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Effect of sumatriptan in different models of pain in rats

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Abstract

The effect of sumatriptan in two standard algesimetric tests and in a model of cephalalgia was evaluated in rats. The pain threshold was measured by the hot-plate and the writhing tests; cephalalgia was produced by injecting bradykinin (10 μg in a volume of 10 μl) into a common carotid artery. Sumatriptan was subcutaneously (s.c.) injected at the doses of 4, 8, 24 or 42 mg/kg; morphine (5 or 10 mg/kg s.c.) and indomethacin (5 or 10 mg/kg s.c) were used as standard analgesic drugs. Sumatriptan had no analgesic activity either in the hot-plate test or in the writhing test. On the other hand, at 24 and 42 mg/kg it dose-dependently reduced the response to the intracarotid injection of bradykinin (vocalization and tachypnea), this effect being prevented by the 5-HT_{1B} receptor antagonist, isamoltane. The 5-HT_{1D} receptor antagonist BRL15572 prevented the effect of sumatriptan on bradykinin-induced tachypnea, but not the effect of sumatriptan on bradykinin-induced vocalization. These data demonstrate that sumatriptan is significantly effective in a reliable animal model of cephalalgia, while having no systemic analgesic activity.

Keywords: Hot-plate; Writhing test; Migraine-like model; Bradykinin; Rat; Sumatriptan

1. Introduction

Triptans still represent the most specific pharmacologic treatment for neurovascular headaches, such as migraine and cluster headache (Ferrari, 1998; Ferrari and Saxena, 1993; Goadsby et al., 2002).

This effect seems to be exquisitely selective, as they have no analgesic activity in other types of headache, such as tension-type headache. Of key relevance to the mechanism of action of triptans in migraine is their agonist activity at serotonin 5-$HT_{1B/1D/1F}$ receptors (Fowel et al., 1991; Goadsby et al., 2002; Hoyer et al., 1994).

Activation of serotonin 5-HT_{1B} receptors—abundantly expressed on vascular smooth muscle cells, primarily in the cranial circulation [but also in the coronary circulation (Longmore et al., 1997)]—causes constriction of arteriovenous anastomoses in the carotid bed, and of external cranial vasculature (De Vries et al., 1999; Verheggen et al., 1998). Activation of serotonin 5-HT_{1D} receptors—preferentially located on sensory trigeminal terminals (Longmore et al., 1997)—inhibits the release of vasoactive and sensory neuropeptides [substance P; calcitonin gene-related peptide (CGRP); vasoactive intestinal peptide (VIP); neurokinin A] and of other vasodilator transmitters, such as nitric oxide (NO), that reinforce vasodilatation and perivascular sensory nerve activity, cause plasma protein extravasation across dural vessels, and trigger a sterile neurogenic inflammatory process in the dura (Reuter et al., 2002; Saxena et al., 1998). Activation of serotonin 5-HT_{1F} receptors—preferentially expressed in the neuronal bodies—inhibits neuronal activity, including the release of vasodilating and pain-producing neuropeptides from sensory terminals (Johnson et al., 1997).

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However, some experimental data have been produced suggesting the possibility that triptans may have in addition a non-specific antinociceptive effect, exerted through the central nervous system (Ghelardini et al., 1996, 1997).

The present experimental study was designed with the aim to clarify whether the analgesic effect of triptans is specifically restricted to a migraine-like kind of pain or can be demonstrated also in other kinds of pain.

2. Materials and methods

2.1. Animals

Adult male rats of a Wistar SPF strain, weighing 180–200 g on arrival from Harlan Italy (Correzzana, Milano), were used. They were housed in groups of four to five, in plexiglass cages (40×25×15 cm), in climatised colony rooms (21±1 °C; 60% humidity), with food in pellets and tap water continuously available, under a 12 h/12 h light/dark cycle (lights on from 07:00 to 19:00). Housing conditions and experimentation procedures were strictly in accordance with the European Community ethical regulation on the care and use of animals for scientific research; the present research was moreover approved by the Ethical Committee for animal experimentation of the University of Modena and Reggio Emilia. The rats were accustomed to our housing conditions for at least 1 week before being used.

2.2. Hot-plate test

Responsiveness to nociceptive stimulation was measured by means of a conventional hot-plate apparatus (Socrel DS-35, Ugo Basile, Comerio, VA, Italy). The animals were placed one at a time on an electrically heated metal plate that was kept at the constant temperature of 54±0.4 °C. The latency either to forepaw licking or to jumping was recorded by means of an electronic timer started and stopped by a foot switch. In our conditions, the baseline latencies obtained in pre-experimental tests, with groups of six to eight rats, ranged from 6.3±0.4 to 6.7±0.5 s (means±S.E.M.; $p>0.05$, ANOVA). A cut-off time of 30 s was adopted. The analgesic effect was calculated as a percentage of the maximum possible effect (%MPE) according to the formula: (TL−BL)/(30−BL)×100, where TL=test latency, BL=baseline latency, 30=cut-off time in seconds (Eddy and Leimbach, 1953; Woolfe and MacDonald, 1944).

2.3. Abdominal constriction test (writhing test)

The writhing test (Koster et al., 1959) was performed by intraperitoneally (i.p.) injecting 2 ml/kg body weight of a 1% aqueous acetic acid solution. Before acetic acid injection, rats were placed individually in the test cage (33×56×20 cm) and habituated for 10 min to the new environment. Stretching movements—consisting of arching of the back, development of tension in the abdominal muscles, elongation of the body and extension of forelimbs—were counted for 30 min after acetic acid injection by an experimenter unaware of the treatment. The analgesic activity was expressed also in terms of percentage of inhibition: **% inhibition (%I)**=$n-n'$ / $n\times$**100**, where n=mean number of writhes of control group (vehicle-injected animals) and n' =mean number of writhes of test group (**%I<70**=absence of analgesic activity).

2.4. Migraine-like model

Rats were anaesthesized with propofol (75 mg/kg i.p.), and surgically prepared: a common carotid artery and a femoral vein were exposed and cannulated with indwelling polyethylene catheters; three needle electrodes were subcutaneously implanted on the chest and connected to a polygraph (Battaglia-Rangoni, Bologna, Italy) for the recording of the respiratory rate; a microphone was placed a few cm over the snout of the rat, and connected to the polygraph for the recording of vocalization; finally, the lead II electrocardiogram (ECG) was also recorded on the polygraph by means of needle electrodes subcutaneously implanted on the limbs. Bradykinin was bolus injected into the arterial catheter at the dose of 10 μg, in the volume of 10 μl. Respiratory tracing and phonogram were recorded before, during and for 5 min after bradykinin injection. The dose of 10 μg of bradykinin was chosen as the one able to induce vocalization and tachypnea in 100% of rats, anesthetized with propofol (75 mg/kg i.p.) on the basis of preliminary experiments.

2.5. Drugs and treatments

Sumatriptan succinate (GlaxoSmithKline, Stevenage, Hertfordshire, UK) was dissolved in saline and subcutaneously (s.c.) administered at the doses of 4, 8, 24 or 42 mg/kg, 10 min before testing [these doses had been used in previous "in vivo" studies concerning the possible antinociceptive effect of sumatriptan (Ghelardini et al., 1996, 1997)]; morphine hydrochloride (Sigma-Aldrich, Milano, Italy) was dissolved in saline and s.c. administered at the dose of 5 or 10 mg/kg, 20 min before testing; indomethacin [Liometacen, Promedica, Parma, Italy (meglumine salt of indomethacin)] was dissolved in saline and s.c. administered at the dose of 5 or 10 mg/kg, 20 min before testing; bradykinin (Sigma-Aldrich, Milano, Italy) was dissolved in saline. The 5-HT1B-receptor antagonist, isamoltane hemifumarate , and the 5-HT1D-receptor antagonist 3-[4-(4-chlorophenyl)piperazin-1-yl]-1,1-diphenyl-2-propanol hydrochloride [BRL15572 hydro-

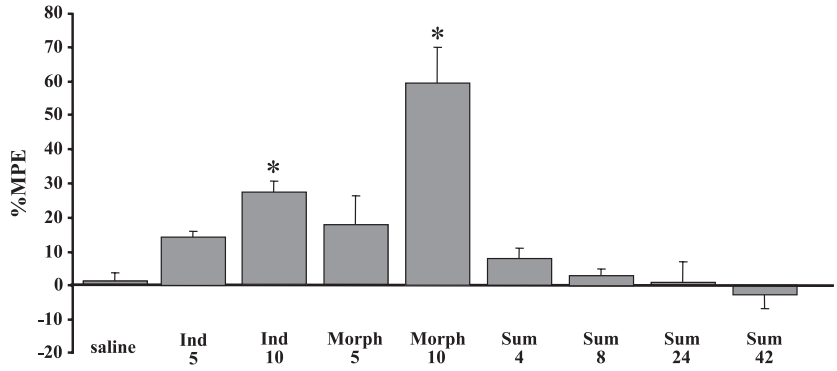

Fig. 1. Effect of sumatriptan in the hot-plate test in the rat % MPE=percentage of the maximum possible effect. Indomethacin (Ind, 5 or 10 mg/kg, s.c.), morphine (Morph, 5 or 10 mg/kg, s.c.) and sumatriptan (Sum, 4, 8, 24 or 42 mg/kg, s.c.) were administered 20, 20 and 10 min before testing, respectively. Means±S.E.M.; 12 animals per group. *P<0.05 vs. saline-treated group (ANOVA followed by Student–Newman–Keuls' test).

chloride (Tocris Cookson, Bristol, UK)] were dissolved in water or dimethyl sulfoxide (100 mM), respectively, and intravenously (i.v.) injected 10 min before sumatriptan at the doses of 4 and 0.3 mg/kg, respectively. These doses were chosen because fully effective for the "in vivo" blockade of serotonon 5-HT1B and 5-HT1D receptors, respectively (Ahlenius and Larsson, 1999; Centurion et al., 2001; Dawson and Nguyen, 2000; Sanchez-Lopez et al., 2004).

All drug solutions were freshly prepared. The number of animals in each experimental group is specified in figures and tables captions.

2.6. Statistical analysis

Data from the hot-plate test and the writhing test were analysed using the analysis of variance (one way analysis of variance, ANOVA) followed by the Student–Newman–Keuls' test (SNK test). Data from the migraine test (tachypnea and vocalization) were analysed using the chi-square test (χ^2 test). Level of significance: P<0.05.

3. Results

3.1. Hot-plate test

Sumatriptan, at all doses used, was completely ineffective, with MPE values not significantly different from those of saline-treated rats. On the other hand, as expected, morphine and indomethacin (both at the higher dose) inhibited the nociceptive response, with a significant increase in %MPE [F(8,99)=10.42, P=0.000] (Fig. 1).

3.2. Abdominal constriction test (writhing test)

Only morphine and indomethacin had a clear antinociceptive effect, with a significant reduction of the number of writhings [F(8,63)=19.07, P=0.000], while sumatriptan was ineffective at any dose (Fig. 2).

3.3. Migraine-like model

Sumatriptan prevented the effects produced by the intracarotid injection of bradykinin; at the dose of 24 mg/

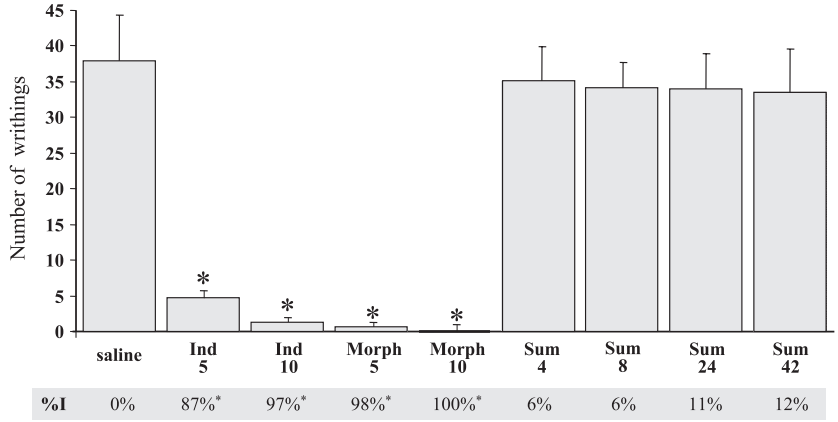

Fig. 2. Effect of sumatriptan in the writhing test in the rat. Indomethacin (Ind, 5 or 10 mg/kg, s.c.), morphine (Morph, 5 or 10 mg/kg, s.c.) and sumatriptan (Sum, 4, 8, 24 or 42 mg/kg, s.c.) were administered 20, 20 and 10 min before testing, respectively. Means±S.E.M. of the number of writhings obtained from each treatment group (8 animals per group), during a 30-min observation period. The numbers under each bar represent the percentage of inhibition (%I). *P<0.05 vs. saline-treated group (ANOVA followed by Student–Newman–Keuls' test).

Table 1
Effect of sumatriptan in the migraine-like model in the rat

Treatment (mg/kg)	*Tachypnea*	Vocalization
	%	%
Saline	100 (10/10)	100 (10/10)
Indomethacin 10, s.c.	70 (7/10)	60 (6/10)
Morphine 10, s.c.	60 (6/10)	60 (6/10)
Sumatriptan 24, s.c.	50 (5/10)[a]	60 (6/10)
Sumatriptan 42, s.c.	10 (1/10)[a]	10 (1/10)[a]

Indomethacin, morphine and sumatriptan were administered 20, 20 and 10 min, respectively, before the intracarotid injection of bradykinin (10 μg in a volume of 10 μl). In brackets: the number of animals displaying the behaviour.

[a] $P<0.05$ vs. saline-treated group (χ^2-test).

kg the number of rats with tachypnea was significantly reduced ($\chi^2=4.267$, $P=0.039$), while the effect on vocalization was not statistically significant; at the highest dose (42 mg/kg), both tachypnea and vocalization were prevented in 90% of animals [($\chi^2=12.929$, $P=0.000$]. On the other hand, indomethacin and morphine had no significant effect (Table 1). The effect of sumatriptan was almost completely prevented by the 5-HT_{1B} receptor antagonist, isamoltane [$\chi^2=5.62$, $P=0.018$ and $\chi^2=7.9$, $P=0.005$ for tachypnea and vocalization, respectively], whereas the 5-HT_{1D} receptor antagonist BRL15572 only slightly influenced bradykinin-induced tachypnea [$\chi^2=3.225$, $P=0.073$] (Table 2).

4. Discussion

Our present results show that sumatriptan has a dose-dependent analgesic effect in a rat model of migraine-like pain. In this model, both morphine and indomethacin are much less effective. On the other hand, sumatriptan is completely ineffective in two classical models of pain, where both morphine and indomethacin are strongly effective.

Our present data disagree with those obtained by Ghelardini et al. (1996, 1997), but are in agreement with those obtained by Skingle et al. (1990). In the hot-plate test, Ghelardini et al., chose a temperature of the plate (52.5 °C) lower than that chosen by Skingle et al. (55 °C) and by ourselves (54 °C), a different animal species (mouse), and a different method to calculate the analgesic effect (difference between the mean licking latencies on the different groups, instead of difference between the percentages of the maximum possible effect). Thus, it is possible that the inconsistency between the results obtained by Ghelardini et al., and those obtained by Skingle et al. and by ourselves may depend on these methodological differences.

The effect of sumatriptan in our migraine-like model is mostly antagonized by the blockade of serotonin 5-HT_{1B} receptors, and to a much lesser degree by the blockade of serotonin 5-HT_{1D} receptors, indicating that such effect is mainly the consequence of the activation of serotonin 5-HT_{1B} receptors.

Bradykinin is well known to be of primary relevance for cerebral circulation, either under normal or pathological conditions (Hardman et al., 1996; Volpe et al., 1999). Moreover, bradykinin is one of the most potent algogenic mediators and regulators of the noxious sensitivity of nociceptors (Couture et al., 2001; Dray and Perkins, 1997). Through the activation of bradykinin B_2 receptors, constitutively expressed on sensory terminals (Steranka et al., 1988; Lopes et al., 1995), it facilitates the release of neuromediators such as substance P, CGRP, neurokinin A and glutamate from sensory neurons as well as from peripheral terminals of capsaicin-sensitive primary afferents (Geppetti, 1993; Lopes et al., 1995; MacLean et al., 1990).

For these reasons this kinin is considered to play an important role in microvessels dilatation and in the genesis of vascular pain. It potently dilates arterial cerebral vessels and contributes to the vasodilatation, oedema and pain during migraine (Hardman et al., 1996; Volpe et al., 1999). Bradykinin was indeed suggested as a possible pathogenetic factor of migraine several years ago (Bertolini et al., 1966, 1968; Sicuteri et al., 1966): the injection of a few micrograms of bradykinin into a common carotid artery or into the cisterna magna of rabbits was shown to cause intense vocalization and flight; vocalization was observed also following the intracarotid injection of bradykinin into rabbits under general anesthesia [in the absence of verbal reporting, vocalization has long been accepted as a signal of pain in animals; indeed, among the many responses evoked by nociception, vocalization is perhaps the only one uniquely associated with nociception on the one hand, and the perception of pain on the other (Guzman et al., 1962).

The effect of sumatriptan on the migraine-like symptoms induced by the intracarotid injection of bradykinin is

Table 2
Influence of 5-HT_{1B} and 5-HT_{1D} antagonists on the effect of sumatriptan in the migraine-like model in the rat

Treatment (mg/kg)	*Tachypnea*	Vocalization
	%	%
Saline	100 (6/6)	100 (6/6)
Sumatriptan	12.5 (1/8)[a]	12.5 (1/8)[a]
Isamoltane+sumatriptan	80 (8/10)[b]	90 (9/10)[b]
BRL15572+sumatriptan	71.4 (5/7)[b]	42.8 (3/7)

Sumatriptan (42 mg/kg, s.c.) was administered 10 min before the intracarotid injection of bradykinin (10μg in a volume of 10 μl). Isamoltane (4 mg/kg, i.v.) and BRL15572 (0.3 mg/kg, i.v.) were administered 10 min before sumatriptan. In brackets: the number of animals displaying the behaviour.

[a] $P<0.05$ vs. saline-treated group.

[b] $P<0.05$ vs. sumatriptan-treated group (χ^2-test).

likely the consequence of a functional antagonism. Mainly through the activation of serotonin 5-HT_{1B} receptors, sumatriptan causes in fact vasoconstriction of external cranial vasculature and of arteriovenous anastomoses in the carotid bed; moreover, mainly through the activation of serotonon 5-HT_{1D} receptors, sumatriptan inhibits the release of several vasoactive and sensory neurpeptides (substance P, CGRP, VIP, neurokinin A) and of other vasodilator transmitters, such as NO (Dechant and Clissold, 1992; Fowel et al., 1991; Humphrey and Feniuk, 1991; Humphrey et al., 1989).

In conclusion, our present data confirm in the rat that sumatriptan is specifically effective in migraneous pain, while being completely ineffective—at the same dose levels—in other kinds of pain. Furthermore, our data further support the possible role of bradykinin in the pathophysiology of migraine.

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