Pergolide and Cabergoline But not Lisuride Exhibit Agonist Efficacy at Serotonin 5-HT_{2B} Receptors

Jähnichen S.[1], Horowski R.[2] & Pertz H.H.[1]

[1]Institut für Pharmazie, Freie Universität Berlin, 14195 Berlin, Germany

[2]NeuroBiotec GmbH, 13353 Berlin, Germany

Risk of Valvular Heart Disease

Articles

Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease

Guy Van Camp, Anja Flamez, Bernard Cosyns, Caroline Weytjens, Luc Muyldermans, Michel Van Zandijcke, Johan De Sutter, Patrick Santens, Pierre Decoodt, Christian Moerman, Danny Schoors

Van Camp et al. (2004). Lancet **363**:1179-1183

Nebenwirkungen

HERZKLAPPENERKRANKUNGEN UNTER PERGOLID (PARKOTIL)

Pleurafibrosen, Perikarderguss, retroperitoneale Fibrosen und andere fibrotische Erkrankungen sind unter der PARKINSON-Behandlung mit dem Mutterkornalkaloid Pergolid (PARKOTIL) beschrieben (vgl. a-t 2002; 33: 96). Seit 2002 weisen mehrere Einzelberichte auch auf einen Zusammenhang mit klinisch relevanten Herzklappenerkrankungen hin.[1,2] In einer einjährigen Beobachtungsstudie mit PARKINSON-Patienten wird jetzt versucht, Häufigkeit und Ausmaß der Klappenveränderungen bei Dauerbehandlung mit Pergolid zu

arznei-telegramm (2004) **35**:52

Food and Drug Administration
MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program

2003 Safety Alert - Permax (pergolide mesylate)

Dear Health Care Professional,

During postmarketing surveillance for Permax®, a small number of individuals ha been identified as developing cardiac valvulopathy involving one or more valves during Permax therapy. Based on Lilly safety data and scientific publications, the pathological assessment of valves that were surgically removed was consistent with the valvulopathy associated with carcinoid syndrome and with the use of othe ergot alkaloid drugs. While a clear causal relationship between pergolide and the

FDA (2003). http://www.fda.gov/medwatch/...

Risk of Valvular Heart Disease

- Pergolide has been associated with:
  - Retroperitoneal, pleural, and pericardial fibrosis
  - Valvular heart disease[1]
- Possible involvement of 5-HT_{2B} receptors:
  - Fibrotic changes were also observed for ergolines (eg, methysergide), anorectics (fenfluramine, aminorex)[2], and MDMA[3]
  - These compounds or their metabolites are agonists at 5-HT_{2B} receptors
  - 5-HT produces mitogenic effects in cardiac fibromyoblasts via activation of 5-HT_{2B} receptors[3]

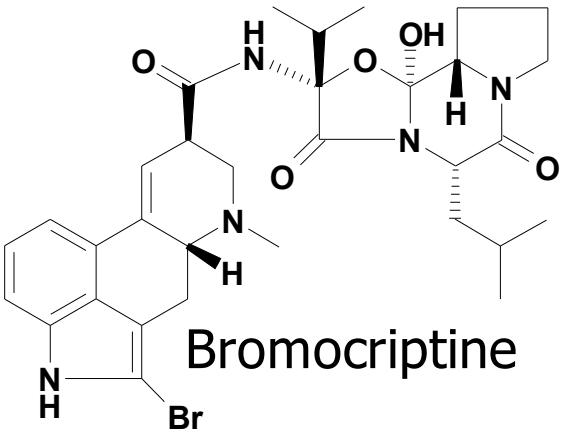
[1]Van Camp *et al*. (2004). *Lancet* **363**:1179-1183 [2]Launay *et al*. (2002). *Nature Med*. **8**:1129-1135
[3]Setola *et al*. (2003). *Mol. Pharmacol*. **63**:1223-1229

Aims

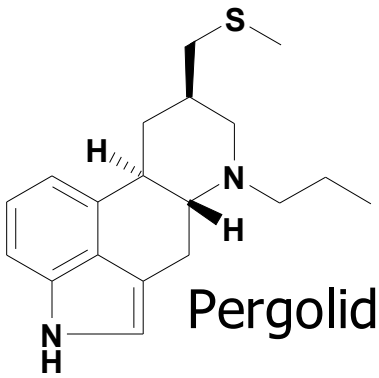
1. Can the cardiac valvulopathy induced by ergolines be related to their agonist properties at 5-HT_{2B} receptors?

2. Are the pergolide-induced cardiovascular effects mediated by 5-HT_{2B} receptors a general phenomenon of the ergoline-class?

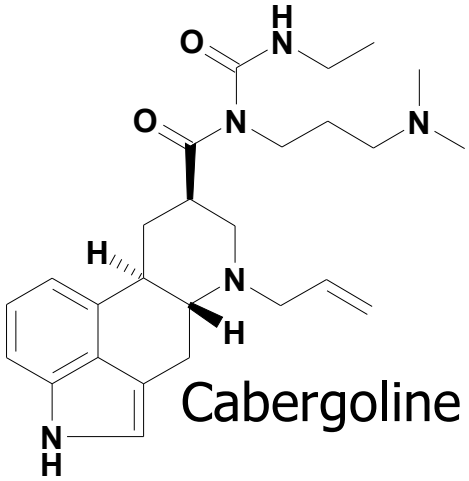
Ergolines in Therapy of Parkinson‘s Disease



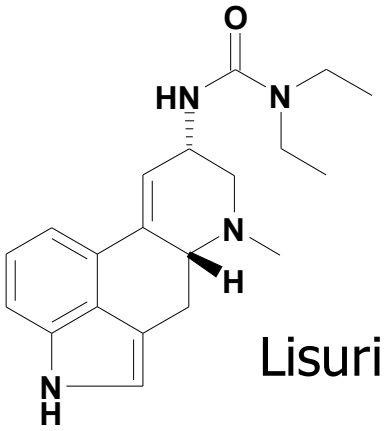
Bromocriptine



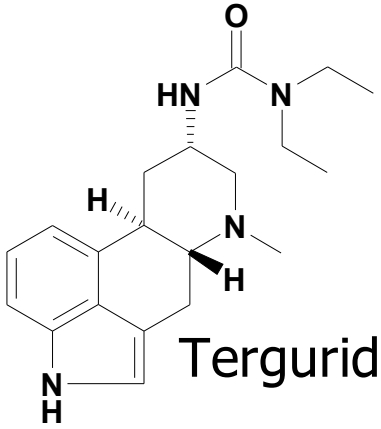
Pergolide



Cabergoline



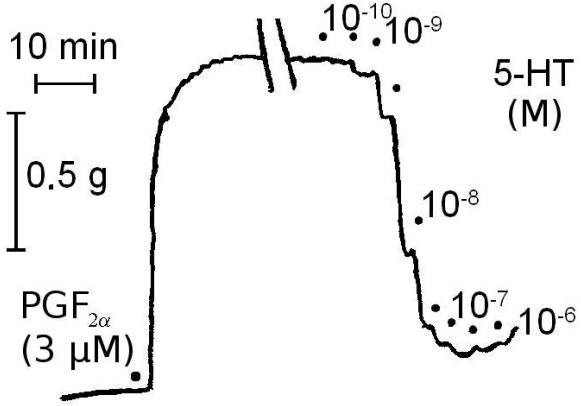
Lisuride

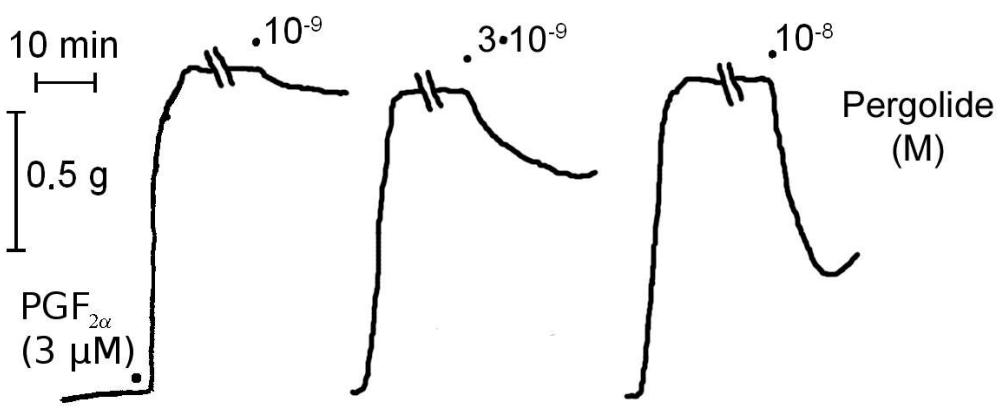


Terguride

Pig Pulmonary Arteries (PPAs)

- Pharmacological characterization of ergolines in $PGF_{2\alpha}$-precontracted PPAs
- 5-HT relaxes PPAs via
  - Activation of endothelial $5\text{-}HT_{2B}$ receptors[1]
  - Release of NO[1]

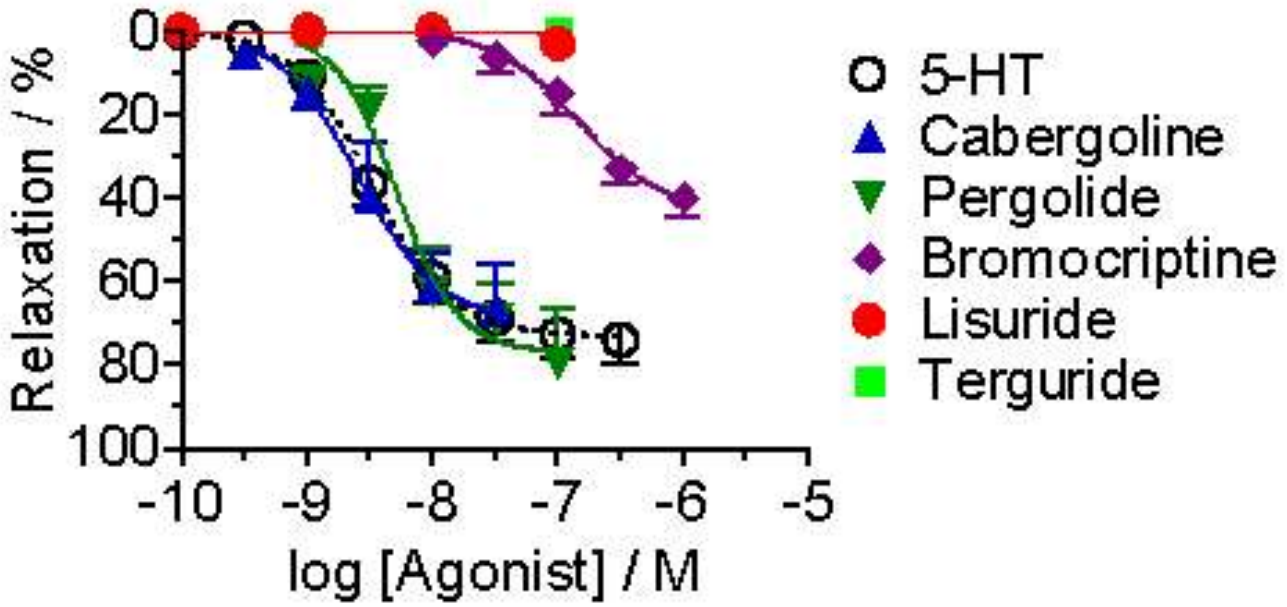




[1]Glusa & Pertz (2000). *Br. J. Pharmacol.* **130**:692-698

Relaxation of PPAs

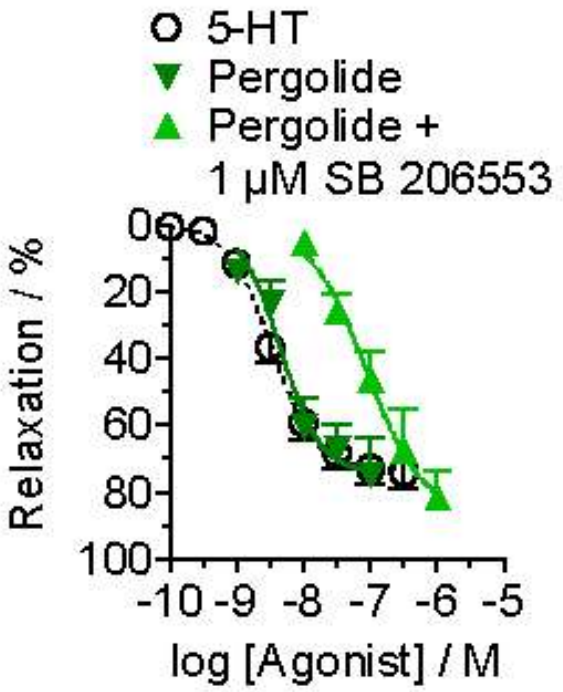
- Pergolide and cabergoline are full agonists in PPAs
- Bromocriptine acts as a partial agonist in PPAs
- No relaxant response to lisuride and terguride in PPAs

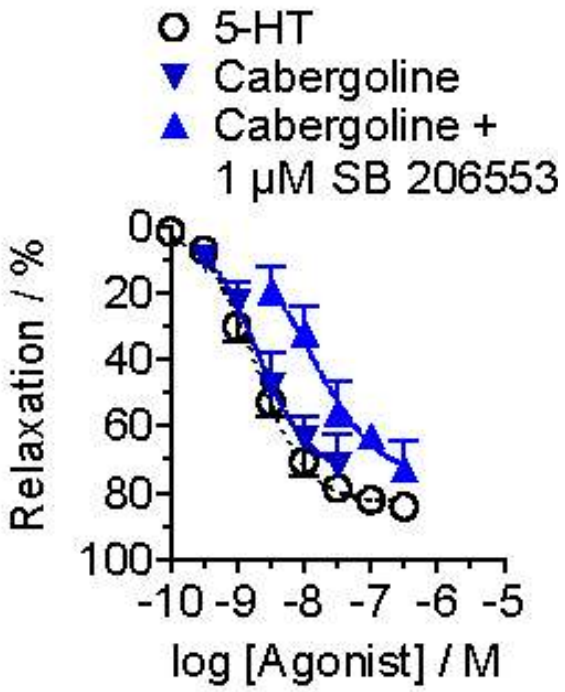


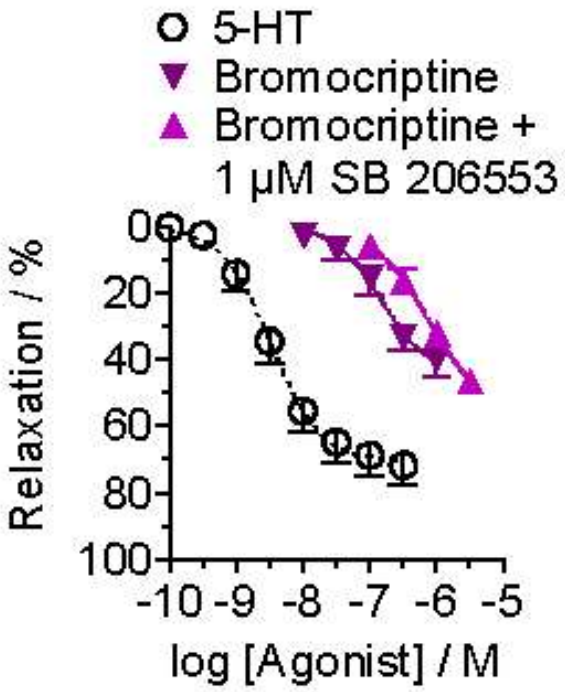
Relaxation of PPAs

- Relaxant responses to pergolide, cabergoline, and bromocriptine were antagonized by SB 206553

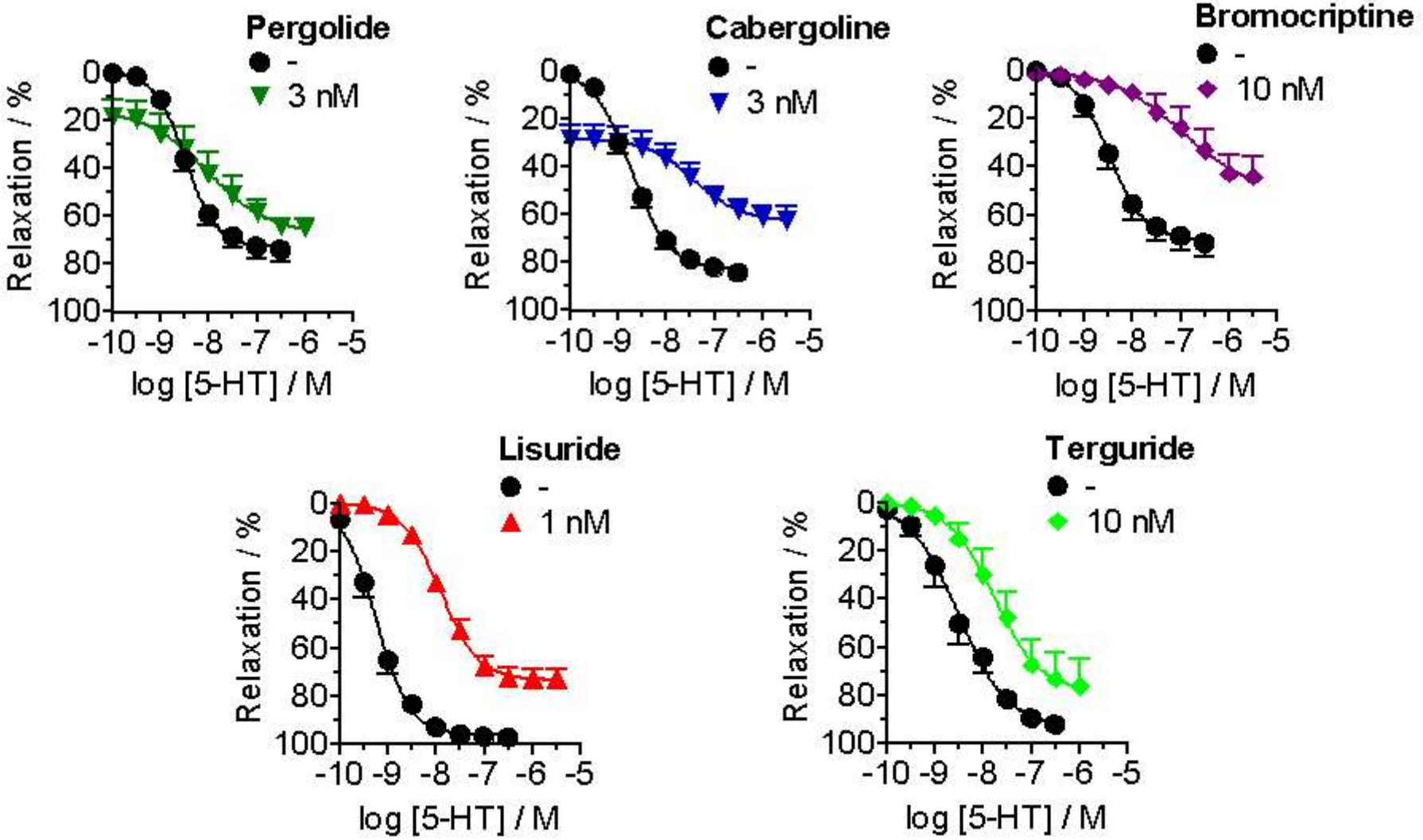
⇨ 5-HT_{2B} receptors are involved in relaxation to the agonists







Inhibition of the 5-HT-Response



Pharmacological Parameters

	Agonist profile			Antagonist profile	
	n	pEC_{50}	E_{max} (%)[a]	n	pK_P or pK_B
Pergolide	5	8.42 ± 0.11	98 ± 12	5	9.14 ± 0.23
Cabergoline	5	8.72 ± 0.14	86 ± 7	4	9.54 ± 0.20
Bromocriptine	4	6.86 ± 0.12	64 ± 8	4	9.39 ± 0.21
Lisuride	3	-	0	4	10.32 ± 0.10
Terguride	3	-	0	5	8.49 ± 0.11

[a]E_{max}(5-HT) = 100%

- Rank order of agonist potency:

cabergoline > pergolide >> bromocriptine

Correlation with Valvular Heart Disease

	Agonist potency (5-HT_{2B})	Valvular heart disease	Pulm. fibrosis[1]	Pleural fibrosis[1]	Retroper. fibrosis[1]
Pergolide	+++	+++	++	++	++
Cabergoline	+++	+	+	+	-
Bromocriptine	+	+	++	+	+
Lisuride	-	-	-	(+)	(+)
Terguride	-	-	-	-	-

- Ergoline induced cardiac valvulopathy and fibrosis correlates with agonist potency at 5-HT_{2B} receptors

[1]*Curr. Probl. Pharmacovigilance* (2002) **28**:3 (modified)

Conclusions

- Pergolide, cabergoline, and bromocriptine behave as (partial) agonists at 5-HT_{2B} receptors, whereas lisuride and terguride are silent antagonists
- Ergoline induced valvular heart disease correlates with agonist potency at 5-HT_{2B} receptors

⇨ Agonism at 5-HT_{2B} receptors is not a class effect of ergolines

⇨ Further clinical investigations are required

Acknowledgments

- NeuroBiotec GmbH, Berlin (financial support and supporting informations)

B. Schurad	NeuroBiotec, Berlin
K. Ackermann	FU Berlin
T. Görnemann	FU Berlin

Thank you !