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THE ROLE OF NORADRENALINE AND 5-HYDROXYTRYPTAMINE IN THE CENTRAL ACTION OF RAUWOLFIA ALKALOIDS AND BENZOQUINOLIZINE DERIVATIVES

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Abstract—Sedative-like Rauwolfia alkaloids lower the content of 5-hydroxytryptamine and noradrenaline in brain and other tissues. Benzoquinolizine derivatives lacking an indole group have a similar effect upon these amines. A difference in these two classes of compounds was found when the latter substances produced a short sedative effect and brief depression of the amines. In general the results suggest a causal relation between the pharmacological action of the two types of drugs upon the central nervous system and monoamine metabolism. Studies with other benzoquinolizine compounds show a differential effect upon the two amines so that noradrenaline depletion may cause sedation. Reserpine-like drugs do not have identical effects upon brain and peripheral amines. It is possible that tranquilizing effects are exerted through depletion of noradrenaline or its precursors or of other substances yet unknown.

FOLLOWING the work of Pletscher *et al.*[1], Carlsson and Hillarp[2] and Holzbauer and Vogt[3] several reports have been published, which show that reserpine lowers the content of 5-hydroxytryptamine (5-HT) and catechol amines, particularly noradrenaline (NA), in the brain and various other tissues. Among Rauwolfia alkaloids only those with sedative action (reserpine, raunescine, deserpidine, rescinnamine) produce depression of the two amines.[4, 5] Pletscher *et al.*[6, 7] have found a second group of substances, which, like Rauwolfia alkaloids, cause sedation as well as NA and 5-HT depletion in the brain. These are synthetic benzoquinolizine derivatives having no indole group.

After Rauwolfia administration the content of NA and 5-HT diminishes gradually during several hours and the sedative action also becomes clear only after a considerable latent period. Reserpine, apart from small traces, is metabolized in most tissues long before the pharmacological effects have been fully developed.[8, 9] Benzoquinolizines, on the other hand, produce a comparatively short-lasting depletion of these brain amines and the sedative effect is also short-lived.[7] Based on these findings, among others, it has been postulated that a causal connexion exists between the pharmacological action of the afore-mentioned drugs on the central nervous system and their influence on monoamine metabolism.

According to the theory of Brodie and co-workers[10, 11] 5-HT exists in the tissues in "bound" form and only minute quantities are in "free" state. If the pharmacological activity is due to the unbound fraction the sedative action of Rauwolfia could be produced by the free 5-HT liberated from the cellular binding sites. A relative increase in this free amine would then be more important than the decrease of the total 5-HT present. It is difficult to explain, for instance, why Rauwolfia alkaloids

produce stimulation instead of sedation in animals pretreated with monoamine oxidase inhibitors, like iproniazid.[11] After iproniazid treatment these alkaloids can even increase the total 5-HT content in the brain[12] and at the same time probably also elevate the amount of unbound amine. More evidence for the role of 5-HT has been presented,[13] but many of the recent results indicate that the pharmacological effects of these compounds on the central nervous system may possibly be related to the depression of NA but probably not to that of 5-HT.

Carlsson *et al.*[14] have shown that 3 : 4-dihydroxyphenylalanine (DOPA), the precursor of NA, when given to reserpinized mice and rabbits, will restore normal activity presumably by restoring the central catechol amine. The precursor of 5-HT, 5-hydroxytryptophane, however, was unable to antagonize the tranquilizing effect of reserpine. Essentially similar results have been obtained while using monkeys treated with deserpidine.[15] Carlsson *et al.*[16] have also found that, like NA, the precursor of it, 3-hydroxytyramine (Dopamine) is made to disappear almost completely from the brain by reserpine.

It has been demonstrated by Brodie *et al.*[10] while using fluorometric methods that reserpine depletes 5-HT and NA in the rabbit brain stem to the same degree and at the same rate, the two curves being superimposable. With biological methods we found, however, that after raunescine in rats the depletion of NA in the brain was much more pronounced than that of 5-HT.[17, 18] This happened also after a suitable dose of reserpine, although not as consistently.[17] There was a clear sedative action after a dose of raunescine which was able to lower the NA but not the 5-HT content in the brain.

This selective action on brain monoamines has been demonstrated by Pletscher *et al.*[19] by using two benzoquinolizine derivatives. These were found to affect the brain content of 5-HT in mice almost equally but the brain content of NA differently. One of the compounds was able to release more NA than the other and only the NA-releasing compound had a marked sedative effect.

It is of interest that some new drugs, which have some of the actions of reserpine, cause depression of the amines mainly in that part of the organism where their site of action is most obvious, i.e. centrally or peripherally. Ro 1–9569 (tetrabenazine) a benzoquinolizine derivative, releases NA and 5-HT in the brain but does not appreciably affect NA at peripheral nerve endings.[13,20] It also elicits reserpine-like central effects but has no marked action on the blood pressure.[20] From synthetic reserpine analogues SU 5171 exhibits sedative activity and depletes brain 5-HT in low doses, but does not depress the blood pressure. On the other hand, another analogue, SU 3118 (syrosingopine) is effective in decreasing the blood pressure and releasing peripheral NA, but considerable higher doses of this compound are necessary to produce sedation and depletion of brain NA and 5-HT.[21–23]

In the periphery the reserpine-like drugs probably produce their typical effects by making cells unable to bind NA. Which of the two amines is more important in the mechanism of the central action of these drugs is not clear. It is also possible that other substances present in the brain cells will still enter the picture.

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