

Perspectives and directions in the development of new anthelmintic drugs in veterinary medicine

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The growing level of resistance of parasites to antiparasitic drugs, as well as the rigorous standards for maximum residue levels of drug in edible animal tissues are significant challenges for modern veterinary pharmacotherapy. Parasitic nematodes cause substantial morbidity and mortality in animals and people globally and major losses to food production annually. Control of these nematode parasites relies on an effective supply of anthelmintics, but continued use of anthelmintic compounds for mass chemotherapy will lead to drug resistance. There is a need to identify novel compounds for anthelmintic development. The neuromuscular system of parasitic nematodes has proven to be an efficient pharmacological target for antihelmintics. Some of the most frequently used antiparasitic drugs are agonists of nicotinic acetylcholine receptors (nAChRs) (imidazothiazoles and tetrahydropyrimidines) or activators of both glutamate-gated chloride channels (GluCl) and GABA-receptors (macrocylic lactones). Cholinergic agonists such as levamisole, pyrantel and oxantel selectively open ligand-gated acetylcholine ion channels expressed in nematode body wall muscles to induce spastic contraction of muscle cells leading to paralysis of the worms.

We propose research in the following directions to improve existing pharmacotherapy and development of new drugs: 1. Investigation of effectiveness of combinations of existing GABAergic and cholinergic drugs to enhance efficacy; 2. Investigation of potential new targets for anthelmintics (muscarinic ACh receptor and serotonergic MOD 1 receptor); 3) The repurposing of existing drugs that exhibit potential anthelmintic properties; 4) The antinematodal properties of terpenoid Active Ingredients (AIs) of plant essential oils and potential of combinations of AIs and existing drugs.

Perspektive i pravci razvoja novih antihelmintika u veterinarskoj medicini

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Rastući nivo rezistencije parazita na antiparazitske lekove, kao i rigorozni standardi za maksimalne nivoe rezidua lekova u jestivim životinjskim tkivima, predstavljaju značajan izazov za savremenu veterinarsku farmakoterapiju. Parazitske nematode uzrokuju značajan morbiditet i smrtnost životinja ali i ljudi širom sveta. Takođe, uzrok su velikih gubitaka u proizvodnji hrane. Kontrola infekcija ovim parazitima oslanja se na efikasnu primenu anthelmintika, ali učestala primena istih anthelmintičkih jedinjenja za masovnu hemoterapiju dovodi do razvoja rezistencije na lekove. Konstantno postoji potreba da se identifikuju nova jedinjenja za razvoj potencijalnih anthelmintika. Sa druge strane, neuromišićni sistem parazitskih nematoda se pokazao kao efikasna farmakološka meta za ove lekove. Neki od najčešće korišćenih antiparazitskih lekova su agonisti nikotinskih acetilholinskih receptora (nAChRs) (imidazotiazoli i tetrahidropirimidini) ili aktivatori glutamat-zavisnih hloridnih kanala (GluCl) i GABA-receptora (makrociklični laktoni). Holinergički agonisti kao što su levamisol, pirantel i oksantel selektivno otvaraju ligand-zavisne acetilholinske jonske kanale

ekspimirane u mišićima zida tela nematoda da izazovu spastičnu kontrakciju mišićnih ćelija što dovodi do paralize crva.

Predlažemo u cilju poboljšanja postojeće farmakoterapije i razvoja novih lekova istraživanja u sledećim pravcima: 1. Istraživanje efikasnosti kombinacija postojećih GABAergičnih i holinergičkih lekova za povećanje efikasnosti; 2. Istraživanje potencijalnih novih meta za anthelmintike (muskarinski ACh receptor i serotonergički MOD 1 receptor); 3) Novu namenu postojećih lekova, namenjenim drugim indikacijama koji ispoljavaju potencijalna antihelmintička svojstva; 4) Antinematodna svojstva terpenoidnih aktivnih sastojaka (AI) biljnih esencijalnih ulja i potencijalne kombinacija AI i postojećih lekova.

Treatment of filarial nematodes of humans and domestic animals.

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Filarial nematodes are significant pathogens of humans and domestic animals. Unlike most of the gut dwelling nematode parasites the filariae require an arthropod vector for transmission. *Burgia malayi*, *Wucheria bancrofti*, *Onchocerca volvulus* and *Loa loa* are significant pathogens of humans in sub-saharan Africa and south east Asia. *Brugia* spp. are responsible for the condition "elephantiasis"; a swelling of the lower extremities due to oedema and coarsening of the skin. This condition is both debilitating and also causes social stigma with sufferers unable to do productive work. While pathology of the eye leading to blindness is caused by the larvae of *O. volvulus*: so called "river blindness" is the leading infective cause of blindness in sub-Saharan Africa with about 30 million cases. In companion animals *Dirofilaria repens* is increasing in prevalence in Europe, while cases of *Dirofilaria immitis* (heartworm) are increasing in the USA. For *Dirofilaria* spp. a large component of the spread of disease is being attributed to climate change; as the planet warms the areas where mosquito vectors are detected are expanding. For all filarial species there is a significant gap in the pharmacopeia, there are no safe drugs for killing the adult worms. Treatment of adults in companion animals is possible with melarsomine but is suboptimal, while there are no safe treatments for filarial disease in humans used to kill adult worms. Control of these diseases relies almost entirely on prophylaxis using either Diethylcarbamazine or Ivermectin to kill the infective stages of the parasite. The recent development of emodepside is offering hope of new treatments against these parasites in humans but is likely to remain problematic for adult *D. immitis* in cats and dogs.

Lečenje infekcija filarijaza ljudi i domaćih životinja

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Filarijalne nematode su značajni patogeni ljudi i domaćih životinja. Za razliku od većine parazitskih nematoda koji žive u crevima, filarije zahtevaju vektor artropoda za prenos na domaćina. *Burgia malayi*, *Wucheria bancrofti*, *Onchocerca volvulus* i *Loa loa* su značajni patogeni ljudi u podsaharskoj Africi i jugoistočnoj Aziji. *Brugia* spp. odgovorni su za stanje "elefantijaza"; otok donjih ekstremiteta zbog edema i grubosti kože. Ovo stanje je istovremeno iscrpljujuće i takođe izaziva društvenu stigmu kod pacijenata koji nisu u stanju da obavljaju produktivan posao. Sa druge strane do promena na oku izazivaju larve *O. volvulus*: takozvano „rečno slepilo“ je vodeći infektivni uzrok slepila u podsaharskoj Africi sa oko 30 miliona slučajeva. Kod kućnih ljubimaca *Dirofilaria repens* je u konstantnom porastu u Evropi, dok su slučajevi *Dirofilaria immitis* (srčani crv) u porastu u SAD. Za *Dirofilaria* spp. velika uticaj na širenje bolesti pripisuje se klimatskim promenama; kako se planeta zagreva, oblasti u kojima se otkrivaju vektori, komarci se šire. Za sve filarijaze postoji značajan problemu farmakopeji, ne postoje bezbedni lekovi za uništavanje odraslih oblika parazita. Lečenje odraslih životinja moguće melarsominom, ali terapija nije optimalna, dok ne postoje bezbedni adulticidni tretmani za filarijaze kod ljudi. Kontrola ovih bolesti se gotovo u potpunosti oslanja na profilaksu korišćenjem dietilkarbamazina ili ivermektina za uništavanje infektivnih stadijuma parazita. Nedavni razvoj emodepsida pruža nadu za nove tretmane protiv ovih parazita kod ljudi, ali će verovatno ostati problematičan za odrasle *D. immitis* kod mačaka i pasa.