New sympathomimetic amines: actions on catecholamine receptors

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Saligenin analogues of catecholamines have been reported to be potent, long acting sympathomimetic agents, active at α- and β-receptors and not susceptible to catechol-O-methyl transferase (Brittain, Farmer, Jack, Martin & Simpson, 1968; Hartley, Jack, Lunts & Ritchie, 1968). The activities of noradrenaline, adrenaline and isoprenaline at typical α- and β-adrenergic receptors are compared in Table 1 with those of their saligenin analogues—that is, AH.3364, AH.4053, AH.3021 respectively. Results are also given for AH.3365, the N-tertiary butyl homologue of AH.3021.

TABLE 1. *Relative activities at α- and β-receptors of N-substituted catechol and saligenin ethanolamines (isoprenaline or noradrenaline were assigned an activity of* 100 *as shown)*

Structure			Inhibition of acetylcholine induced bronchoconstriction in anaesthetized guinea-pigs (drugs and spasmogen injection i.v.)	Inhibition of response of isolated guinea-pig trachea to electrical stimulation	Positive inotropic action on isolated guinea-pig atria	Effects of drugs injected i.v. on diastolic blood pressure and heart rate of anaesthetized rats			
						Heart rate		Diastolic blood pressure	
Drug	R_1	R_2				Inc.	Dec.	Inc.	Dec.
Noradrenaline	HO	H	2	1	2	9	100	100	0
Adrenaline	HO	CH_3	73	19	5	7	200	141	5
Isoprenaline	HO	$CH(CH_3)_2$	100	100	100	100	0	0	100
AH.3364	$HOCH_2$	H	2	0·04	0·08	0	68	25	0
AH.4053	$HOCH_2$	CH_3	3	0·02	0·02	0	63	45	0
AH.3021	$HOCH_2$	$CH(CH_3)_2$	46	12·5	0·09	9	0	0	11
AH.3365	$HOCH_2$	$C(CH_3)_3$	66	38	0·04	2	0	0	7

Of the compounds described AH.3365 has the most selective action on β-adrenergic receptors in bronchial smooth muscle. This result has been confirmed in conscious animals. For example AH.3365 (1 and 5 mg/kg orally) increased the time to dyspnoea in guinea-pigs exposed to acetylcholine aerosol. This effect lasted for 4–8 hr with only a minimal effect on heart rate at the higher dose level. Isoprenaline (1 and 5 mg/kg orally) was poorly active in preventing dyspnoea and both doses caused marked tachycardia. By aerosol, the protection afforded by AH.3365 greatly exceeded that afforded by isoprenaline, both in intensity and duration. In this test the heart rate increased only after isoprenaline aerosol.

Early human clinical results indicate that AH.3365 by aerosol or by mouth can cause long lasting maximal bronchodilatation without cardiovascular effect.

REFERENCES

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