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SECOND SESSION. CHAIRMAN: P. HOLTZ

H. INTRODUCTORY REMARKS

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As a pharmacologist I have always been impressed, on nearly all levels of biological life, be it bacteria and other unicellular organisms, be it plants or lower animals, to be confronted with chemical compounds which have striking pharmacological actions in higher animals and in man, and in them serve even as hormones or chemical transmitters of nervous activity. I should like only to mention the occurrence of acetylcholine in paramecia and in the secretion of stinging nettle, and the occurrence of dopamine and other catecholamines in the broom and in bananas. It is fascinating to see how nature by entirely different metabolic routes and by means of different enzymes may reach the same results.

The first paper of this afternoon's session, given by Dr. Sekeris, will be concerned with the metabolism of catecholamines and other sympathomimetic amines in insects. Dr. Sekeris will deal with investigations on the hormonal control of enzymatic amine metabolism and how hormonal control causes, at a certain developmental stage of the insect, the blowfly, a shift of the amine metabolism from a "lower" monophenolic to a "higher" diphenolic level.

The following papers are devoted to the action and physiological role of two enzymes, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO), which in both animals and man probably are the most important ones for the breakdown of the catecholamines, a process which sometimes is identical with their pharmacological inactivation. Indeed, as early as 1905, Dakin found the O-dimethylated adrenaline pharmacologically inactive. Today, mainly from the work of Dr. Armstrong and of Dr. Axelrod, we know that 3-O-methylation is one of the most important enzymatic mechanisms, involved particularly in the inactivation of exogenous, extraneuronal, circulating catecholamines. On the other hand, recent investigations have shown that methylation of the phenolic hydroxy group in the 4-position can result in compounds with marked central effects producing muscular rigidity, and resembling the actions of bulbocapnine (2).

Oxidative deamination of amines means the formation of the corresponding aldehydes. These are usually pharmacologically inert as recently shown by Renson *et al.* (6a) to be true also for the aldehydes formed from noradrenaline (NE) and adrenaline (E) by incubation with purified MAO preparations. However, about 25 years ago we found that dopamine, which is usually a pressor agent in the cat, was transformed by incubation with MAO into a compound lowering the cat's blood pressure (3). The assumption that the deamination product of dopamine, dihydroxyphenylacetaldehyde, might be the depressor agent had to be abandoned since later experiments revealed that epinine, the N-methylated derivative of dopamine, on incubation with MAO, was not converted to a blood

pressure-lowering agent although the enzyme would also deaminate epinine to dihydroxyphenylacetaldehyde. In contrast to dopamine, epinine was only inactivated (4).

The different behavior of the two catecholamines found its explanation in that the aldehyde formed in the dopamine-containing incubates condensed with unchanged dopamine to yield tetrahydropapaveroline (THP), while under the same experimental conditions epinine, being a secondary amine, was unable to do so (fig. 1). We were able to show by thin-layer chromatography that with increasing incubation time dopamine disappeared gradually while THP was formed. As was to be expected, the MAO inhibitor Mo 911 (pargyline) prevented the transformation of dopamine to the hydrogenated and demethylated derivative of papaverine. The intravenous injection of an incubate with inhibited MAO into cats raised the blood pressure, as did dopamine which had not been incubated. An incubate in which THP had been formed exerted a pressure-lowering effect, as did authentic THP. The depressor effect of THP, however, differed from that of papaverine in that it could be blocked by the β-adrenergic blocking agent pronethalol (nethalide), thus resembling the depressor action of the β-sympathomimetic agent isoproterenol (5).

Apparently, two requirements have to be fulfilled for the "musculotropic" papaverine to acquire affinity for adrenergic β-receptors: 1) the N-containing benzene ring has to be hydrogenated giving a $-CH_2 \cdot CH_2 \cdot N\begin{matrix}H\\ \diagup\\ \diagdown\\ R\end{matrix}$ configuration,

and 2) at least two of the four methoxy-groups have to be demethylated to give free phenolic hydroxy-groups (fig. 2). Therefore, papaveroline, the demethylated but not hydrogenated derivative of papaverine, as well as tetrahydropapaverine, the hydrogenated but not demethylated derivative, proved to be musculotropic

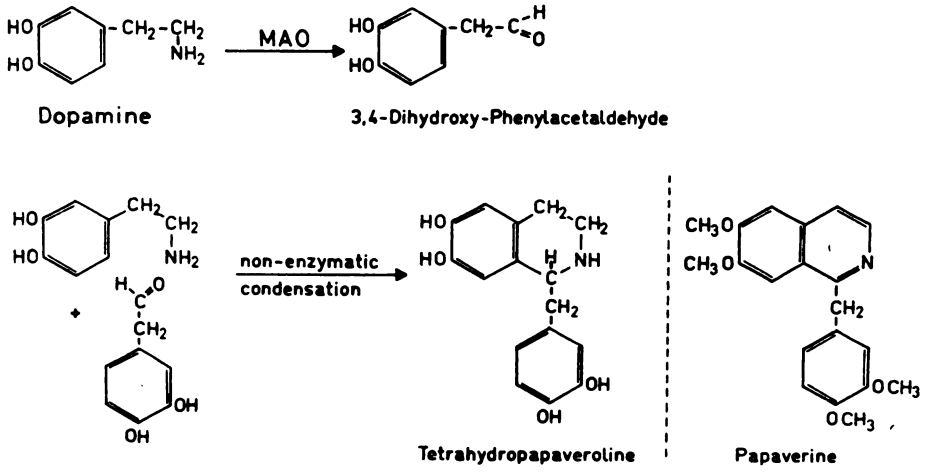

FIG. 1

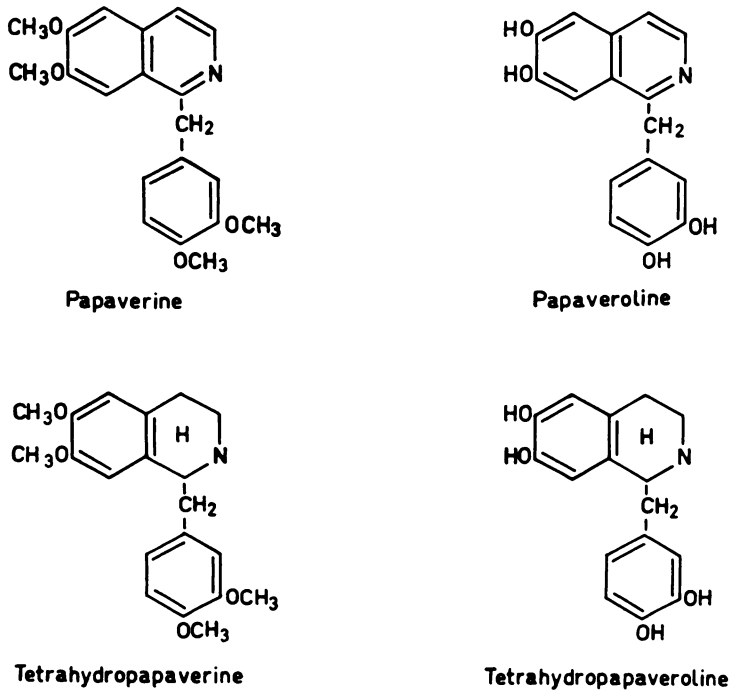

FIG. 2

like papaverine itself: their pressure-lowering action in the cat was not blocked by pronethalol (6).

From these results it may be concluded that two structural elements are essential for the β-sympathomimetic activity of THP: 1) two free phenolic hydroxy groups in 3,4-position and 2) the bulky substituent on the amino group (see 1).

The condensing reaction between dopamine and dihydroxyphenylacetaldehyde to yield THP has been demonstrated so far only *in vitro*. It remains to be clarified whether the formation of THP can occur *in vivo*, and whether its β-stimulatory action is responsible for some pharmacologic effects of dopamine. It is known that condensation reactions of this kind underlie the biosynthesis of many plant alkaloids (7, 8).

However, discussion of these interrelations is better postponed. The last paper of this afternoon's session will be concerned with the nature of adrenergic receptors and thus with a basic problem which has been with us since the days of Ehrlich in Frankfurt and of Langley in Cambridge. During the last year Dr. Belleau has developed an interesting and stimulating concept of pharmacologic receptors, based on physicochemical considerations. We are glad to have the opportunity to hear from him the newest developments.

REFERENCES

1. BELLEAU, B.: An analysis of drug-receptor interactions. Proc. 1st. Int. Pharmacol. Meeting, Vol. 7, pp. 75-95, 1963.
2. ERNST, A. M.: Phenomena of the hypokinetic rigid type caused by O-methylation of dopamine in the *para*-position. Nature, Lond. 193: 178-179, 1962.

3. HOLTZ, P. UND HEISE, R.: Fermentativer Abbau von L-Dioxyphenylalanin (Dopa) durch Niere. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **191**: 87–118, 1938.
4. HOLTZ, P., STOCK, K. UND WESTERMANN, E.: Ueber die Blutdruckwirkung des Dopamin. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **246**: 133–146, 1963.
5. HOLTZ, P., STOCK, K. UND WESTERMANN, E.: Pharmakologie des Tetrahydropapaverolins und seine Entstehung aus Dopamin. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **248**: 387–405, 1964.
6. HOLTZ, P. UND PALM, D.: In preparation, 1965.
6a. RENSON, J., WEISSBACH, H. AND UDENFRIEND, S.: Studies on the biological activities of the aldehydes derived from norepinephrine, serotonin, tryptamine and histamine. J. Pharmacol. **143**: 326–331, 1964.
7. SCHOEPF, C. UND BAYERLE, H.: Zur Frage der Biogenese der Isochinolinalkaloide. Ann. Chem. **513**: 190–202, 1934.
8. SCHOEPF, C. UND SALZER, W.: Zur Frage der Biogenese der 1-Benzyl-1,2,3,4-tetrahydro-isochinolin-Alkaloide. Ann. Chem. **544**: 1–30, 1940.