REGULATION OF STEROIDOGENESIS BY UBIQUINONE

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Thorp and Waring (1962) reported that feeding α-p-chlorophenoxyisobutyrate (CPIB) to rats was effective in depressing the concentration of cholesterol in the plasma by 30-40%, and that in the liver by about 10%, without change in growth rate or food consumption. The hypolipidemic effect of this drug had been confirmed in several laboratories (Atromid Symposium, 1963) and it is now being used for treatment of hypercholesteremic patients under the trade name Atromid-S. Gould and coworkers (1965, 1966) found that the rate of synthesis of cholesterol, as estimated by the incorporation of acetate-1-^{14}C, decreased to the extent of 30-50% without any decrease in that of ketone bodies and triglycerides in the livers of CPIB-fed rats. Since incorporation of mevalonate-2-^{14}C into cholesterol was unaffected, the site of inhibitory action of the drug was considered to be at an early stage in the sequence of reactions of isoprene synthesis. Also, the action of the drug was considered indirect since these effects were observed only in intact animals

but not when the drug was added in the homogenate system synthesizing cholesterol. (Avoy, Swyryd and Gould, 1965).

Ramasarma and coworkers (1967) observed identical effects in ubiquinone-fed rats with respect to the decrease in the incorporation of acetate-1-^{14}C, but not mevalonate-2-^{14}C, into sterols to the extent of 30-50% with no decrease in fatty acids. It is now found that feeding CPIB to rats increased liver-ubiquinone concentration two-fold (Table 1).

Table 1. Liver-ubiquinone concentration in CPIB-fed rats

	μmole/liver
Normal	0.96 ± 0.05
CPIB-fed	2.14 ± 0.26

The values are mean and standard deviation from independent analysis of six rats in each group.

The pattern of incorporation of radioactive tracers into lipid components was similar, confirming the earlier observations of inhibition of isoprene synthesis in the liver at some step between acetate and mevalonate in both conditions of feeding CPIB or ubiquinone (Table 2).

Liver-cholesterol being the source of cholesterol in the serum, inhibition of its synthesis in the liver under the above feeding conditions should reflect in lowering serum-sterol concentration and this is experimentally confirmed (Fig. 1).

Table 2. Incorporation of acetate-1-^{14}C and mevalonate-2-^{14}C into lipid components of the liver of rats fed ubiquinone or CPIB

Status of rats	Sterols		Ubiquinone		Fatty acids
	counts/ min.	mg.	counts/ min.	µmoles	counts/ min.
Tracer: Acetate					
Normal	3400	11.5	45	0.8	11800
Ubiquinone -fed	1200	12.5	30	1.5	21700
Normal	2200	15.9	35	1.0	13400
CPIB-fed	1300	16.4	60	2.4	51400
Tracer: Mevalonate					
Normal	45700	14.0	2600	0.8	-
Ubiquinone -fed	41200	10.6	1100	1.4	-
Normal	22800	21.0	2400	0.6	-
CPIB-fed	20500	19.0	3000	1.4	-

Ubiquinone-9 (1.5 mg./day/rat) was fed orally for 5 days and CPIB was fed at 0.5% in the diet for 10 days. The rats were then dosed orally with acetate-1-^{14}C (20 µc/rat) or with mevalonate-2-^{14}C (2 µc/rat) and killed after 4 hr. Average values per liver of three independent determinations are given. The diet consisted of casein (20%), starch (60%), sugar (10%), peanut oil (5%), salt mixture (5%)and vitamins according to U.S.P. (but contained no cholesterol). The methods used are the same as described earlier (Krishnaiah, Joshi and Ramasarma, 1967).

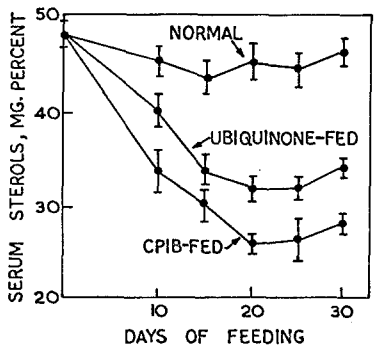

Fig. 1. Concentration of serum sterols in normal rats fed ubiquinone or CPIB. The experimental conditions are the same as described in the legend of Table 2. Each value represents mean and range of independent determinations from six rats.

Ubiquinone (prenyl side chain) and cholesterol, the two end products of isoprene synthesis, seem to depend for their synthesis on a common step between acetate and mevalonate which appears to be subject to inhibition by increased liver-ubiquinone concentration achieved either by direct feeding of ubiquinone or by the indirect action of CPIB. The twin effects of inhibition of liver-sterol synthesis from acetate-1-^{14}C and the decrease in serum-sterol concentration were elicited by ubiquinone-9, but not ubiquinone-10, suggesting high specificity of the natural, major homologue. These results prompt the hypothesis that ubiquinone functions as a regulatory molecule in steroidogenesis in the liver.

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