Structural requirements for activity of catecholamines at beta-receptors

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The investigations which we carried out on the relationships between molecular properties and biological activity of catecholamines allowed a chemical interpretation of the interaction mechanisms responsible for α- and β-receptor activity (Pratesi, 1963; Pratesi & Grana, 1965).

Apart from steric factors, α-receptor reactivity is probably linked to the tendency of a catecholamine to give up one proton. Beta-receptor reactivity appears mainly linked to the strength of the base and to an appropriate geometry of the cationic ending of the base itself so as to enable this part of the molecule to come within a critical reaction distance of the receptor.

We have studied the pharmacodynamic activity of a series of N-isopropylphenylethanolamines in which the catechol system in position 3 and 4 is replaced by atoms or groups with different inductive effects and with different hydrophylic or lipophylic natures (Pratesi, Grana & Villa, 1968). The results suggest that there is a lipophylic region in the surroundings of the receptor. Here we may consider that the molecule is linked hydrophobically through its aromatic portion. Such hydrophobic binding may modify the condition of fit and thus reduce the number of effective interactions even though it contributes to the total affinity of the molecule for the receptor.

We have now found that, when the value of the hydrophobic binding constant is less than 1.5, the intrinsic activity is appreciably higher for *meta*-substituted derivatives than for *para*-substituted, while the affinity is practically the same. Substitution in the *ortho*-position generally produces a more dramatic fall of intrinsic activity as well as of affinity.

A series of 1-phenoxy-2-hydroxy-3-isopropylaminopropanes variously substituted in the ring has also been examined. All the compounds were devoid of intrinsic activity; their affinity values were constantly higher than in the corresponding phenylethanolamines. The unsubstituted compound possesses the highest affinity. This shows the importance of the CH_2O group in determining the fit of the molecule on the receptor area, a conclusion which is confirmed by the results obtained with an isosteric series of compounds in which the oxygen atom of the CH_2O group is replaced with S or CH_2.

These findings enable us to draw a rational chemical picture of the β-receptor which may explain differences in activity of compounds and at same time to formulate a hypothesis on the mechanism of activation of the receptor.

REFERENCES

PRATESI, P. (1963). Chemical structure and biological activity of catecholamines. *International Symposium on Pharmaceutical Chemistry*, Florence, 1962, pp. 435–449. London: Butterworths.

PRATESI, P. & GRANA, E. (1965). Structure and activity at adrenergic receptors of catecholamines and certain related compounds. *Advances in Drug Research*, vol. 2, pp. 127–142. New York: Academic Press.

PRATESI, P., GRANA, E. & VILLA, L. (1968). Molecular properties and biological activity of catecholamines and certain related compounds. *Proceedings of the Third International Pharmacological Meeting*, vol. 7, pp. 283–294. New York: Pergamon Press.