Selectivity Profile of 1-Allylergopeptines at Different 5-HT Receptors and α_1 Adrenoceptors

Sven Jähnichen[1], Erika Glusa[2], Heinz H. Pertz[1]

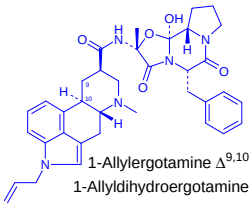
[1]Institute of Pharmacy, Free University of Berlin, Königin-Luise-Str. 2+4, 14195 Berlin, Germany
[2]Center for Vascular Biology and Medicine, Friedrich-Schiller-Universisty Jena, Nordhäuser Str. 78, 99089 Erfurt, Germany

P:P13

Introduction

Ergotamine and dihydroergotamine (DHE) are used in migraine therapy for over 50 years. It has been shown that both compounds possess high affinity for α-adrenoceptors, dopamine receptors and nearly all subtypes of 5-HT receptors with low or missing selectivity among the different subtypes [1]. The efficacy of ergotamine and DHE in migraine therapy has been associated with the potent partial agonism of both at cerebral 5-$HT_{1B/1D}$ receptors. However, other vascular receptors, such as α_{1B} adrenoceptors and 5-HT_{2B} receptors, may also be involved in migraine headache [2,3].

The aim of the present study was to show, whether the pharmacological properties of ergotamine and DHE at different 5-HT receptors and α_1 adrenoceptor subtypes might be influenced, if their structure was modified by introduction of an allyl group at the indole nitrogen.



1-Allylergotamine $\Delta^{9,10}$
1-Allyldihydroergotamine

Methods

Agonist and antagonist effects of ergotamine, DHE, 1-allylergotamine and 1-allyl-DHE were studied in ring preparations of rat thoracic aorta (RA: α_{1D}), guinea-pig iliac artery (GPIA: 5-HT_{1B}), rat tail artery (RTA: 5-HT_{2A}), and porcine pulmonary artery (PPA: 5-HT_{2B}) [4-6]. The effects of the compounds were further studied in prostatic portions of rat vas deferens (RVD: α_{1A}; non-cumulative CRCs) and in strips of guinea-pig spleen (GPS: α_{1B}) as previously described [7,8].

Effects at α_1 adrenoceptors

1. 1-Allylergotamine and 1-allyl-DHE were silent antagonists exhibiting moderate affinities at α_{1A}, α_{1B} and α_{1D} adrenoceptors and low discrimination between the three subtypes (Fig. 1-3).

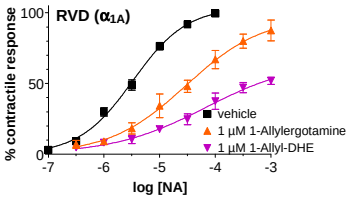


Fig. 1: Inhibition of NA-induced contractions in RVD.

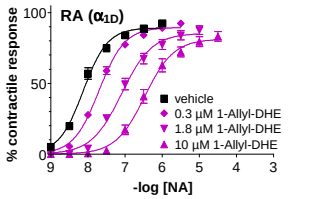


Fig. 2: Inhibition of NA-induced contractions in RA by 1-allyl-DHE.

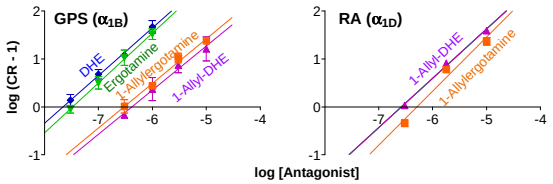


Fig. 3: Schild-Plots at α_{1B} adrenoceptors in GPS (left) and at α_{1D} adrenoceptors in RA (right).

Effects at 5-HT_{1B} receptors

1. In contrast to ergotamine and DHE, the allyl-substituted derivatives showed no agonist activity at concentrations up to 1 µM.
2. Antagonist affinities (pK_B) for 1-allyl-substituted compounds were approximately 30-fold lower than the partial agonist affinities (pK_P) for ergotamine and DHE (Fig. 4).

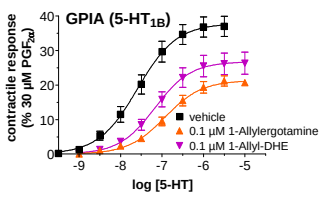


Fig. 4: Inhibition of 5-HT induced contractions in GPIA.

Effects at 5-HT_2 receptors

1. 1-Allyl-substitution reduced the intrinsic activities of ergotamine and DHE at 5-HT_{2A} receptors in rat tail artery. The affinities at 5-HT_{2A} receptors were moderately reduced (Fig. 5).
2. At 5-HT_{2B} receptors in porcine pulmonary arteries both, 1-allylergotamine and 1-allyl-DHE, were silent but insurmountable antagonists showing subnanomolar affinities (Fig. 6).

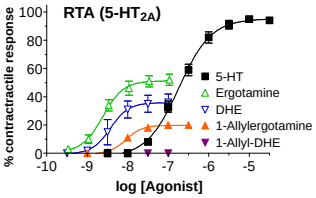


Fig. 5: Contractions in RTA.

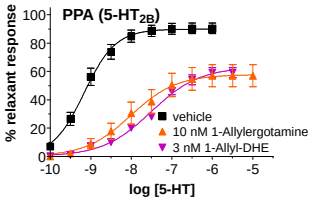


Fig. 6: Inhibition of relaxation to 5-HT in precontracted PPA.

Tab. 1: Agonist and antagonist affinities

	1-Allylergotamine				Ergotamine				
	conc. (µM)	*n*	*E_{max} (%)*	*affinity (pK_B, pK_P)*	*conc. (µM)*	*n*	*E_{max} (%)*	*affinity (pK_B, pK_P)*	*affinity ratio[e]*
RVD (α_{1A})	1	4	0	6.90 ± 0.09	0.03	3	0	8.17 ± 0.01[c]	0.05
GPS (α_{1B})	0.3 - 10	12	0	6.48 ± 0.05[d]	0.03 - 1	12	0	7.51 ± 0.06[d]	0.09
RA (α_{1D})	0.3 - 10	12	0	6.36 ± 0.06[d]		6	14±5	7.51 ± 0.14	0.07
GPIA (5-HT_{1B})	0.1 - 0.3	6	0	7.55 ± 0.25[c]	0.003	4	29±5	8.97 ± 0.06	0.04
RTA (5-HT_{2A})		5	21±3	7.85 ± 0.05			52± 4[a]	8.36 ± 0.11[a]	0.31
PPA (5-HT_{2B})	0.01	6	0	9.11 ± 0.18[c]			73[b]	8.17 ± 0.07[b]	8.3
	1-Allyldihydroergotamine				Dihydroergotamine				
	conc. (µM)	*n*	*E_{max} (%)*	*affinity (pK_B, pK_P)*	*conc. (µM)*	*n*	*E_{max} (%)*	*affinity (pK_B, pK_P)*	*affinity ratio[e]*
RVD (α_{1A})	1	4	0	7.22 ± 0.08[c]	0.03	3	0	8.03 ± 0.13[c]	0.15
GPS (α_{1B})	0.3 - 10	12	0	6.33 ± 0.09[d]	0.3 - 10	12	0	7.65 ± 0.05[d]	0.05
RA (α_{1D})	0.3 - 10	12	0	6.60 ± 0.04[d]		6	2±1	7.87 ± 0.15	0.05
GPIA (5-HT_{1B})	0.1 - 0.3	6	0	7.13 ± 0.16[c]	0.003	4	25±3	8.61 ± 0.09	0.03
RTA (5-HT_{2A})	0.1	5	0	7.65 ± 0.05[c]		5	38±6	8.23 ± 0.13	0.26
PPA (5-HT_{2B})	0.01	6	0	9.30 ± 0.07[c]			70[b]	7.70 ± 0.11[b]	40

[a] Data from [5]; [b] Data from [6]; [c] Insurmountable antagonism; [d] From Schild regression analysis (slope not significantly different from unity); [e] ratio of affinities (K_B or K_P) between unsubstituted and 1-allyl-substituted ergopeptines.

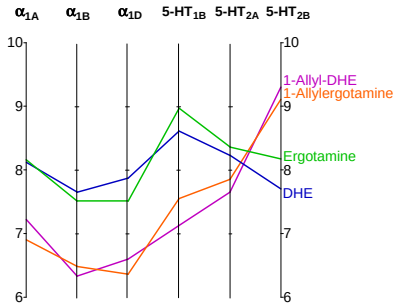


Fig. 7: Comparison of the affinities (pK_B or pK_P) for ergotamine, DHE, 1-allylergotamine and 1-allyl-DHE at different α_1 adrenergic, 5-HT_1 and 5-HT_2 receptor subtypes.

Conclusions

- Introduction of an allyl substituent at the indole nitrogen in ergopeptines causes decreased affinities at rodent 5-HT_{1B} receptors and at α_1 adrenoceptor subtypes but increases affinities at porcine 5-HT_{2B} receptors (Fig. 7).
- 1-Allylergotamine and 1-allyldihydroergotamine are selective but insurmountable antagonists exhibiting subnanomolar affinities at porcine 5-HT_{2B} receptor.
- Due to their potent 5-HT_{2B} receptor antagonism, 1-allylergopeptines might be effective drugs in migraine prophylaxis.

References

[1] Tfelt-Hansen P. et al. (2000); Brain 123: 9-18.
[2] Schmuck K. et al. (1996); Eur. J. Neurosci. 8: 959-967.
[3] Willems E.W. et al. (2001); Cephalalgia 21: 110-119.
[4] Pertz H.H. (1993); Naunyn-Schmiedeberg's Arch. Pharmacol 348: 558-565.
[5] Schöning C. et al. (2001); J. Anim. Sci. 79: 2202-2009.
[6] Glusa E. and Pertz H.H. (2000); Br. J. Pharmacol. 130: 692-698.
[7] Eltze M. and Boer R. (1992); Eur. J. Pharmacol. 224: 125-136.
[8] Eltze M. (1994); Eur. J. Pharmacol. 260: 211-220.

Acknowledgements. The authors are indebted to Dr. W. Schunack for generous support of the studies and to Dr. M. Flieger for the generous gifts of drugs.