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.

Department of Pharmacology,
Faculty of Medicine of Ribeirão Prêto, U.S.P.,
Ribeirão Prêto, São Paulo, Brazil.

M. ROCHA E SILVA

July 8, 1969

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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

and centrifuged. The supernatant fluids from three hearts were combined and the [^{3}H]noradrenaline contents from the acetic acid eluates from alumina columns measured (Whitby, Axelrod & Weil-Malherbe, 1961).

Diethyldithiocarbamate, ethyldithiocarbamate, dimethyldithiocarbamate, disulfiram (tetraethylthiuram disulphide), tetramethylthiuram disulphide and tetramethylthiuram monosulphide at 125 mg/kg, intraperitoneally, neither prevented the uptake nor caused an increased release of [^{3}H]noradrenaline from the heart (Table 1). Although decreases in radioactivity were noted with some compounds, none was statistically significant.

Table 1. *The effect of diethyldithiocarbamate and structurally related compounds on the uptake of* [^{3}H]*noradrenaline in the rat heart*

Compound	[^{3}H]Noradrenaline counts/min g^{-1} ± s.e.	*P* value	% Control
Control	14,100 ± 600	—	100
Diethyldithiocarbamate	14,200 ± 1,000	<0·9	101
Ethyldithiocarbamate	12,500 ± 600	<0·2	89
Dimethyldithiocarbamate	13,300 ± 1,000	<0·7	95
Tetramethylthiuram disulphide	12,000 ± 1,000	<0·2	87
Tetramethylthiuram monosulphide	13,300 ± 1,000	<0·7	94
Disulfiram	13,700 ± 1,300	<0·9	97

Diethyldithiocarbamate and disulfiram are inhibitors of dopamine-β-hydroxylase in the rat heart (Goldstein, Anagnoste & others, 1964). Recently we have shown that dimethyldithiocarbamate (Lippmann & Lloyd, 1969), ethyldithiocarbamate (Lippmann & Lloyd, 1969), tetramethylthiuram disulphide and tetramethylthiuram monosulphide (Lippmann & Lloyd, unpublished observations) also inhibit the formation of [^{14}C]noradrenaline from [^{14}C]dopamine in the rat heart. Although it is known that disulfiram (400 mg/kg) does not interfere with the uptake, storage, metabolism or release of noradrenaline, nor the uptake, storage or release of dopamine in the rat heart (Goldstein & others, 1964; Musacchio, Goldstein & others, 1966; Musacchio, Kopin & Snyder, 1969), it was not known whether any of the active related compounds affected the ability of the heart to take up and store noradrenaline.

The experiments now reported indicate that these inhibitors of dopamine-β-hydroxylase which are structurally-related to disulfiram do not cause alterations in the uptake, short-term storage or release of exogenously administered noradrenaline in the rat heart.

The authors acknowledge the technical assistance of Miss Dorothy Mulrooney.

Biogenic Amines Laboratory,
Ayerst Laboratories,
Montreal, Quebec, Canada.

W. LIPPMANN
K. LLOYD

July 25, 1969

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