As previously suggested (Furtado, 1966), bradykinin seems to compete with neurohypophysial hormones for the receptor site through ionic, hydrogen, and hydrophobic bonds rather than by breaking the S—S bridge of the hormones. If bradykinin and cysteine are actually competing for a common site in the receptor this fact makes it probable that thiols might also directly act at a receptor level rather than by solely reducing the hormones.

Acknowledgements. The author is indebted to Prof. Rocha e Silva for helpful criticism and for creating facilities to work in his department; also to Sandoz Ltd., Basle, Switzerland, for generous supplies of synthetic bradykinin. The investigation was partly supported by a grant from F.A.P.E. S.P., Brazil.

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Decrease of homovanillic and 5-hydroxyindoleacetic acids in the brain after hypothalamic lesions

SIR,—Destruction of the medial forebrain bundle (MFB) in the lateral hypothalamus decreases the 5-hydroxytryptamine (5-HT), noradrenaline and dopamine content in various parts of the rat brain (Heller & Moore, 1965; Andén, Dahlström, Fuxe & others, 1966). These changes occur not only in areas directly innervated by the axons of the MFB, e.g. the hypothalamus and limbic forebrain, but also in regions not directly connected with the MFB, possibly as a consequence of lesions of other fibres, e.g. nigro-striatal (Andén & others, 1966). The decrease of the cerebral monoamines might be due to different mechanisms, for example diminution of the storage or inhibition of the synthesis of the amines. The finding of a diminished activity of decarboxylase of aromatic amino-acids after lesion of the MFB reported by Heller, Seiden, Porcher & Moore (1965) does not necessarily indicate an impaired synthesis of catecholamines and 5-HT, since decarboxylation of 3,4-dihydroxyphenylalanine and 5-hydroxytryptophan do not seem to be a limiting step in the biosynthesis of these amines (Hess, Connamacher, Ozaki & Udenfriend, 1961). By influencing the cerebral content of homovanillic and 5-hydroxyindoleacetic acids, the major metabolites of dopamine and 5-HT respectively, further information might be gained on the mechanism which leads to a decrease of the aromatic monoamines. Therefore these acids, as well as the chlorpromazine-induced increase of homovanillic acid, were measured in the basal parts of each brain side after unilateral lesions of the MFB. Chlorpromazine was chosen since the drug enhances the hydroxylation of tyrosine *in vivo* and increases the formation of homovanillic acid in the brain possibly as a consequence of a primary blockade of dopaminergic receptors (Andén, Roos & Werdinius, 1964; Burkard, Gey & Pletscher, 1967).

TABLE 1. EFFECT OF ELECTROLYTIC LESIONS OF THE MEDIAL FOREBRAIN BUNDLE (MFB) ON THE CONTENT OF MONOAMINES AND METABOLITES AS WELL AS ON THE CHLORPROMAZINE-INDUCED RISE OF HOMOVANILLIC ACID (HVA) IN THE BASAL BRAIN PARTS OF RATS

Monoamine or metabolite	Control side	Side with lesion	
	Absolute values (μg/g)	Absolute value (μg/g)	value %
Dopamine	2·56 ± 0·19	0·82 ± 0·35	31 ± 11 (I)
Homovanillic acid	0·11 ± 0·01	0·05 ± 0·01	48 ± 4 (II)
Homovanillic acid after chlorpromazine	0·38 ± 0·06	0·11 ± 0·01	32 ± 7 (III)
Noradrenaline	0·78 ± 0·19	0·46 ± 0·06	62 ± 4 (IV)
5-Hydroxytryptamine	1·03 ± 0·12	0·72 ± 0·08	71 ± 2 (V)
5-Hydroxyindoleacetic acid	0·53 ± 0·01	0·43 ± 0·03	81 ± 3 (VI)

The determinations were made 15 days after the lesion. 10 mg/kg chlorpromazine were administered i.p. 2 hr before death. Each figure represents an average ± s.e. of 3–6 experiments. The percentage values were calculated for each individual experiment, the side without lesion serving as the control.

Significance: I, II, III, IV, V, VI $P<0.01$
I: IV $0.01<P<0.05$
I: V $P<0.01$
II: VI $P<0.01$

In male albino rats, unilateral (right side) electrolytic lesions were made according to Heller, Harvey & Moore (1962). The left side was sham-operated performing all the surgical procedures of the right side, but introducing the electrode in the brain above the target area without delivering current. Since most of the MFB fibres are uncrossed (Guillery, 1957), the left side was used as a control for the biochemical determinations. The animals were killed 15 days later after a fasting period of 16 hr. Histological controls indicated that the electrolytic lesions were located in the region of the MFB. Partial damage of the nigro-striatal fibres can, however, not be excluded.

In addition, in the basal parts (basal ganglia including limbic structures, thalamus and hypothalamus) of each brain side, dopamine, homovanillic acid, 5-HT, 5-hydroxyindoleacetic acid and noradrenaline were measured by spectrophotofluorimetric procedures (ref. Pletscher, Bartholini, Bruderer & others, 1964). Furthermore, estimations of homovanillic acid were made 2 hr after intraperitoneal injection of 10 mg/kg chlorpromazine, the animals being kept in an environment of 31° to prevent the development of hypothermia.

The present results (Table 1) confirm earlier reports (Heller & Moore, 1965; Andén & others, 1966) by demonstrating that unilateral lesions of the MFB cause a decrease of dopamine, noradrenaline and 5-HT. The dopamine is more markedly affected than 5-HT and noradrenaline. Our findings furthermore show that, together with the diminution of the amines, a significant decrease of homovanillic and to a lesser extent also of 5-hydroxyindoleacetic acid occurs on the injured side. In addition, the chlorpromazine-induced increase of homovanillic acid as observed on the control side is markedly attenuated on the side with the lesion.

These findings indicate that by lesions of the MFB the synthesis of dopamine, 5-HT and possibly noradrenaline in the basal brain parts might be impaired.

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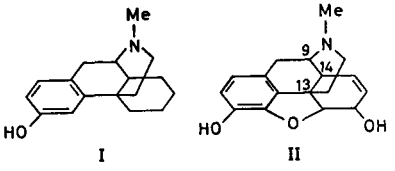
Optical rotatory dispersion characteristics of (−)-3-hydroxy-*N*-methylmorphinan and (−)-morphine

SIR,—The relative configurations of (−)-3-hydroxy-*N*-methylmorphinan (I, levorphanol) and (−)-morphine (II) are of interest in view of the established stereoselectivity of the analgesic receptor towards many classes of analgesics (Beckett & Casy, 1965). In the absence of direct chemical methods, the use of optical rotatory dispersion (o.r.d.) data (Crabbé, 1965) offers the most promising physical method for the stereochemical correlation of (−)-I and (−)-II. The following results were obtained using a Polarmatic 62 photo-electric spectropolarimeter. The o.r.d. curve of (−)-morphine base (*c*, 0·02% in ethanol, 0·05 dm cell) showed a negative Cotton effect, $[\phi]^{25}_{340}-1499$, $[\phi]^{25}_{303}-4123$, $[\phi]^{25}_{291}-5620$ (trough), $[\phi]^{25}_{281}+4120$ (inflection), $[\phi]^{25}_{256}+13490$ (peak), $[\phi]^{25}_{244}-30240$ (limit of measurement); the curve for (−)-morphine hydrochloride was similar with trough characteristics, $[\phi]^{25}_{290}-5223$. Bobbitt, Weiss & Henessian (1959), using a less sensitive spectropolarimeter, recorded the o.r.d. curves of morphine, codeine and dihydrocodeine in dioxane and observed negative Cotton effects with troughs near 300 mμ in each case; values beyond 298 mμ could not be obtained. The o.r.d. curve of levorphanol base (*c*, 0·01% in ethanol, 0·05 dm cell) also showed a negative Cotton effect, $[\phi]^{25}_{400}-3375$, $[\phi]^{25}_{313}-15520$, $[\phi]^{25}_{290}-40460$ (trough), $[\phi]^{25}_{288}-33050$ and $[\phi]^{25}_{278}-35780$ (fine structure, absent in the salt), $[\phi]^{25}_{268}+16190$ (peak); in 0·1N hydrochloric acid-ethanol, trough and peak characteristics were $[\phi]^{25}_{291}-45320$ and $[\phi]^{25}_{270}+18880$ respectively.



I II

The negative Cotton effects of (−)-I and (−)-II are attributed to the optically active phenolic chromophore because the Cotton effect mid-points (near 286 mμ for morphine and 280 mμ for levorphanol) are close to the phenolic ultraviolet absorption maxima of the two compounds [morphine λ_{max} 285 (base), 288 mμ (salt); levorphanol λ_{max} 284 (base), 283 mμ (salt) in ethanol]. Differences in the o.r.d. curves of I and II, viz. characteristics at wavelengths below 280 mμ and the lower $[\phi]^{25}_{291}$ (trough) value for (−)-II, probably arise as a result of the presence in (−)-II of optically active chromophores (additional to the phenolic function) that are absent in (−)-I, a compound of simpler structure.