

Effect of Polyene Macrolides on Cholesterol Metabolism of the Chick¹ (34190)

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Substances, ranging from plant sterols to, as yet, unidentified constituents of oat hulls, and including such diverse materials as pectin and cholestyramine, have been shown to interfere with the absorption and utilization of both dietary and circulating enterohepatic lipids and cholesterol (1-4). An unusual observation on the effect of polyene macrolides by the oral route on canine prostatic glandular hyperplasia (5) suggested the possibility that these antifungal agents might possess interesting properties relative to lipid, and, in particular, to cholesterol utilization. Studies in dogs, indeed, demonstrated the remarkable property of the polyene macrolides to affect serum cholesterol levels (6). The present paper reports on the efficacy of relatively small amounts of dietary polyene macrolides in relation to plasma cholesterol levels, and fecal lipid and sterol excretion of the cholesterol-fed chick.

Materials and Methods. The egg powder-containing diet and the methods used in determining plasma cholesterol and fecal sterol and total lipids have been previously described (2). Duplicate groups of 6-8 male, day-old chicks, were used for each treatment group. Since some of the polyene macrolides are known to be unstable, in one experiment they were daily mixed into the feed. Preliminary tests had also shown reduced drug activity from feed exposed to sunlight; the experiments were therefore carried out in artificial light.

Results and Discussion. The results of a comparison between a number of related aromatic heptaene macrolides² added at a level of 200 mg/kg diet are given in Table I. At

this dosage level hamycin was toxic (8 of 16 chicks died) but there was no mortality from any of the other compounds tested, although food consumption and body weight were also depressed by candicidin and aureofungin. In comparison with the control group, all of the aromatic heptaene macrolides tested reduced plasma cholesterol levels and concomitantly increased fecal lipid and sterol excretion. The latter observation rules out the possibility that reduced food intake was responsible for the lower plasma cholesterol levels. Even with normal food consumption, fungimycin exhibited similar effects on plasma and fecal lipid levels with minor effects on body weight. This is an important consideration because food intake reduced below normal is known to cause elevated plasma cholesterol levels of chicks (7).

In a second experiment the aromatic heptaene macrolide, candicidin, was compared with a variety of other polyene macrolides belonging to the nonaromatic heptaene (amphotericin B), pentaene (filipin) and tetraene (nystatin) macrolide groups (Table II). None of these compounds affected food intake significantly. Whereas the plasma cholesterol-lowering effect of candicidin was greatest, reductions were also noted with filipin and amphotericin B; nystatin had essentially no effect. However, all compounds showed markedly increased effects on fecal sterol and lipid excretion.

²The following compounds were used in this study: candicidin (S. B. Penick, lot 8487-NHF-1, micronized, 60%), fungimycin (Institute of Microbiology, lot 8-7-68, 70%), aureofungin (Hindustan Antibiotics, crude, 25%), hamycin (Cooper Laboratories, lot 72C8-3704, micronized, 50%), nystatin (E. R. Squibb, lot 36982-013, 4230 units/mg), filipin (Upjohn, lot U5956, 96%) and amphotericin B (E. R. Squibb, lot 38675-001, 90%).

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In the third experiment (Table III) two levels of candicidin were fed, both of which reduced body weight and food consumption. As before, there were significant reductions in plasma cholesterol. Unlike the findings in the other studies with candicidin, there was no increased fecal sterol excretion, whereas total fecal lipid excretion increased almost

TABLE I. Effect of Dietary Aromatic Heptaene Macrolide Additions on 3-Week Body Weight, Food Consumption, Plasma Cholesterol, and Fecal Lipid Excretion.

Polyene macrolide supplement ^a (200 mg/kg of diet)	Body wt (g)	Food consumption (g/bird)	Plasma cholesterol (mg/100 ml)	Fecal (% dry wt)	
				Sterol	Lipid
None	307 ± 7 ^b	359	218 ± 10 ^b	0.76 ^d	4.22
Candicidin	174 ± 10	253	155 ± 8	1.72	9.78
Fungimycin	291 ± 9	369	178 ± 8	1.15	5.10
Aureofungin	237 ± 12	311	183 ± 9	1.42	7.04
Hamycin ^c	134 ± 12	195	126 ± 13	1.44	9.89

^a The drugs were mixed into the feed daily.

^b Mean ± SE for duplicate groups of 8 male chicks.

^c Half of the 16 chicks fed this drug died during the 3-week experiment; no deaths occurred in any of the other groups listed in this table.

^d Fecal analyses were carried out in duplicate on each of the 2 groups comprising a dietary treatment.

TABLE II. Effect of Miscellaneous Dietary Polyene Macrolide Additions on 3-Week Body Weight, Food Consumption, Plasma Cholesterol, and Fecal Lipid Excretion.

Polyene macrolide supplement ^a (200 mg/kg of diet)	Body wt (g)	Food consumption (g/bird)	Plasma cholesterol (mg/100 ml)	Fecal (% dry wt)	
				Sterol	Lipid
None	267 ± 10 ^b	335	197 ± 11 ^b	0.62 ^c	6.70
Nystatin	301 ± 10	346	209 ± 16	0.84	8.27
Filipin	285 ± 9	340	179 ± 12	1.09	11.37
Amphotericin B	286 ± 12	347	170 ± 9	0.97	9.09
Candicidin	215 ± 9	279	131 ± 8	1.47	13.70

^a The drugs were added to the feed when diet was mixed.

^b Mean ± SE for duplicate groups of 7 male chicks.

^c Fecal analyses were carried out in duplicate on each of the 2 groups comprising a dietary treatment.

TABLE III. Effect of Dietary Candicidin on 3-Week Body Weight, Food Consumption, Plasma Cholesterol, and Fecal Lipid Excretion.

Candicidin supplement ^a (mg/kg of diet)	Body wt (g)	Food consumption (g/bird)	Plasma cholesterol (mg/100 ml)	Fecal (% dry wt)	
				Sterol	Lipid
None	304 ± 8 ^b	341	213 ± 18 ^b	0.80 ^c	5.40
40	274 ± 13	337	171 ± 12	0.67	13.20
200	201 ± 11	290	130 ± 9	0.78	15.85

^a The drug was added to the feed when diet was mixed.

^b Mean ± SE for duplicate groups of 6 male chicks.

^c Fecal analyses were carried out in duplicate on each of the 2 groups comprising a dietary treatment.

threefold. The absence of a fecal sterol response in this experiment may be due to a different bacterial flora in these chicks, perhaps resulting in greater cholesterol conversion to coprosterol which is not detected by the colorimetric method employed for the sterol determination.

Summary. It was shown that small concentrations of certain dietary polyene macrolides, and in particular the aromatic heptaenes, effectively reduce plasma cholesterol of cholesterol-fed chicks, presumably through a mechanism which involves binding of lipids, particularly cholesterol, in the digestive tract.

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