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Short communication

Rizatriptan has central antinociceptive effects against durally evoked responses

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Abstract

The 5-$HT_{1B/1D}$ receptor agonist rizatriptan constricts intracranial, extracerebral blood vessels, inhibits neurogenic vasodilation and extravasation in the meninges and is effective clinically against migraine. The present study has investigated whether rizatriptan may also have activity at 5-$HT_{1B/1D}$ receptors within the central nervous system (CNS) that contributes to its antimigraine effects. Action potentials evoked by electrical stimulation of the dura-mater were recorded extracellularly from single neurones in the trigeminal nucleus caudalis in anaesthetized rats. Rizatriptan dose dependently inhibited these nociceptive dural responses by up to $63 \pm 9\%$ after 3 mg/kg, i.v. Rizatriptan therefore has central activity which may contribute to its efficacy against migraine headache.

Keywords: 5-$HT_{1B/1D}$ receptor agonist; Rizatriptan; Trigeminal nucleus caudalis; Migraine; Electrophysiology

1. Introduction

The trigeminal (V) caudal nucleus is the primary relay site for somatosensory information from pericranial and intracranial tissues (see Cooper and Sessle, 1993). This site of nociceptive processing is believed to underlie some aspects of migraine head pain since noxious stimulation of the dura and meningeal blood vessels can evoke electrophysiological responses (Strassman et al., 1986) and c-*fos* expression (Kaube et al., 1993b; Strassman et al., 1994) in the trigeminal nucleus caudalis.

Rizatriptan is a potent selective 5-$HT_{1B/1D}$ receptor agonist which has been shown to be clinically useful in the treatment of migraine headache (Visser et al., 1996). Rizatriptan selectively constricts isolated human middle meningeal arteries (Longmore et al., 1997) and inhibits neurogenic dural vasodilatation (Hargreaves et al., 1997) and extravasation (Shepheard et al., 1994). These peripheral actions are thought to contribute to the antimigraine activity of rizatriptan. The observation that 5-HT_1 receptor agonists have general antinociceptive properties in the spinal cord (Zemlan et al., 1988) prompted experimental studies to assess the involvement of central trigeminal 5-$HT_{1B/1D}$ receptors in the modulation of nociceptive neurotransmission from cranial structures since these sites could also be involved in the antimigraine effects of brain penetrant 5-$HT_{1B/1D}$ receptor agonists. Systemic sumatriptan has been shown electrophysiologically to attenuate dural nociceptive responses (Kaube et al., 1993a) and c-*fos* expression (Shepheard et al., 1995) in the nucleus caudalis under experimental conditions where the blood–brain barrier is disrupted. Furthermore, anatomical studies show a high concentration of 5-$HT_{1B/1D}$ receptors in the trigeminal ganglion of animals and humans (Bruinvels et al., 1992; Rebeck et al., 1994; Bouchelet et al., 1996) and in the V caudal nucleus (Mills and Martin, 1995). Clinical studies with rizatriptan showed that it produced good dose-related pain relief in migraine patients but that at high dose levels there was a concomitant increase in the incidence of central adverse events (Visser et al., 1996). This response profile indicated that rizatriptan penetrated the CNS and suggests that central actions may contribute to its antimigraine efficacy. The present studies in vivo have therefore investigated whether the selective 5-$HT_{1B/1D}$ receptor agonist rizatriptan has a central antinociceptive site of action within the trigeminal nucleus caudalis in the presence of an intact blood–brain barrier.

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2. Materials and methods

2.1. Animal preparation

Male Sprague-Dawley rats ($n = 12$, 320–420 g) were anaesthetized with halothane (2% in O_2); the trachea, a carotid artery and the jugular veins were cannulated for artificial ventilation, monitoring animal vital signs (blood pressure and end tidal CO_2) and for administering anaesthetics and drugs intravenously. The animal was immobilized in a stereotaxic frame, the brainstem was exposed and the temporal bone was thinned to allow visualisation of the meningeal blood vessels. The exposed surfaces were then covered with mineral oil to prevent desiccation. A constant infusion of sodium pentobarbitone (30 mg/kg/h) was used for the remainder of the experiment. The animal was paralyzed with pancuronium bromide (1 mg/kg/h); adequate anaesthesia was ensured by monitoring the cardiovascular response to a noxious stimulus. Blood pressure was monitored continuously and the experiment terminated if the systolic pressure remained below 90 mmHg. Body temperature was kept within 36.5–37.5°C.

2.2. Electrophysiological recordings

A single barrelled glass microelectrode (7–10 MΩ; NaCl (1.5 M)) was stereotaxically positioned in the caudal trigeminal nucleus and the cell depth relative to the pial surface was recorded. Extracellular single unit action potentials were evoked by electrical stimulation of the middle meningeal artery using a tungsten bipolar electrode; single square wave pulses (70–500 μs duration; threshold intensities of 1.8–5.7 mA) were applied at 0.2–0.3 mA above threshold at 1 Hz for 20 s; this was repeated every 200 s. Action potentials were counted using a window discriminator and the total counts over the 20 s of stimulation were used to calculate drug effects. Rizatriptan (MK-462; L-705,126; *N*,*N*-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethyl-amine) was tested on responses to dural stimulation by i.v. administration in a cumulative dose regimen of 0.3, 1 and 3 mg/kg (base weight), with a 10 min dose interval; in separate experiments equivalent volumes of saline were given every 10 min as repeated vehicle controls. Effects of rizatriptan or vehicle were calculated as a % inhibition of the three stable responses immediately before dosing. Mean values are expressed ± S.E.M. Statistical tests were performed using a 2-way analysis of variance (ANOVA) with repeated measures; a probability of $P < 0.05$ was deemed to be significant.

3. Results

3.1. Trigeminal cell classification

Pharmacological data were obtained from 12 single neurones in the trigeminal caudal nucleus 1–2 mm caudal to obex, 400–1210 μm from the pial surface. All neurones responded to noxious electrical dural stimulation and the mean latency for the first action potential was 3.5 ms (range of 2–8 ms).

3.2. Effects of rizatriptan on durally evoked responses

Fig. 1 shows an example of the effects of the 5-$HT_{1B/1D}$ receptor agonist rizatriptan on the responses of a single neurone to dural stimulation, represented as a series of post-stimulus histograms. Rizatriptan potently and dose dependently inhibited the nociceptive responses with marked blockade at 10 and 26 min after the 3 mg/kg dose. With this cell, each stimulus evoked more than one action potential, so that the total activity was 38 spikes/20 s. Overall in the rizatriptan group the mean data for the control electrical stimulation was 23 ± 5 spikes/20 s. Fig.

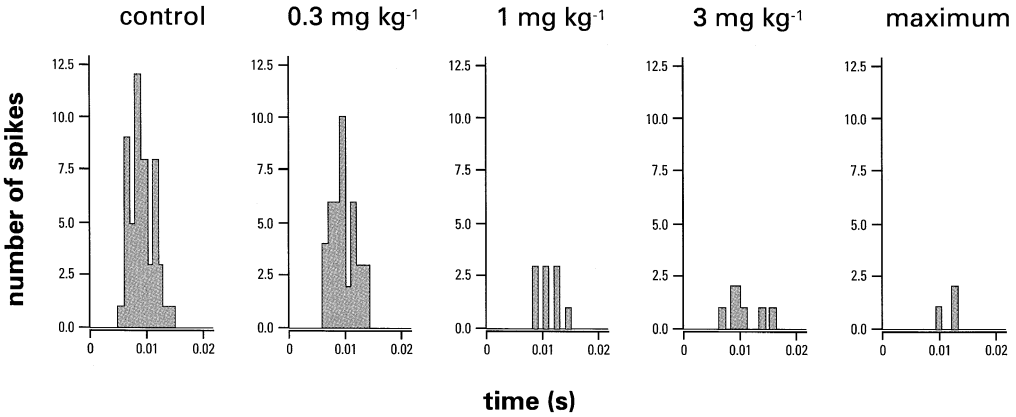

Fig. 1. Example recording from a single cell in the trigeminal nucleus caudalis (500 μm from the pial surface). The figure shows the cumulative post-stimulus histograms of the single unit responses to 20 electrical stimuli (2.7 mA; 200 μs) applied to the dura at 1 Hz. These responses were dose dependently depressed by cumulative i.v. doses of 0.3, 1 and 3 mg/kg rizatriptan, reaching a maximum effect 26 min after the 3 mg/kg dose.

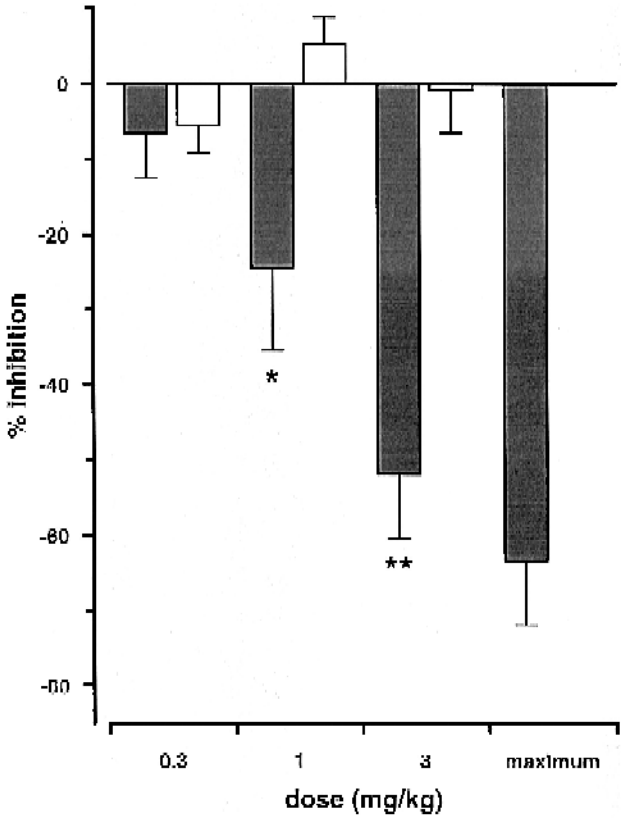

Fig. 2. The mean data for rizatriptan (filled bars, $n = 6$) and the repeat vehicle controls (open bars, $n = 5$). All data (mean ± S.E.M.) are expressed as a % inhibition compared to control. Significant differences between rizatriptan and saline controls are indicated by * and **; $P < 0.05$ and 0.005, respectively.

2 shows the mean data for rizatriptan on those cells where it produced consistent dose dependent inhibitions (6 cells; see Fig. 2); on one cell rizatriptan had no effect (< 10% inhibition at 3 mg/kg) and this result was not included in the analysis. The reason for this lack of effect is currently unknown but may reflect the absence of pre-junctional 5-$HT_{1B/1D}$ receptors on some dural primary afferent fibres. A mean maximum effect of 63 ± 9% was attained 19 ± 4 min after the 3 mg/kg dose. In all these cells the durally evoked responses remained depressed for the remainder of the experiment (up to 1 h after the 3 mg/kg dose). Repeated doses of vehicle (saline; $n = 5$) had no effect (see Fig. 2). Using an ANOVA test there was a significant difference ($P < 0.05$) between these controls and the effects of rizatriptan (see Fig. 2). Rizatriptan had no significant effects on blood pressure.

4. Discussion

These data show that the clinically effective antimigraine 5-$HT_{1B/1D}$ receptor selective agonist rizatriptan can penetrate the intact blood–brain barrier and inhibit central nociceptive neurotransmission arising from noxious dural stimulation. Since the meninges are thought to be a primary source of headache pain the present studies suggest that rizatriptan may have a central antimigraine locus of action in addition to its peripheral vasoconstrictor effects in intracranial, extracerebral blood vessels. 5-$HT_{1B/1D}$ receptors are thought to modulate the release of neuropeptides from peripheral terminals of the trigeminal fibres in the dura-mater (Moskowitz, 1992) and the release of substance P/calcitonin gene-related peptide (CGRP; Arvieu et al., 1996) and monoamines (Davidson and Stamford, 1995) from central terminals. Since studies have shown that sumatriptan has no effect on isolated trigeminal ganglion cells (O'Shaughnessy et al., 1993) it is likely that rizatriptan acts through the former mechanism to modulate nociceptive neuropeptide neurotransmission at the central terminals of dural trigeminal afferents.

In the present study we have used stimulus intensities which are at or slightly above threshold. Since there is evidence only for dural afferent fibres with C- and Aδ-fibre conduction velocities (Strassman et al., 1995; Bove and Moskowitz, 1995), and any stimulation of the dura is intensely painful, the stimulation parameters used should be adequate to activate nociceptive primary afferent fibres and would thus be described as noxious. Indeed, the latencies measured in the current study suggest afferents with conduction velocities towards the Aδ-fibre range (4–15 m/s).

Previous experiments have shown that the 5-$HT_{1B/1D}$ receptor agonist sumatriptan reduced durally evoked electrophysiological responses to electrical stimulation of the superior sagittal sinus (Kaube et al., 1993a) and reduced c-*fos* mRNA expression following electrical stimulation of the trigeminal ganglion (Shepheard et al., 1995), but only after disruption of the blood–brain barrier with mannitol. The inhibitory effect of rizatriptan with an intact blood–brain barrier in the present study suggests that this agonist may be more brain penetrant than sumatriptan. Another 5-$HT_{1B/1D}$ receptor agonist, zolmitriptan, has also been shown to attenuate dural nociceptive responses under conditions of an intact blood–brain barrier (Goadsby and Hoskin, 1996).

The present data clearly show that rizatriptan penetrates the blood–brain barrier and has significant inhibitory effects on durally mediated nociceptive responses in the CNS. These findings support a role for 5-$HT_{1B/1D}$ receptors in the modulation of central trigeminal nociceptive neurotransmission. Whether this effect is specific to the division of the trigeminal system that innervates the meninges or applies to all trigeminal sensory input, such as that from the face, requires further investigation.

Rizatriptan therefore has central trigeminal antinociceptive activity, as well as peripheral vasoconstrictor and inhibitory effects on the trigeminovasculature, that could contribute to its clinical effectiveness against migraine headache pain.

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