Structure-activity relationship of compounds which block receptors for 5-hydroxytryptamine on the sympathetic nerves of the rabbit heart

J.R. FOZARD, A.T.M. MOBAROK ALI & E. MUSCHOLL

Department of Pharmacology, Materia Medica and Therapeutics, The University, Manchester M13 9PT

5-Hydroxytryptamine (5-HT) stimulates noradrenaline release from the sympathetic nerves of the rabbit heart by activating tryptamine receptor sites (Fozard & Mobarok Ali, 1976a). Responses can be selectively inhibited by 5-HT and several of its analogues (Fozard & Mobarok Ali, 1976b) and by (−)- and (+)-cocaine (Fozard, Mobarok Ali & Newgrosh, 1977). This report details the changes in 5-HT inhibitory activity as a result of changes in structure in a series of compounds related to cocaine.

Rabbit hearts were perfused as previously described (Fozard & Muscholl, 1971) and pA_2 values (Schild, 1947) were determined using cardiac rate as the index of the response. DMPP was used as the reference substance since it acts on a different population of neuronal receptors. The results are as shown in the table.

The fact that both (+)-cocaine and neopsicaine were as active against 5-HT as (−)-cocaine suggests that substitution at the 2 position is not important for the blocking activity. This is confirmed by the data with tropacocaine which shows both potency and selectivity as an antagonist of 5-HT but has no substituent at position 2. If the substituent in position 3 is replaced by −OH (tropine) or tropic acid (atropine) introduced in the trans position to the bridge nitrogen atom, both potency and selectivity is lost. Thus the position of the aromatic ring relative to the bridge nitrogen seems to be critical for 5-HT inhibitory activity. The much simpler compounds, procaine and metoclopramide, which are similar to the cocaine derivatives with respect to the distance between an aromatic ring and a nitrogen atom, also show selective 5-HT blocking activity. In contrast, lignocaine, although a potent local anaesthetic, has one less atom in the chain connecting its aromatic ring with the terminal nitrogen atom and is neither potent nor selective as an antagonist of 5-HT.

References

FOZARD, J.R. & MOBAROK ALI, A.T.M. (1976a). Evidence for tryptamine receptors on cardiac sympathetic nerves. *Br. J. Pharmac.*, **58**, 276P–277P.

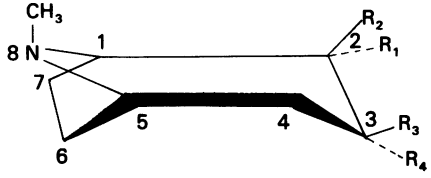
FOZARD, J.R. & MOBAROK ALI, A.T.M. (1976b). Inhibition of the stimulant effect of 5-hydroxytryptamine on cardiac sympathetic nerves by 5-hydroxytryptamine and related compounds. *Br. J. Pharmac.*, **58**, 416P–417P.

FOZARD, J.R., MOBAROK ALI, A.T.M. & NEWGROSH, G. (1977). Selective blockade of presynaptic tryptamine receptors by (−)-cocaine and (+)-cocaine. *Br. J. Pharmac.* (in press).

FOZARD, J.R. & MUSCHOLL, E. (1971). A useful muscarinic parameter and the differential recording of atrial and ventricular tension in the perfused rabbit heart. *Naunyn-Schmiedeberg's Arch. Pharmak.*, **270**, 319–325.

SCHILD, H.O. (1947). pA, a new scale for the measurement of drug antagonism. *Br. J. Pharmac. Chemother.*, **2**, 189–206.

Table 1 Structure activity relationship of compounds which block the cardiac stimulant responses to 5-hydroxytryptamine (5-HT) and dimethylphenylpiperazinium (DMPP)



Compound	R_1	R_2	R_3	R_4	pA_2 *vs 5-HT**	n	pA_2 *vs DMPP**	n	pA_2*(5-HT)*–pA_2*(DMPP)*
(–)-Cocaine	H	$COOCH_3$	OCO⟨⟩	H	6.24 ± 0.08	4	4.95 ± 0.09	3	1.29
(+)-Cocaine	$COOCH_3$	H	OCO⟨⟩	H	6.90 ± 0.07	3	5.02 ± 0.003	3	1.88
Neopsicaine	$COOC_3H_7$	H	OCO⟨⟩	H	6.35 ± 0.13	3	5.14 ± 0.02	3	1.21
Tropacocaine	H	H	OCO⟨⟩	H	6.77 ± 0.08	3	4.83 ± 0.12	3	1.94
Tropine	H	H	H	OH	4.17 ± 0.11	3	4.26 ± 0.15	3	–0.09
Atropine	H	H	H	OCOCH(⟨⟩)CH_2OH	4.83 ± 0.09	3	4.63 ± 0.04	3	0.20
Procaine	$(C_2H_5)_2$ N CH_2CH_2OCO⟨⟩			NH_2	5.58 ± 0.07	3	4.13 ± 0.06	3	1.45
Metoclopramide	$(C_2H_5)_2$ N CH_2CH_2NHCO(2-OCH_3, 5-Cl⟨⟩)			NH_2	7.26 ± 0.09	3	4.51 ± 0.11	3	2.75
Lignocaine	$(C_2H_5)_2$ N CH_2CONH(2,6-CH_3⟨⟩)				3.87 ± 0.09	3	4.16 ± 0.09	3	0.29

* Mean values with standard errors.