STUDIES ON THE ABSORPTION, DISTRIBUTION AND METABOLISM OF 1-α-TOCOPHEROL*) IN THE RAT

F. Weber, U. Gloor, J. Würsch and O. Wiss

Department of Vitamin and Nutritional Research and Physical Research Department of F. Hoffmann-La Roche & Co. Ltd., Basle (Switzerland)

Received October 21, 1963

From previous extensive studies comparing d-α-tocopherol with dl-α-tocopherol by various biological assay methods, it was concluded that the biopotency of l-α-tocopherol is lower than that of the d-form. Based on these results, a conversion factor of 1.22 to 1.36 for the biopotency of d-α-tocopherol in relation to dl-α-tocopherol was established (Nutr.Revs. 19, 146 (1961)). The availability of pure l-α-tocopherol obtained by chemical synthesis (Mayer et al., 1963) facilitated the examination whether besides quantitative also qualitative differences exist between the d- and l-form of α-tocopherol.

Simon et al. (1956) have found that, after administration of d-α- and dl-α-tocopherol, the glucuronide of the γ-lactone of 2-(3-hydroxy-3-methyl-5-carboxypentyl)-3,5,6-trimethyl-1,4-benzoquinone was excreted in the urine of human beings and rabbits. The same metabolite could now be detected in the urine of rats dosed with labeled d-α- or l-α-tocopherol, indicating that no differences exist in the metabolism of these two forms of α-tocopherol. Up to now, however, it was not possible to decide whether an inversion of the configuration occurs during the metabolic degradation. In these experiments, 2 mg-doses of (1',2'-^{3}H)-d-α- and (1',2'-^{3}H)-l-α-tocopheryl acetate (specific activity = 101.9 μC/mg and 106.2 μC/mg, resp.) were administered orally to fasted rats (weighing about 140 to 150 g) as an emulsion in 0.5 ml of 0.9 % saline containing 2 % Tween 80. The urine was collected for a period of four days and the metabolite identified as described previously (Weber and Wiss, 1963).

The absorption of d-α- and l-α-tocopheryl acetate was studied by determining the radioactivity in various organs, half an hour, two and

*) The d-α- and l-α-tocopherol preparations used correspond to (2R,4'RS,8'RS)-α- and (2S,4'RS,8'RS)-α-tocopherol, resp., synthesized by Mayer et al. (1963).

twenty-four hours after administration. The results are shown in Fig. 1 to 3 from which it can be seen that l-α-tocopherol is absorbed better and excreted somewhat more rapidly than the d-form. The better absorption of l-α-tocopherol is confirmed by a higher excretion of the metabolite, the amount of which was found to be about three times higher after administration of l-α-tocopherol than after administration of d-α-tocopherol within a period of twenty-four hours.

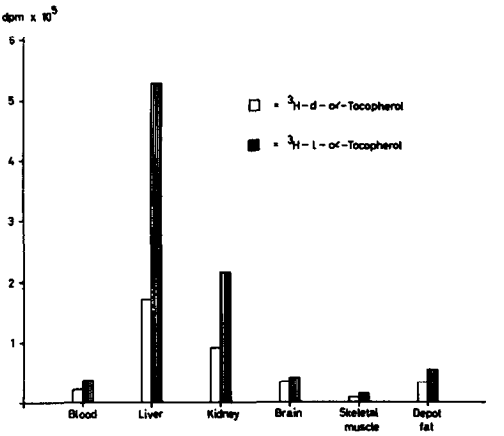

Fig.1. Distribution of the radioactivity (dpm/g fresh tissue) in blood, liver, kidney, brain, skeletal muscle (from the thigh), and depot fat (testicular fat) of rats, half an hour after the oral administration of 2 mg of ^{3}H-d-α- or ^{3}H-l-α-tocopheryl acetate. The columns represent mean values of three animals each.

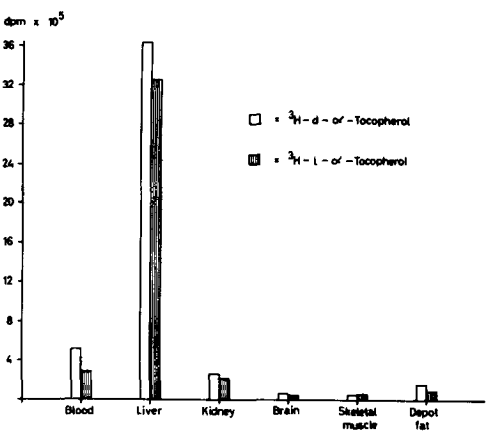

Fig.2. Distribution of the radioactivity (dpm/g fresh tissue) in various tissues of rats, 2 hours after the oral administration of 2 mg of ^{3}H-d-α- or ^{3}H-l-α-tocopheryl acetate. Mean values of two animals each.

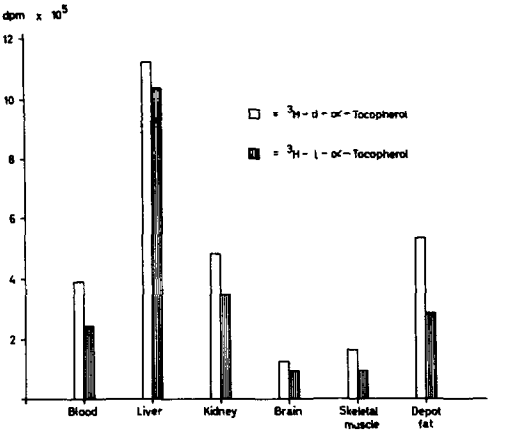

Fig.3. Distribution of the radioactivity (dpm/g fresh tissue) in various tissues of rats, 24 hours after the oral administration of 2 mg of ^{3}H-d-α- or ^{3}H-l-α-tocopheryl acetate. Mean values of two animals each.

In previous investigations (Wiss et al., 1962), it was shown that d-α-tocopherol exhibits a characteristic distribution pattern in various organs and cell particles which differs markedly from that of the unnatural antioxidant ethoxyquin*). It was, therefore, of interest to compare d-α- and l-α-tocopherol in this respect. As shown in Fig. 2, the distribution patterns of d-α- and l-α-tocopherol are very similar. The same could be found when comparing the accumulation of α-tocopherol in the adrenals. Twenty-four hours after administration, the concentration of d-α-tocopherol in the adrenals was 37 times higher than in the blood (on a weight basis), whereas the corresponding factor for l-α-tocopherol was found to be 32.

By separating the cell particles of liver homogenate, it was previously demonstrated that d-α- and dl-α-tocopherol were especially enriched in the microsomes (Cowlishaw et al., 1957; Draper and Alaupovic, 1959; Weber et al., 1962). Comparative studies with ^{3}H-labeled d-α- and l-α-tocopherol revealed that the same applies to l-α-tocopherol.

References

Cowlishaw, B., Søndergaard, E., Prange, I., and Dam, H., Biochim.Biophys. Acta 25, 644 (1957).
Draper, H.H., and Alaupovic, P., Federation Proc. 18, 218 (1959).

*) Ethoxyquin = 2-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline

Mayer, H., Schudel, P., Rüegg, R., and Isler, O., Helv.Chim.Acta 46, 650 (1963).
Simon, E.J., Gross, C.S., and Milhorat, A.T., J.Biol.Chem. 221, 797 (1956)
Simon, E.J., Eisengart, A., Sundheim, L., and Milhorat, A.T., J.Biol.Chem. 221, 807 (1956).
Weber, F., Gloor, U., and Wiss, O., Fette-Seifen-Anstrichmittel 64, 1149 (1962).
Weber, F., and Wiss, O., Helv.Physiol.Pharmacol.Acta 21, 131 (1963).
Wiss, O., Bunnell, R.H., and Gloor, U., Vitamins Hormones 20, 441 (1962).