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The effect of adrenergic compounds on neurogenic dural vasodilatation ☆

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Abstract

The pharmacology of neurogenic trigeminovascular vasodilator responses in the dura mater is of interest for understanding the pathophysiology of migraine and to develop new therapies for this disabling common condition. Aminergic mechanisms have been implicated in migraine through direct study of amines in patients, and by inference from the pharmacology of many effective anti-migraine compounds, particularly preventative agents. This study used intravital microscopy to assess the role of aminergic transmission in neurogenic dural vasodilatation (NDV) by measuring directly the diameter of dural arteries in sodium pentobarbitone anaesthetised rats. Electrical stimulation of a closed cranial window produces, by local depolarisation of nerves, dural vessel dilation that is monitored continuously on-line using video-microscopy and a video dimension analyser. This dural vasodilatation was not affected by pre-treatment with an α_1-adrenoceptor agonist (phenylephrine, 1 and 5 μg/kg), or antagonist (corynanthine, 1 and 2 mg/kg), nor by an α_2-adrenoceptor agonist (UK14,304, 5 μg/kg) or antagonist (yohimbine, 1 and 3 mg/kg). Similarly, we saw no effect of β-adrenoceptor blockade (propranolol, 1 and 3 mg/kg). The lack of an inhibitory effect of UK14,304 the model of neurogenic dural *vasodilation* contrasts with its effect in neurogenic dural *plasma protein extravasation model*. The lack of inhibition of β-adrenoceptor antagonists in the neurogenic vasodilatation model contrasts with their usefulness as migraine prophylactics, and suggests that their mechanism of action in migraine is unlikely to be through sensory trigeminal fibre terminals at the neurovascular junction. Moreover, the data indicate that the adrenergic system does not play a significant role in neurogenic dural vasodilation.

Keywords: Trigeminovascular; Migraine; Headache; Adrenergic compound

1. Introduction

Migraine is a common (Stewart et al., 1992) and disabling (Menken et al., 2000) condition whose pathogenesis is not yet completely understood. The often reported throbbing quality of the pain (Headache Classification Committee of The International Headache Society, 1988) has suggested a pivotal role for the cranial blood vessels and their trigeminal innervation (Wolff, 1963). One approach to studying the pharmacology of the trigeminal innervation of the dural vessels has been to directly observe changes in meningeal vessel diameter while activating the neurovascular bundle with electrical stimulation (Williamson et al., 1997b). This approach offers the opportunity to study receptor systems that are implicated in migraine, such as those implicated through therapeutic responses, in a controlled, stable model system in vivo.

The trigeminal sensory fibres that innervate the dural vessels contain the potent vasodilator peptides calcitonin gene-related peptide (CGRP) and substance P (Uddman, 1989). CGRP and substance P both cause dilation of dural vessels when given intravenously in the rat (Williamson et al., 1997a), and are released upon trigeminal ganglion stimulation in the human and cat (Goadsby et al., 1988). Stimulation of the trigeminal ganglion at sufficient intensities will cause plasma protein extravasation in the dura mater (Markowitz et al., 1987), with associated local neuropeptide release (Buzzi et al., 1991). Neurogenic stimulation of the cranial window causes vasodilatation of dural vessels, such as the middle meningeal artery, and this is mediated by CGRP release from trigeminal sensory fibres (Williamson et al., 1997b).

Adrenergic receptor systems have been implicated in migraine by virtue of studies of catecholamines in migraineurs and by the pharmacology of a number of anti-

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migraine compounds. The α_1-adrenoceptor has been implicated by the pharmacology of ergotamine (Leysen and Gommeren, 1984), and its long-standing use as an anti-migraine drug (Tfelt-Hansen et al., 2000). An α-adrenoceptor antagonist acting post-synaptically was able to abort the nitroglycerin-induced migraine without aura, while pre-treatment with an α_1-adrenoceptor agonist was able to inhibit the ability of ergotamine to abort this migraine (Bonuso et al., 1994). Vatz (1997) has reported from 10 patients with migraine that they responded to α_1-adrenoceptor antagonists better than or equal to other commonly used migraine prophylactics. Using the extravasation model, an α_1-adrenoceptor agonist was found to have no effect on electrically induced extravasation, but did enhance capsaicin-stimulated protein leakage (Markowitz et al., 1988).

Clonidine, an α_2-adrenoceptor agonist, used as a migraine prophylactic (Anthony and Lance, 1972; Kallanranta et al., 1977) has stimulated some interest in α_2-adrenoceptor mechanisms. Clonidine has some utility in a histamine-induced experimental migraine model (Denaro et al., 1985). Mianserin, which has α_2-adrenoceptor antagonist properties, decreased headache in the same study after 30 days use (Denaro et al., 1985). Agonists at α_2-adrenoceptors have been shown to block dural plasma protein extravasation after trigeminal ganglion stimulation, but not substance P-induced extravasation, while the α_2-adrenoceptor antagonists did not block extravasation (Matsubara et al., 1992). These data provide evidence for the localisation of α_2-adrenoceptors in rodent dura mater, and some functional relationship for those receptors with the dural trigeminovascular innervation.

β-Adrenoceptor antagonists are among the best-established preventative anti-migraine agents (Silberstein and Rosenberg, 2000). However, the mechanism of action of β-blockers in migraine prophylaxis is unknown. Certainly an action at the dural neurovascular interface is plausible. In this context, it is noteworthy that β-adrenoceptor antagonists do not block trigeminal-evoked dural plasma protein extravasation (Markowitz et al., 1988).

In this study, we utilised an intravital dural microscopy system (Williamson et al., 1997b) to test adrenergic compounds across the range of receptors that have been implicated by clinical studies or pre-clinical observations relevant to migraine. We sought to compare the results in this model of neurogenic dural vasodilatation with those from the dural plasma protein extravasation model (Markowitz et al., 1987).

2. Materials and methods

2.1. Surgical preparation

Male Sprague–Dawley rats (300–400 g) were anaesthetised throughout the experiments with sodium pentobarbitone (60 mg/kg i.p. and then 18 mg/kg/h, i.v. infusion). The left femoral artery and vein were cannulated for blood pressure recording and injection of drugs intravenously, respectively. Temperature was maintained throughout using a homeothermic blanket system. The rats were placed in a stereotaxic frame, the skull exposed and the right parietal bone thinned by drilling with a saline-cooled drill until the blood vessels of the dura were clearly visible through the intact skull.

2.2. Intravital microscopy

The cranial window was covered with mineral oil (37 °C). A branch of the middle meningeal artery viewed using an intravital microscope (Microvision MV2100, UK) and the image displayed on a television monitor. Dural blood vessel diameter was continuously measured using a video dimension analyser (Living Systems Instrumentation, USA) and displayed with blood pressure on a chart recorder and a data analysis system (MI^2, Modular Instruments, UK). Measurements were taken after the blood pressure effect of the test substance had dissipated. A bipolar stimulating electrode (NE 200X, Clark Electromedical) was placed on the surface of the cranial window approximately 200 μm from the vessel of interest.

2.3. Experimental protocols

2.3.1. Defining electrical stimulation parameters

In each preparation, electrical stimulation was used to evoke dilation of the dural blood vessels. The surface of the cranial window was stimulated at 5 Hz, 1 ms for 10 s (Grass Stimulator S88, Grass Instrumentation) with increasing voltage until a maximal dilation was observed. Subsequent electrically induced responses in the same animal were then evoked using that voltage.

2.3.2. Effects of adrenergic drugs on neurogenic dural vessel diameter

The effects of an α_1-adrenoceptor agonist phenylephrine (1 μg/kg) on neurogenically produced vasodilation were studied. The compound was administered 10 min after the control response to electrical stimulation, with further stimulation repeated 15 and 30 min later. A further 10 min after the final electrical stimulation, an increased dose of phenylephrine (5 μg/kg) was given followed by two more electrical stimulations, again after 15 and 30 min (Henderson et al., 2000). This protocol was used for the α_1-adrenoceptor antagonist corynanthine (1 and 2 mg/kg) (Hey and Koss, 1988). The effects of an α_2-adrenoceptor agonist (UK14,304) (Bayorh et al., 1997) on neurogenically produced vasodilatation was studied similarly. A control response to electrical stimulation was produced and, 10 min later, UK14,304 (5 μg/kg) was given and the electrical stimulation then repeated after 15 and 30 min. This protocol was also used for UK14,304 at 10 μg/kg.

An α_2-adrenoceptor antagonist, yohimbine (1 and 3 mg/kg) (Allard et al., 1995), with electrical stimulation repeated at 15 min. The protocol for β-blocker (propanolol) testing at doses of 1 and 3 mg/kg (Nichols et al., 1991) was the same as for UK14,304.

2.4. Data analysis

The effects of electrical stimulation on dural vessel diameter were calculated as a percentage increase from the pre-stimulation baseline diameter and the effects of the post-drug stimulation were then compared to the control response elicited after electrical stimulation. Data are presented as mean ± S.E.M. Dural vessel diameter was measured in arbitrary units. An ANOVA with repeated measures (SPSS v9.0) was used to test the effect of the test compounds at the various doses over time with significance assessed at the $P < 0.05$ level.

2.5. Drugs

UK14,304 (Tocris Cookson, UK) was dissolved in 0.1% 1 M HCl and 99.9% saline (0.9%). Corynanthine (Tocris Cookson) was dissolved in 45% w/v 2-Hydroxy-β-cyclodextrin (RBI, UK). Phenylephrine (Sigma-Aldrich, UK) was dissolved in 0.9% saline, yohimbine (Sigma-Aldrich) was dissolved in water and propanolol hydrochloride was purchased pre-dissolved in 0.9% saline (Inderal, Zeneca).

3. Results

3.1. Effects of electrical stimulation on dural vessel diameter

As has been shown previously (Williamson et al., 1997b), electrical stimulation of the surface of the cranial window produces a short-lasting decrease in vessel diameter. This was followed by an increase in the vessel diameter of 119 ± 6% ($n = 42$), as determined across the entire stimulated cohort, with duration of approximately 5 min. In all experiments electrical stimulation had no effect on mean arterial blood pressure.

3.2. Effect of α_1-adrenoceptor agonist—phenylephrine

Electrical stimulation of the cranial window produced a baseline increase in vessel diameter of 114 ± 16%. Following i.v. injection of phenylephrine (1 and 5 μg/kg, $n = 5$), the response evoked by electrical stimulation after 15 and 30 min was 121 ± 27% and 99 ± 18%, respectively, for 1 μg/kg, and 105 ± 16% and 101 ± 23%, respectively, for 5 μg/kg. There was no persistent effect of phenylephrine on vessel diameter, although immediately after injection the baseline dropped, corresponding to an increase in blood pressure. These recovered to baseline before the next electrical stimulation (Fig. 1A).

3.3. Effects of α_1-adrenoceoptor antagonist—corynanthine

Electrical stimulation of the cranial window produced baseline increases in vessel diameter of 106 ± 9% (1 mg/kg) and 110 ± 9% (2 mg/kg). Following i.v. injection of corynanthine (1 mg/kg, $n = 7$, and 2 mg/kg, $n = 5$), the response evoked by electrical stimulation after 15 and 30 min was 97 ± 6% and 100 ± 13%, respectively (1 mg/kg), and 141 ± 24 and 104 ± 15%, respectively (2 mg/kg). There was no persistent effect of corynanthine on vessel diameter, although baseline did drop slightly immediately after injection. This had returned to baseline by the next electrical stimulation (Fig. 1B).

3.4. Effect of α_2-adrenoceptor agonist—UK14,304

Electrical stimulation of the cranial window produced baseline increases in vessel diameter of 108 ± 18% (5 μg/kg) and 96 ± 10% (10 μg/kg). Following intravenous injection (i.v.) of UK14,304 (5 μg/kg, $n = 5$ and 10 μg/kg, $n = 8$) the responses evoked by electrical stimulation after 15 min were increases in vessel diameter of 95 ± 19% and 95 ± 8%, respectively. These increases were not significant compared to the baseline increases. The responses were similar after 30 min with 5 μg/kg ($n = 4$) dose leaving a 94 ± 18% vessel response to stimulation, and 10 μg/kg dose leaving a 122 ± 20% ($n = 4$) increase. There was no persistent effect of UK14,304 on vessel diameter, although immediately after injection, the baseline dropped slightly, recovering to its pre-injection level by the time of the next electrical stimulation (Fig. 2A). There was a similar dip in blood pressure after injection that returned to baseline levels soon after.

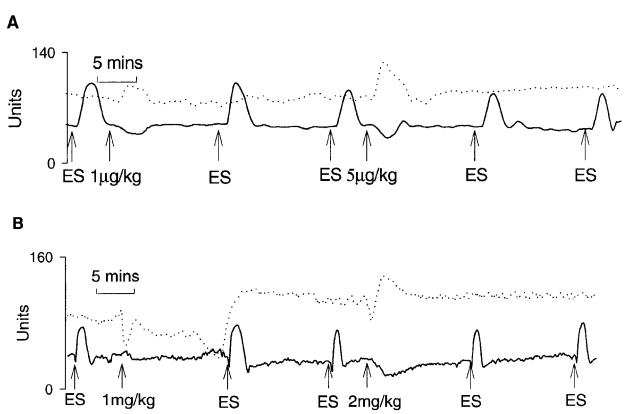

Fig. 1. Original tracings showing the effects of (A) the α_1-adrenoceptor agonist phenylephrine (1 and 5 μg/kg) and (B) α_1-adrenoceptor antagonist corynanthine (1 and 2 mg/kg) on mean arterial blood pressure (dotted line—mm Hg) and increase in vessel diameter (black line—arbitrary units), following electrical stimulation (ES) of the cranial window.

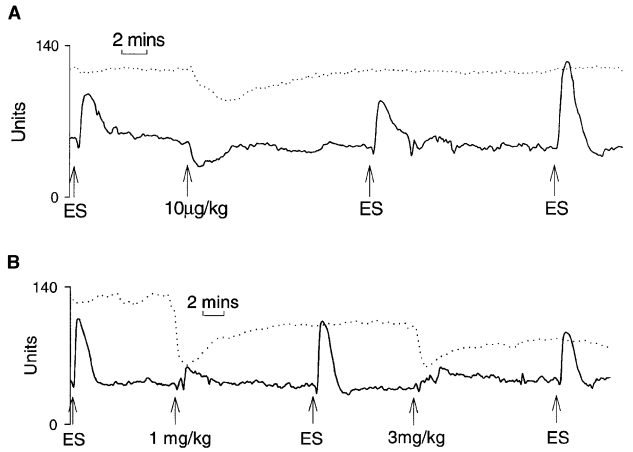

Fig. 2. Original tracings showing the effects of (A) the α_2-adrenoceptor agonist UK14,304 (10 μg/kg) and (B) α_2-adrenoceptor antagonist yohimbine (1 and 3 mg/kg) on mean arterial blood pressure (dotted line —mm Hg) and increase in vessel diameter (black line—arbitrary units) following electrical stimulation (ES) of the cranial window.

3.5. Effect of α_2-adrenoceptor antagonist—yohimbine

Electrical stimulation of the cranial window produced baseline increases in vessel diameter of $138 \pm 16\%$ (1 mg/kg) and $140 \pm 15\%$ (3 mg/kg). Following i.v. injection of yohimbine (1 and 3 mg/kg, $n = 6$), the responses evoked by electrical stimulation after 15 min were $117 \pm 18\%$ and $118 \pm 9\%$, respectively. There was no persistent effect of yohimbine on vessel diameter, although the baseline did increase slightly after injection, returning to normal by the time of the next electrical stimulation (Fig. 2B).

3.6. Effect of β-adrenoceptor antagonist—propranolol

Electrical stimulation of the cranial window produced baseline increases in vessel diameter of $171 \pm 22\%$ (1 mg/kg) and $109 \pm 15\%$ (3 mg/kg). Following i.v. injection of propanolol (1 mg/kg, $n = 6$, and 3 mg/kg, $n = 3$), the response evoked by electrical stimulation after 15 and 30 min was $170 \pm 23\%$ and $146 \pm 23\%$, respectively (1 mg/kg), and $109 \pm 15\%$ and $109 \pm 14\%$, respectively (3 mg/kg). There were no persistent effects of propanolol on the vessel diameter, although there was an increase in vessel diameter immediately after bolus injection that could be accounted for by the drop in blood pressure. This had returned to baseline by the time of the next electrical stimulation.

4. Discussion

In this study, we have reproduced comparable increases in dural vessel diameter by electrical stimulation of the closed cranial window as those first shown by Williamson et al. (1997a,b). In this study, we have observed no evidence for involvement of α-adrenergic or β-adrenoceptor mechanisms in neurogenic dural vasodilatation. The results suggest that neither α-adrenoceptors nor β-adrenoceptors are likely to share the mechanisms by which triptans modulate neurogenic dural vasolidatation. Furthermore, since the β-adrenoceptor antagonist propanolol is effective as a migraine preventative, the results suggest another, probably non-peripheral, site of action for this class of compounds in their prophylactic effects.

There are similarities and differences between neurogenic plasma protein extravasation (Markowitz et al., 1987) and neurogenic dural vasodilatation (NDV) (Williamson et al., 1997b). Plasma protein extravasation involves both vasodilatation and leakage of plasma proteins, whereas neurogenic dural vasodilatation only requires vasodilatation. The intravital model uses low intensity brief electrical stimulation as opposed to high intensity sustained stimulation in plasma protein extravasation. This difference may activate different populations of nerve fibres. The intravital method preferentially activating A-delta fibres, causing CGRP release, with the extravasation model activating C-fibres and substance P release (Lee et al., 1985; O'Connor and Van der Kooy, 1988). In contrast, the most clear-cut similarity between the approaches is seen with the triptans, 5-$HT_{1B/1D}$ receptor agonists, such as sumatriptan, which are inhibitory in both settings (Buzzi and Moskowitz, 1990; Williamson et al., 1997b).

A notable difference in the pharmacology of these models is the different role of substance P mechanisms. RP 67580, a substance P receptor antagonist at the tachykinin (NK_1) receptor, does not inhibit neurogenic dural vasodilatation after electrical stimulation of the closed window (Williamson et al., 1997a). However, RP 67580 has been shown to prevent extravasation after trigeminal ganglion stimulation in rat dura mater (Shepheard et al., 1993) and retina (May et al., 1998), and substance P-induced extravasation (Hirayama et al., 1993), as has RPR-100893 (Lee et al., 1994). Substance P-induced dilatation in the intravital model was antagonised by RP67580 but not the CGRP receptor antagonist human $\alpha CGRP_{(8-37)}$ (Williamson et al., 1997a), consistent with well-controlled nature of the intravital model. The fact that the α_1-adrenoceptor agonist phenylephrine had no impact on the neurogenic dural vasodilatation, while enhancing capsaicin, effectively C-fibre, activated extravasation (Markowitz et al., 1988) is consistent with the neurogenic dural vasodilatation being largely A-delta mediated. Perhaps the most striking difference between these new data and those published for plasma protein extravasation is the results for the α_2-adrenoceptor agonist UK14,304. It was effective at inhibiting the plasma protein leakage after trigeminal stimulation (Matsubara et al., 1992), but does not effect neurogenic dural vasodilatation. Given that CGRP but not substance P is elevated in migraine (Goadsby et al., 1990), the neurogenic dural vasodilatation model suggests a pivotal role for A-delta fibres in the pathophysiology of acute migraine.

A common theme in the compounds that inhibit neurogenic dural vasodilatation is that they are 5-$HT_{1B/1D}$ receptor agonists, such as sumatriptan (Williamson et al., 1997b), rizatriptan (Williamson et al., 1997c), electriptan, and dihyroegotamine (Williamson, unpublished data), and are established acute anti-migraine treatments (Ferrari, 1998). A number of the compounds tested in this series of experiments have been suggested to act as prophylactics in migraine, although the evidence is only really clear for the β-blocker propranolol (Silberstein and Rosenberg, 2000). Compounds that successfully inhibit neurogenic dural vasodilatation have the common feature that they probably act on the A-delta fibres present on trigeminal afferents, or they act pre-synaptically to inhibit the release of CGRP in the trigeminal necleus, or both. A preliminary conclusion might be that this model system will not be helpful, at least acutely, in determining the effects of putative prophylactic anti-migraine compounds.

In conclusion, this study demonstrates no effect of α_1-adrenoceptor agonist or antagonist activity, or α_2-adrenoceptor agonist or antagonist activity on neurogenic dural vasodilatation as monitored by intravital microscopy. Similarly, the β-adrenoceptor antagonist and migraine preventative, propranolol, had no effect on neurogenic dural vasodilatation. The dural neurogenic vasodilator model is a useful and stable model system to dissect the pharmacology of the trigeminovascular system.

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