, 1994; Ferrari and Saxena, 1995), which have been shown to be accompanied by increases in regional cerebral blood flow (Olesen et al., 1990; Goadsby and Edvinsson, 1993). We were interested in examining possible inhibitory effects of 5-HT_1 receptor agonists on the dural arterial flow in our model, paralleling the inhibitory effects of these substances on the plasma extravasation in the dura mater (Buzzi and Moskowitz, 1990; Buzzi et al., 1991b). For this study we used (i) sumatriptan as a clinically approved 5-HT_1 receptor agonist and (ii) CP 93,129, the latter being highly effective in inhibiting plasma extravasation in particular in the rat dura mater (Buzzi and Moskowitz, 1990; Matsubara et al., 1991; Moskowitz and Cutrer, 1994). Since it has been proposed that one subtype of the 5-HT_1 receptor is located on dural blood vessels mediating vasoconstriction and another subtype on trigeminal fibers inhibiting neuropeptide release (Humphrey et al., 1988; Rebeck et al., 1994; Moskowitz, 1994), we measured both the basal resting blood flow and the changes evoked by local electrical stimulation before and after administration of the 5-HT_1 receptor agonists. In summary, we found inhibitory effects on both these flow parameters. However, the doses of 5-HT_1 receptor agonists required for these effects were much higher than those described for the inhibition of plasma extravasation after trigeminal ganglion stimulation (Buzzi and Moskowitz, 1990; Matsubara et al., 1991).

2. Materials and methods

2.1. Anaesthesia and general preparation

Thirty-one male Wistar rats (210–360 g) were used. The experiments were performed in accordance with the regulations for animal care and treatment and supervised by a committee of the local government. The animals were anaesthetized by an initial dose of 140–150 mg/kg thiopental (Trapanal, Byk Gulden, Konstanz, Germany) i.p., followed by additional doses of 25–30 mg/kg thiopental i.p. when required. Depth of anaesthesia was routinely assessed and held at a level in which noxious stimuli failed to elicit nociceptive motor reflexes or changes of the systemic arterial pressure. A catheter was inserted into the right femoral vein for the infusion of solutions. Arterial blood pressure was continuously recorded with a pressure transducer via a catheter in the right femoral artery and maintained above 90 mmHg (mean) by i.v. infusion of 4% Ficoll 70 (Serva, Heidelberg, Germany) and 5% glucose solutions if required. The animal's body temperature was maintained at 37.0–37.5°C with a thermostatically regulated heating plate. Usually the animals were tracheotomized but respirated spontaneously. For comparison, in two experiments the animals were paralyzed with pancuronium bromide (Pancuronium Organon, Organon Teknika, Eppelheim, Germany) and artificially ventilated; the end-expiratory CO_2 was around 4%. These and other experiments not included in this study showed no difference between spontaneously breathing and ventilated animals regarding maintenance of blood pressure and dural blood flow.

2.2. Preparation for stimulation and recording

The preparation for stimulation of dural afferents and the recording of dural blood flow has previously been reported in detail (Kurosawa et al., 1995). Briefly, the animal's head was fixed in a stereotaxic frame and, using an electric drill, the skull was trepanized while being cooled with Tyrode solution (4°C). Two cranial windows, one of about 2×6 mm (for stimulation) and one of 4×7 mm (for recording), were drilled into the parietal bone to expose the dura mater (see Fig. 1 in Kurosawa et al., 1995). In the small opening parallel to the sagittal suture, a pair of stimulating electrodes (platin wires with a diameter of 0.2 mm and a length of about 4 mm, separation 1 mm, cathode placed laterally) was lowered on the dural surface and covered with paraffin oil. In the recording window, a needle type probe (tip diameter 0.8 mm) of a laser Doppler flowmeter was positioned over a branch of the medial meningeal artery (MMA) at a distance of 2–3 mm from the lateral stimulation electrode. The laser Doppler flow signal (flux) measured at these sites was usually more than 10-times higher than the flux when the probe was located between the dural arterial branches (pial background flow). In correspondence with this finding a thin piece of black plastic inserted between dura and pia mater in some control experiments did not significantly change the flow values (Kurosawa et al., 1995, and unpublished experiments). The recording window was covered with pieces of gauze soaked with Tyrode solution to prevent drying and to maintain a fluid medium between probe and dura.

2.3. Recording of blood flow and electrical stimulation

Blood flow was recorded by a laser Doppler system (Moor Instruments, MBF3D or DRT4; time constant 1.0 s). The output was displayed on-line with a chart recorder

(Rikadenki R-10) or with a computer using the DRT4 software (Moor Instruments). Systemic arterial blood pressure was recorded simultaneously with the flow. The dura was electrically stimulated with rectangular pulses of 0.5 ms length for periods of 30 s at intervals of 5 min, the lateral electrode being used as the cathode. This type of stimulation usually causes transient increases in blood flow, the magnitude of which depends on the strength and the frequency of stimuli, but are very reproducible in magnitude when constant stimulation parameters are used (Kurosawa et al., 1995). The stimuli are appropriate for exciting sensory and autonomic nerve fibers in the dura mater. Stimulation near the sagittal superior sinus is suggested to activate preferably the terminals of perivascular afferent nerve fibers, most of which accompany the dural arteries running in rough direction towards the sagittal line (Messlinger et al., 1993), thereby crossing the parallel stimulation electrodes. In few experiments the blood flow during stimulation decreased. This effect could be abolished by phentolamine suggesting a dominant activation of sympathetic fibers in these rare cases (Kurosawa et al., 1995).

To account for individual variations, stimulus strength and frequency were optimized at the beginning of each experiment to elicit substantial and stable (but not maximal) increases in local blood flow without changes of the blood pressure. The stimulation strengths ranged from 7.5 to 17.5 V; in most of the experiments it was 10 V. The pulse frequency was usually 10 Hz, in some experiments 5 Hz. Although there is no evidence that any of the effects of 5-HT_1 receptor agonists on the registered flow parameters are influenced by stimulation strength and frequency, care was taken to avoid systematic differences in the stimulus parameters between experimental groups. Each drug test was preceded by at least three control stimulation intervals. The vehicle or the test substance were i.v. injected or topically applied to the exposed dural surface only if the control stimulations elicited stable increases in flow. Administration was always two minutes prior to the next stimulation, and was followed by 4–5 further stimulation periods (see Figs. 1 and 4).

2.4. Drug administration

For topical administration, the cotton swab lying on the dura was replaced by another one soaked with Tyrode solution (pH 7.4; 285 mosm/l) or sumatriptan hydrogensuccinate (Imigran 16.8 mg/ml; Glaxo, Bad Oldesloe, Germany) containing sumatriptan at a concentration of 40.6 mM (12 mg/ml (305 mosm/l)). For systemic (i.v.) administration, sumatriptan hydrogensuccinate was diluted immediately before the experiment in sterile 0.9% saline to final doses of 0.1, 0.3 and 1.5 mg/kg body weight, i.e., 0.24, 0.72 and 3.6 μmol/kg. The 5-HT_{1B} receptor agonist CP 93,129 (3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one; a gift from Pfizer, Groton, CT, USA) was dissolved in saline with 5% dimethylsulfoxide (DMSO) as a stock solution of 0.1 M and kept frozen. Immediately before use it was diluted with saline for final doses of 0.46, 4.6 and 23 μmol/kg body weight. Vehicles were saline (for sumatriptan) and DMSO in saline (same concentration as in the highest dose of the CP 93,129 solution). All solutions had a final volume of 0.3 ml and were slowly injected into the femoral vein within 1 min.

2.5. Measuring and evaluation of data

Blood flow was determined by morphometry of the chart records as described previously (Kurosawa et al., 1995). Basal flow values were determined by measuring the area between the zero line (laser light switched off) and the midline of the curve of the basal (unstimulated) flow at intervals of 5 min, i.e., from the beginning of one stimulation to the next one (Fig. 1A); the interval in which the drug was given was excluded. Increases in blood flow were determined by measuring the area circumscribed by the curve of the evoked responses above basal (unstimulated) flow (Fig. 1A). All measurements of basal or evoked flow, respectively, were calculated relative to the mean of the two control measurements immediately before the test sequence. The results were grouped according to drugs and doses, and mean values ± S.E.M. were calculated for each time after drug administration (Figs. 2, 3 and 5); the number of experiments in these groups is shown in the figures. A comprehensive analysis of variance with extensions for repeated measures was performed within these groups and between different doses and vehicle. A modified *t*-test with Bonferroni correction was employed to compare measurements after drug administration with corresponding values after vehicle. Significance was assessed at the 5% level.

3. Results

3.1. Effects of local sumatriptan on basal and evoked blood flow

In 6 experiments, sumatriptan (12 mg/ml) was locally administered on the exposed dura mater in the recording opening. Within 2 min the basal blood flow and the stimulation-induced increases in flow (evoked flow) were reduced (Fig. 1B). On average, the basal flow was lowered by about 15% during the first minutes and tended to further decrease as long as the cotton with the sumatriptan was left on the dura (Fig. 2A). This effect was significant within the whole observation time of 30 min compared to the values after Tyrode solution, which did not lower basal and evoked flow (Fig. 1A, Fig. 2A). The evoked increases in flow were reduced to nearly 80% compared with the values before administration of sumatriptan, with a maximal effect observed after 7 min (Fig. 2B). This reduction was significant for 12 min after sumatriptan, compared to the control experiments with Tyrode solution (Fig. 2B).

The systemic arterial pressure was not changed after local administration of sumatriptan or Tyrode solution.

3.2. Effects of systemical sumatriptan on basal and stimulated blood flow

In 16 experiments sumatriptan was i.v. injected. Within the whole range of doses used (0.24–3.6 μmol/kg) sumatriptan did not significantly change the basal arterial flow ($n = 15$ experiments) compared with vehicle (saline), although there was a tendency towards a decrease after the higher doses (Fig. 3A). The electrically-evoked increases in flow ($n = 16$ experiments) were significantly reduced two minutes after the injection of sumatriptan only at the higher doses of 0.72 and 3.6 μmol/kg for some minutes (Fig. 3B). The mean systemic arterial pressure (90–100 mmHg) decreased after the i.v. administration of sumatriptan by 6–7% on average without any correlation with the dose applied.

3.3. Effects of systemical CP 93,129 on basal and evoked blood flow

Like sumatriptan, CP 93,129 was systemically administered at doses that have been shown to inhibit plasma extravasation in the rat dura mater (Matsubara et al., 1991; Huang et al., 1993). Doses of 0.46 and 4.6 μmol/kg of CP 93,129 ($n = 10$ experiments) had no significant effects on either the basal blood flow or the stimulation-evoked

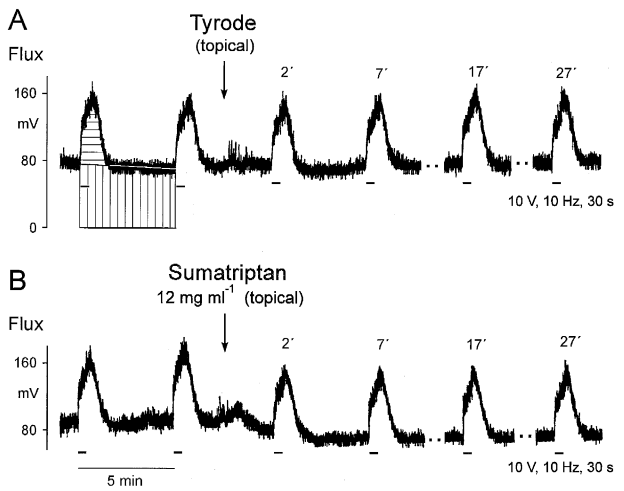

Fig. 1. Chart records of basal and stimulus-evoked dural arterial flow (flux = output of the flowmeter in mV). Increases in flow were evoked by electrical stimulation (pulses of 0.5 ms at 10 Hz for 30 s) indicated by bars below the records. (A) Basal flow values were determined as the areas between zero flux (0 mV, laser light switched off) and basal flux within stimulation–post-stimulation intervals of 5 min (vertically hatched area). Values of evoked flow were determined as the areas under the flux increases above basal flux (horizontally hatched area). Tyrode solution, topically administered at time 0, did not change basal and evoked flow. (B) Effects of topical administration of sumatriptan on the basal and evoked flow in a typical specimen.

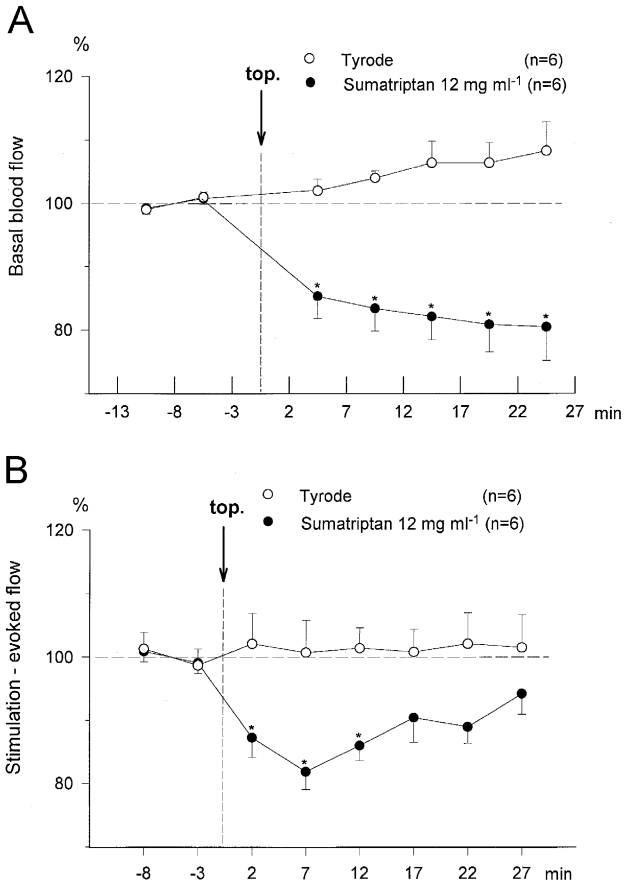

Fig. 2. Effects of topically administered Tyrode solution and sumatriptan on basal and evoked flow. The time-course of mean values (±S.E.M.) of n experiments (animals) plotted in (A) (basal flow) and (B) (evoked flow) shows significant differences between Tyrode solution and sumatriptan (* $P < 0.05$).

increases in blood flow (Fig. 5A, B). CP 93,129 at the high dose of 23 μmol/kg clearly lowered both flow parameters in all 5 experiments (Fig. 4B, Fig. 5A,B). On average, the basal flow was reduced to about 80% of the control values (before drug administration) throughout the observation period of 30 min, which was significantly different to the values after vehicle (Fig. 5A). The stimulation-evoked flow was reduced to about 70% of the control during 4 stimulation periods (2–17 min). Later the evoked increases in flow gradually recovered but were still different to the values after vehicle (Fig. 5B). The mean systemic arterial pressure (90–100 mmHg) decreased after CP 93,129 by 4–6% on average without any dose-dependency.

4. Discussion

4.1. Stimulation of trigeminal afferents causing elements of neurogenic inflammation

This study examined the effects of two 5-HT_1 receptor agonists, sumatriptan and CP 93,129, on the dural arterial

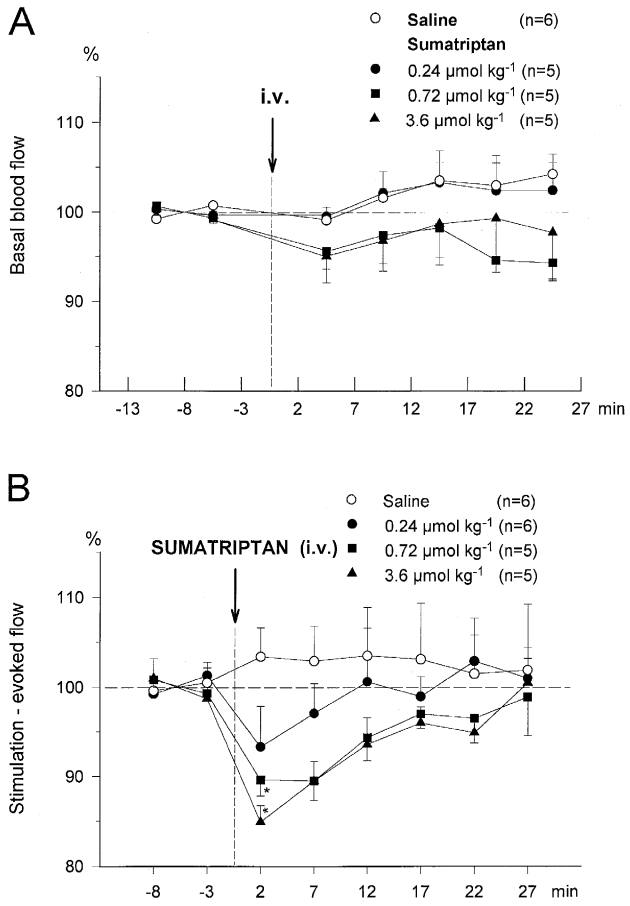

Fig. 3. Effects of systemically administered sumatriptan on basal (A) and evoked flow (B). The dose–response curves of mean values (±S.E.M.) of *n* experiments (animals) show differences between vehicle and drug (* $P < 0.05$) in the evoked flow curves only.

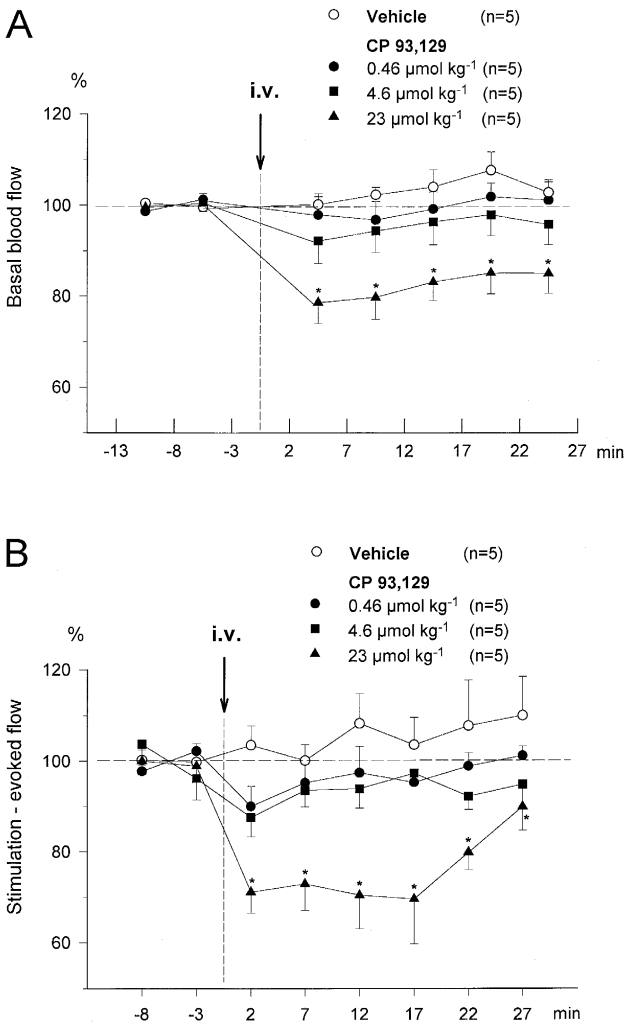

Fig. 5. Effects of systemically administered CP 93,129 on basal (A) and evoked flow (B). The dose–response curves of mean values (±S.E.M.) of *n* experiments (animals) show significant differences between vehicle and drug at the highest dose (* $P < 0.05$).

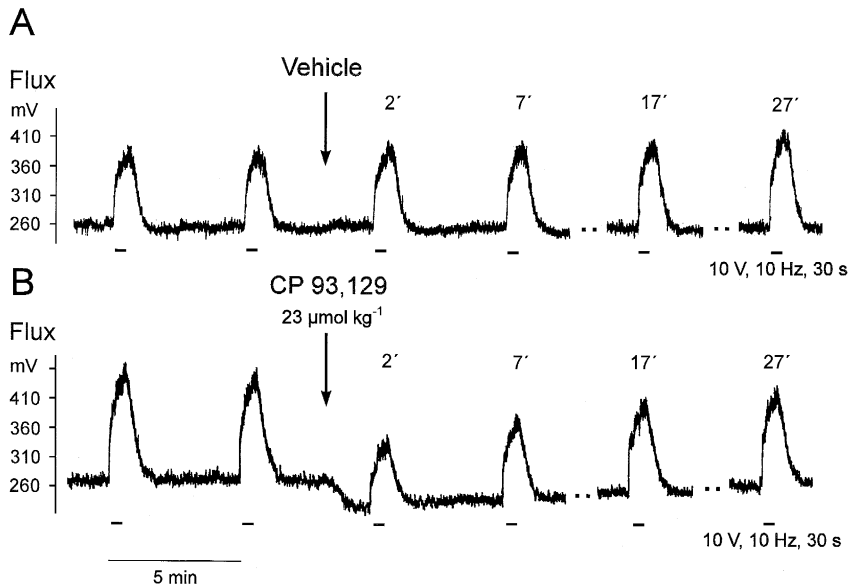

Fig. 4. Specimen records of basal and stimulated dural arterial flow. (A) No change occurred after i.v. administration of the vehicle. (B) Injection of CP 93,129 lowered basal and evoked flow.

blood flow and the increases in flow evoked by local electrical stimulation. The stimulation-evoked increases in flow are probably due to the excitation of primary afferent nerve fibers, because they can be blocked by local application of lidocaine and procaine, and by local administration of tetrodotoxin (unpublished results). They can also dose-dependently be reduced by the CGRP receptor antagonist human-CGRP-(8-37), which at a concentration of 10^{-5} M caused almost nearly total inhibition of these responses (Kurosawa et al., 1995), whereas they were not altered by the tachykinin NK_1 receptor antagonist RP 67580 (Carmody et al., 1996). Thus there is evidence that the stimulation-evoked increases in flow are mediated by CGRP but not by substance P. Neurogenic plasma extravasation in the dura mater, on the other hand, is probably mediated by substance P through the activation of NK_1 receptors (Markowitz et al., 1987; Moussaoui et al., 1993; O'Shaughnessy and Connor, 1993).

The 5-HT_1 receptor agonists sumatriptan and CP 93,129 have been shown to block plasma extravasation and other elements of neurogenic inflammation such as endothelial secretion and platelet aggregation in the dura mater of the rat and the guinea pig (Buzzi and Moskowitz, 1990; Matsubara et al., 1991; Buzzi et al., 1992). In the present experiments, we therefore initially used similar doses of sumatriptan (0.24 and 0.72 μmol/kg, i.e., 71 and 214 μg/kg) and CP 93,129 (4.6 μmol/kg) as those effectively reducing plasma extravasation (Buzzi and Moskowitz, 1990; Matsubara et al., 1991). These doses were not effective in inhibiting the evoked increases in dural arterial flow (see Fig. 3B; Fig. 5B), or the effect was very short-lasting (after sumatriptan at 0.72 μmol/kg). Only much higher doses of CP 93,129 (23 μmol/kg) reduced both the basal and the evoked flow by about 20 and 30%, respectively (see Fig. 5A,B). An inhibitory effect was also achieved with local application of sumatriptan at a very high concentration (12 mg/ml, i.e., 40.6 mM) which lowered the basal and evoked flow by maximally 20% (Fig. 2B, Fig. 3B). The threshold doses for inhibiting the evoked flow were at least 10 times higher than those necessary for inhibiting plasma extravasation (Buzzi and Moskowitz, 1990; Matsubara et al., 1991; Shepheard et al., 1995). This means that sumatriptan at clinical doses (80–100 μg/kg) can inhibit neurogenic plasma extravasation in the rat, but was not able to reduce the evoked blood flow in our experiments. One possible reason for this discrepancy may be that different experimental approaches (local orthodromic stimulation in our experiments vs. antidromic ganglion stimulation in the studies mentioned above) have been used. On the other hand, in a recent study Lambert and Michalicek (1996) stimulated the trigeminal ganglion in the cat to induce vasodilatation and increase of blood flow in the medial meningeal artery. Consistent with our results they found no reduction of this response after systemic administration of sumatriptan and dihydroergotamine at clinically conventional doses. Unlike these results, Goadsby and Edvinsson (1993) have reported on increases of the cerebral blood flow following trigeminal ganglion stimulation in the cat, which could be reduced by i.v. administration of sumatriptan and dihydroergotamine at clinical doses. Unfortunately, the authors did not describe the time course of blood flow changes nor did they mention at which time after sumatriptan the blood flow was measured.

Stimulation of trigeminal afferents may degranulate dural mast cells, which contain 5-HT, histamine and heparin (Edvinsson et al., 1977; Dimitriadou et al., 1991; Dimlich et al., 1991). The significance of this effect on the meningeal blood flow is not yet clear. However, we have found no systematic changes of the dural arterial flow after topical administration of 5-HT at concentrations up to 10^{-3} M (unpublished).

4.2. Effect of 5-HT_1 receptor agonists on the release of neuropeptides from primary afferent nerve fibers (prejunctional action)

According to the concept of neurogenic inflammation, neuropeptides are released from peptidergic afferent nerve fibers upon electrical or chemical stimulation and mediate their effects by binding to neuropeptide receptors on several target tissues such as vascular endothelium, smooth muscle and mast cells (Basbaum and Levine, 1991; Donnerer and Amann, 1993). There is plenty of evidence that these mechanisms take place in the meninges too (Markowitz et al., 1987; Goadsby et al., 1988; Buzzi and Moskowitz, 1990; Zagami et al., 1990; Dimitriadou et al., 1991, 1992; O'Shaughnessy and Connor, 1993; Goadsby and Edvinsson, 1993; Moskowitz and Cutrer, 1994). Using immunocytochemistry, we have recently found signs of secretion of CGRP from dural nerve fibers upon electrical stimulation with the same parameters as used in the present study and a depletion of CGRP immunoreactivity after continuous stimulation for longer than 20 min (Messlinger et al., 1995a). Similar observations have been described by Knyihar-Csillik et al. (1995) after trigeminal ganglion stimulation. An increased level of CGRP has been found in the venous compartment after electrical stimulation of the trigeminal ganglion and the superior sagittal sinus in rats and cats (Zagami et al., 1990; Buzzi et al., 1991a; Goadsby and Edvinsson, 1993, 1994a). This CGRP increase (which was paralleled by an increase in cerebral blood flow) could be reduced by 5-HT_1 receptor agonists such as sumatriptan, dihydroergotamine and 311C90 (Buzzi et al., 1991a; Goadsby and Edvinsson, 1993, 1994a). The inhibition of plasma extravasation in the rat dura mater by 5-HT_1 receptor agonists could be reversed by substance P and neurokinin A (Saito et al., 1988; Buzzi and Moskowitz, 1990). Taken together, it is very likely that there are prejunctional inhibitory actions of 5-HT_1 agonists on elements of the neurogenic inflammation in the dura mater, probably by inhibiting the neu-

ropeptide release.

In regard to the different threshold doses required to inhibit plasma extravasation and stimulus-evoked blood flow increases, it may be significant that substance P and CGRP immunoreactivities have been found to be colocalized in 17% of trigeminal afferents projecting to intracranial vessels, while another 21% of these afferents were CGRP-, but not substance P-immunoreactive (O'Connor and Van der Kooy, 1988). Using high pressure liquid chromatography, Jansen et al. (1992) have assessed much higher concentrations of CGRP than substance P in extracts of human middle meningeal arteries. Since neurogenic plasma extravasation is inhibited by much lower doses of 5-HT_1 receptor agonists than neurogenic blood flow increase, it may be speculated that these drugs are more effective in inhibiting neuropeptide release from substance P/CGRP containing afferents than from nerve fibers which contain only CGRP.

4.3. Vasoconstrictor effects of 5-HT_1 receptor agonists (postjunctional action)

5-HT_1 receptors in the dura mater of the guinea pig and man have been suggested to be located both on nerve fibers and blood vessels, controlling neuropeptide release and vasotonus (Moskowitz and Cutrer, 1994; Rebeck et al., 1994). The 5-$HT_{1D\alpha}$ subtype (human 5-HT_{1D} receptor according the new classification of 5-HT_1 receptors; Hartig et al., 1996) is thought to mediate inhibition of plasma extravasation, the 5-$HT_{1D\beta}$ subtype (human 5-HT_{1B} receptor) vasoconstriction. Intracranial arterial vessels are constricted by 5-HT_1 receptor agonists such as sumatriptan in vitro and in vivo (Friberg et al., 1991; Connor et al., 1992; Jansen et al., 1993; Saxena and Tfelt-Hansen, 1993) although the effect on the middle meningeal artery in cats has been reported to be small and evanescent (Lambert and Michalicek, 1996). In the present study only high doses of CP 93,129 were able to reduce the basal flow, while i.v. sumatriptan was not effective at all. Using the microsphere technique, Den Boer et al. (1992) have found no significant effect of sumatriptan and ergot alkaloids on arteriovenous anastomoses in the dura mater of the pig. On the other hand, sumatriptan has been shown by subselective angiography to constrict human intracranial arteries in vivo (Henkes et al., 1996). Thus a direct vasoconstrictor effect of 5-HT_1 receptor agonists contributing to a reduction of increased intracranial blood flow during migraine attacks cannot be ruled out.

4.4. Relevance of CGRP and sumatriptan actions to migraine and headache

During migraine attacks and cluster headache, increased levels of CGRP (but not substance P) have been measured in the venous outflow from the head, suggesting the release of neuropeptides from the trigeminal afferent system (Goadsby et al., 1990; Goadsby and Edvinsson, 1993, 1994b). The increased CGRP levels could be reduced by sumatriptan at clinically effective doses in parallel with the relief of migraine pain in most of the patients (Goadsby and Edvinsson, 1993, 1994b). These results raise the question whether CGRP is directly involved in nociceptive mechanisms leading to migraine pain and other headaches, since dilatation of intracranial vessels, e.g. by CGRP, has been considered to be a noxious stimulus (Friberg et al., 1991; Humphrey and Goadsby, 1994). However, it seems just as possible that the CGRP-induced vasodilatation does not constitute the noxious stimulus itself, but is rather a response to the nociceptive processes in the dura mater. In this way CGRP may have a protective function, possibly accelerating the wash-out of noxious substances from the affected tissue by increasing the blood flow. The dural arterial flow may be rather robust being not affected by those doses of 5-HT_1 receptor agonists that inhibit plasma extravasation in the rat (0.1–0.3 mg kg^{-1} sumatriptan i.v.; Buzzi and Moskowitz, 1990; Buzzi et al., 1991a) and that are used for treatment of migraine pain (e.g., 6 mg sumatriptan s.c.). Recent clinical studies with the endothelin antagonist bosentan, which has been found to block plasma extravasation in the dura mater of the rat (Brändli et al., 1995), however, have failed to show any significant antimigraine effect (May et al., 1996). Thus it appears questionable if the inhibition of neurogenic inflammation is the only essential antinociceptive mechanism of 5-HT_1 receptor agonists in the treatment of migraine pain. Other mechanisms such as inhibitory effects of 5-HT_1 receptor agonists on the activation of primary meningeal afferents and central neurons of the trigeminovascular system may be important, as has been suggested by some authors (Nozaki et al., 1992; Kaube et al., 1993; Goadsby and Edvinsson, 1994a)

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