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REVIEW

Present-day anthelmintics and perspectives on future new targets

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Abstract In absence of vaccines for the majority of helminths, chemotherapy is still the mainstay for controlling human helminthiases. However, a limited number of drugs are available in the market to combat parasitic helminths in human. Besides, the development and spread of drug resistance have declined the use of most currently available anthelmintics. Clearly, availability of new anthelmintic agents will be essential in the next few years. More research into the mechanisms of drug actions and their targets are eminent for the discovery and development of novel anthelmintic agents. Recent drug discovery techniques mostly rely on mechanism-based screening of compounds on heterologously expressed targets in bacterial, mammalian or yeast cells. Although this is usually a successful approach, it is money- and time-consuming; meanwhile, pharmaceutical companies prefer the tested target that is chosen based on basic research. The nervous system is the site of action of several chemotherapeutics including pesticides and antinematode drugs; accordingly, the nervous system continues to be a promising target. Recent advances in exploring helminths' nervous system, neurotransmitters and receptors have paved the way for the development of potential agents targeting the nervous system and its components.

Keywords Anthelmintics · Flatworms · *Schistosoma mansoni* · Praziquantel · Artemether · Nervous system

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Introduction

Helminth infections are a major health problem particularly in poor tropic and subtropic countries. Morbidity caused by helminths can vary from asymptomatic infection to serious and fatal disease depending on the type and localization of the causative worm. According to recent estimates, approximately two pillion people are suffering from the effects of intestinal nematodes in the form of diarrhoea, low growth rates, frequent illness and death in 2 % of cases (Martin and Robertson 2010). More than 205 million people are infected with schistosomiasis, which causes more than 200,000 deaths annually, and 56 million people are suffering from one or more foodborne trematode infection worldwide (WHO 2014a, b).

Unfortunately, there is no effective vaccine for controlling helminthic diseases; therefore, treatment and prophylaxis count on anthelmintic drugs, which are intended for killing and eliminating helminths from the host body through affecting different targets with various mechanisms. However, there are concerns about their efficacy, and currently, there is a degree of resistance to the available anthelmintic agents which developed due to continuous drug exposure, consequently creating selection pressure that is expected to increase with further drug using (Albonico et al. 2003). The development of new agents that work through different targets is a pressing need, and it is the only way to combat this resistance. In parasitic helminths, the nervous system controls vital functions, including feeding, locomotion and reproduction (Ribeiro et al. 2005). Therapies acting on the nervous system have the advantage of rapid therapeutic effect after administration. Interestingly, the commonly used antiparasitic drugs, ivermectin, levamisole, piperazine and pyrantel, are conducting their effect through the parasite's nervous system particularly that of nematodes. Few drugs are available for treating parasitic flatworms affecting human, but recent advances in exploring neurobiology of the blood fluke

Schistosoma mansoni indicated that targeting the nervous system, transmitters and receptors is a promising way for developing new anthelmintic agents.

Herein, we review the currently available anthelmintics, their mechanism of action and targets in parasitic helminths affecting human, and we also discuss the flatworm nervous system, focusing on receptors recently identified in *S. mansoni* to elaborate their potential as new drug target candidates.

Benzimidazole

Benzimidazoles are a class of synthetic compounds with broad-spectrum anthelmintic activity. Four benzimidazole drugs can be used in human: albendazole, mebendazole, thiabendazole and triclabendazole (van den Enden 2009). Benzimidazoles target the free β-tubulin. It binds the parasite tubulin, the essential protein component of microtubules with higher affinity than the human protein, leading to inhibition of tubulin polymerization and loss of cytoplasmic microtubules in worms; moreover, inhibition of glucose uptake and depletion of glycogen storage are an additional mechanism recorded in some helminths (Lacey 1990). Benzimidazoles are used in global control programs for soil-transmitted helminthiases targeting school-aged children and in filaria control programs. In cestodes, simultaneous administration with cimetidine increases the serum concentration of benzimidazole and enhances their therapeutic effect especially in cystic echinococcosis (Wen et al. 1994), and more recent, a novel benzimidazole-derived compound (BTP-Iso) showed promising results as antischistosomal agents in experimentally infected mice (El-Bialy et al. 2013). In general, benzimidazoles are well-tolerated, and minor side effects in the form of mild gastrointestinal symptoms have been reported, but prolonged treatment in high doses is occasionally complicated by bone marrow depression, alopecia and hepatocellular injury. Experimentally, albendazole and mebendazole are embryotoxic and teratogenic, so it is recommended to avoid their use during the first trimester of pregnancy (de Silva et al. 1999). Using benzimidazoles during the second and third trimester in pregnant females infected with hookworms is beneficial to improve iron-deficiency anaemia (Bradley and Horton 2001), and the WHO recommended using benzimidazoles in infested children more than 1-year age to avoid development of consequences caused by soil-transmitted helminthiases (Montresor et al. 2003).

Albendazole

Albendazole is one of the most commonly used drugs for treatment and control of soil-transmitted helminthiases, with broad activity against *Ascaris lumbricoides*, hookworms and *Trichuris trichiura*; therefore, it is used on wide scale in mass treatment programs in developing countries. Albendazole is also used in the global elimination of lymphatic filariasis (Gyapong et al. 2005); better results are achieved especially when albendazole is combined with ivermectin (Addiss et al. 1997). It is also effective against other nematodes as *Enterobius vermicularis*, *Trichostrongylus* and *Capillaria philippinensis* with minor side effects. In cestodes, albendazole is used in the treatment of hydatid disease and gives good results when used in treating neurocysticercosis (Garcia 2008).

Thiabendazole

Thiabendazole is the first anthelmintic of the benzimidazole class, effective against several nematodes, but causes severe and frequent side effects which limit its use; therefore at present, it is not considered as the first choice therapy for any helminth infection (Bradley and Horton 2001). Side effects include nausea, vomiting, diarrhoea, convulsions, neuropsychiatric disturbance and intrahepatic cholestasis (van den Enden 2009).

Triclabendazole

Although triclabendazole is a benzimidazole derivative, it has no activity against nematodes, but reported activity against adult *Fasciola*, and its immature stages identified it as the drug of choice in fascioliasis (El-Morshedy et al. 1999). Triclabendazole is very effective in treating *Paragonimus* infection (Calvopina et al. 1998) but has weak and inconsistent activity against schistosomes (Keiser et al. 2006). The mechanism of action of triclabendazole is proposed to be similar to other benzimidazole, but other actions of triclabendazole and its sulphoxide metabolite have been recorded, including inhibition of protein synthesis and uncoupling of oxidative phosphorylation (Carr et al. 1993).

Flubendazole

The benzimidazole flubendazole has recently been approved for human use in the treatment of gastrointestinal nematodes (Geary and Mackenzie 2011). In injection formula, flubendazole has a macrofilaricidal activity against lymphatic filariasis and onchocerciasis, as oral administration has low bioavailability (Mackenzie and Geary 2011).

Bithionol

A bacteriostatic drug acts by the inhibiting or uncoupling of oxidative phosphorylation in the parasite, resulting in

blocking of adenosine triphosphate (ATP) synthesis and energy production (James and Gilles 1985). It was previously used for the treatment of fascioliasis, but now, its use is restricted to countries where triclabendazole is not available (Keiser and Utzinger 2007a). Bithionol has been used for the treatment of *Paragonimus* infection with high cure rate (Kim 1970). Bithionol administration may be accompanied with minor gastrointestinal symptoms in the form of abdominal pain, vomiting and diarrhoea, but the long treatment course for bithionol is the main disadvantage being given in multiple doses on alternate days for 10–15 doses, which makes the patients less compliant with the recommended regimen (Keiser and Utzinger 2007a).

Praziquantel

Praziquantel (PZQ) is a pyrazino-isoquinoline derivative and is the drug of choice in all cases of human schistosomiasis. Schistosomes have a biphasic sensitivity to PZQ; early migrating larval stages and mature adult are sensitive, while immature adult is less or even non-susceptible (Pica-Mattoccia and Cioli 2004). Despite the initial effects of PZQ that included an influx of calcium into the worm resulting in calcium-dependent muscle contraction, spastic paralysis and tegumental destruction, the exact mode of action of PZQ has to be elucidated (Mehlhorn et al. 1981). The β subunits of Ca^{2+} channels have been hypothesized as a potential target for PZQ, and these subunits in *S. mansoni* and *Schistosoma japonicum* have different structure from other β subunits known in other creatures (Kohn et al. 2001; Greenberg 2005).

Recently, PZQ was recorded to inhibit uptake of adenosine and uridine by schistosomes (Angelucci et al. 2007). Increased exposed antigens on the worm surface are a detectable effect of PZQ, which will lead to immune attack of the schistosomes, but this is still a point of debate. PZQ also inhibits the excretory system of worms and induces a rapid hepatic shift (5 min to an hour after administration) of schistosome worms from the mesenteric plexuses to the liver (Mehlhorn et al. 1981), and that was postulated to be due to the increased muscular contraction following the rapid uptake of the drug by the worms (Greenberg 2005).

PZQ is highly effective against most of trematodes and cestodes including, *Clonorchis sinensis* and *Opisthorchis viverinni*, the intestinal flukes *Fasciolopsis buski*, *Heterophes heterophes*, *Metagonimus yokogawai* and the lung fluke *Paragonimus westermani*, in addition to *Taenia saginata*, *Taenia solium*, *Diphyllobothrium latum*, *Dipylidium caninum* and *Hymenolepis nana* (Chai 2013); however, only the liver flukes, *Fasciola hepatica* and *Fasciola gigantica*, are resistant to PZQ (Mehlhorn et al. 1981). In general, PZQ is a safe, well-tolerated drug and can be used in pregnant and lactating females (Allen et al. 2002). Adverse effects in the form of headache, dizziness, drowsiness, abdominal discomfort, pain, nausea and diarrhoea have been recorded with PZQ. These symptoms are transient and dose-related. Fever, pruritus, urticaria, rashes, arthralgia, myalgia and eosinophilia are noted occasionally as a result of released worm antigens.

Niclosamide

Niclosamide is a halogenated salicylanilide derivative, which inhibits the mitochondrial oxidative phosphorylation process and simultaneously inhibits oxygen and glucose uptake by the parasite (Weinbach and Garbus 1969). It is used as a PZQ alternative for the treatment of infection with *D. latum*, *T. saginata* and *H. nana*, but it is not recommended in treatment for *T. solium* infection due to the risk of cysticercosis (Craig and Ito 2007). Niclosamide ethanolamine salt can be used as molluscicide for controlling schistosomiasis snails (van den Enden 2009).

Levamisole

Levamisole is a synthetic phenylimidazolthiazole, with anthelmintic effect against soil-transmitted nematodes. Levamisole is an agonist of nicotinic receptors of acetylcholine-gated membrane ion (nAChR) channels. Stimulation of these receptors leads to depolarization and entry of calcium through the opened AChR channels leading to increase calcium ions in the sarcoplasmic reticulum, causing muscle contractions and spastic paralysis of the worms, which will be swept out of the alimentary tract (Williamson et al. 2009). Moreover, it is presumed that levamisole has an immunostimulant effect on the host (Renoux 1980); therefore, it is used as an adjuvant therapy in the treatment of colon carcinoma. Moreover, using levamisole in combination with mebendazole delays the development of benzimidazole resistance (Albonico et al. 2003).

Pyrantel pamoate

Pyrantel pamoate is a depolarizing neuromuscular blocking agent derived from pyrimidine. It interferes with neurotransmission by inhibiting acetylcholine esterase enzyme in helminths and induces persistent activation of nAChR, resulting in worm irreversible spastic paralysis. Pyrantel is active against several nematodes including *Ascaris* and *Strongyloides stercoralis*, but repeated doses are needed in hookworms, *E. vermicularis* and *T. trichiura* infection to achieve high cure rate (Keiser and Utzinger 2008). Generally, it is well-tolerated, but mild and transient

gastrointestinal tract (GIT) symptoms are recorded, and it is not recommended for use during pregnancy.

Piperazine derivatives

Piperazine

Piperazine is a cyclic secondary amine, acts as gamma-aminobutyric acid (GABA) receptor agonist and causes flaccid paralysis of the worm resulting in its expulsion by the normal intestinal peristalsis, but in the absence of intestinal movement, worm may recover and resume their parasitic life (Martin et al. 1997). It can be used as an alternative for mebendazole or pyrantel pamoate in the treatment of ascariasis and enterobiasis. Side effects include GIT upset, headache, dizziness, urticaria and transient neurological effects such as tremors, ataxia and muscular weakness. Convulsion and respiratory depression can occur with higher and lethal doses. It is contraindicated in patients suffering from epilepsy (van den Enden 2009).

Diethylcarbamazine

Diethylcarbamazine (DEC) is a derivative of piperazine, which affects microfilaria by unknown mechanism, although interference with arachidonic acid and nitric oxide metabolic pathways are possible ones (McGarry et al. 2005), but alteration of the host immune system is another suggested mechanism, which could explain its effects (Geary et al. 2010). The microfilaricidal effect of DEC includes loss of microfilaria sheath, in addition to damage and apoptosis of organelles (Peixoto et al. 2004).

DEC is presumed to have a macrofilaricidal activity as well in lymphatic filariasis; therefore, it is the drug of choice for lymphatic filariasis caused by *Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*, *Mansonella streptocerca* and *Loa loa*. Although DEC does not reverse the existing lymphatic damage happened in filariasis, it prevents new lymphatic damage. Using DEC during acute lymphangitis is not recommended due to severe allergic response to parasite products. In loiasis treatment, pre-treatment with antihistamines is preferable to reduce adverse reactions to dying microfilaria and adult worms. Adverse effects of DEC are mainly due to the release of lipopolysaccharides from *Wolbachia*, the symbiotic bacteria in *W. bancrofti*, and include headache, fever and dizziness.

DEC is no longer used in the treatment of onchocerciasis. Mazzotti reaction can happen in a few hours of drug administration, and patient may complain of itching, fever, tachycardia, headache and enlarged tender lymph nodes; in addition, severe eye complications can lead to visual loss and even blindness (Cross et al. 2001).

Avermectins

Several compounds belong to the avermectin group including ivermectin, milbemycin, moxidectin, abamectin, doramectin and selamectin. These compounds selectively activate the glutamate-gated chloride channels (GGCC), which present only in invertebrates as nematodes, insects and crustaceans. At higher doses, avermectins can activate some subtypes of $GABA_a$ ion channel receptors, resulting in the release of inhibitory neurotransmitter γ-butyric acid in the parasite causing muscle paralysis and eventually parasite death (Cully et al. 1996).

Ivermectin used in human is active against wide range of nematodes, insects, mites and ticks but not cestodes and trematodes due to lack of high-affinity receptors for avermectin, although recently, Diab et al. (2010) reported in vitro tegumental destruction caused by ivermectin application to *F. gigantica*. In nematodes, avermectins inhibit pharyngeal pumping and feeding or inhibit egg laying or muscle motility (Wolstenholme and Rogers 2005).

Ivermectin is widely used for treatment and elimination programs of onchocerciasis. It affects mainly microfilaria, suppressing production and release of microfilariae from adult females for at least 6 months, but it has little or no effect on adult worm in lymphatic filariasis and onchocerciasis (Ottesen et al. 2008; Cupp et al. 2010), so it is mainly used for transmission control rather than treatment. In *Onchocerca volvulus*, ivermectin administration results in the reversal of lymphadenopathy and improvement of ocular manifestations due to microfilaria. Ivermectin is used in combination with albendazole or DEC for mass treatment for elimination of lymphatic filariasis, which was launched by the WHO. Moreover, it can be used in areas where onchocerciasis, loiasis or both are endemic. Nevertheless, in patients with high level of *L. loa* microfilaraemia, who were treated with ivermectin, encephalopathy was frequently recorded (Twum-Danso 2003). Ivermectin is also effective against several nematodes as *Ascaris*, *Trichuris* and *E. vermicularis*. Moreover, it is efficient in the treatment of cutaneous larva migrans, cutaneous gnathostomiasis, intestinal strongyloidiasis, refractory strongyloidiasis and hyperinfection with *S. stercoralis* in patients with AIDS (Torres et al. 1993). In addition to nematodes, ectoparasites as scabies mites and lice were found susceptible to ivermectin, and it is efficiently used in controlling outbreaks (Strong and Johnstone 2007).

Side effects due to ivermectin treatment are mild and transient. In filariasis, dying of microfilariae and release of proinflammatory substances from the endosymbiotic *Wolbachia* are the main causes of the adverse allergic effects in the form of pruritus, rash, dizziness and facial oedema (Keiser et al. 2002). Although no significant adverse effects have been observed in accidently treated pregnant women (Pacqué et al. 1990), ivermectin is contraindicated in

pregnancy. Clinical records of ivermectin resistance are a threat, and its prevention requires adequate monitoring of mass drug administration.

Artemisinins

Artemisinins are derived from the extracts of sweet wormwood (*Artemisia annua*) and are now making a crucial contribution to the management of malaria. Artemether (ART) and artesunate with others, including artemisone, arteether, artelinic acid and the active metabolite dihydroartemisinin (DHA), are generically known as 'artemisinins' (Krishna et al. 2008). Artemisinin was effective against schistosomes and was later found to possess a broad spectrum of activity against a wide range of trematodes, including *S. japonicum*, *S. mansoni*, *Schistosoma haematobium*, *C. sinensis*, *F. hepatica* and *Opisthorchis viverrini* (Keiser and Utzinger 2007b). Artemisinin derivative plus PZQ used in combination significantly increase the cure rates of schistosomiasis in comparison with PZQ alone (Liu et al. 2011).

Among the artemisinin derivatives, ART and artesunate were found of particular importance as antischistosomal agents (Utzinger et al. 2003). ART is more toxic than artesunate but exhibits consistently higher levels of activity against *S. mansoni* parasites of different ages than artesunate (Utzinger et al. 2002). ART is highly effective against juvenile stages of schistosomes, while adult worms are less susceptible (El-Beshbishi et al. 2013a), and has the ability to induce high-level resistance against *S. mansoni* reinfection in mice (Bergquist et al. 2004). Abdel Aziz and el-Badawy (2000) proved that DHA is equally effective as PZQ in the treatment of *S. mansoni*-infected mice as evidenced by decreased worm burden and controlled pathological effects on liver cells. The in vivo activity of DHA against the schistosomula and adult worms of *S. mansoni* is dose-dependent and is obvious against the 21-day schistosomula in particular (Li et al. 2012). The three artemisinin derivatives were comparably effective against juvenile and adult *S. japonicum* at the same dose (Li et al. 2011).

The precise mechanism of action of the artemisinins against either malaria or schistosomiasis is yet unknown. However, it is thought to involve an interaction with heme that cleaves the endoperoxide bond of the drug to produce carbon-centred free radicals that then alter the biochemical pathways within the parasite (Golenser et al. 2006). Reduction of glycogen and protein content and inhibition of ATPase activity in schistosomes are recorded in *S. japonicum* (Xiao et al. 1997). Tegumental changes have been reported in schistosomula including swelling, erosion, peeling, vesiculation and collapse of tegumental ridges with exposure to ART alone (Xiao et al. 2000) and combined with haemin in adult schistosomes (Xiao et al. 2001). Almost all worms died within 48 to 72 h possibly due to a certain toxic effect on the worms ensuing from artemether interaction with haemin (Abdul-Ghani et al. 2009).

Recently, researchers reported the potential therapeutic effect of artemisinins in *Toxoplasma gondii* (D'Angelo et al. 2009) and the lethal in vitro effect on *Trypanosoma cruzi* and *Trypanosoma brucei rhodesiense* (Mishina et al. 2007; Nibret and Wink 2010).

Artemisinin-based combination therapy

The recommendation to using artemisinin-based combination therapy (ACT) came first by the WHO (2006), in face of uncomplicated malaria, in areas experiencing resistance to monotherapy.

Several ACTs are currently available, including artemether-lumefantrine (AL), DHA-piperaquine (DHA-PPQ), artesunate-amodiaquine (AS+AQ), artesunate-mefloquine (AS+MQ) and now artemisinin-naphthoquine (ARCO®). The later combination is of particular interest because, unlike other artemisinin-based combinations which require a 3-day regimen, ARCO® requires either a single-dose treatment or a two-dose treatment over 24-h (Hombhanje and Huang 2010). Multiple clinical studies validated the effectiveness of this very short therapeutic regimen of ARCO® against uncomplicated *falciparum* malaria (Hombhanje et al. 2009). Naphthoquine compound was developed in China in the late 1980s. It belongs to the 4-aminoquinoline family that interferes with hemozoin formation pathway, which is peculiar to blood-feeding parasites (including *S. mansoni*) and is absent in the host, which makes it an exceptionally attractive drug target (Krishna et al. 2008).

Artemisinin and naphthoquine complement each other such that the delay time for parasiticidal action of naphthoquine is covered by artemisinin's immediate onset of lethal effect, and the short circulating half-life of artemisinin would be extended over several days (covering several asexual cycles) by the long circulating half-life of naphthoquine (Hombhanje and Huang 2010).

Based on studies on artemether (Bergquist et al. 2004; El-Beshbishi et al. 2013a) and 4-aminoquinoline derivatives (Oliveira et al. 2004) as efficient schistosomicidal agents, El-Beshbishi et al. (2013b) provided the first glance at the impetus of possible antischistosomal activity of artemisinin-naphthoquine combination (CO-ArNp) against Egyptian strain of *S. mansoni* experimentally. The results of this study showed the advantages of Co-ArNp therapy over PZQ against both juvenile and adult *S. mansoni* worms, the subsequent effects on egg deposition and improved hepatic pathology. Noteworthy, this study showed that the use of CO-ArNp single oral dose therapy, as an antischistosomal agent whenever failure of standard monotherapy with PZQ is reported, is

a viable option. The CO-ArNp dosing protocols showed potent effects more than those previously reported for the activity of artemsinins against *S. mansoni* worms. Evidently, artemisinins exert a therapeutic activity on the Egyptian strain of *S. mansoni* more than other strains previously tested experimentally, and the response extends for a long period beyond the juvenile stages, conferring some degree of therapeutic activity on the adult worms (Abdul-Ghani et al. 2011). Moreover, this major activity of CO-ArNp against all tested *S. mansoni*-developing stages might be explained by a significant synergistic interaction between artemisinin and naphthoquine phosphate (El-Beshbishi et al. 2013b).

Flatworm nervous system as drug target

The nervous system of flatworms is well-organized, composed of the central nervous system (CNS) and peripheral nervous system (PNS). The archaic brain and the two longitudinal nerve cords are the components of the CNS, while the PNS consists of smaller nerve cords and plexus, which supply all body structures, particularly the tegument, alimentary tract, somatic musculature and reproductive organs (Ribeiro et al. 2005). Since flatworms are acoelomate organisms and lack the endocrine secretion, the coordination of different body functions is expected to be done by the nervous system and a network of neurotransmitters, receptors and neuromodulators (Halton 1996).

Classical neurotransmitters including ACh, dopamine (DA), histamine (HA), serotonin (5HT) and glutamate are implicated in the regulation of vital activities in flatworms such as metabolism, movement, transport and reproduction and thus are important for the survival of the parasite (Ribeiro et al. 2005). Within the parasitic flatworms, schistosomes have attracted researchers to elucidate its neurobiology in the past decades, and now, we have a wealth of information about neurotransmitters present in schistosomes, their effects and receptors mediating these effects.

Comprehensive research in schistosomes reported the role of several neurotransmitters in modulating the locomotory behaviour in which serotonin, histamine and glutamate have stimulatory effect, while dopamine inhibits the motility of the adult worms (Ribeiro et al. 2005; El-Shehabi et al. 2012). Moreover, additional important functions have been attributed to these neurotransmitters such as the role of serotonin in carbohydrate metabolism (Pax 1996), glutamate in controlling female's egg production (Taman and Ribeiro 2011a), dopamine in worm attachment and digestive functions (El-Shehabi et al. 2009; Taman and Ribeiro 2009).

Several transmitter receptors have been identified in schistosomes recently. Sm5HTR, a G protein-coupled receptor (GPCR) responsive to serotonin (Patocka et al. 2014), was detected in the adult and larval stage (schistosomula). In both, the signals of Sm5HTR were detected in the central nervous system, including the cerebral ganglia and main nerve cords besides peripheral innervations of the oesophagus, caecum, oral and ventral suckers. In addition, marked expression was recorded in the peripheral nerve fibres supplying the body wall musculature and tegument extending to the outer surface of the male worms. Based on expression pattern of this serotonin receptor and RNA interference (RNAi) experiments done by the authors, it is clear that Sm5HTR plays an important role in the motor control of larva and adult worm, and no doubt, targeting this receptor could be vital for parasite survival.

Apart from serotonergic receptor, two histamine receptors have been identified in *S. mansoni*, SmGPR-1, which is expressed in muscles of the body wall including suckers (Hamdan et al. 2002; El-Shehabi et al. 2009) and SmGPR-2, located in the neurons of submuscular nerve plexus (El-Shehabi and Ribeiro 2010). The neuromuscular expression of these two receptors indicated their possible role in modulating motor activity in schistosomes.

More recent, two DA have been cloned from *S .mansoni*, SmD2 (Taman and Ribeiro 2009) and SmGPR-3 (El-Shehabi et al. 2012). Of interest is SmGPR-3, which is divergent from vertebrate DA receptors and has a mixed pharmacological profile that is not similar to any known mammalian receptor. Immunolocalization of both receptors indicates their importance in central and peripheral controlling of schistosomes locomotory behaviour.

For glutamate, a putative ionotropic glutamate receptor has been identified (Mendonça-Silva et al. 2002), but recently, two glutamate receptors have been cloned and characterized from *S. mansoni*.

The first is the metabotropic glutamate receptor (SmGluR) which is distantly related to glutamate receptors from other organisms and does not belong to any of the existing subtypes of metabotropic glutamate receptor and have a specific pharmacological profile; all may indicate that this receptor could be a new type of glutamate receptor. SmGluR is expressed in adult and larvae nervous system, in addition to neurons innervating adult somatic musculature including acetabulum and body wall muscles. The detection of SmGluR in female worm reproductive system highlights its possible role in the regulation of ova production and its importance as a probable drug target as interference with oogenesis will reduce or even eliminate ova, which is the main cause of pathology in schistosomiasis (Taman and Ribeiro 2011a).

The second characterized glutamate receptor (SmGBP) is a truncated one, which has the glutamate-binding site but lacks the seven transmembrane domains characterizing the metabotropic glutamate receptors (Taman and Ribeiro 2011b). Immunolocalization identified the expression of SmGBP in adult male tubercles but not expressed in female or larval stages. The gender and surface-specific expression of

SmGBP suggest its likely role in the transport mechanism across the tegument or host-parasite interaction, which make it ideal for drug targeting. Consequently, more research is needed to determine the exact role of this receptor in schistosomes.

Conclusions

Interestingly, most of nematode anthelmintics in use bind to receptors gated by classical neurotransmitters such as GABA, glutamate or acetylcholine leading to the disruption of the worm neuromuscular function and eventually worm elimination. In the same way, the sophisticated nervous system of flatworms controls vital functions in the worm and contains neurotransmitter receptors with unusual pharmacological properties. Taken together, these data suggest that nervous system and transmitter receptors might serve as attractive targets for anthelmintic agents in parasitic trematodes, especially schistosomes.

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