Concerning the histamine receptor (H_1)

A few years ago we proposed a model for the histamine receptor in the ileum of the guinea-pig (Rocha e Silva, 1960, 1966). This model was constructed on the basis of the following ideas then accepted: (*a*) the active form of histamine under physiological conditions was that in which hydrogen bonding was possible between the amine nitrogen (N^+) and the pyridine (N) nitrogen of the imidazole ring; (*b*) the secondary anchorage group of histamine to fit its receptor site, could be the imine (=NH) radical of the imidazole ring; (*c*) the pK of the receptor site was found to be around pH = 7·10–7·0, thus suggesting a histidine moiety at the receptor site. Having these facts in mind, a fit of the agonist to its receptor site might involve electrostatic attractions between the "pyridine" nitrogen of the imidazole of the agonist and the carbonyl oxygen (=O) of the peptide link in the receptor amino-acid chain. The function of histamine would be to protonate the "pyridine" nitrogen of the receptor histidine, shifting the double bond and releasing a high energy radical hypothetically bound to the "pyrrole" nitrogen of the histidine moiety, as shown in Fig. 1.

A reappraisal of this concept was made possible, after a recent publication by Kier (1968) in which the author reached the conclusion that the configuration of histamine acting upon H_1 receptors, would preclude any hydrogen bonding between the (N^+) amine nitrogen and the pyridine nitrogen of the imidazole ring. The distance between the two nitrogens is of the order of 4·55 Å, and therefore too large to allow for the occurrence of any hydrogen bonding, as shown in Fig. 2a.

On the basis of his calculations, Kier (1968) concludes that the nitrogen of the lateral chain of histamine forms a quaternary link and it is strongly positively charged. Furthermore, "if the quaternary nitrogen atom of the side-chain is regarded as a primary binding site to a receptor, it is quite likely . . . that the secondary site is the pyridine nitrogen (tr^2 tr tr π)N" and it is highly electron rich. The distribution of charges in the histamine molecule is indicated in Fig. 2b.

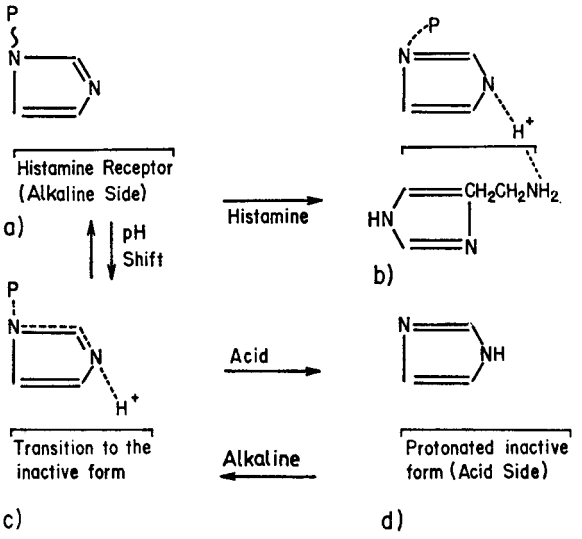

FIG. 1. The previous schematic representation of the receptor for histamine in different conditions of pH: (a) resting condition at pH about 7·0; (b) interaction of a histamine molecule to protonate the "pyridine" N of the imidazole ring of the receptor site; (c) activated form of the receptor, when the pH is shifted from a higher to lower values; (d) inactive form, in acid medium, when the receptor is "discharged" of its hypothetical metabolite ~P. (According to Rocha e Silva, 1961.)

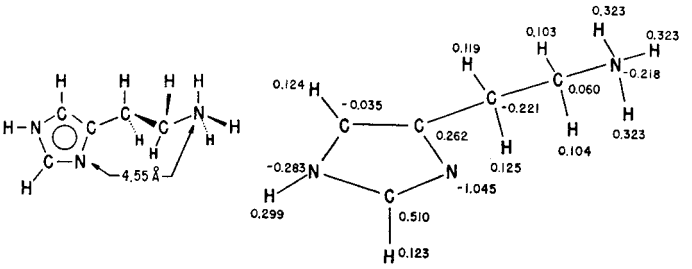

FIG. 2. (a) Configuration of the histamine cation under physiological conditions. The N^+-to-(tr^2 tr tr $\sigma + \pi$) N distance is too large to allow any hydrogen bonding to occur; (b) net charges ($\sigma + \pi$) distribution in the histamine monocation; note that the carbon flanking the two nitrogens in the imidazole ring is positively charged. (According to Kier, 1968.)

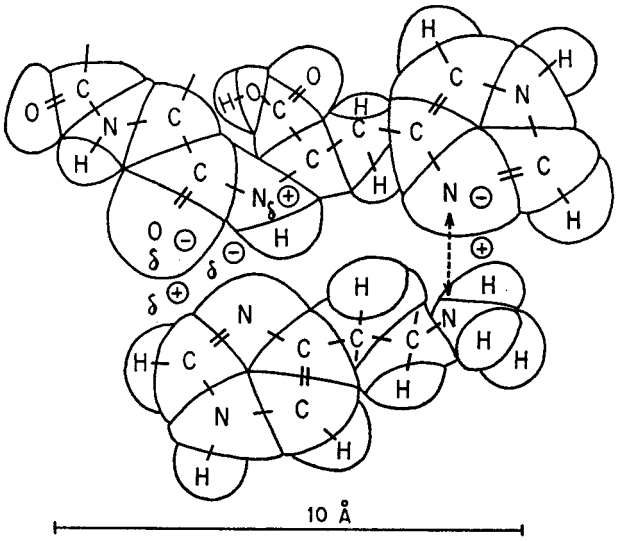

FIG. 3. A new version on the interaction of the histamine cation with the histidyl moiety supposedly existing in the H_1 receptor in the ileum of the guinea-pig.

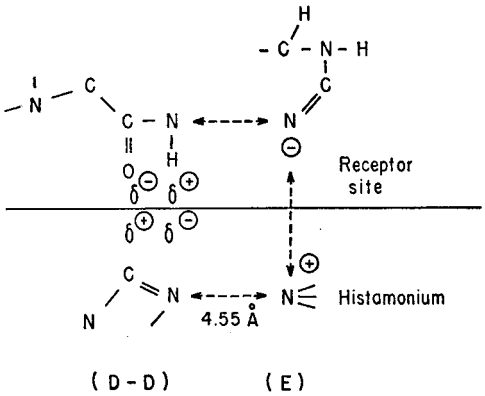

FIG. 4. Schematic representation of the forces involved in the interaction of histamine with its hypothetical receptor site. (E), electrostatic; (D–D) dipole-dipole interactions. Protonation of the pyridine (–N=) nitrogen of the histidyl moiety of the receptor would shift double bond to –C=N– position.

As indicated in Fig. 2b, a substantial positive charge is generated on the carbon flanked by the two nitrogen atoms, in the imidazole ring.

These findings contribute a great deal towards improving our previous model, since in this way a dipole appears in the imidazole ring that can fit the inverted dipole of the peptide link in the receptor model presented in Fig. 3.

We can therefore suggest that histamine is attracted to its specific receptor site (H_1) by: (*a*) strong electrostatic interaction between the pyridine (N^-) nitrogen of the histidine moiety and the strongly charged quaternary nitrogen (N^+) of the histamonium ion, and (*b*) the reciprocally inverted dipoles in the peptide link of the receptor and the carbon (C^+)–pyridine nitrogen (N^-) of the imidazole ring of the agonist (Fig. 4).

The other implications of the model are not changed, and rather are improved by the new scheme.

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Diethyldithiocarbamate and structurally-related compounds and the uptake and release of noradrenaline in the heart of the rat

Disulfiram, tetraethylthiuram disulphide, and its reduction product diethyldithiocarbamate have been demonstrated to inhibit dopamine-β-hydroxylase [3,4-dihydroxyphenylethylamine, ascorbate: O_2 oxidoreductase (hydroxylating), E.C. 1.14.2.1] (Goldstein, Anagnoste & others, 1964; Green, 1964). Structurally-related compounds, such as phenylethyldithiocarbamate (Jonsson, 1967) and dimethyldithiocarbamate (Lippmann & Lloyd, 1969), also inhibit the *in vivo* conversion of exogenous dopamine to noradrenaline. The possibility exists that these compounds might cause an increased release of noradrenaline and that this might influence the activity observed. Whether compounds structurally-related to diethyldithiocarbamate and disulfiram affect the [^{3}H]noradrenaline content of the rat heart in animals injected with [^{3}H]noradrenaline is now reported.

Male albino rats (60–80 g) were injected intraperitoneally with the compounds which were in aqueous suspension of polysorbate (Tween) 80. Control animals were injected with an equal volume of the vehicle. After 45 min the animals were injected, in the tail vein, with 2·5 μCi($\pm$)-[^{3}H]noradrenaline (Radiochemical Centre, Amersham, U.K.) in a 0·25 ml solution of 0·75% sodium chloride and 0·01N HCl. The animals were killed 15 min later, and the hearts removed, rinsed, blotted, weighed and placed on dry ice; they were then homogenized in ice-cold 0·4N perchloric acid