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α_1-Adrenoceptor agonist activity of α_2-adrenoceptor antagonists in the pithed rat preparation

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The selective α_2-adrenoceptor antagonist, RX781094, evoked a dose-related pressor response in the pithed rat preparation when administered in bolus doses by the intravenous route. This response was enhanced following depletion of endogenous amines by reserpine, and inhibited by the selective α_1-adrenoceptor antagonist, prazosin. Two other selective α_2-adrenoceptor antagonists, Wy 26703 and Wy 26392, had no marked effect on the blood pressure of this preparation. Pretreatment of the preparation with Wy 26703 had no significant effect on the pressor response evoked by RX781094.

It is concluded that RX781094 is an α_1-adrenoceptor agonist at similar doses to those at which it exhibits α_2-adrenoceptor antagonist properties. The agonist activity exhibited by RX781094 is not a general property of all α_2-adrenoceptor antagonists and should be considered when this compound is employed as an α_2-adrenoceptor antagonist.

Introduction Following the classification of α-adrenoceptors into α_1- and α_2-subgroups (Langer, 1974), compounds have been sought which exhibit selectivity for each of these receptors. Antagonists with selectivity for the α_1-subtype, such as prazosin (Cambridge, Davey & Massingham, 1977) and indoramin (Rhodes & Waterfall, 1978), have been available for several years, but it is only comparatively recently that antagonists selective for the α_2-subtype have been described. The pharmacological profile of these new compounds is incomplete and one of them, RX781094 (Chapleo, Doxey, Myers & Roach, 1981), has been reported to have partial agonist activity *in vivo* and *in vitro* (Dalrymple, Hamilton, Hannah & Reid, 1983). In order to determine whether this property is a common feature of α_2-adrenoceptor antagonists we have compared the effects of two selective antagonists Wy 26703 and Wy 26392 (Pierce & Waterfall, 1982) with that of RX781094 in the pithed rat preparation.

Methods Female Sprague-Dawley rats (230–270 g) were anaesthetized with halothane (5% in O_2). The trachea, left carotid artery and jugular vein were cannulated. After bilateral vagotomy the rats were pithed with a steel rod and artificially ventilated (55 strokes min^{-1}, 10 ml kg^{-1}). Blood pressure was recorded on a Grass polygraph via a Statham P23D pressure transducer. Drugs were administered via the jugular vein. Deep body temperature was maintained at 37°C by means of a heating blanket.

Following a period of equilibration, saline (1.0 ml kg^{-1}), prazosin (0.1 mg kg^{-1}), Wy 26703 (1.0 mg kg^{-1}) or a combination of the latter two were administered intravenously. Fifteen minutes later a cumulative dose-response curve was constructed for RX781094. In a further series of experiments saline (1.0 ml kg^{-1}) was administered and 15 min later a cumulative dose-response curve was constructed to either Wy 26703 or Wy 26392.

One group of rats was pretreated 24 h before use with reserpine (5 mg kg^{-1} s.c.). Noradrenaline concentrations (measured in the atria) were decreased by 96% by this treatment (Dr M. Wyllie, personal communication).

The dose of RX781094 required to evoke a 50 mmHg rise in diastolic blood pressure (ED_{50} mmHg) was calculated for each experimental group and is given as the mean ± s.e.mean for each group.

The following compounds were used: RX781094 (2 - (2(1,4 - benzodioxanyl)) - 2 - imidazoline HCl), Wy 26392 (N - methyl - N - (1,3,4,6,7,11b α - hexahydro - 2H - benzo - [a] - quinolizin - 2β - yl) propane - 1 - sulphonamide HCl), Wy 26703 (N - methyl - N - (1,3,4,6,7,11bα - hexahydro - 2*H* - benzo - [a] - quinolizin - 2β - yl) - i - butanesulphonamide HCl) synthesized in the Department of Chemistry, Wyeth Laboratories, prazosin (Pfizer Ltd,) and reserpine (Koch-Light).

Statistical testing between the pressor response curves to RX781094, Wy 26703, Wy 26392 and saline vehicle was performed by nested analysis of variance.

Log dose-response curves to RX781094 alone and in the presence of prazosin and/or Wy 26703 were checked for parallelism and the significance of the differences between them determined by a probit transformation and an analysis of covariance on regression (Snedecor & Cochran, 1980; Sokal & Rohlf, 1981).

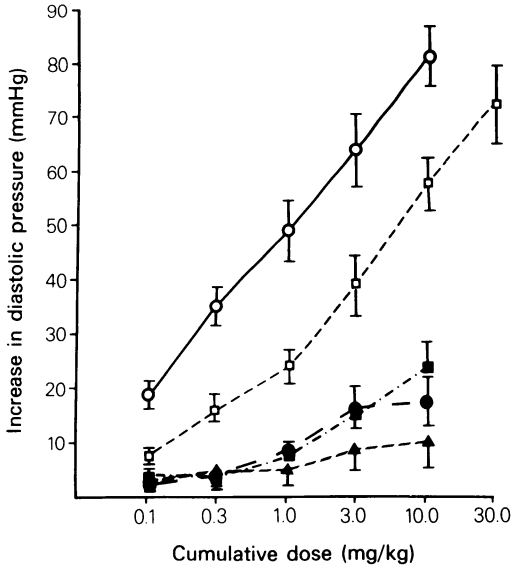

Figure 1 Pressor responses evoked by intravenous doses of RX781094 (○, $n = 4$), Wy 26703 (■, $n = 4$), Wy 26392 (●, $n = 4$). In one group of experiments the preparation was pretreated with prazosin (0.1 mg/kg) 15 min before constructing the dose-response curve to RX781094 (□, $n = 4$). In the control curve (▲, $n = 4$) saline alone was administered in volumes equivalent to those employed for the administration of each of the α_2-adrenoceptor antagonists. Diastolic pressure before drug administration was 39.5 ± 1.2 mmHg (mean ± s.e.mean; $n = 20$).

Results Cumulative administration of RX781094 ($0.1-10.0$ mg kg^{-1}) evoked a dose-dependent pressor response in the pithed rat (Figure 1, ED_{50} mmHg $= 1.63 \pm 0.8$ mg kg^{-1}).

Depletion of the endogenous noradrenaline content of the preparation by reserpine pretreatment shifted the dose-response curve to the left (ED_{50} mmHg, 0.09 ± 0.03 mg kg^{-1}). Prazosin (0.1 mg kg^{-1}) evoked a significant ($P < 0.001$) and parallel shift in the RX781094 dose-response curve to the right (Figure 1, ED_{50} mmHg $= 7.9 \pm 3.2$ mg kg^{-1}). Wy 26703 (1.0 mg kg^{-1}) had no significant effect on the response curve to RX781094 (ED_{50} mmHg $= 1.7 \pm 0.7$ mg kg^{-1}). A combination of prazosin (0.1 mg kg^{-1}) and Wy 26703 (1.0 mg kg^{-1}) evoked a parallel shift to the right in the response curve to RX781094 of the same magnitude (ED_{50} mmHg $= 6.1 \pm 0.2$ mg kg^{-1}) as that obtained with prazosin alone.

Cumulative administration of saline (1.0 ml kg^{-1}) evoked small pressor responses in the pithed rat which did not exceed 10.0 ± 4.6 mmHg ($n = 4$) following the last dose (Figure 1). Cumulative dosing of the preparation with Wy 26703 or Wy 26392 ($0.1-10.0$ mg kg^{-1}) evoked pressor responses of 23.8 ± 4.7 and 17.5 ± 4.3 mmHg respectively at a dose of 10 mg kg^{-1} (Figure 1). Statistical analysis (nested analysis of variance) between treatment groups showed that there was no significant difference between saline and Wy 26703 or Wy 26392 treatment. However, analysis of individual points on the dose-response curves revealed a significant difference between saline and both α_2-adrenoceptor antagonists at doses of 3 and 10 mg kg^{-1} ($P < 0.05$, Student's t test).

Discussion The selective α_2-adrenoceptor antagonist, RX781094, has been reported to evoke a pressor response in the conscious rabbit and a contractile response from the rabbit isolated aortic strip (Dalrymple *et al.*, 1983).

The pressor response to intravenous doses of RX781094 has now been confirmed in the pithed rat preparation. In this preparation RX781094 was both more potent and produced a greater pressor response than that observed in the rabbit. In the series of experiments described here, the maximum response was not obtained as the doses which could be given were limited by the solubility of the compound and the volume administered.

The response evoked by RX781094 was observed in pithed rats with and without reserpine treatment. Thus, neither endogenous noradrenaline, nor a tonically active sympathetic nervous system appears to be involved in the response. This indicates that blockade of presynaptic α_2-adrenoceptors, leading to an enhancement of neuronal release of noradrenaline (Langer, 1974) is not responsible for the pressor response.

Dalrymple *et al.* (1983) were unable to define the receptor subtype involved in the response to RX781094 and concluded that both postsynaptic α_1- and α_2-adrenoceptors may contribute. In the pithed rat the pressor response evoked by RX781094 was reduced by prazosin but not by the α_2-antagonist, Wy 26703, suggesting that only α_1-adrenoceptors mediate the response.

From results described here it is concluded that RX781094 is an α_1-adrenoceptor agonist in the pithed rat over the dose-range $0.1-10$ mg kg^{-1} i.v. Under very similar experimental conditions to those employed in this study, we have found this compound to be an α_2-adrenoceptor antagonist over the range $0.3-3$ mg kg^{-1} i.v. (Paciorek & Shepperson, unpublished observations).

A comparison of the effects of RX781094 with those of two other α_2-adrenoceptor antagonists, Wy 26703 and Wy 26392, revealed that only RX781094 evoked a marked pressor response in the

pithed rat. Thus, this α_1-adrenoceptor-mediated response appears to be a property of RX781094 in particular, and not of α_2-adrenoceptor antagonists in general. This pharmacological profile, combining α_1-agonism and α_2-antagonism is not unique, other compounds of this type have been described in the literature (BDF 6143 for example, Armah & Cohnen, 1982). In some experimental situations the effect of presynaptic α_2-adrenoceptor blockade and α_1-adrenoceptor agonism may be similar, and a compound having both properties may therefore exaggerate the response to presynaptic blockade. For this reason, the possibility that compounds may possess this profile must be considered when experiments are conducted to examine the effect of α_2-adrenoceptor blockade.

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