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Interaction of 2-[β-(4-hydroxyphenyl)ethylaminomethyl]tetralone (BE-2254: 'HEAT') with catecholamine receptors in rat brain membranes

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2-[β-(4-Hydroxyphenyl)ethylaminomethyl]-tetralone (BE-2254: 'HEAT') has been shown to block peripheral α-adrenoceptors (Benthe, Gothert & Tuchinda, 1972; Baumgarten, Gothert & others, 1972). Indirect pharmacological evidence indicates that BE-2254 administered systemically can also block central catecholamine receptors and impair catecholamine receptor-mediated responses (Clineschmidt, Pflueger & others, 1975a). In this latter study, BE-2254 was found to be approximately equipotent with chlorpromazine in blocking central noradrenaline receptors but was much less active than either chlorpromazine or haloperidol as a blocker of central dopamine receptors. Biochemical examination of the effects of BE-2254 on central catecholamine metabolism also indicated a preference of this compound for noradrenaline rather than dopamine receptors (Clineschmidt, Totaro & others, 1975b).

These studies have now been extended to the *in vitro* level by examining the affinity of BE-2254 for central α-, β- and dopaminergic catecholamine receptors using the following binding assays: α-receptor; binding of [^{3}H]dihydroergocryptine (^{3}H-DHE) (Greenberg & Snyder, 1977) and [^{3}H](2-([2′,6′-dimethoxy]phenoxyethylamino)methyl benzodioxan) (^{3}H-WB-4101) (Greenberg, U'Prichard & Snyder, 1976) to rat cerebral cortical membranes; β-receptor; binding of[^{3}H]dihydroalprenolol (^{3}H-DHA) to rat brain crude synaptosomal membranes (Alexander, Davis & Lefkowitz, 1975); dopamine receptor; binding of [^{3}H]haloperidol (^{3}H-HAL) to rat caudate membranes (Burt, Creese & Snyder, 1976). The ligand concentrations used, total radioactivity bound (d min^{-1} mg^{-1} original wet weight of tissue), total counts bound per assay tube and per cent specific binding were as follows: ^{3}H-DHE; 0·4 nM; 128 d min^{-1}; 1000 c min^{-1}; 70%: ^{3}H-WB-4101; 0·22 nM; 70 d min^{-1}; 530 c min^{-1}; 75%: ^{3}H-DHA; 18 nM; 168 d min^{-1}; 1600 c min^{-1}; 80%: ^{3}H-HAL; 1 nM, 840 d min^{-1}; 1600 c min^{-1}; 50%. Counting efficiency for the ^{3}H-ligand/filter disk complexes in Amersham PCS Scintillation cocktail was 38–40%.

* Correspondence.

^{3}H-DHE and ^{3}H-HAL were obtained from New England Nuclear (Boston, Mass.) and ^{3}H-DHA from Amersham (Clearbrook Heights, Chicago, Ill.). ^{3}H-WB-4101 was custom tritiated by New England Nuclear. Chlorpromazine, haloperidol, phentolamine and propranolol were tested as reference compounds. IC50 values were obtained by examining the compounds at three or four concentrations in triplicate in each experiment. Data thus obtained were analysed using a log concentration-percent response linear regression.

BE-2254 was effective in preventing the binding of ^{3}H-DHE and ^{3}H-HAL to their respective receptors (Table 1). The IC50 for the α-receptor ligand was about 10 times lower than that of the ligand for dopamine receptors. Because of the controversy related to the specificity of ^{3}H-DHE as an α-receptor ligand (Davis, Strittmatter & others, 1977; Tittler, Weinreich & Seeman, 1977), the effects of BE-2254 were also examined using ^{3}H-WB-4101, an α-antagonist. The IC50 of BE-2254 in the WB-4101 assay was 200 times lower than that seen in the ^{3}H-HAL binding assay. Whether this difference in the IC50 values in the α-binding assays represents different classes of binding sites remains to be seen (U'Prichard, Greenberg & Snyder, 1977); however the reported K_D's of the two α-ligands are similar (^{3}H-DHE; 0·8 nM [Greenberg & Snyder, 1977]; ^{3}H-WB-4101; 0·6 nM [Greenberg & others, 1976]). The binding of ^{3}H-DHA was not affected by BE-2254. This profile indicates that BE-2254 binds preferentially to central α-adrenoceptors, but, as previously reported does have some affinity for central dopamine receptors.

Chlorpromazine and haloperidol had, as expected, a high affinity for caudate dopamine receptors. Both compounds also showed a weaker affinity for the α-receptor, chlorpromazine being the more potent of the two. Neither of these neuroleptics affected ^{3}H-DHA binding, although propranolol, a reference β-adrenoceptor blocker, was effective in this assay.

Although BE-2254, haloperidol and chlorpromazine interact with both α-adrenoceptors and dopamine receptors, their ratios between the two binding assays

Table 1. *Effect of BE-2254 on binding of radiolabelled ligands to α-, β- and dopamine receptors in rat brain membrane preparations.* *Values given as the mean for three separate observations with the s.d where applicable.

	IC50 (nM)*				^{3}H-DHE	^{3}H-WB-4101
Compound	^{3}H-DHE	^{3}H-WB-4101	^{3}H-DHA	^{3}H-HAL	^{3}H-HAL	^{3}H-HAL
BE-2254	18·1 s.d. 2·6	0·94 s.d. 0·02	>10000	185 s.d. 50	0·1	0·005
Chlorpromazine	155·7 s.d. 59·0	5·3 s.d. 1·6	>10000	16·8 s.d. 1·6	9·3	0·32
Haloperidol	367·0 s.d. 135·0	38 s.d. 4	>10000	2·0 s.d. 0·2	181·0	19·0
Phentolamine	1·7 s.d. 0·3	7·4 s.d. 0·3	—	—	—	—
(—)-Propranolol	—	—	12·2 s.d. 1·0	—	—	—

indicate a degree of selectivity. Thus, while chlorpromazine and especially haloperidol exhibit a preference for dopamine receptors, BE-2254 has a preference for α-receptors (see Table 1). Compared with phentolamine, BE-2254 was about 10 times less potent in inhibiting the binding of ^{3}H-DHE but was, however, 8 times *more* potent than phentolamine in the ^{3}H-WB-4101 binding assay, once again raising the possibility of the existence of more than one type of α-receptor as defined by the binding of these two ligands. Since BE-2254 given systemically can antagonize central noradrenergic receptor-mediated responses, whereas phentolamine is ineffective in doing this (Clineschmidt & others, 1975a), it would appear that BE-2254 can be utilized *in vivo* for assessing the involvement of central-adrenoceptors in various behavioural and pharmacological responses. However, it is clear that the compound must be used at doses that delineate between its effects on central noradrenergic and dopaminergic mechanisms (Clineschmidt & others, 1975a).

The judicious use of BE-2254 together wih compounds such as haloperidol and dopamine-β-hydroxylase inhibitors, e.g. FLA-63, should prove useful in attempting to differentiate between noradrenaline and dopamine as the mediators of *in vivo* effects thought to have an underlying catecholaminergic basis.

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