Parasite neuromusculature and its utility as a drug target

EDITED BY A. G. MAULE AND T. A. DAY
CO-ORDINATING EDITOR L. H. CHAPPELL

Preface

Uncoordinating motor function in parasites – is this still a valid goal?

As in all multicellular animals that display motor activities, nerve and muscle systems in helminth parasites interact in a highly co-ordinated manner to control movements associated with alimentation, reproduction, locomotion and attachment. All metazoan parasites rely on some or all of these activities for their survival, a fact that has been exploited by many of the available chemotherapeutics that compromise normal nerve-muscle function in parasites. However, research on the nerve and muscle systems of helminths has been confined to a handful of laboratories, with most efforts directed at other target systems, vaccine development or investigations of anthelmintic mechanisms of action. Work in all of these areas is critical to the development of a knowledge base that will underpin the continued and longer term control of parasites. Nevertheless, given the success of the available anthelmintics that disrupt coordinated motor activities, it is somewhat surprising that more effort has not been directed towards novel target discovery from within this system. Attention could be deflected from the neuromuscular system on the basis that many of the current drugs already target motor function, and it could be rational to assume that new targets need to be sourced elsewhere. The reviews in this supplement question that notion and indicate that we should not overlook seams of good targets just because they have been mined previously (see reviews in this supplement by Greenwood, Williams & Geary; Kimber & Fleming; McVeigh *et al.*; Mousley, Maule & Marks; Ribeiro, El-Shehabi & Patocka; Selkirk, Lazari & Matthews; Vermeire, Humphries & Yoshino).

Even though research that has focused directly on neuromuscular systems in helminth parasites has been restricted, the fact that many of the front-line anthelmintics target neuromuscular function has meant that efforts to unravel their mechanisms of action have provided much data on the molecular biology, physiology and biochemistry of these systems. In this way, the information flow has been both ways, from target protein to chemotherapeutics and from chemotherapeutics to target protein (see reviews in this supplement by Sangster, Song & Demler; Greenberg; Wolstenholme & Rogers; Martin *et al.*).

For a long time we have known that neuromuscular function is susceptible to chemotherapeutic attack and that compromising this aspect of parasite biology is sufficient to cure many parasite infections. But why is this system so amenable to drug intervention? Most obviously, it is critical to parasite motor/behavioural responses that are essential to survival. But also, it is made amenable as a drug target by the fact that the body wall of all helminth parasites is invested with muscle and the openings through the cuticle or tegument are, invariably, controlled by neuromuscular systems – relatively easy drug access could be another key. So, although it is easy to hypothesise why the neuromusculature is a good target, it is difficult to pinpoint the exact reasons for the success of drugs that have targeted motor function such as the imidazothiazoles (levamisole), the macrocyclic lactones (avermectin/milbemycin), selected organophosphates (dichlorvos), heterocyclic compounds (piperazine), tetrahydropyrimidines (pyrantel, morantel) and praziquantel. However, what is clear is that their number and success serve to highlight the utility of the neuromuscular system as a source of drug targets – there is no evidence that this resource has been either thoroughly exploited or exhausted such that it warrants continued study. Indeed, the ever-growing databases of molecular information on

Parasitology (2005), **131**, S1–S2.
doi:10.1017/S0031182005009388 Printed in the United Kingdom

helminths have provided a significant impetus to the discovery of novel drug targets, especially in helminth parasites for which major expressed sequence tag submissions have been made.

The neuromuscular system contains a considerable range of potential targets, such that a significant impediment to novel drug discovery is not only our ability to characterize these targets but to select those that have most relevance in down-stream screening programmes. For example, classical signalling pathways have proven to be good targets and have been exploited by many of the available anthelmintics, albeit serendipitously since they were all discovered empirically. Now that additional proteins (receptors, channels, transporters, regulatory enzymes) involved in neuromuscular-based classical signalling systems are being uncovered (see reviews in this supplement by Selkirk, Lazari & Matthews; Ribeiro, El-Shehabi & Patocka; Vermeire, Humphries & Yoshino), there is increased potential for the identification of new ways to compromise these classical transmitter pathways. However, classical transmitters represent only one cohort of the intercellular signalling molecules that regulate motor function – the best known of the others are the neuropeptides that provide evidence for a raft of new targets about which relatively little is known. Of particular note here are the neuropeptide receptors that provide the first real opportunity to exploit this signalling system for parasite control (see reviews in this supplement by McVeigh *et al.*; Greenwood, Williams & Geary; Kimber & Fleming; Mousley, Maule & Marks). Indeed, in nematodes and arthropods, we are now in a period of receptor characterization and deorphanization that should facilitate screen development and drug discovery programmes (see Greenwood, Williams & Geary, in this supplement). This breakthrough in arthropods and nematodes has been based, largely, on the utility of the model species, *Caenorhabditis elegans* (see review by Li, in this supplement) and *Drosophila melanogaster*. Unfortunately, the absence of a proven model species has meant that work on flatworm neuromuscular function has lagged behind that seen in nematodes and arthropods. Even in the absence of such a tractable model species, progress in flatworms is being made and will, undoubtedly, be assisted by the nematode and arthropod data (see review by McVeigh *et al.*, in this supplement). Developing suitable molecular tools in the flatworms to allow transgenic and gene silencing studies is a major requirement for significant progress in this area.

Largely inspired by David Halton's 1996 Parasitology supplement, *Molecular Biochemistry and Physiology of Helminth Neuromuscular Function*, this offering encompasses reviews on actual and potential targets from parasitic helminth neuromuscular function and serves to highlight the fact that this source of drug targets continues to display remarkable potential. We hope that this compilation of review articles will encourage more parasitologists to undertake research on parasite nerve and muscle systems.

https://doi.org/10.1017/S0031182005009388 Published online by Cambridge University Press