programme drawn up jointly by agro-meteorologists and plant pathologists and carried out over a number of years.

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ADRENERGIC RECEPTOR(S) AND CALCIUM

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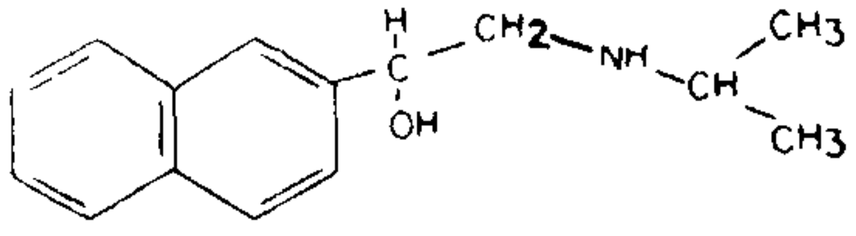
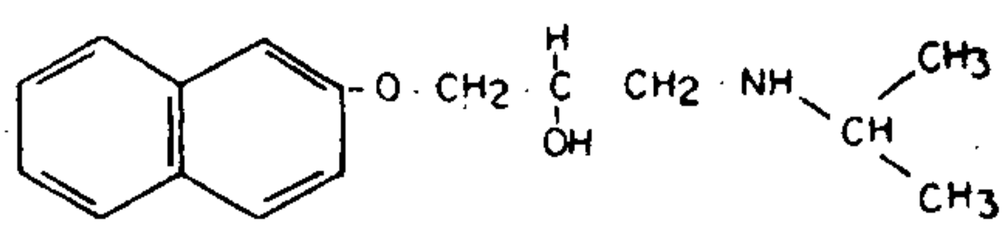
THE nature of the adrenergic receptor(s) has been the subject of intense study particularly since Ahlquist's classification of these into α- and β-types.[1] Based on the available data Belleau[2] suggested a model of the α- and β-receptors and the mode of their interaction with the catecholamines and related compounds. In a recent paper he has elaborated his earlier ideas to take into account new data.[3]

We wish, herein, to deal with an aspect not emphasised earlier and which appears to us as of considerable importance in the further understanding of the subject. The role of calcium ions in adrenergic activity is well known and Belleau[3] has in fact taken this factor into consideration while elaborating his picture of interaction with the α-receptor. However, he has not discussed its role with regard to the β-activity, though data are not lacking on the importance of calcium ions in β-adrenergic activity. In this context the recent interesting observations of Naylor[4] on the influence of adrenaline and some adrenergic blocking drugs on the 'lipid facilitated transport' of calcium ions deserve careful consideration. Naylor found that lipids extracted from microsomal and mitochondrial fractions of the hearts of rabbit, guinea-pig and other animals facilitated transport of calcium ions from the Ringer's solution into a lipid solvent phase. This transport was inhibited by the addition of pronethalol (I) and propranolol (II), the two typical β-adrenergic blocking agents to the Ringer's solution, whereas it was potentiated by the addition of adrenaline (III) and nor-adrenaline (IV) and not altered by the addition of tyramine (V).

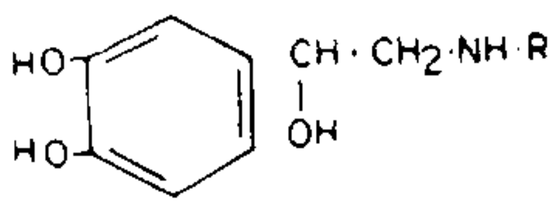
An interpretation of the above data is the following and could lead to interesting corollaries. From Naylor's data,[4] it may be inferred that the adrenergic blocking drugs as well as adrenaline and nor-adrenaline are able to bind calcium, whereas tyramine is unable to do so, and this appears more probable as the drugs under study were added to the Ringer's solution containing calcium prior to extraction with the lipid. Under the experimental conditions interaction of the drugs with the lipid as the primary process is unlikely. Further the calcium-pronethalol/propranolol combination is obviously lipid insoluble, thus keeping down the calcium in the aqueous phase in contrast to the calcium-catecholamine combination which is lipid soluble. The capacity of these compounds to bind calcium can be traced to the presence of an alcoholic hydroxyl, which is absent in tyramine. On the other hand, it is likely that the catechol group in adrenaline and nor-adrenaline enables their complexes to link on to appropriate polar functions in the bio-lipids and thus get transported to the lipid phase. The absence of such a functional group in the β-blocking drugs would then explain



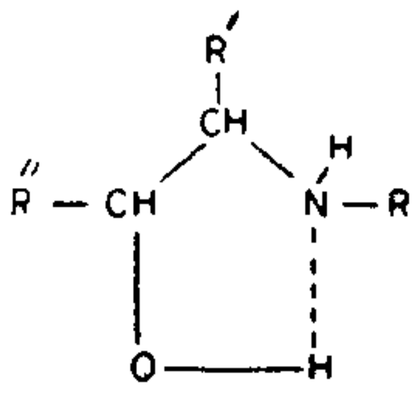
I



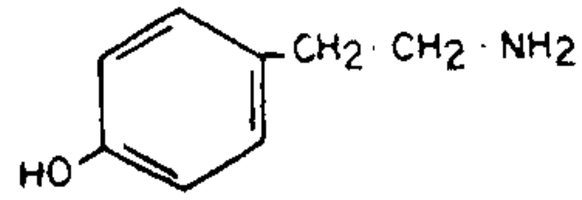
II



III R = CH_3
IV R = H



VI



V

the lack of affinity of their calcium complexes for the lipid phase. At any rate what appears to differentiate between adrenaline and nor-adrenaline on the one hand and the adrenergic blocking drugs on the other is the lipid phase solubility of the calcium-complex of the former and the insolubility of the latter; both types, however, bind calcium. In view of the fact that phospholipids form part of the adrenergic receptor structure, the above observations may have deeper significance and herein may lie a clue to the mode of action of adrenergic blocking drug. Further Naylor's data show that adrenaline binds calcium more efficiently than nor-adrenaline and from the arguments below one could expect isoprenaline to be even more efficient. The catecholamine and allied compounds such as ephedrine, can be considered as ethanolamine derivatives and it is known,[5] that in the ethanolamines and ephedrine the alcoholic hydroxyl is hydrogen-bonded to the nitrogen as shown in (VI). They also form metal complexes and it is logical to expect the catecholamines to exhibit similar properties. The strength of the intramolecular H-bonding and hence the capacity to bind calcium among related compounds of this type would depend upon the nature of the substituents on the nitrogen and should increase as the (+) inductive effect of the group R increases, *i.e.*, in the order, nor-adrenaline < adrenaline < isoprenaline. Interestingly enough, the same is the order in which the β-adrenergic activity increases. We thus find, that there is a definite parallelism between calcium binding capacity and adrenergic activity both depending, in an identical manner upon the structural parameters pointed out earlier by Pratesi and Grana.[6] Pratesi and Grana further pointed out, that when a predominantly α-active substance is allowed to act on an organ containing only β-receptors, a β-type effect is obtained and *vice versa*. In terms of the arguments set out above this could mean that, apart from the structure of the catecholamine, availability of calcium ions in the environment of the receptor could be a major factor in deciding the character of the response. More studies are, however, necessary before the theme could be further delineated.

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