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Serotonin 5-HT$_{1B}$ Receptor-Mediated Contractions to Triptans in Guinea-Pig Iliac Artery

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Introduction

Sumatriptan has been used in acute migraine therapy for nearly one decade. Activation of cerebral vascular 5-HT$_{1B}$ receptors and inhibition of trigeminal nerve-mediated dural extravasion mediated by prejunctional 5-HT$_{1B/1D/1F}$ receptors are responsible for the beneficial effect of sumatriptan [1,2]. In the last years 2nd generation triptans have been developed which display differences in bioavailability and tolerability [3].

Vascular 5-HT$_{1B}$ receptors have not only been detected in cerebral arteries but also in peripheral blood vessels such as coronary arteries and saphenous veins in humans and other species. Activation of vascular 5-HT$_{1B}$ receptors in the periphery seems to be associated with the angina pectoris-like side effects induced by triptans [4].

This study was designed to demonstrate that the guinea-pig iliac artery is a reliable rodent model to study 5-HT$_{1B}$-receptor-mediated vasoconstrictions by potential antimigraine drugs.

Methods

Ring segments of each guinea-pig common iliac artery were prepared and isometrically mounted in organ baths filled with modified Krebs-Henseleit solution and aerated with 95% O_2 and 5% CO_2 as previously described [5]. The preparations were exposed to 30 µM $PGF_{2\alpha}$ to observe the maximal contractile response. After reequilibration one cumulative concentration-response curve to 5-HT, 5-CT or triptans was recorded in the absence or presence of antagonist (1 or 10 nM GR127935; 3 or 10 nM SB216641; 30 min incubation) following moderate precontraction with $PGF_{2\alpha}$ (10-20% maximal contraction). Effects mediated by 5-HT$_{2A}$ receptors were prevented by addition of 1 µM ketanserin.

Effects of 5-HT, 5-CT, and triptans

1. 5-HT, 5-CT, and triptans caused concentration-dependent contractions in guinea-pig iliac artery (Fig. 1, Tab. 1).
2. The CRCs to 5-HT, 5-CT, sumatriptan, almotriptan, rizatriptan, and naratriptan were monophasic, but the CRC to eletriptan was biphasic (1st phase: 0.01 - 3 µM; 2nd phase >10 µM).
3. Triptans showed differences in their onset kinetics. Contractions by eletriptan were slower than those induced by other triptans (Fig. 2).

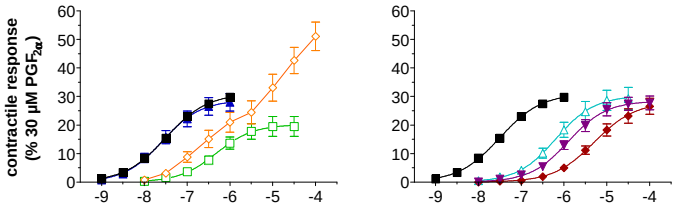

Fig. 1: Contractile responses to 5-HT (■), 5-CT (▲), eletriptan (◇), rizatriptan (□), naratriptan (△), sumatriptan (▼), and almotriptan (◆).

Tab. 1: Agonist efficacies and potencies of triptans in guinea-pig iliac artery

	n	E_{max} [a]	pD_2
5-HT	46	31 ± 1	7.50 ± 0.02
5-CT	12	29 ± 3	7.55 ± 0.06
Sumatriptan	12	28 ± 2	5.88 ± 0.05
Almotriptan	11	28 ± 3	5.25 ± 0.06
Eletriptan	9	26 ± 4	6.62 ± 0.05
Rizatriptan	6	20 ± 4	6.34 ± 0.06
Naratriptan	6	30 ± 4	6.18 ± 0.06

[a] % 30 µM $PGF_{2\alpha}$

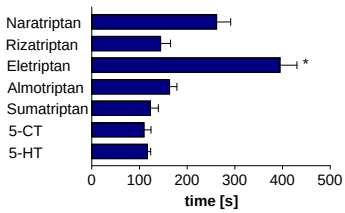

Fig. 2: Time to attain the contractile response at the EC_{50} value.* P < 0.05

References

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Acknowledgements. The authors are indebted to Dr. W. Schunack for generous support of the studies. The generous gifts of drugs by the pharmaceutical companies are gratefully acknowledged.

Effects of GR127935 and SB216641

1. GR127935 and SB216641 inhibited the contractile effects to 5-HT, 5-CT, and triptans at low nanomolar concentrations (1 - 10 nM; Fig. 3).
2. Both GR127935 and SB216641 inibited the contractions to low concentrations of eletriptan but failed to inhibit those of high concentrations (Fig. 3).

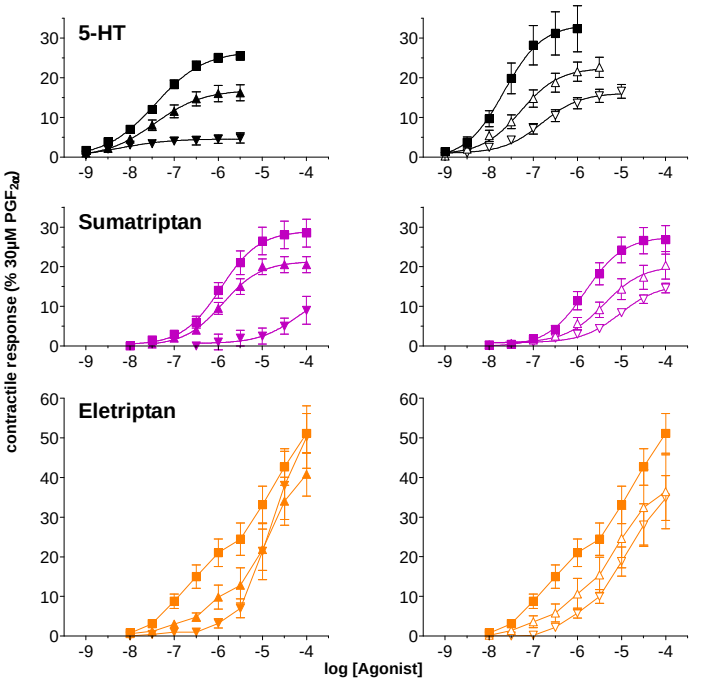

Fig. 3: Inhibition of the contractile responses to 5-HT (top), sumatriptan (middle), and eletriptan (bottom) by 1 nM (▲, ▲, ▲), 10 nM (▼, ▼, ▼) GR127935, and by 3 nM (△, △, △) and 10 nM (▽, ▽, ▽) SB216641.

Correlation analysis

1. The pD_2 values of 5-HT, 5-CT, sumatriptan, rizatriptan, and naratriptan in guinea-pig iliac artery positively correlate with the pD_2 values at native rodent 5-HT$_{1B}$ receptors [6] and with binding affinities (pK_i) at recombinant gp 5-HT$_{1B}$ receptors [7] (Fig 4).

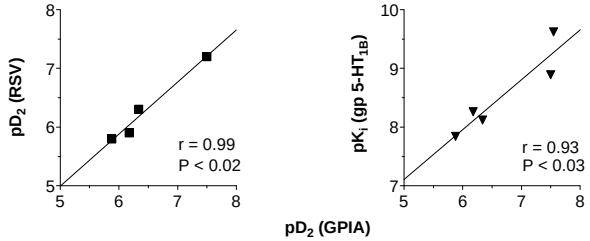

Fig. 4: Correlation between pD_2 values in guinea-pig iliac artery and in rabbit saphenous vein (left). Correlation between pD_2 values in guinea-pig iliac artery and binding affinities at recombinant guinea-pig 5-HT$_{1B}$ receptors (right).

Conclusions

- 5-HT, 5-CT, and triptans mediate contractions in guinea-pig iliac artery via 5-HT$_{1B}$ receptors.
- The guinea-pig iliac artery is a convenient functional assay to describe vascular effects of potential antimigraine drugs.
- Contractions to high concentrations of eletriptan were mediated by other receptors than 5-HT$_{1B}$ or 5-HT$_{1D}$. Further investigations are required.