J Headache Pain (2010) 11:5–12
DOI 10.1007/s10194-009-0170-y

REVIEW ARTICLE

Does sumatriptan cross the blood–brain barrier in animals and man?

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Received: 24 August 2009 / Accepted: 27 October 2009 / Published online: 10 December 2009

Abstract Sumatriptan, a relatively hydrophilic triptan, based on several animal studies has been regarded to be unable to cross the blood–brain barrier (BBB). In more recent animal studies there are strong indications that sumatriptan to some extent can cross the BBB. The CNS adverse events of sumatriptan in migraine patients and normal volunteers also indicate a more general effect of sumatriptan on CNS indicating that the drug can cross the BBB in man. It has been discussed whether a defect in the BBB during migraine attacks could be responsible for a possible central effect of sumatriptan in migraine. This review suggests that there is no need for a breakdown in the BBB to occur in order to explain a possible central CNS effect of sumatriptan.

Keywords Blood–brain barrier · Sumatriptan · Migraine · CNS · Animal studies · Human studies

Introduction

The triptans, 5-$HT_{1B/1D}$ receptor agonists, are effective drugs in the treatment of migraine attacks [1–4]. It has been debated for a long time whether the triptans act during migraine attacks on the peripheral nociceptive input or on the nociceptive system in the CNS [5, 6]. Triptans can theoretically decrease peripheral nociception either by a selective cranial vasoconstriction, the rationale for its development [6, 7] or an effect on trigeminovascular nerves [6]. A peripheral effect on trigeminal vascular nerves was indicated by the blocking effect of sumatriptan of neurogenically mediated plasma extravasation [8]. Inhibitors of neurogenic inflammation (NI) were, however, ineffective in the treatment of migraine [9] and it is thus difficult to ascribe a pivotal role for NI in migraine. In 1996 it was, based on the effect of zolmitriptan, suggested that inhibition of trigeminal neurons in the brain stem by lipophilic triptans may play a role in the anti-migraine effect of these drugs and that these results offered the prospect of a third pathophysiological target site for triptans [10].

The prototype of a triptan is sumatriptan, the first developed triptan [7]. Apparently this drug, which is relatively hydrophilic, did not in several animal studies [5, 11–14] cross the blood–brain barrier (BBB) in sufficient amount to cause a pharmacological effect in the trigeminal nucleus caudalis [5, 12, 13] or frontal cortex [11]. In contrast, other more lipophilic triptans, such as zolmitriptan [5, 15], naratriptan [16], rizatriptan [17], and eletriptan [18], caused an inhibition of nociception in the trigeminal nucleus caudalis in these animal models of migraine.

In contrast to earlier studies [7, 19] it was recently stated that "this central site of action is consistent with the evidence that sumatriptan can rapidly cross the blood–brain barrier into the central nervous system after systemic administration". This was, however, based on a pharmacokinetic study using sumatriptan 3.2 mg/kg [20] far above the therapeutic dose of 100 μg/kg.

In recent studies from 2004 and 2009 a presynaptic inhibition of sumatriptan (300–600 μg/kg) in the trigeminal nucleus caudalis was found [21] and reversal of facial allodynia by sumatriptan [22] was observed.

In the following, animal studies on sumatriptan will be reviewed and possible explanation for the discrepancy

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among studies will be suggested. Next, CNS adverse events after triptans in migraine patients and normal subjects will be reviewed.

It is concluded that both the animal and the human studies suggest that sumatriptan to some minor extent can penetrate into the CNS across the BBB both in animals and in man. The minor penetration of sumatriptan into the CNS is, however, sufficient to cause pharmacological effects most likely because the drug is potent 5-$HT_{1B/1D}$ receptor agonist [1, 3].

Review of studies in animals

The penetration of systemically administered ^{14}C-labeled sumatriptan into the central nervous system was investigated in the mouse [7]. Only 0.006% of total radioactivity was found in the brain indicating poor brain penetration by sumatriptan [7]. In another study no sumatriptan was found in the brain with whole body assay in rats [19].

An overview of 21 animal studies investigating the possible effect of sumatriptan on the CNS is presented in the Table 1. For an overview of used animal models of migraine, see [23].

The clinically used dose of subcutaneous sumatriptan 6 mg corresponds to approximately 100 μg/kg, but the dose used in animal studies varied widely from 50 μg/kg to 100 mg/kg (Table 1). In nine studies [5, 11–14, 24–27], there was no effect of sumatriptan in the animal model. In one study an antinociceptive effect was found after 5–30 mg/kg, most likely mediated by the 5-HT_{1A} receptor [28]. In contrast, an effect of sumatriptan 100–1,000 μg/kg on the CNS was found in nine studies [21, 22, 29–35].

In one study sumatriptan 300 μg/kg blocked c-fos protein-like immunoreactivity within trigeminal nucleus caudalis following irritation of meningeal afferents induced by blood [36]. In another study from the same group of investigators sumatriptan 300 μg/kg reduced c-fos protein-like immunoreactivity in the trigeminal nucleus caudalis (TNC) after repeated cortical spreading depression [37]. In the authors opinion the effects of sumatriptan were most likely due to an effect on the peripheral part of the afferent fibres of the trigeminal nerve but they add: "of course, the studies reported herein do not exclude the unlikely possibility that this hydrophilic 5-HT analogue blocks c-fos protein-like immunoreactibility within the TNC directly" [37].

In a later study from 1997 with the same problem it was found that morphine 3 mg/kg, but not sumatriptan 300 μg/kg, decreased c-fos expression in TNC after multiple CSD [27]. These results have been disputed [38].

In one study sumatriptan acutely in a dose of 100 μg/kg and 1 mg/kg, as well as zolmitriptan 100 μg/kg, decreased 5-HT synthesis rate in many brain region in rats including the dorsal raphe nucleus [34]. Chronically, sumatriptan (300 μg/kg per day) induced significant increases in the 5-HT synthesis rate in many projection areas but had no effect in the dorsal raphe nucleus [33]. Overall, these findings indicate that not only zolmitriptan, but also sumatriptan affect brain serotonergic neurotransmission [34].

One study used very high doses of sumatriptan: in a pharmacokinetic–pharmacodynamic study in rats from 2001 [20] on the serotonergic effects and extracellular levels of eletriptan, zolmitriptan and sumatriptan, using a very high dose of 2.5 mg/kg i.v., it was shown that the three drugs with different lipophilicity had similar extracellular levels in the brain. On the other hand, sumatriptan did not exert a serotonergic effect, as did zolmitriptan and eletriptan, most likely because sumatriptan is less potent in this system than the two other triptans [20]. In addition, non-equipotent doses of the two triptans compared with sumatriptan were used, see later. The problem with this study is evident: the usual subcutaneous dose of sumatriptan in man is 6 mg, corresponding to 100 μg/kg, whereas the dose is 32 times higher in this rat study [20]. This could indicate that a saturable, expulsion process limiting the access of the three triptans to the CNS exists. In fact, eletriptan distribution in the CNS is limited by the P-glycoprotein-mediated efflux [39, 40] whereas sumatriptan and zolmitriptan are subjected to non-P-glycoprotein-mediated efflux [41].

What could be the explanation for this different effect of sumatriptan in these various animal models of migraine? In two of these studies in which sumatriptan had no effect [12, 13], an effect of sumatriptan was observed after disruption of the BBB with mannitol. The potential for a CNS effect of a triptan, including sumatriptan, is thus present in the animal models used [12, 13] as also demonstrated by the effect of zolmitriptan [5, 15], naratriptan [16], rizatriptan [17] and eletriptan [18] in these models with intact BBB.

The dictum was thus in the beginning, based on pharmacokinetic studies [7, 19] that sumatriptan had only minimal or no passage within the central nervous system. Most early animal studies apparently supported, with different methodology, the lack of penetration of sumatriptan across the BBB [11–13, 24]. Later animal studies have shown in some but not in all (Table 1) investigations that sumatriptan in these animal models, mostly of migraine, did exert an effect inside the BBB.

CNS effects in migraine patients and other subjects

In human postmortem brains [3H]sumatriptan binding sites have been found in among others, globus pallidus >

Table 1 Studies on the central nervous system effect of sumatriptan in animals

References	Dose of sumatriptan	Parameter used	Results	Indicates passage of sumatriptan across BBB
Sleight et al. (1990) [11]	50 and 500 μg/kg (i.p.) (guinea pig)	Extracellular 5-HT levels in the frontal cortex as measured by microdialysis	No effect of systemic sumatriptan (sumatriptan 10^{-8}–10^{-7} M in microlysate caused a decrease of 5-HT)	–
Skingle et al. (1990) [24]	Dose 1–100 mg/kg (rodents)	Antinociceptive effect by (various tests)	No antinociceptive effect (in some tests 100 mg/kg had an effect)	–
Nozaki et al. (1992) [36]	720 nmol/kg (300 μg/kg) (rat)	c-fos expression in the trigeminal nucleus caudalis after autologous blood in cisterna magna	Sumatriptan reduced c-fos positive cells in trigeminal nucleus caudalis by 31%	(−/+) see comment[a]
Moskowitz et al. (1993) [37]	300 μg/kg (rats	c-fos expression in trigeminal nucleus caudalis after repeated CSD	Sumatriptan reduced c-fos expression	(−/+) see comment[a]
Kaube et al. (1993) [12]	100 μg/kg (cat)	Single units activity and trigeminal somatosensory evoked potentials after SSS stimulation	No effect of sumatriptan (after blood–brain barrier disruption with mannitol sumatriptan decreased the peak-to-peak amplitude of evoked potentials)	–
Shepheard et al. (1995) [13]	1,000 μg/kg (rat)	Expression of c-fos mRNA in trigeminal nucleus caudalis after stimulation of trigeminal ganglion	No effect of sumatriptan (after blood–brain barrier disruption with mannitol sumatriptan decreased expression of c-fos mRNA with 63%	–
Ghehardini et al. 1996 [28]	5–30 mg/kg (mouse))	Antinociceptive effect (hot-plate test)	There was an antinociceptive effect, most likely mediated by the 5-HT_{1A} receptor	?
Mitsikostas et al. (1996) [30]	0.3–0.9 mg/kg (rat)	Brain monoamines concentration	0.6 mg/kg decreased hypothalamic serotonin concentration	+
Hoskin and Goadsby (1996) [29]	85 μg/kg (cat)	c-fos expression in trigeminal nucleus caudalis after dilatation of SSS	Reduction of c-fos expression	(+/−) see comments[b]
Knyihár-Csillik et al. (1997) [14]	120 μg/kg (rat)	c-fos in caudal trigeminal nucleus after stereo electrical stimulation of the trigeminal ganglion	No effect of sumatriptan on c-fos expression	–
Ingvardsen et al. (1997) [27]	300 μg/kg (rat)	c-fos in TNC after CSD	No effect of sumatriptan on c-fos expression	–
Hoskin and Goadsby (1998) [5]	85 μg/kg (rat)	c-fos expression in trigeminal nucleus caudalis after SSS stimulation	No effect on c-fos expression[b]	–
Read et al. (1999) [31]	300 μg/kg (rat)	Nitric oxide formation in the cerebral cortex after nitroglycerin	Decrease of NO formation	+
Read and Parsons [32]	300 μg/kg (rat and cat)	Nitric oxide formation in the cerebral after CSD	Decrease of NO formation and decrease of partial oxygen tension	+
Read et al. (2001) [25]	300 μg/kg (rat)	CGMP after CSD	No effect on brain stem cGMP after 3 days	–
Johnson et al. (2001) [20]	3.2 mg/kg (rat)	Measurements of sumatriptan concentrations in microdialysate. Central release of 5-HT	Concentrations of sumatriptan up to 8 nM was observed. No effect on central release of 5-HT	+

Table 1 continued

References	Dose of sumatriptan	Parameter used	Results	Indicates passage of sumatriptan across BBB
Kayser et al. (2002) [33]	100 μg/kg (rat)	Mechanical allodynia-like behaviour after ligature of n. infraorbitalis	A significant reduction of mechanical allodynia-like behaviour on injured and contralateral side of the face[c]	+
Dobson et al. (2004) [34]	300–1,000 μg/kg (rat)	Serotonin synthesis in brain	Given acutely a decrease in 5-HT synthesis in certain regions of the brain was observed	+
Pardutz et al. (2004) [26]	600 μg/kg (rat)	Nitroglycerin-induced nNOS immunoreactive neurones in trigeminal nucleus caudalis	nNOS expression could not be prevented	–
Levy et al. (2004) [21]	300 μg/kg (rat)	Changes in spontaneous activity of trigeminal peripheral and central neurones after inflammatory soup on dura	Sumatriptan blocked the induction of central sensitization most likely by a presynaptic inhibition	+
Edelmayer et al. (2009) [22]	600 μg/kg (rat)	Prevention of facial allodynia after inflammatory mediators on the dura	Sumatriptan prevented or reversed facial allodynia	+
Bates et al. (2009) [35]	600 μg/kg i.p. and 0.06 μg intrathecal (mouse)	Prevention of thermal and mechanical allodynia	Systemic sumatriptan inhibited thermal allodynia but not mechanical allodynia. Intrathecal sumatriptan inhibited both	+

[a] The authors considered that this was a peripheral effect on the trigeminal nerve [34], see text

[b] The authors concluded: "The simplest reasonable conclusion is that sumatriptan inhibited trigeminal afferent by a direct neuronal mechanism at the peripheral terminal."[22]. They found a central effect unlikely because no central effect of sumatriptan was observed in previous studies [9, 10]

[c] Zolmitriptan 30 μg/kg caused a decrease in c-fos expression in trigeminal nucleus caudalis

[d] The site of action is not totally clear but is most likely a CNS effect because a reduction of contralateral allodynia [29]

cortex > hippocampus [42]. In the brain stem the highest [3H]sumatriptan binding sites were seen in the substantia nigra, the trigeminal nucleus, nucleus of the tractus solitarius and periaqueductal gray [43]. If sumatriptan can cross the BBB in sufficient amounts, one would thus expect CNS adverse events after therapeutic use of the drug.

Some migraine patients complain of sleepiness/tiredness, difficulty in thinking and dizziness [44] after sumatriptan. In a meta-analysis of oral triptans, sumatriptan 100 mg caused 6% (95% CI 3–9%) more CNS adverse events than placebo [2]. This could indicate a CNS effect of sumatriptan. Similarly, zolmitriptan 2.5 mg caused 9% (965 CI 4–14%) more CNS adverse events than placebo [2]. The CNS adverse events of triptans can, however, be partly ascribed to migraine symptoms being unmasked by effective treatment since responders to eletriptan had more CNS AEs than non-responders to eletriptan [45]. However, in one large RCT [46] any CNS adverse events were more frequent after sumatriptan 100 mg (29.6%) ($n = 386$) than after rizatriptan 10 mg (22.5%) ($n = 385$) [47] despite the fact that the two drugs were equipotent for headache relief after 2 h [46]. In addition, rare cases of central nervous system AEs such as akathesia, acute dystonia and pathological laughter have been described after subcutaneous and oral sumatriptan used in the treatment of migraine and cluster headache [48–50].

That CNS adverse events can occur after triptans outside migraine attacks was shown in a placebo-controlled study in female healthy volunteers [51]. The results showed that sumatriptan 50 mg and rizatriptan 10 mg caused small but clear effects on the CNS, mainly mild sedative effects, which were less than sedation after the active control drug, temazepam 20 mg [51]. In addition, sumatriptan caused a significant increase in the EEG alpha power compared with placebo for the frontal leads, whereas this was not the case for rizatriptan [51]. In another study it was shown that zolmitriptan 5 and 10 mg, but not sumatriptan 100 mg, had an effect on cortical auditory-evoked potential in man [52]. In one placebo-controlled study in male subjects with a history of substance abuse subcutaneous sumatriptan 8 and 16 mg was psychoactive, was discriminated from placebo, produced a dose-related decrease on euphoria score and elevated scores on measures of apathic sedation and disliking [53]. These studies demonstrate that normal

therapeutic doses do exert a CNS effect in non-migrainous subjects.

In a recent positron emission tomographic (PET) study in six migraine patients, it was shown that subcutaneous sumatriptan 6 mg normalizes the migraine attack-related increase in brain serotonin synthesis [54], thus demonstrating convincingly that sumatriptan can exert an effect on the brain in migraineurs during an attack.

In a double-blind, placebo-controlled study in migraine patients, subcutaneous sumatriptan 6 mg caused an increase of the duration of the early exteroceptive suppression period of temporalis muscle activity both during the migraine attack and during the migraine interval [55], whereas there was no effect on contingent negative variation [56].

In another study on glyceryl trinitrate-induced migraine, during attacks there was an increase in slow rhythmic activity of the theta and delta range and a decrease of activity in the alpha and beta range [57]. The abnormalities disappeared after a sumatriptan injection [57]. One cannot exclude, however, that the effect of sumatriptan in this study is due to an effect on migraine per se.

In one study on obsessive–compulsive disorder (OCD) the sumatriptan treated subjects' OCD symptoms worsening, as measured by The Yale Brown scale, was significant compared to placebo ($p < 0.02$) [58]. In another study no such effect was observed [59].

Exercise capacity was decreased after subcutaneous sumatriptan 6 mg in one placebo-controlled study [60]. The authors' conclusion was that it could be a peripheral effect of the drug because "sumatriptan is a selective 5-HT (1B/1D) receptor agonist that does not cross the blood–brain barrier" [60]. It was thus regarded as an established fact, based on [12, 13], that sumatriptan does not penetrate the BBB.

In one review it was concluded that the incidence of CNS adverse events is correlated ($r = 0.68$) to the lipophilic attributes of the triptans [61], whereas in two other reviews this was not the case [62, 63]. Re-analysing of the data from the first review [61] with the use of equipotent triptan doses sumatriptan 100 mg (instead of 50 mg) and eletriptan 40 mg (instead of 80 mg) shows, however, that there is no correlation ($r = 0.324$, $p = 0.438$, Spearman's nonparametric test), as would be expected since the triptans are subjected to different efflux systems from the brain [41].

Overall, the triptans, apart from almotriptan 12.5 mg and the low dose of naratriptan, 2.5 mg [2], result in CNS adverse events with a relatively low incidence which indicates an effect on the CNS. These CNS adverse events of triptans, especially sleepiness/tiredness, can in some cases be a problem in the clinical use of the drugs, including sumatriptan [3].

Comments on the possible effects of sumatriptan inside the BBB

Are the doses of the different triptans used in these animal studies comparable? In one study investigating parenteral sumatriptan and zolmitriptan, it was stated that clinically comparable doses were used [5]. Thus sumatriptan 85 μg/kg and zolmitriptan 30 μg/kg were used. There are RCTs with subcutaneous sumatriptan [64, 65], but none with parenteral zolmitriptan. Equipotency must therefore be judged from oral comparative RCTs. Based on one large comparative RCTs, zolmitriptan 5 mg is comparable with sumatriptan 100 mg [66]. This is also the case in the well-known meta-analysis [2]. Thus is seems reasonable to compare the systemic availability of these doses. Sumatriptan has an oral bioavailability of 14% [1, 3] and 100 mg thus results in sumatriptan 14 mg being available, whereas zolmitriptan 5 mg with an bioavailability of 39% [1, 3] results in zolmitriptan 1.95 mg being systemically available. The ratio between the systemically available doses is thus 7.2. In the animal study [5] of sumatriptan and zolmitriptan mentioned above, the dose ratio was 85/30 = 2.8. So either too little sumatriptan or too much zolmitriptan was used. The sumatriptan 85 μg/kg dose is near the subcutaneously used dose of 6 mg in man. So most likely a too high dose of zolmitriptan was used if the two drugs are equipotent.

The different results for sumatriptan in these animal models is most likely not a consequence of different doses of the drug used. Thus, in "negative" studies the dose range of sumatriptan was 85 μg/kg to 6 mg/kg, whereas in the "positive" studies the dose range was 100–1,000 μg/kg (Table 1). The results most likely depend on the animal model used. Whether an inhibitory CNS effect of sumatriptan is observed in an animal study is most likely the result of the ratio between stimulus used, electrical stimulation [5, 13] or inflammatory mediators [20, 21], and the inhibitory effect of sumatriptan. If the stimulus is very strong, such as superior sagittal stimulation (SSS), for 1 h in one study [5] and described in one study as a supramaximal stimulation [12] or trigeminal ganglion stimulation [13, 14] even "normal" levels of sumatriptan in the CNS are most likely unable to inhibit the response. In contrast, "more" physiological stimuli such as inflammatory mediators [21, 22] can probably be inhibited by "normal" levels of sumatriptan. It should be noted, however, that the more lipophilic triptans such as zolmitriptan [5], naratriptan [16], rizatriptan [17] and eletriptan [18] were effective in the SSS model without a breakdown of the BBB. This higher efficacy of these triptans than sumatriptan in this SSS model does not, however, result in increased effect of these triptans in the acute treatment of migraine [1, 2].

The presence of triptan binding sites and triptan receptor mRNA within the CNS leaves little doubt as to the potential for CNS effects of the triptans [67–69]. It is recognized that the triptan class of compounds do generally have poor penetration characteristics with brain/plasma partition coefficient ($K_{p,brain}$) [41] well below 1, when compared with typical CNS marketed drugs (e.g. diphenhydramine with a $K_{p,brain}$ of 9) [42]. The $K_{p,brain}$ in P-glycoprotein-competent (mdrla +/+) mice were 0.13 (sumatriptan), 0.42 (naratriptan), 0.20 (rizatriptan),0.038 (zolmitriptan), and 0.30 (eletriptan) [41].

The extent of brain penetration is, however, a poor guide to central activity, especially with potent agonists such as the triptans, since they, in contrast to most other CNS agents that are antagonists, will require only low fractional receptor occupancy to exert central effects [40].

The original hypothesis when sumatriptan was developed was that the drug was a specific cranial vasoconstrictor [6, 7] and that it did not or only to a very minor extent penetrate across the BBB into the CNS [7, 19]. The best way to substantiate a hypothesis is to try to falsify it *ad modum* Popper [70]. The intended falsifying experiment should have a suitable design and should be of high quality. In the present case the hypothesis was that sumatriptan cannot cross the BBB, and the falsifying experiment would be an investigation aimed at and demonstrating an effect in CNS of sumatriptan in an animal and if possible in man. Until 1996 the investigations failed to unequivocally falsify the hypothesis (Table 1). Thus in two studies [12, 13] the BBB had to be broken down by hyperosmolar mannitol before sumatriptan could exert an inhibitory effect in the trigeminal nucleus caudalis (TNC). There were two animal studies 1992 [36] and 1993 [37] which by the authors were interpreted as showing a peripheral inhibitory effect of sumatriptan on primary afferents of the trigeminovascular system but which, as mentioned above, could not exclude an inhibitory effect in the TNC [37]. From 1996 on several high-quality animal studies, see Table 1, demonstrated a CNS effect of sumatriptan. In addition, it was shown that sumatriptan induced more CNS adverse events than placebo when used in the acute treatment of migraine [2]. Among the studies, two investigations are the most convincing as falsifying experiments both in animals and man: in one study in rats sumatriptan blocked the induction of central sensitization after an inflammatory soup on dura most likely by presynaptic inhibition [21]. In a recent PET investigation in six migraine patients during an actual attack, subcutaneous sumatriptan 6 mg normalizes the attack-related increase in brain serotonin synthesis [54].

There is a debate as to whether the anti-migraine action of triptans is solely through peripheral effects, cranial vasoconstriction [6, 7] and inhibition of release of neuropeptide from the trigeminovascular nerve endings, or whether antinociceptive activity within the brain stem is partly responsible [61].

Sumatriptan can most likely, in addition to a possible peripheral trigeminovascular effect, exert an effect in the brain stem when used for migraine treatment. The BBB is most likely intact during migraine attacks [22, 71] and there is therefore no need to consider a leakage of the BBB [9] for sumatriptan to exert a CNS effect in migraine.

Finally, it is noteworthy, that the increased activity during migraine attacks in the brain stem, as measured with PET [72, 73], still persisted after successful treatment of migraine attacks with subcutaneous sumatriptan. The drug was thus unable to "extinguish" the "migraine generator" and this is most likely the cause of headache recurrence after sumatriptan. This is likely also the case for other brain penetrating triptans with which recurrence also occurs [1, 2].

Acknowledgments The study was supported by the Lundbeck Foundation via the Lundbeck Foundation Center for Neurovascular Signaling (LUCENS).

Conflict of interest None.

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