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Studies on Chemotherapy of Parasitic Helminths (X), *In Vitro* Effects of Known Antischistosomal and Neuropharmacological Drugs on the Motor Activity of Adult *Schistosoma japonicum*

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For the development of more effective and less toxic anthelminthics, it has been useful to study the biochemical and physiological mechanisms, and pharmacological responses of the helminthic worms (Mansour, 1964; Saz and Bueding, 1966; Woolhause, 1979). As to the schistosomes, there have been many reports regarding *in vitro* effects of various drugs on energy metabolism, ion-movements, and neuromuscular junctions of *Schistosoma mansoni* (Woolhause, 1979), whereas there have been few reports on such *in vitro* effects of drugs on those of *S. japonicum*.

We have undertaken comparative and systematic studies regarding drug actions on various helminths and isolated host tissue preparations using the isotonic transducer and visual observation methods that we recently developed (Sano *et al.*, 1981; Terada *et al.*, 1982). In the present study, effects of various drugs on the motor activity of *S. japonicum* were examined by the visual observation method to determine whether this method can be actually applied for detecting anthelminthic effects against the worm and also to determine preliminarily the neuropharmacological responses of the worm.

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Materials and Methods

1. Visual observation method

Mice (ddY strain) were experimentally infected with cercariae of *Schistosoma japonicum* (Yamanashi strain) liberated from *Oncomelania nosophora* (Yamanashi strain) maintained in laboratory. After 3 to 5 months of infection, adult worms in the mesenteric or portal veins of the mice were collected by the perfusion method (Smithers and Terry, 1965) with Earle's balanced salt solution as a perfusion medium. This medium was buffered at pH 7.4 to 7.5 with sodium bicarbonate, and added with 100 units of penicillin G (potassium salt, Meiji), 100 μg of streptomycin sulfate (Meiji), and 10% horse serum (M.A. Bioproducts) per ml. Thereafter, the worms were transferred into the same medium in test tubes (2.2× 5.0 cm) kept in a water bath at 35 C. Two ml of medium were used per paired worms or a male worm. No difference between a single male and paired worms was observed

Table 1 Quantification of the motor activity of adult *S. japonicum*

Changes in motor activity	Value	
	Head portion	Other sites (x 2)
Remarkably stimulated	4.0	2.0
Moderately stimulated	3.0	1.5
Little influenced	2.0	1.0
Control activity	2.0	1.0
Little influenced	2.0	1.0
Moderately inhibited	1.0	0.5
Remarkably inhibited	0.0	0.0

in their susceptibility to drugs tested.

After the motor activity was observed under a dissecting microscope, drugs were added into each test tube except control ones. The medium was sealed with one ml of liquid paraffin in order to prevent evaporation. The motor activity of male worms in both experimental and control tubes was observed at 1/4, 1/2, 1, 2, 3, 6, and 24 hr after the addition of drugs.

The estimation of the motor activity was carried out as follows. The movement at three sites was separately observed: displacemental or groping movement of head portion with acetabulum, peristaltic movement of the body, and undulating movement of the posterior portion. The control activity at these three sites was given as a score of 2.0, 1.0, and 1.0, respectively. The motor activity of worms in test tubes with or without drugs was evaluated with criteria such as rate and amplitude of contraction, and was ranked as remarkable, moderate or little as shown in Table 1. Finally, motor activity of the male worms at each drug concentration was expressed by a total score from three sites: control or little influenced, total score=4.0; inhibition, $0.0 \leqq$ total score < 4.0; and stimulation, $4.0 <$ total score $\leqq 8.0$. Changes in tone (paralysis or spastic paralysis was caused or not) were also observed. Tables 2 and 3 show the results obtained at 1, 3, and 24 hr exposure as mean ± S.E. Values at each time in tables are regarded as following effects: rapid effect at 1 hr, delayed effect at 24 hr, and effect at 3 hr probably related to the drug concentration in blood after oral administration.

2. Compounds tested

1) Known antischistosomal drugs: sodium antimonyl tartrate (Stibnal) [Banyu], niridazole [Ciba], hycanthone methanesulfonate [Sterling-Winthrop], oxamniquine [Pfeizer], and praziquantel [Bayer]. Trans-5-amino-3-[2-(5-nitro-2-furyl)-vinyl]-1,2,4-oxadiazole (SQ-18506) and 4-isothiocyano-4′-nitro-diphenylamine (CGP-4540) were kindly provided by Dr. E. Bueding, School of Medicine, The Johns Hopkins University.

2) Neuropharmacological agents: eserine salicylate, carbamylcholine chloride (Carbachol), γ-aminobutyric acid (GABA) [Sigma], metrifonate, dichlorvos [Kumiaikagaku], 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) [Aldrich], nicotine tartrate, pilocarpine hydrochloride, 5-hydroxytryptamine (5-HT, serotonin) [Tokyokasei], phenylephrine hydrochloride [Wako], isoproterenol hydrochloride [Nikkenkagaku], and clonidine hydrochloride [Tanabe].

Each drug was dissolved in an appropriate solvent [0.9% NaCl, ethanol or dimethylsulfoxide (DMSO)] and then added into the incubation medium. The final concentration (1% or less) of two organic solvents in the incubation medium did not affect the motor activity of the worms.

Results

The concentration of drugs is shown as g/ml, unless otherwise stated in the text.

1. Effects of various known antischistosomal drugs on the motor activity of adult *S. japonicum* (Table 2)

Stibnal (3×10^{-7}–3×10^{-5}) and praziquantel (10^{-7}–10^{-5}) spastically inhibited the motor activity and caused spastic paralysis in *S.*

Table 2 Effects of various known antischistosomal drugs on the motor activity of adult *S. japonicum*

Drug	Concentration (g/ml)	N*	Motility at 1 hr	Motility at 3 hr	Motility at 24 hr
No drugs		39	4.0±0.0†	4.0±0.0	4.0±0.0
Stibnal	3×10^{-8}	5	4.0±0.0	4.0±0.0	4.0±0.0
	10^{-7}	3	4.0±0.0	4.0±0.0	4.0±0.0
	3×10^{-7}	6	3.8±0.3	2.3±0.2	2.1±0.2
	4.6×10^{-7}	8	3.5±0.2	0.9±0.3	0.8±0.5
	10^{-6}	3	3.2±0.8	1.5±0.0	0.5±0.3
	3×10^{-6}	4	0.9±0.1	0.0±0.0	0.0±0.0
	10^{-5}	4	1.0±0.0	0.1±0.1	0.0±0.0
	3×10^{-5}	3	0.0±0.0	0.0±0.0	0.0±0.0
Niridazole	10^{-6}	3	4.0±0.0	4.0±0.0	3.7±0.3
	10^{-5}	3	4.0±0.0	4.0±0.0	1.8±0.2
	2.1×10^{-5}	12	3.5±0.2	3.4±0.2	1.9±0.3
	10^{-4}	3	3.7±0.3	3.7±0.3	1.2±0.2
Hycanthone	10^{-6}	6	4.0±0.0	4.0±0.0	4.0±0.0
	4.5×10^{-6}	6	3.8±0.2	2.4±0.4	3.8±0.5
	10^{-5}	3	1.3±0.2	0.5±0.0	0.8±0.2
	4.5×10^{-5}	4	0.8±0.3	0.3±0.1	0.3±0.3
	10^{-4}	3	0.0±0.0	0.0±0.0	0.0±0.0
Oxamniqine	10^{-5}	3	4.0±0.0	4.0±0.0	4.0±0.0
	2.7×10^{-5}	6	4.3±0.2	4.0±0.0	4.0±0.0
	10^{-4}	3	3.3±0.3	3.0±0.0	1.2±0.2
SQ-18506	10^{-6}	3	4.0±0.0	4.0±0.0	4.0±0.0
	10^{-5}	3	4.0±0.0	4.0±0.0	0.2±0.2
	10^{-4}	3	0.7±0.2	0.7±0.2	0.0±0.0
Praziquantel	10^{-8}	8	3.4±0.2	3.9±0.1	3.9±0.1
	10^{-7}	16	1.8±0.2	1.6±0.2	1.8±0.2
	10^{-6}	5	0.2±0.1	0.1±0.1	0.1±0.1
	10^{-5}	4	0.3±0.1	0.0±0.0	0.0±0.1
CGP-4540	10^{-6}	9	4.0±0.0	4.0±0.0	4.0±0.0
	2.7×10^{-6}	10	4.0±0.0	3.5±0.3	2.3±0.6
	10^{-5}	3	0.8±0.4	0.8±0.4	0.7±0.2
	10^{-4}	3	1.2±0.2	0.0±0.0	0.0±0.0

*: Number of experiments, †: All values are shown as mean ± S. E.

japonicum (Photo. 1).

On the other hand, other antischistosomal drugs were less effective. In higher concentrations, however, hycanthone (10^{-5}–10^{-4}), CGP-4540 (10^{-5}–10^{-4}), and SQ-18506 (10^{-4}) were rather effective throughout the observation period, whereas niridazole (10^{-5}–10^{-4}), oxamniquine (10^{-4}), and SQ-18506 (10^{-5}) showed slight effects only at 24 hr. The effects of hycanthone were characterized by a remarkable relaxation, especially in the head portion (Photo. 1).

2. Effects of various neuropharmacological agents on the motor activity of adult *S. japonicum* (Table 3)

1) Cholinergic drugs: Inhibition of the motor activity of *S. japonicum* was remarkably shown by eserine (4×10^{-7}–4×10^{-5}), metrifonate (2.6×10^{-7}–2.6×10^{-6}), and dichlorvos (2.2×10^{-7}–2.2×10^{-6}), and slightly by carbachol (10^{-4}), but not by DMPP (10^{-5}–10^{-4}), nicotine (10^{-5}–10^{-4}) and pilocarpine

Table 3 Effects of various neurophrmacological agents on the motor activity of adult *S. japonicum*

Drug	Concentration (g/ml)	N*	Motility at 1 hr	Motility at 3 hr	Motility at 24 hr
No drugs		30	4.0±0.0†	3.9±0.0	3.9±0.0
Eserine	$4x10^{-8}$	3	3.8±0.2	4.0±0.0	4.0±0.0
	10^{-7}	3	4.0±0.0	3.7±0.3	4.0±0.0
	$4x10^{-7}$	4	1.8±0.3	1.5±0.3	3.0±0.0
	10^{-6}	3	2.0±0.5	1.8±0.3	2.7±0.2
	10^{-5}	4	0.3±0.3	0.1±0.1	2.1±0.2
	$4x10^{-5}$	3	0.2±0.2	0.2±0.2	0.7±0.2
Metrifonate	10^{-7}	3	4.0±0.0	4.0±0.0	4.0±0.0
	$2.6x10^{-7}$	10	2.3±0.5	0.6±0.2	3.5±0.2
	10^{-6}	3	1.7±0.2	1.5±0.0	4.0±0.0
	$2.6x10^{-6}$	12	0.3±0.1	0.3±0.1	3.2±0.3
Dichlorvos	10^{-7}	3	3.3±0.3	4.0±0.0	4.0±0.0
	$2.2x10^{-7}$	9	1.0±0.3	2.2±0.2	3.7±0.2
	10^{-6}	3	0.8±0.4	1.5±0.0	4.0±0.0
	$2.2x10^{-6}$	7	0.1±0.1	0.4±0.2	2.5±0.2
Carbachol	10^{-5}	5	3.8±0.2	3.8±0.2	3.6±0.2
	10^{-4}	5	2.1±0.4	1.7±0.4	3.0±0.4
DMPP	10^{-5}	4	3.8±0.3	3.3±0.3	3.0±0.0
	10^{-4}	5	3.0±0.0	3.0±0.0	2.7±0.1
Nicotine	10^{-5}	3	4.0±0.0	4.0±0.0	4.0±0.0
	10^{-4}	3	3.7±0.2	4.0±0.0	4.0±0.0
Pilocarpine	10^{-4}	4	4.0±0.0	4.0±0.0	4.0±0.0
5-HT	10^{-7}	8	4.3±0.2	4.1±0.1	4.0±0.3
	10^{-6}	6	4.6±0.3	4.4±0.3	6.2±0.3
	10^{-5}	7	5.3±0.4	5.5±0.2	6.4±0.3
	10^{-4}	3	5.3±0.3	5.0±0.0	5.3±0.4
	10^{-3}	10	5.9±0.3	5.2±0.3	2.9±0.6
GABA	10^{-4}	4	4.0±0.0	4.5±0.5	4.0±0.0
phenylephrine	10^{-5}	3	4.0±0.0	4.0±0.0	4.0±0.0
clonidine	10^{-5}	3	4.0±0.0	4.0±0.0	4.0±0.0
isoproterenol	10^{-5}	3	4.0±0.0	4.0±0.0	4.0±0.0

*: Number of experiments, †: All values are shown as mean ± S. E.

(10^{-4}). The effects of cholinesterase inhibitors were characterized by a remarkable relaxation, though they were transient.

2) Other drugs: 5-HT (10^{-6}–10^{-3}) stimulated the motor activity of the worm. The stimulant effect of 5-HT was characterized by an increase of rate and amplitude, and spastic paralysis was observed in some worms treated with higher concentration (10^{-3}) at 24 hr. On the other hand, other agents such as GABA (10^{-4}), phenylephrine (10^{-5}), clonidine (10^{-5}), and isoproterenol (10^{-5}) had little effect.

Discussion

Regarding *in vivo* effects, it was reported that a few anthelminthics such as trivalent organic antimonials and praziquantel were remarkably effective against *S. japonicum* as well as *S. mansoni* and *S. haematobium*, and that many others including oxamniquine and niridazole were not effective against *S. japonicum* (Rollo, 1975; Katz,

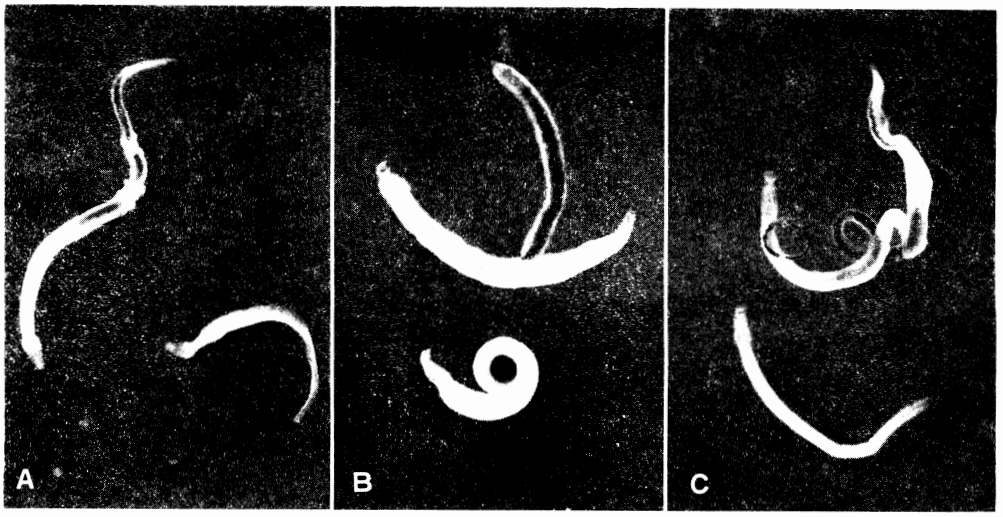

Photo. 1 Effects of Stibnal and hycanthone on the motor activity of *S. japonicum*.
A) Control. B) Worms treated with Stibnal (10^{-5}) for 3 hr.
C) Worms treated with hycanthone (10^{-4}) for 3 hr.

1977; Gönnert and Andrews, 1977; Woolhause, 1979). In the present *in vitro* experiment, the motor activity of adult *S. japonicum* was also remarkably inhibited by these effective drugs, but little influenced by non-effective drugs. This experiment also showed whether drug actions were caused rapidly or slowly, and transiently or sustainedly. It was reported that praziquantel acts rapidly, whereas oxamniquine and niridazole act slowly against sensitive worms such as *S. mansoni* and *S. haematobium* (Thomas and Andrews, 1977; Pax *et al.*, 1978; Woolhause, 1979). In the present study, praziquantel also rapidly affected the motor activity of adult *S. japonicum*, whereas oxamniquine and niridazole affected only at 24 hr even at higher concentrations. On the other hand, the motor activity was inhibited sustainedly by Stibnal and praziquantel, but transiently by metrifonate and dichlorvos. Thus, it is probable that this *in vitro* experiment by the visual observation method actually permits us to detect and determine anthelminthic effects against adult *S. japonicum* by a relatively simple procedure and in a short time.

Using various *in vitro* methods, mechanisms of actions of drugs on energy metabolism, ion-movements or neuromuscular junctions have been studied in *S. mansoni* (Woolhause, 1979). For example, it was reported that trivalent organic antimonials inhibit the activity of phosphofructokinase, a rate limiting enzyme in glycolysis (Bueding and Mansour, 1957), and that niridazole and SQ-18506 act on the activity of glycogen phosphorylase (Bueding and Fisher, 1970; Bueding *et al.*, 1971). It was also reported that metrifonate, dichlorvos and hycanthone affect neuromuscular junctions consisting of inhibitory cholinergic and excitatory serotonergic mechanisms (Baker *et al.*, 1966; Bennett *et al.*, 1969; Bueding *et al.*, 1972; Bueding and Bennett, 1972; Tomosky *et al.*, 1974; Hillman and Cibler, 1975; Hillman and Senft, 1975; Tomosky-Sykes and Bueding, 1977). Praziquantel is known to contract *S. mansoni* through inhibiting Na^+, K^+-ATPase-like functions (Pax *et al.*, 1978; Fetterer *et al.*, 1980, 1981).

In the present study, cholinergic drugs such as eserine, metrifonate, dichlorvos, and

carbachol showed paralytic effects on the motor activity of *S. japonicum*, while 5-HT (serotonin) and praziquantel showed contractive effects. Little effect by other cholinergic drugs, adrenergic drugs, and GABA on the motor activity of *S. japonicum* also agreed well with those reported in *S. mansoni* (Bueding, 1968; Tomosky *et al.*, 1974). It was reported that hycanthone stimulated the motor activity of *S. mansoni* at lower concentrations (10^{-6}–10^{-5} M, 4.5×10^{-7}–4.5×10^{-6} g/ml), but inhibited at higher concentrations (10^{-4}–10^{-3} M) (Hillman and Cibler, 1975; Hillman and Senft, 1975; Woolhause, 1979). And complicated mechanisms of action of this drug have been reported, including an inhibition of cholinesterase activity, a competition at the acetylcholine receptors, and a stimulation of the uptake of 5-HT probably at extraneural sites (Woolhause, 1979). In our experiment, however, remarkable relaxation was observed at higher concentrations of hycanthone (10^{-5}–10^{-4}), whereas little effect was observed at its lower ones (10^{-6}–4.5×10^{-6}). These results suggest that *S. japonicum* may have mechanisms basically similar to those reported in *S. mansoni* regarding ion-movements and neuromuscular junctions.

It was suggested from the results on the inhibitory effects of Stibnal, niridazole, and SQ-18506 that these drugs may similarly affect the glycolytic enzymes in *S. japonicum*. It was also suggested in *S. japonicum* as well as *S. mansoni* that the slow onset of actions of niridazole, oxamniquine and SQ-18506 are probably due to the fact that these drugs gradually cause a reduction in the glycogen stores of the worms (Bueding and Fisher, 1970; Bueding *et al.*, 1971; Woolhause, 1979). Thus, it is likely that *S. japonicum* derives its energy by the processes basically similar to those of *S. mansoni*.

Though many drugs were suggested to affect intrinsically similar mechanisms in *S. japonicum* as well as *S. mansoni*, the sensitivity of *S. japonicum* to drugs seems to be lower than those of *S. mansoni* and *S. haematobium* (Bueding, 1968; Rollo, 1975; Katz, 1977; Woolhause, 1979). These differences in the sensitivity to drugs may be attributed to structural and functional differences such as those in tegumental layers and in permeability to drugs, besides differences in the susceptibility in receptor sites. Probably, less development of anthelminthics against *S. japonicum* is due to this lower sensitivity to drugs.

When the sensitivity is compared within the species, however, the *in vitro* sensitivity of *S. japonicum* to drugs seems to be rather agreed with that *in vivo*. Therefore, *in vitro* experiments on various drugs may be useful for the development of anthelminthics against *S. japonicum* as well as other schistosomes.

Summary

Effects of known antischistosomal drugs and neuropharmacological agents on the motor activity of adult *Schistosoma japonicum* were examined by the visual observation method that we recently developed. The motor activity of *S. japonicum* was affected remarkably by Stibnal and praziquantel, slightly by CGP-4540, hycanthone and SQ-18506, and little influenced by niridazole and oxamniquine. The motor activity was inhibited by cholinergic drugs such as eserine, metrifonate, dichlorvos, and carbachol, but stimulated by 5-HT. From these results, it was suggested that our visual observation method can be actually applied for detecting and determining the anthelminthic effects against *S. japonicum*, and that this worm has mechanisms basically similar to those reported in the physiology and pharmacology of *S. mansoni*.

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寄生虫症の化学療法に関する研究（X）
日本住血吸虫の自動運動に及ぼす既知抗住血吸虫薬および神経薬理学的薬物の影響

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駆虫薬の研究を目的として，著者らが改良した肉眼的観察法を用い，日本住血吸虫の自動運動に及ぼす既知の抗住血吸虫薬および神経薬理学的薬物の作用を検討し，以下の如き結果を得た．

1)　既知の抗住血吸虫薬のうち，*in vivo* 実験で日本住血吸虫に対し有効なもの（Stibnal, praziquantel）は今回の *in vitro* 実験でも著明な作用を示した．一方，*in vivo* 実験で無効なもの（oxamniquine, niridazole）は *in vitro* 実験でもほとんど作用を示さなかったが，CGP-4540, hycanthone および SQ-18506 は弱い作用を示した．これらの結果は，今回の肉眼的観察法が抗日本住血吸虫薬の *in vitro* スクリーニング法として，充分適用しうることを示している．

2)　日本住血吸虫の自動運動は，eserine, metrifonate, dichlorvos, carbachol などにより抑制され，一方，5-hydroxytryptamine によって促進された．これら神経薬理学的薬物および既知抗住血吸虫薬の作用からみると，日本住血吸虫も基本的にはマンソン住血吸虫と同様の生理学的ないし薬理学的機構を有することが示唆された．