Hypocholesterolemic Effect of 3-Hydroxy-3-methylglutaric Acid

In bacterial system, 3-hydroxy-3-methylglutaric acid (HMG) has been evaluated as an antimetabolite of mevalonic acid[1]. FIMOGNARI[2] has shown that HMG inhibits the incorporation of acetate into mevalonate in rat liver preparations. This may explain the HMG inhibition of cholesterol synthesis from acetate as described by RABINOWITZ and GURIN[3]. There is certain rationale to the fact that a compound active as an inhibitor of cholesterol biosynthesis may have utility in the treatment of hypercholesterolemia and atherosclerosis, e.g. nicotinic acid[4], α-phenylbutyric acid and α-p-biphenylbutyric acid[5]. This prompted us to investigate the hypocholesterolemic property of HMG in normal as well as hypercholesterolemic animals.

Materials and methods. 4 groups of young male albino rats, C.D.R.I. strain[6], weighing 50 g and each group containing 6 animals were selected for experimental studies (Table I). Group I was kept as control and fed on basal diet[7]. In addition to this diet, groups II, III and IV received orally, varying doses of HMG in water (as indicated) for 7 or 14 days. At the end of treatment, the total serum cholesterol was determined by Bloor's method. For studies made in Table II, young male albino rats weighing about 100 g were maintained for 2 weeks on an experimental diet (basal diet containing 2% hydrogenated vegetable oils; 20 mg cholesterol and 10 mg sodium cholate as homogeneous water suspension, by intubation) in order to produce hypercholesterolemic conditions. The serum cholesterol level of such rats was found to be significantly elevated (192 ± 19 mg%; $p < 0.001$) as compared to rats kept on basal diet only (118 ± 5 mg%). The rats were then divided into groups of 5 each. The cholesterol-fed and cholesterol plus HMG-fed groups continued receiving experimental diet. However, in addition, the latter group received 50 mg HMG/kg/day in water. The experimental diet was replaced by basal diet for hypercholesterolemic control groups and HMG-fed groups. The latter received 50 mg HMG/kg/day in water. At varying periods of HMG treatment (as indicated), the serum cholesterol was determined.

Results. From Table I is evident that HMG administration to normal rats for 1 or 2 weeks significantly lowers the total serum cholesterol content. From the statistical evaluation of the data presented in Table II, it becomes clear that HMG feeding causes a significant depression in serum cholesterol levels of HMG-fed groups as compared to parallel hypercholesterolemic control groups. It was also observed that combined feeding of cholesterol along with HMG also significantly declines the serum cholesterol levels as compared to parallel cholesterol-fed groups. This further supports the hypocholesterolemic property of HMG. It is interesting to mention that no apparent harmful effects of HMG feeding were noticed on animals during the course of investigation. From other works it is known that, in vivo, HMG arises from HMG-CoA by the action of HMG-CoA hydrolase (EC 3.1.2.5), which strongly and competitively inhibits the HMG-CoA reductase (EC 1.1.1.34) activity in bacterial[8] as well as rat liver preparations[2]. These observations, coupled with the hypocholesterolemic property of HMG, suggest that HMG, like other inhibitors of cholesterol biosynthesis, may find a use in the treatment of hypercholesterolemia provided that in men this substance acts in the same way and is well tolerated. The detailed pharmacological screening of this compound is in progress and will be reported elsewhere in detail[9].

Table I. Effect of HMG feeding on serum cholesterol of normal rats[a]

	Group No. I	II	III	IV
	Treatment			
	Basal diet	Basal diet + 10 mg HMG[b]	Basal diet + 20 mg HMG	Basal diet + 30 mg HMG
7 days	151 ± 10	145 ± 2	136 ± 5	128 ± 5[c]
14 days	164 ± 4	147 ± 3[d]	133 ± 8[d]	130 ± 9[e]

[a] All figures are average values expressed as total cholesterol content in mg% with standard error; [b] dose of HMG/kg/day; [c] difference as compared with control group statistically significant $p < 0.05$; [d] $p < 0.01$; [e] $p < 0.001$.

Table II. Effect of HMG and cholesterol + HMG feeding on serum cholesterol of hypercholesterolemic rats (average ± S.E.)

HMG treatment (day)	Total cholesterol content, mg%			
	Cholesterol-fed group	Cholesterol + HMG-fed group	Hypercholesterolemic control group	HMG-fed group
1st	207 ± 10	139 ± 5[a]	200 ± 6	133 ± 3[a]
2nd	203 ± 4	129 ± 15[a]	181 ± 4	138 ± 4[a]
3rd	208 ± 2	172 ± 8[a]	192 ± 6	165 ± 4[a]
4th	–	–	181 ± 5	148 ± 3[a]
5th	211 ± 14	167 ± 5[b]	158 ± 5	162 ± 4
6th	–	–	139 ± 5	137 ± 7

[a] Difference as compared to respective control group statistically significant $p < 0.001$; [b] $p = 0.01$.

Zusammenfassung. Bei Fütterung mit 3-hydroxy-3-methylglutarsäure (HMG) wurde eine bedeutende Senkung des Serum-Cholesterinspiegels sowohl in normalen, als auch in hypercholesterin-ämischen Ratten beobachtet. Bei gleichzeitiger Verabreichung von HMG und Cholesterol blieb die erwartete Zunahme beim Serumcholesterin aus und gleichzeitig wurde eine Abnahme des Cholesterinspiegels festgestellt.

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