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Inhibition of Respiration in a Flagellate Protozoon by Hypocholesterolemic Drugs

Several hypocholesterolemic drugs uncouple oxidative phosphorylation in rat liver mitochondria[1]. Also some of these drugs, for example, benzmalecene and triparanol ("*MER*-29"), inhibit multiplication of *Ochromonas danica*, a phytoflagellate; oleic acid annuls this inhibition, but sterols or sterol precursors do not[2]. Do these drugs inhibit synthesis of ATP in *O. danica*? It remains to be seen if there is an especially close relation between ATP synthesis and lipid synthesis.

O. danica was grown in chemically defined medium[3] for 5 days at 25° under fluorescent lights. Cells were collected by centrifugation, washed once in carbon- and nitrogen-free growth medium (minus all carbon and amino-acid nitrogen sources) and resuspended as a 1 per cent cell suspension in carbon- and nitrogen-free medium. Air was bubbled vigorously through cell suspensions before use. Drugs were dissolved in 95 per cent ethanol; ethanol had no effect or stimulated endogenous respiration slightly at the concentrations used. Respiration was measured as consumption of oxygen in a cuvette containing a Clark oxygen electrode connected to a power supply and a Varian *G*14 recorder. Cell suspensions were continuously agitated in the cuvette by a glass-encased spinning magnet.

Triparanol stimulated respiration slightly at low concentrations (0·11 and 0·34 mM). Higher concentrations of triparanol and benzmalecene inhibited endogenous respiration (Table 1). In rat mitochondria 0·7 mM triparanol had no effect on oxidative phosphorylation. In *O. danica* c. 0·7 mM triparanol and a higher concentration of benzmalecene markedly inhibited endogenous respiration. Hypocholesterolemic agents apparently act in the protozoon—as in mammals—by inhibiting synthesis of ATP along with lipid synthesis.

Inhibitors of oxidative phosphorylation block sterol synthesis in rat liver homogenates[4]; conversely the hypocholesterolemic drugs inhibit ATP-linked reactions in lipid synthesis[5,6]. Lauric acid, which actively uncouples oxidative phosphorylation in rat liver mitochondria[1], also effectively inhibits conversion of mevalonic acid-2-^{14}C to cholesterol in rat liver homogenates[7]. It is tempting to speculate that hypocholesterolemic drugs, including thyroxine and perhaps nicotinic acid, may exert a potent but indirect inhibitory effect on sterol synthesis by depleting ATP reserves, and also by directly inhibiting steps in sterol synthesis[8].

Table 1. Effect of Hypocholesterolemic Drugs on Endogenous Respiration of *O. danica*

Compound	Concentration (mM)	Ratio Inhibited rate / Normal rate of respiration*
Triparanol	0·11	1·05
	0·34	1·10
	0·68	0·58
	1·14	0·50
Benzmalecene	0·68	0·93
	1·14	0·30

* μmoles of oxygen utilized/min by 5·0 ml. of a 1 per cent cell suspension containing 668 μg protein/ml.

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Dental Abnormalities in European and New Zealand Hedgehogs

Herter[1] examined the skulls of six hedgehogs, *Erinaceus europaeus* L., from Hawke's Bay, New Zealand, and found that three of them had dental abnormalities. One animal lacked both lower second incisors and the gap between the first and second premolars was wider than usual. The first two right premolars had not erupted in another animal, while a third hedgehog lacked a second lower incisor, and the canine on that side had moved forward to take its place. All thirty North European hedgehogs, compared with these New Zealand animals, had normal sets of teeth. Herter suggests that this abnormality may have resulted from a mutation which has occurred since the hedgehog's introduction to New Zealand seventy years ago.

I have examined 67 sets of adult hedgehogs' teeth from the North Island and four sets of teeth from the South Island of New Zealand, collected between 1956 and 1958. Only 34 sets were complete. Thirty-five hedgehogs lacked certain teeth, two had extra teeth, and five had teeth which had erupted abnormally. The lower second incisors were the most variable teeth: twenty animals lacked one or both. One had an extra pair of incisors in both upper and lower jaws. The second premolar in the upper jaw was quite variable in shape and occurrence, being absent in 14 animals and abnormally erupted in two others. No anomaly was noticed in molars.

Combining these and Herter's observations we find that 39 of the 77 New Zealand hedgehogs examined showed some dental abnormality, usually a deficiency or faulty eruption of the incisors or premolars, whereas 30 animals from northern Europe had a normal complement. Thus the difference between northern European and New Zealand hedgehogs appears to be well established.

However, New Zealand animals are not the only ones to show this characteristic: Barrett-Hamilton[2] observed that the second premolar of British hedgehogs was often variable in shape and occurrence. Though he does not give any indications of the number of specimens he examined, I have been able to examine 24 sets of British hedgehogs'