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Hypotensive and sedative properties of α-adrenoceptor agonists: relation to pre- and post-synaptic stimulation

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We have previously reported on the separation between antihypertensive and sedative effects in a series of centrally acting α-adrenoceptor stimulants when compared with clonidine (Clough, Hatton, Pettinger, Samuels & Shaw, 1978). The potency of the same compounds as sedatives has been further investigated using halothane sleeping time and locomotor activity in rats. Hypotensive activity was measured in the anaesthetized rat and potency at pre-synaptic α-adrenoceptors was measured in the pithed rat (Drew, 1976) and in the field stimulated mouse vas deferens. Potency at post-synaptic α-adrenoceptors was measured in the pithed rat.

ICI 106270 was 4.5 times less potent as a hypotensive agent, 33 times less potent as a sedative in the sleeping time test, and 16 times less potent on locomotor activity relative to clonidine (Table 1). ICI 110802, which lowered blood pressure as effectively as ICI 106270 was 20 times less potent on locomotor activity and did not effect halothane sleeping time (Table 1). There is thus a separation between sedative and hypotensive activity in these compounds compared with clonidine.

In the pithed rat there was no significant difference between ICI 101187, ICI 106270, and clonidine at post-synaptic α-adrenoceceptors. This could therefore not explain the difference in sedative properties of these compounds.

ICI 101187 and clonidine also had similar effects as pre-synaptic α-adrenoceptor stimulants so this also could not explain the different sedative effects. However the two least potent compounds as pre-synaptic α-adrenoceptor agonists, ICI 106270 and ICI 110802, were also considerably less active as sedatives (Table 1).

Two other α-adrenoceptor stimulants, lofexidine and guanfacine, have been compared with clonidine in the halothane sleeping time test and also in the pithed rat (Table 1). The relative lack of sedation with guanfacine was also associated with reduced potency as a pre-synaptic α-adrenoceptor agonist while sedation approaching that of clonidine was observed with lofexidine, an equally potent pre-synaptic α-adrenoceptor agonist. Thus it would appear that the occurrence of sedation in these α-adrenoceptor stimulants was related in some way to their pre-synaptic but not to their post-synaptic properties. However, clonidine was more active as a sedative than this data alone would predict and this may be attributed to a further undefined property of clonidine. The ability to lower BP was unrelated to the pre-synaptic α-adrenoceptor agonist actions of the compounds but appeared to be more related to the post-synaptic activity. Again clonidine was more potent than would be predicted from this data alone.

References

CLOUGH, D.P., HATTON, R., PETTINGER, S.J., SAMUELS, GILLIAN M.R. & SHAW, A. (1978). Substituted aryltetrahydro pyrrolo imidazoles: a new class of centrally acting antihypertensives. *Br. J. Pharmac.*, **62**, 385–386P.

DREW, G.M. (1976). Effects of α-adrenoceptor agonists and antagonists on pre- and post-synaptically located α-adrenoceptors. *Eur. J. Pharmac.*, **36**, 313–320.

Table 1 The potency of various α-adrenoceptor stimulants as hypotensive and sedative agents; relation to potency at pre- and post-synaptic α-adrenoceptors.

Compound ICI No.	*Anaesthetized rat BP ED_{50} μg/kg i.v. (Mean and s.e. mean)*	*Relative sleeping time clonidine = 1*	*Locomotor activity ED_{50} μg/kg i.v. (Mean and s.e. mean)*	*Pithed rat $ED_{50}HR$ μg/kg i.v. mean ± s.e. mean*	*Pithed rat $ED_{50}BP$ μg/kg i.v. mean ± s.e. mean*	*Pithed rat $ED_{50}BP$ / $ED_{50}HR$ mean ± s.e. mean*	*Vas deferens $I.C._{50}$ ng/ml mean ± s.e. mean*
Clonidine	1.2 (0.6–2.3)	1	15.3 (10.1–23.3)	19.4 ± 4.4	8.3 ± 2.1	0.54 ± 0.16	2.5 ± 0.27
101187	5.1 (4.2–6.2)	0.1	194.2 (130.6–288.7)	9.3 ± 1.5	5.3 ± 1.1	0.66 ± 0.18	2.6 ± 0.60
106270	5.5 (4.1–7.2)	0.03	237.5 (163.6–344.9)	63.2 ± 13.1	8.7 ± 3.1	0.20 ± 0.11	15.7 ± 3.80
110802	5.4 (3.9–7.6)	0	312.5 (186.7–521.1)	78.5 ± 18.0	3.2 ± 0.2	0.08 ± 0.04	>20
Lofexidine	—	0.3	—	13.6 ± 4.85	9.0 ± 1.9	1.05 ± 0.34	—
Guanfacine	—	0.1	—	82.2 ± 4.98	138.6 ± 62.0	2.33 ± 0.94	—

Anaesthetized rat BP ED_{50} = dose to lower BP by 20 mmHg.
Locomotor activity ED_{50} = dose to reduce control activity by 50%.
Pithed rat ED_{50} HR = dose to reduce increment in HR due to stimulation by 50%.
Pithed rat ED_{50} BP = dose to increase BP by 50 mm Hg.
Vas deferens IC_{50} = dose to decrease twitch response by 50%.