Veterinary Parasitology 212 (2015) 18–24

Contents lists available at ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Anthelmintics: The best way to predict the future is to create it

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ARTICLE INFO

Article history:
Received 25 March 2015
Received in revised form 8 May 2015
Accepted 20 May 2015

Keywords:
Anthelmintic
Mode of action
Tribendimidine
Emodepside
Diethylcarbamazine

ABSTRACT

'The best way to predict the future is to create it.' When we look at drugs that are used to control parasites, we see that new knowledge has been created (discovered) about their modes of action. This knowledge will allow us to predict combinations of drugs which can be used together rationally to increase the spectrum of action and to slow the development of anthelmintic resistance. In this paper we comment on some recent observations of ours on the modes of action of emodepside, diethylcarbamazine and tribendimidine. Emodepside increases the activation of a SLO-1 K^+ current inhibiting movement, and diethylcarbamazine has a synergistic effect on the effect of emodepside on the SLO-1 K^+ current, increasing the size of the response. The combination may be considered for further testing for therapeutic use. Tribendimidine is a selective cholinergic nematode B-subtype nAChR agonist, producing muscle depolarization and contraction. It has different subtype selectivity to levamisole and may be effective in the presence of some types of levamisole resistance. The new information about the modes of action may aid the design of rational drug combinations designed to slow the development of resistance or increase the spectrum of action.

1. Introduction

'The best way to predict the future is to create it.' This quote is usually ascribed to Abraham Lincoln and leads to some interesting thoughts when applied to different research fields including our own field of study, that is, anthelmintics. What are we creating and what can we see for the future for anti-parasitic drugs? We are creating new techniques for the screening of anthelmintic drugs, we are creating new methods for studying the modes of actions of anthelmintics and we are creating new ways for detecting anthelmintic resistance (Gilleard and Beech, 2007; Lanusse et al., 2014). We are also creating better awareness of the 'neglected tropical diseases' (Hotez et al., 2008) of humans which include ascariasis, hookworm and trichuriasis and better awareness of the link between human and animal medicine, the 'One Health' concept. Our western economic system has also produced a more favorable economic environment for the development of animal anthelmintics, than anthelmintics for humans. Currently, we limit the damage done by nematode parasites of animals with pasture management, and improved targeted metaphylactic and therapeutic use of anthelmintics; for humans, clean water and sanitation are

Fig. 1. Paul Erlich in his Frankfurt office, *circa* 1900, the father of modern chemotherapy, who worked on trypanosome diseases and popularized the concept of the 'magic bullet' (magische Kugel, the perfect therapeutic agent).

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http://dx.doi.org/10.1016/j.vetpar.2015.05.016
0304-4017/

limiting factors (like clean pasture for animals) while mass drug administration (MDA) has similarities to the regular metaphylactic use of anthelmintics for animals. Vaccinations against parasites for both humans and animals are very desirable but so far they have limited efficacy.

The advances and creations listed above lead to a number of logical predictions for the future use and development of anthelmintics. We are confident that the development and better understanding of anthelmintic properties will continue, at a steady but modest pace, driven by economic, human and animal needs. We think that the economic pressures associated with animal medicine will remain greater than for human medicine and focused on the development of novel 'resistance-busting' anthelmintics. Success in research can be limited by funding as was said by the father of modern drug development, Paul Ehrlich Fig. 1 (1854–1915), who recognized success required the four Gs: *Gluck, Geduld, Geshcick und Geld* (luck, patience, skill and money, (Perutz, 1988). The 'money' for animal anthelmintics comes from the market for anti-parasitic drugs and chemicals for small animals and livestock which was estimated at $11 billion (Evans and Chapple, 2002). This contrasts with the market for human anthelmintics which is only $0.5 billion despite some 2 billion humans being infected in developing countries, around 25 cents per person annually! Given that the out of pocket costs of new human drugs may be $403 million (at year 2000 valuations (DiMasi et al., 2003) or more, we can see that the commercial development of human anthelmintic drugs is not favorable. It seems more likely that the economics of animal health will drive the development and advance of the knowledge base of animal anthelmintics and that these developments will be applied and adapted for human use (ivermectin and perhaps emodepside) unless private charities, governments and foundations overcome the financial limitations. In addition to the gradual development

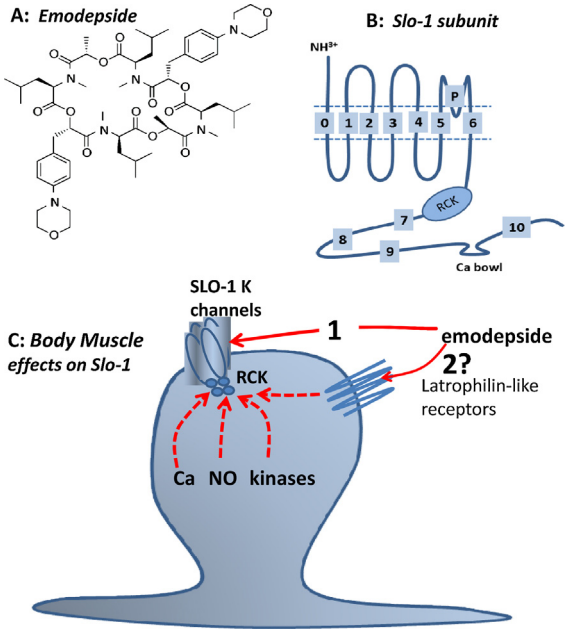

Fig. 2. Summary diagrams of emodepside structure, Slo-1 subunit and a model of the mode action of emodepside on nematode body muscle. A: Emodepside. B: Line diagram of structure of one SLO-1 subunit; each SLO-1 K^+ channel is made up of 4 of these subunits. C. Putative mode of action of emodepside on SLO-1K^+ channels in the muscle: act directly (1) or indirectly by stimulating latrophilin-like receptors (2) and signaling cascades that may involve NO, protein Kinase C and/or calcium. It is unlikely that emodepside acts at the extracellular surface of the SLO-1 K^+ channel because of the slow time course of its action. It is very lipophilic and could act in the lipid membrane phase on the SLO-1 K^+ channel or move into the cytoplasm and act intracellularly. A SLO-1 K^+ channel (C) is shown composed of 4 subunits along with the 'RCK' cytoplasmic regulatory region of the channel. (Martin et al., 2012).

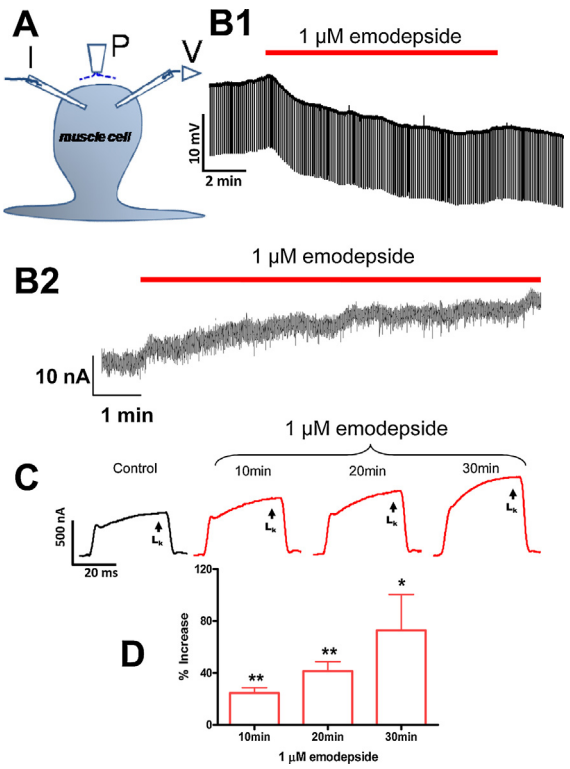

Fig. 3. Electrophysiological techniques (two micropipette current-clamp and voltage-clamps) for recording from *Ascaris suum*. A: *A. suum* muscle bag showing the current (I) and voltage (V) micropipettes in the bag, and the perfusion needle (P). B1: Representative current-clamp trace showing the slow hyperpolarizing membrane potential during and after 10 min application of 1 μM emodepside. B2: Outward current response to 1 μM emodepside at higher time resolution. Holding potential −35 mV. Notice that emodepside produces a gradually increasing current after a delay of some 30 seconds. The response does not plateau in the time period of this recording. C: Voltage-clamp traces of control K^+ current and the time-dependent effects of 1 μM emodepside on the K^+ currents, all to a step potential of 0 mV from a holding potential of −35 mV. D: Bar chart (mean ± S.E.) of 1 μM emodepside effect on steady state(LK) currents. Comparison was made between the control 0 mV step current at 30–40 ms and the corresponding current increased by emodepside at 10, 20 and 30 min. Emodepside increased LK currents at 10 min ($p < 0.01$, $n = 4$, paired t-test), 20 min ($p < 0.01$, $n = 4$, paired t-test) and 30 min ($p < 0.05$, $n = 4$, paired t-test). (Martin et al., 2012).

of resistance-busting anthelmintics we see: developments in our understanding of the modes of action of anthelmintics; we see more logical combinations of anthelmintics to slow down or counter the development of resistance and; also new methods for detecting anthelmintic resistance.

Our lab has focused on understanding of the modes of action of anthelmintics and in this paper we illustrate some of our recent observations and developments in our understanding of the actions of emodepside, diethylcarbamazine and tribendimidine. The mode of action of these anthelmintics involves effects on membrane ion-channels and has required us to use electrophysiological techniques for their study (Martin et al., 1996b). We think that better knowledge of the mode of action of these compounds will allow rational combination with other anthelmintics to increase potency, spectra and allow a slowing of the speed of development of resistance in animal and human parasites. This paper is based on a lecture given to the World Association for the Advancement of Veterinary Parasitology (WAAVP) in Liverpool, 2015 and covers: (1) emodepside, an anthelmintic used for small animals, which has the potential for being used for human use to control filarial parasites; (2) diethylcarbamazine, a long serving anthelmintic still used for the control of filariasis in humans and; (3) tribendimidine, a recent anthelmintic developed by China for human use.