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A use of the isomeric ratio as a criterion to differentiate adrenergic receptors

The general concept of α- and β-adrenergic receptors is well recognized. Rossum (1965) indicated, however, that different tissues may contain different types of α-adrenergic receptors. Although this is a theoretical possibility, Furchgott (1967) found similar K_B values for phentolamine in three different tissues of the rabbit and, on this basis, suggested that the α-adrenergic receptors in thoracic aorta, muscle from the corpus of the stomach and duodenum of rabbit are of a single type.

As with other pharmacologic receptors, a very characteristic property of adrenergic receptors is that of stereoselectivity. If α-adrenergic receptors in various tissues are of a single type, and if their ability to interact with optical isomers is stereoselective, it follows that the activity difference or the isomeric ratio between (−) and (+)-noradrenaline should be the same in each tissue. Under normal circumstances, this isomeric ratio is obscured by several factors operative at the adrenergic nerve terminals; the stereoselective uptake, the unequal distribution of antagonistically-acting α- and β-adrenergic receptors in the same tissue, and the presence of enzymes which can cause selective degradation of isomers of noradrenaline. If all these factors were properly controlled, it is possible that the isomeric ratios of noradrenaline in different tissues containing α-adrenergic receptors would be identical. Data in Table 1 were readily available from previous reports from ours and other laboratories. It can be seen that in normal tissues, the isomeric ratios vary from 2 to 64 (a 32 fold variation). Since acute treatment with reserpine does not significantly change the neuronal uptake, it did not change the isomeric ratio. However, if neuronal uptake was inhibited by cocaine or a cocaine-like agent, imipramine, the isomeric ratios were markedly altered. For cat blood pressure, nictitating membrane, spleen and rat vas deferens, the isomeric ratios for noradrenaline in the presence of cocaine or cocaine-like agents only ranges between 50 and 80. These ratios, within the limits of experimental error, may be considered as essentially equal. Rabbit jejunum has a low density of adrenergic innervation (0·5 μg/g). This is reflected in a high isomeric ratio in the normal tissue. In other words, after inhibiting the uptake, this isomeric ratio of 64 may not change significantly. Similarly, in the rabbit aorta, due to low adrenergic innervation relatively high isomeric ratio was obtained. Thus, the isomeric ratios in all these six tissues which mainly contain α-adrenergic receptors, there is a tendency for isomeric ratios to be equal. It varies from 42 to 80 (*i.e.*,

Table 1. *Relative activities of optical isomers of noradrenaline (NA) on various tissues which mainly contain α-adrenergic receptors*

Test parameter	Procedure or treatment	Approximate ratio[a] (+)-NA (—)-NA	Reference
Cat blood pressure ..	Normal	40	Tye & others (1967);
	Reserpine*	47	Seidehamel & others (1966)
	Cocaine (R)*	60	
Cat nictitating membrane	Normal	8	Tye & others (1967);
	Reserpine*	8	Seidehamel & others (1966)
	Cocaine (R)*	80	
	Denervation (R)*	128	
Cat spleen	Normal	2	Green & Fleming (1968)
	Cocaine (R)*	65	
	Denervation	7	
Rabbit aorta	Normal	42	Swamy, Tye & Patil (unpublished)
Rabbit jejunum ..	Normal	64	Rossum (1965)
Rat vas deferens ..	Normal	5	Patil & others (1967a)
	Reserpine*	5	Patil & others (1967b)
	Desipramine	50	Benvenuti & others (1967)

[a] A dose that will cause equivalent effect was selected as a criterion for calculation of dose ratio.
* Reserpine 3 to 5 mg/kg, i.p. was used 24 to 48 h to deplete catecholamine.

only two fold variation). Furthermore, it should be emphasized that these experiments were not particularly designed to test the present hypothesis. A study of isomeric ratios in different tissues of different animals would be an interesting approach to support or reject the concept of a single type of α-adrenergic receptor. Conversely, if β-adrenergic receptors in the different tissues are of different types, under proper conditions one should obtain markedly different isomeric ratios in different tissues. Unfortunately, at present such information is not available for many tissues containing β-adrenergic receptors. These hypotheses are currently being examined in our laboratories and details will be published elsewhere in the near future.

Furthermore, the same approach can be used to answer the question of a qualitative change in the α-adrenergic receptors after post ganglionic sympathetic denervation (Varma, 1966; Trendelenburg, 1965), and it can be seen that after such a denervation in the cat nictitating membrane and spleen, the isomeric ratios are markedly different than that after cocaine. It is possible that so called qualitative change of α-receptors can alter the steric configuration and hence, its ability to interact with optical isomers of noradrenaline. This is then reflected in the isomeric ratios.

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