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INITIAL STUDIES ON THE EFFECTS OF THE GROWTH FACTOR PRODUCED BY PLEROCERCOIDS OF THE TAPEWORM, SPIROMETRA MANSONOIDES, ON LIVER DRUG METABOLISM

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Plerocercoid larvae of the tapeworm, Spirometra mansonoides, produce a factor that stimulates growth in several mammalian species including intact rats, mice and hamsters, as well as hypophysectomized, thyroidectomized and diabetic rats (1). The actions of the plerocercoid growth factor (PGF) have been compared to those of mammalian growth hormone (2). In addition, PGF was shown to compete with human growth hormone for binding sites in a radioreceptor assay for growth hormone (3). While PGF has many functional similarities to growth hormone, it is immunologically distinct from growth hormone (3).

Injection of exogenous growth hormone into rats has been reported to cause a decrease in hepatic drug metabolism (4). The purpose of this communication is to report that PGF also causes a decrease in hepatic drug metabolism of hypophysectomized rats.

Rats were exposed to PGF by the subcutaneous injection of the PGF-producing plerocercoids. Figure 1 shows that the number of plerocercoids used was sufficient to cause a significant growth response in infected hypophysectomized rats compared to uninfected hypophysectomized rats. However, plerocercoid infection did not increase the growth rate of the intact rats used (data not shown). In earlier studies plerocercoid infection did not affect the growth rate of rapidly growing intact rats (5). However, young, rapidly growing intact rats infected with plerocercoids did exhibit a decrease in pituitary weight and considerably less plasma growth hormone (6).

The data in Table 1 show that the PGF-induced growth response in hypophysectomized rats was accompanied by a 30-50 per cent decrease in the rate of hepatic drug metabolism of drugs that give either a type I (aminopyrine) or a type II (aniline) binding spectrum with hepatic microsomes (7). This inhibitory effect on drug metabolism is similar to that observed in hypophysectomized rats injected with exogenous growth hormone (8). As shown in Table 1, the inhibitory effect on drug metabolism caused by plerocercoid infection was observed at 7 days post-infection and was essentially unaltered for as long as 21 days post-infection. During this same period, the infected hypophysectomized rats were undergoing significant growth compared to the uninfected hypophysectomized controls (Fig. 1).

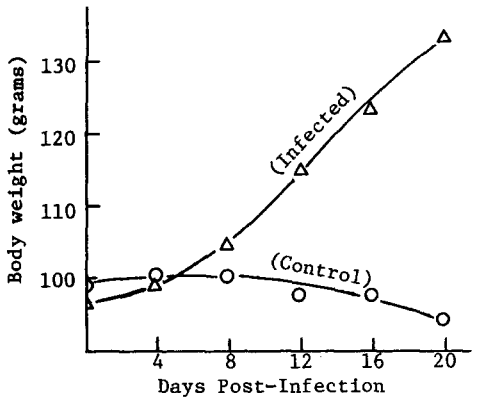

Fig. 1. Effect of S. mansonoides plerocercoids on growth in hypophysectomized rats. Approximately 100 g hypophysectomized male Sprague-Dawley rats were purchased from Hormone Assay, Chicago, Ill. The experimental rats were infected with 10 plerocercoids each by subcutaneous injection 3 weeks after hypophysectomy. The rats were maintained on a purified diet (56% sucrose, 4% salt, 10% corn oil, 30% casein and ample amounts of vitamins) in an animal room with controlled lighting (12 hr light - 12 hr dark) and temperature (80°).

Table 1. Effect of Spirometra mansonoides plerocercoids on hepatic drug metabolism in hypophysectomized rats*

Days post-infection	Drug substrate	Hypophysectomized (nmoles/min/g liver)	Hypophysectomized infected (nmoles/min/g liver)	% Change
7	Aminopyrine	49.96 ± 4.64 (5)	29.88 ± 2.73 (6)	-40†
7	Aniline	6.57 ± 0.35 (4)	3.08 ± 0.46 (3)	-53†
14	Aminopyrine	49.7 ± 5.05 (4)	25.4 ± 5.5 (6)	-49‡
14	Aniline	5.3 ± 0.75 (6)	3.26 ± 0.25 (6)	-38‡
21	Aminopyrine	54.15 ± 5.43 (6)	33.38 ± 4.31 (6)	-38‡
21	Aniline	6.43 ± 0.6 (6)	4.53 ± 0.22 (6)	-30‡

*The hypophysectomized rats used were the same as those described in Fig. 1. All animals were fasted 12 hr prior to sacrifice. The drug metabolism reactions were done with 10,000 g-10 min liver supernatant prepared as described by Mazel (9). The assays used to determine formaldehyde and ρ-aminophenol produced were those described by Mazel (9) except that 20% trichloroacetic acid was used to stop the reactions. The results are expressed as formaldehyde or ρ-aminophenol produced with aminopyrine or aniline as substrate respectively. The numbers given are mean ± S. E. M. (number of animals).

†$P < 0.01$.

‡$P < 0.05$.

The data in Table 2 show that, under the experimental conditions used, PGF (plerocercoid infection) did not affect drug metabolism in the intact rats. Exogenous growth hormone, however, was reported to cause a decrease in drug metabolism in hypophysectomized as well as intact rats (8). The fact that plerocercoid infection of intact rats did not affect drug metabolism in the present experiments could be the result of several factors. It is possible that the plerocercoid infection used did not produce sufficient PGF to overcome the normal controlling influences of endogenous growth hormone present in intact animals. The fact that the growth rate of the intact rats was not influenced under these conditions suggests this. It is also possible that the effect of PGF on drug metabolism is inversely related to PGF-induced growth response as was observed with the hypophysectomized rats (Table 1 and Fig. 1). Such a relationship would make it difficult to observe

Table 2. Effect of Spirometra mansonoides plerocercoids on hepatic drug metabolism in intact rats*

Days post-infection	Drug substrate	Intact (nmoles/min/g liver)	Intact infected (nmoles/min/g liver)	% Change
7	Aminopyrine	83.78 ± 3.71 (4)	89.84 ± 8.5 (5)	+6†
7	Aniline	9.04 ± 0.75 (5)	8.59 ± 1.04(5)	0

*Intact male rats were obtained from Sprague-Dawley, Madison, Wis. and were treated identically to the hypophysectomized rats described in Fig. 1. All other conditions were the same as those described in Table 1. The numbers given are mean ± S. E. M. (number of animals).

†$P > 0.05$.

an effect of PGF on drug metabolism in rapidly growing rats. Whether or not the lack of effect of PGF (plerocercoid infection) on drug metabolism in the young intact rats shown in Table 2 is related to one of these possibilities or is due to other factors can best be answered using injections of purified PGF. Such a preparation will also be required to determine if PGF has an effect at the level of microsomal cytochrome P-450 similar to that reported for growth hormone (4). Efforts are currently in progress to isolate and purify sufficient PGF to conduct the appropriate experiments.

These initial studies clearly show that infection of hypophysectomized rats with plerocercoid larvae of the tapeworm, S. mansonoides, produced effects on growth and hepatic drug metabolism similar to those caused by mammalian growth hormone.

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