Diurnal variation of HMG CoA reductase activity in rat intestine

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Abstract HMG CoA reductase activity of rat intestinal mucosa has a diurnal rhythm which coincides with the diurnal variation of the hepatic HMG CoA reductase but has a lower amplitude. The rhythmic variation of the intestinal reductase was present in both jejunal and ileal crypt cell microsomes and was not abolished by cholestyramine administration.

Supplementary key words cholestyramine · ileum · jejunum · crypt cells · liver

THE RATE OF cholesterol biosynthesis in rat liver has been shown to possess a diurnal rhythm. In animals having unrestricted access to food, synthetic activity is maximal between 12 midnight and 2 AM and is minimal during the morning and early afternoon (1, 2). This rhythmic variation is associated with changes in the concentration of the rate-limiting enzyme of cholesterol biosynthesis, HMG CoA reductase (3). Recently, Edwards, Muroya, and Gould (4) demonstrated that cholesterol biosynthesis from acetate in intestinal mucosa of the rat has a diurnal rhythm which parallels that of the liver but has a lower amplitude. The present studies confirm the work of Edwards et al. (4) and demonstrate that, in the intestine as well as in the liver, the rhythmic changes of cholesterol biosynthesis are associated with changes in the activity of the enzyme HMG CoA reductase. It was shown further that the diurnal variation of hepatic and intestinal HMG CoA reductase persists during administration of the bile acid sequestering agent, cholestyramine.

EXPERIMENTAL PROCEDURES

Male Wistar rats weighing 200–250 g were kept in two rooms from which external illumination was excluded, and light and dark periods (12 hr each) were regulated by electric timers. In one room the light was turned off at 4 PM and turned on at 4 AM (normal illumination). The light cycle in the other room was 180° out of phase (reversed illumination). The animals had access to food (Purina rat chow pellets) and water at all times. The rats were kept in these rooms for at least 3 wk before any enzyme assays were carried out. In the experiments with cholestyramine-treated food, 5 g of the ion exchange resin was mixed with 95 g of finely ground Purina chow, and the controls received ground chow only. Hepatic and intestinal HMG CoA reductase activity was assayed exactly as described previously (5). All determinations were carried out with the microsomal HMG CoA reductase, using duplicate or triplicate samples per tissue per animal.

RESULTS AND DISCUSSION

Fig. 1 illustrates the diurnal rhythm of the microsomal HMG CoA reductase of liver and ileal crypt cells of the rat. In both tissues, maximal HMG CoA reductase activity was observed approximately 6.5 hr after start of the dark period. The activity minimum was relatively broad and occurred between approximately 4 and 10 hr after start of the light cycle. As shown in Table 1, HMG CoA reductase activity was greater in ileum than in jejunum, and the amplitude of the cyclic variation likewise was greater in ileum than in jejunum. The diurnal rhythm of the microsomal HMG CoA reductase activity in ileum and in liver persisted during cholestyramine administration; the maximum and minimum enzyme activities occurred at the same time as in control rats.[1] Ileal reductase activity increased about twofold

Abbreviations: HMG, 3-hydroxy-3-methylglutaryl.

[1] Shefer, S., and E. H. Mosbach. Unpublished observation.

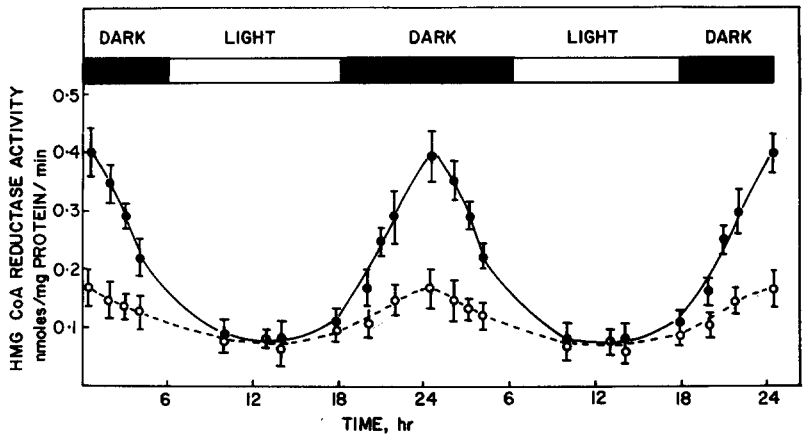

FIG. 1. Diurnal variation of microsomal HMG CoA reductase activity of liver and intestinal crypt cells. ● —— ●, liver; ○ - - -○, ileal crypts. Each point represents the average of 4–9 determinations ± SE.

TABLE 1. Maximal variation in HMG CoA reductase activity of rat intestinal crypt cells[a]

Time	No. of Rats	Diet	Section of Intestine	HMG CoA Reductase Activity	SE[b]
				nmoles/mg protein/min	
6.5 hr after start of light period	5	Stock	Jejunum	0.0554	0.0055
	9	Stock	Ileum	0.0863	0.0032
	4	5% Cholestyramine	Ileum	0.1905	0.0105
6.5 hr after start of dark period	5	Stock	Jejunum	0.0862	0.0032
	9	Stock	Ileum	0.1653	0.0055
	4	5% Cholestyramine	Ileum	0.2758	0.0084

[a] HMG CoA reductase activity of jejunal and ileal crypt cell microsomes was measured at the maximum or minimum of the diurnal cycle. Animals were fed the stock diet or the stock diet plus 5% cholestyramine for 21 days.
[b] Standard error.

TABLE 2. Maximal variation of hepatic microsomal HMG CoA reductase[a]

Time	No. of Rats	Diet	HMG CoA Reductase Activity	SE[b]
			nmoles/mg protein/min	
6.5 hr after start of light period	7	Stock	0.085	0.0032
	4	5% Cholestyramine	0.306	0.0176
6.5 hr after start of dark period	7	Stock	0.395	0.0158
	4	5% Cholestyramine	1.006	0.0494

[a] HMG CoA reductase activity of hepatic microsomes was measured at the maximum or minimum of the diurnal cycle. Animals were fed the stock diet or the stock diet plus 5% cholestyramine for 21 days.
[b] Standard error.

in response to cholestyramine feeding during both the light and the dark periods (Table 1). Persistence of the diurnal rhythm during cholestyramine feeding was also observed with the microsomal HMG CoA reductase of liver (Table 2) (6).

These observations are in good agreement with those of Edwards et al. (4), who did not study intestinal HMG CoA reductase activity directly but measured cholesterol biosynthesis from acetate or tritiated water. It is thus clear that the rhythmic changes of cholesterol synthesis from acetate in ileum and jejunum are associated with parallel changes of HMG CoA reductase. In further agreement with Edwards et al. (4) is the observation that the amplitude of the cyclic change is greater in ileum than in jejunum. HMG CoA reductase activity observed at the peak of the diurnal cycle apparently does not represent maximal activity for a given organ since cholestyramine administration produced a further increase in reductase activity.

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