Mode of Action of Anticestodal Agents

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1. INTRODUCTION

Mode of action of anticestodal agents is a pretentious title for a chapter that can only list the effects of anthelmintics on membranes, organelles, enzymes, and neuromuscular systems. In fact, essential information about the molecular mechanism of action of most anthelmintics is still lacking.

It is surprising that only few scientists are working on the mode of action of anthelmintic drugs, on the biochemical and molecular aspects of helminths, and on the mechanisms regulating host–parasite relationships, considering the myriad of interesting models available. To list just a few examples, many enzymes involved in nucleic acid and protein metabolism and in energy generation still await investigation at the molecular level. A better knowledge of the active sites of these enzymes, of their localization, orientation, and interaction with other cellular components, would be of great help in the study of the underlying mechanisms for the anticestodal activity of the chemical compounds discussed in this chapter. Investigation of the physicochemical properties of membranes, of the transport systems available, and of the neurotransmitters and their receptors will lead to a better understanding of the interaction of many of the anticestodal agents and will contribute to the development of chemicals that might act more selectively against the invader.

This review includes a limited number of publications that deal with the biochemical and biophysical aspects of anticestodal drugs. More details can be found in several comprehensive reviews that have summarized the interactions of common anthelmintics with biochemical and physiological processes in parasitic worms (Mansour, 1979; Rew, 1978; Sharma and Abuzar, 1983; Sharma et al., 1980; Vanden Bossche, 1976, 1978, 1980a,b, 1985; Vanden Bossche et al., 1982).
2. BENZIMIDAZOLES

Mebendazole, or methyl (5-(benzoyl)1H-benzimidazol-2-yl)carbamate has been proved active against a broad spectrum of gastrointestinal (GI) nematodes and cestodes in human and veterinary medicine. After it had been described as larvicidal against *Taenia taeniaeformis* larvae (Thienpont et al., 1974), Heath and Chevis (1974) and Krotov et al. (1974, 1976) were the first to report the efficacy of mebendazole against secondary hydatid cysts in mice. The effects of this benzimidazole carbamate on *Echinococcus granulosus* and *E. multilocularis* have been reported in different experimental animals and in man (Schantz et al., 1982; Bekhti et al., 1977, 1980; Wilson and Rausch, 1980; Witassek et al., 1981; Müller et al., 1982; French, 1984).

The fluorine analogue of mebendazole, flubendazole (Schantz et al., 1982) and of other benzimidazole derivatives, such as albendazole (Saimot et al., 1983), also showed various degrees of larvicidal activity. Mebendazole and related benzimidazole carbamates interact with tubulin and prevent its polymerization. At high concentrations, the benzimidazole derivative, thiabendazole, also affects polymerization of tubulin (Ireland et al., 1979).

The time-related micromorphological changes induced by mebendazole or flubendazole in *T. taeniaeformis* larvae or adult *Hymenolepis nana* have been reported by Borgers et al. (1975), Verheyen et al. (1976), and Laclette et al. (1981). The cytoplasmic microtubules of tegumental cells have almost completely disappeared from the tegument of *H. nana* collected from mice medicated for 6 hr with 500 ppm mebendazole in the food. After the disappearance of the microtubules, vesicles accumulate in the Golgi area, and the absorptive surface of the tegument degenerates. Examination of the hydatid cysts of mice treated with mebendazole revealed the same time-related deteriorative effect of the benzimidazole carbamate as described for other cestode species (Verheyen, 1982). Prolonged treatment with mebendazole of patients with hydatid disease often results in complete necrosis of the germinal layer of *E. granulosus* cysts. These cysts showed only remnants of degenerated germinal layer, including heterogeneous vesicular membranes, electron-dense amorphous structures, myeloid bodies, lipid globules, crystal-like precipitates, and remnants derived from muscular tissue (Verheyen, 1982). The hydatid germinal membrane tissue collected from sheep, treated daily with one or two courses of mebendazole (daily dose 6 g), each lasting 3 weeks, also showed complete degeneration of the tegumental and subtegumental structures (Al-Dabagh et al., 1981).

Although a significant number of interesting studies have been reported, we have yet to learn whether the selective toxicity of mebendazole is attributable to differences between the parasite and host tubulin, to differences in their pharmacokinetic behavior (Köhler and Bachmann, 1980), or to differences in their metabolism.

Possible consequences of the block in transporting secretory substances following interruption of the microtubular system are impaired defense reactions, inadequate nourishment, and cellular autolysis. The inadequate nourishment induced by benzimidazole carbamates has been reported by several investigators. For example, mebendazole affects the glucose uptake by helminths both *in vitro* and *in vivo* (Vanden Bossche,