compare the extents and rates of epoxidation equal concentrations of radiolabeled vitamins K were incubated in separate epoxidation reactions, and the percentage of each converted to its epoxide at the times indicated was determined (Table 1). After 15 min, menadione and DMK_1 were not converted to the epoxide in detectable quantities (i.e. 50 per cent above the zero-time epoxide level). MK-2 and MK-3 as well as K_1 were epoxidized; at 15 min the percentage conversions of MK-2 and MK-3 were about equal and greater than that of K_1. Little further epoxidation occurs with longer incubations. The percentage conversions at the earlier two time points show that the rates of epoxidation of MK-2 and MK-3 are more rapid than that of K_1.

We have demonstrated that vitamins K, other than phylloquinone (K_1), can be converted by the rat liver microsome "phylloquinone epoxidase" to their respective epoxides. In addition, of the vitamins K tested, only those which support carboxylation—K_1, MK-2 and MK-3—are epoxidized in detectable quantities. It is possible, although unlikely, that the hydroquinones of DMK_1 and menadione would be substrates for epoxidation. These were not tested in the current study but were shown previously to be no more active than their respective quinones in carboxylation. The menaquinones, which are more potent than K_1 in the carboxylation reaction, are epoxidized more rapidly and to a greater extent than K_1. Knauer *et al.* [12] have reported that the *cis* isomer of vitamin K_1 which has little biological activity [13], is also epoxidized to only a small extent. In experiments in which tritiated MK-2 and MK-3 epoxide were incubated for 15 min with the microsomes in a N_2 atmosphere, negligible conversion to MK-2 or MK-3 was detected; thus, 1 μM warfarin is sufficient to inhibit the reduction of these epoxides by the microsomal epoxide reductase, and we have not underestimated the amount of epoxide formed because of recycling of the epoxide back to the vitamin.

These data suggest strongly that carboxylation and epoxidation events are linked. The data say nothing about the nature of this linkage. While the epoxidation event may be required for carboxylation, this is not necessarily the situation. Indeed, vitamin K hydroquinone, the active form of the vitamin for carboxylation [5, 9] and an intermediate in the generation of the epoxide [14], may be oxidized to the quinone during carboxylation. If, during this reaction, there is *in situ* generation of H_2O_2, the H_2O_2 could subsequently convert the quinone to its epoxide.

Acknowledgements—This work was supported by USPHS Grants HL 11414 and HD 00023.

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Biochemical Pharmacology, Vol. 28, pp. 938–939.

0006-2952/79/0315-0938 $02.00/0

Equal inhibitory effect of dimethyl- and monomethyl-β-aminopropionylic derivatives of dibenzazepine on the uptake of [^{3}H]noradrenaline by rat brain synaptosomes

(*Received* 12 *July* 1978; *accepted* 10 *August* 1978)

According to the current hypothesis, the relationship of serotonin(5-HT)- and noradrenaline (NA)-positive qualities plays an important role in the action mechanism of tricyclic antidepressants providing the thymoanaleptic and psychoenergising components of antidepressive effect respectively [3,4,9]. It is supposed that the enhancement of central monoaminergic processes by trycyclic antidepressants is connected with their inhibiting effect on the neuronal uptake mechanism (membrane pumps) for monoamines [5,10]. Thus, the evaluation of the effect of drugs, manifesting in the routine screening tests the qualities of antidepressants, on the uptake of 5-HT and NA is of interest.

It was shown that some β-aminopropionylic derivatives of dibenzazepine (DBA) revealed in the routine screening tests the antidepressants activity [8]. In a previous work the effect of these drugs on 5-HT uptake was studied [11].

In the present paper data on the effect of these drugs on the NA uptake is reported.

Transmembrane transport of NA was evaluated by studying the [^{3}H]-NA uptake by a crude fraction of the synaptosomes of brain stem of female Wistar rats [13]. Drugs were introduced into the incubation medium 5 min before [^{3}H]-NA (for detailed method see [6]). The statistical significance of the results was determined by Student's t test.

Table 1. Influence of compounds on the ^{3}H-NA uptake by rat brain synaptosomes

	Inhibition of [^{3}H]-NA uptake (in %) (means ± S.E.M. from 6 experiments). Concentration in the incubation medium (M). 10^{-6}	10^{-5}	10^{-4}
DMI	16.53 ± 3.78	32.77 ± 2.35*	82.34 ±5.76†
N-(β-dimethylaminopropionyl) dibenzazepine	26.54 ± 2.81	27.70 ± 4.65*	70.37 ± 6.31†
N-(β-methylaminopropionyl) dibenzazepine	21.37 ± 1.86	26.70 ± 5.27*	75.84 ± 6.24†

In comparison to control (saline instead of compounds): * $P < 0.05$; † $P < 0.01$.

The effect of the drugs was compared with the action of desipramine (DMI)—the most potent inhibitor of the NA uptake among the imipramine-like drugs [14].

All three drugs studied inhibited the [^{3}H]-NA uptake almost to the same degree (Table 1).

The same degree of the inhibitory effect in tertiary and secondary derivatives of β-aminopropionylic derivatives of DBA corresponds to the equal degree of their antagonism with reserpine in the tests of hypothermia and ptosis, revealing the adrenopositive qualities of the studied drugs [8].

Among aminopropylic derivatives of DBA, the secondary analog (DMI) is known to be a more potent inhibitor of NA uptake than the tertiary one—imipramine [1]. However an equal effect of a tertiary and a secondary derivative on NA uptake was found in this study. At the same time the secondary β-aminopropionylic derivative of DBA has a strong inhibitory effect on 5-HT uptake [11] in contrast to the secondary analog of aminopropylic derivatives of DBA [5, 14]. Thus the secondary analog of this β-aminopropionylic derivative of DBA combines the qualities of both imipramine and DMI in relation to 5-HT and NA uptake respectively. Since for the antidepressive action both 5-HT and NA-potentiating effects are important [12], the combination of such qualities in one and the same drug can offer advantages over other antidepressants, selectively inhibiting the 5-HT or NA uptake.

Another advantage of such kind of drugs is connected with the secondary amine group which they contain. Demethylation of tertiary aminopropylic derivatives of DBA is known to be one of the main reactions of their catabolism *in vivo* [2], while demethylation of the secondary compounds proceeds very slowly [7]. Considering the similarity of chemical structures of aminopropylic and β-aminopropionylic derivatives of DBA, the similarity of the main ways of their catabolism *in vivo* may be suggested. In case this assumption is proved, the use of the secondary β-aminopropionylic compounds, inhibiting 5-HT uptake, would carry at least one advantage over tertiary aminopropylic drugs, since the latter lose their ability to inhibit 5-HT uptake after demethylation.

Acknowledgements—I would like to thank Professor J. Knoll and Dr. K. Magyar (Budapest) for helpful advice and encouragement.

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Biochemical Pharmacology, Vol. 28, pp. 939–940.

0006-2952/79/0315-0939 $02.00/0

Beta adrenergically sensitive adenyl cyclase in turkey erythrocytes—Apparent lack of effect on oxygen carriage

(*Received* 26 *April* 1978; *accepted* 14 *July* 1978)

Epinephrine elicits increases in the levels of cyclic-adenosine-3′, 5′-monophosphate (cAMP) in many tissues [1], including turkey erythrocytes. The turkey erythrocyte has a beta-adrenergic receptor on its outer membrane surface [2], which, when stimulated by the *N*-isopropyl analogue of epinephrine (isoproterenol), elicits an increased cytoplasmic concentration of cAMP [3]. These increased erythrocyte cAMP levels are accompanied by the phosphorylation of a specific membrane protein [4] and bi-directional increases in ion fluxes [5]. Since the only known physiological role of the erythrocyte is the carriage of oxygen, we were intrigued by the possibility that a beta-adrenergic-mediated control of oxygen binding may occur in turkey erythrocytes. Accordingly, we set out to determine whether or not beta-adrenergic agents or