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Review

Ivermectin: An Anthelmintic, an Insecticide, and Much More

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Highlights

Ivermectin and analogs are remarkable broad-spectrum anthelmintics and insecticides, but resistance is now a real concern. Resistance mechanisms have been proposed but they do not appear to account for the resistance seen in parasitic nematodes.

Ivermectin is very effective for controlling microfilaria at low doses but it has limited effects on adult filaria for unclear reasons.

Ivermectin is a positive allosteric modulator of glutamate-gated chloride channels found in both nematodes and insects, and it binds to the channels in their lipid phase.

Ivermectin and analogs also modulate other ion channels and have effects on the mammalian host brain when the blood–brain barrier is impaired.

Preliminary repositioning studies of ivermectin show antiviral, antimalarial, antimetabolic, and anticancer effects at concentrations higher than anthelmintic concentrations in tissue culture.

Here we tell the story of ivermectin, describing its anthelmintic and insecticidal actions and recent studies that have sought to reposition ivermectin for the treatment of other diseases that are not caused by helminth and insect parasites. The standard theory of its anthelmintic and insecticidal mode of action is that it is a selective positive allosteric modulator of glutamate-gated chloride channels found in nematodes and insects. At higher concentrations, ivermectin also acts as an allosteric modulator of ion channels found in host central nervous systems. In addition, in tissue culture, at concentrations higher than anthelmintic concentrations, ivermectin shows antiviral, antimalarial, antimetabolic, and anticancer effects. Caution is required before extrapolating from these preliminary repositioning experiments to clinical use, particularly for Covid-19 treatment, because of the high concentrations of ivermectin used in tissue-culture experiments.

Section snippets

Ivermectin, the Anthelmintic and Insecticide

Ivermectin is a mixture of more than 80% 22,23-dihydroavermectin B1a and B1b (Figure 1). It is a remarkably potent anthelmintic and insecticide when given orally at therapeutic doses of 150 or 200 μg/kg to ruminants, pigs, horses, or humans where it yields C_{max} plasma concentrations of 11–54 ng/ml or 13–63 nM [1,2]. It is generally safe, with acute **LD_{50}** (see Glossary) toxicities seen at 24 000 μg/kg in monkeys [3] and 80 000 μg/kg in beagles [4]; it has a wide spectrum of action against …

Ivermectin and Analogs Are Allosteric Modulators of GluCl Ion Channels

Ivermectin and its analogs are **positive allosteric modulators** (**PAMs**) that selectively open inhibitory glutamate-gated chloride ion channels in the membranes of pharyngeal muscles, motor nerves, female reproductive tracts, and the **excretory/secretory** (**ES**) pores of nematodes and of muscle and nerves of insects and crustaceans [5,6]. The effect is: (i) inhibition of pharyngeal pumping (Figure 2) when the pharyngeal muscle is the target; (ii) inhibition of motility when motor nerves are the main …

Ivermectin Inhibits the Nematode Parasites' Ability to Suppress the Host Immune Response: Immune Modulation Theory

Nematode parasites can modulate the immune response of their host by releasing a complex mixture of immune modulatory compounds [29,30] and thereby survive within the host. Loss of the ability to release the immune modulators would contribute to the elimination of the parasite. Moreno *et al.* [31] have pointed out that ivermectin, at submicromolar concentrations, produces a rapid loss of microfilaria in host blood but fails to affect their motility in culture. An explanation for this …

Effects of Ivermectin on Channels Other Than GluCls in Nematode Parasites and Insects: Additional Channel Theory

Although it is often assumed that ivermectin only acts therapeutically as a PAM on different GluCl channels of nematodes, insects, and arthropods, it also has PAM and inhibitory negative allosteric (NAM) effects on other ion channels. These actions may support the actions of ivermectin on GluCl channels. It has inhibitory effects on **γ-aminobutyric acid** (**GABA**) channel conductances at low concentrations of <0.2 μM in *A. suum* [27], but at higher (10 μM) concentrations it has potentiating effects. …

Ion Channels in the Mammalian Central Nervous System (CNS) Are Also Affected by Ivermectin

Although relatively free from toxicity, ivermectin – when large overdoses are administered – may cross the blood–brain barrier, producing depressant effects on the CNS [38., 39., 40., 41., 42., 43.]. Ivermectin may also enter the brain when there are mutant multiple-drug-resistance transporters in the blood–brain barrier that fail to exclude from the brain drugs that are present in the plasma. In the brain, ivermectin targets the mammalian **glycine receptors** (**GlyRs**), GABA receptors, and nAChRs […

The Spiroketal Groups of Ivermectin Analogs Affect Binding to the Allosteric Site of Ion Channels

Abamectin, doramectin, eprinomectin, emamectin, milbemycin, and moxidectin have a common pharmacophore: a 16-membered macrocyclic lactone ring fused with benzofuran, spiroketal, and disaccharide groups (except that there is no saccharide for moxidectin or milbemycin) (Figure 1). Binding to the ion channels in the transmembrane region involves the benzofuran group, which is inserted deeply into the transmembrane regions, reaching nearly to the pore of the channel. The spiroketal group interacts …

Ivermectin Inhibits NS3 Helicase and Selected Protein Import through Nuclear Pores

The most potent antiviral effects of ivermectin reported appears to be its inhibitory effects, with an EC_{50} of 3–6 nM concentrations, in virus yield reduction assays with cultures of yellow fever virus. The effect is mediated by inhibition of viral NS3 helicase [54]. Ivermectin also inhibits, at higher concentrations, other flaviviruses, such as Japanese encephalitis virus and tick-borne encephalitis virus, with inhibition of replication EC_{50}s of 200–300 nM concentrations.

Ivermectin also …

Antimalarial Effects of Ivermectin

In addition to controlling filariasis, the **mass drug administration** (**MDA**) of ivermectin has also had effects limiting the spread of malaria. Although this is likely due to an inhibitory effect on the mosquito vectors of malaria, there are reports of a direct inhibitory effect of

ivermectin on the liver stages of malarial parasites [65,66]. Singh *et al.* [67] tested a number of novel ivermectin analogs and reported that ivermectin inhibits *Plasmodium falciparum* erythrocyte stages *in vitro*, with …

Antimetabolic Effect of Ivermectin as a Partial Agonist of the Nuclear Farnesoid Receptor (FXR)

FXR is a nuclear receptor, involved in metabolic regulation, that binds to ivermectin with an **EC_{50}** in the 200 nM range [69,70]. It is normally bound by bile acids (as the physiologic agonist) and is expressed highly in the liver, small intestine, kidney, and adrenals [71,72]. Following the binding of bile acid, the FXR translocates to the nucleus to target DNA-regulating genes that are involved in the metabolism of bile acids, lipid, and glucose. Although ivermectin has the potential to treat …

Anticancer Effects of Ivermectin

To overcome the cancer therapeutic bottleneck, repurposing of a number of drugs, including anthelmintics, has been suggested [74]. Juarez *et al.* [75] and Antoszczak *et al.* [76] have reviewed the anticancer effects of ivermectin at high concentrations (0.1–100 μM or doses of 3–40 mg/kg) in tissue culture and in mice. The modes of action of ivermectin on different types of cancer are proposed to involve different mechanisms: (i) the multidrug-resistance transporter protein [77]; (ii) Akt/mTOR [78 …

Resistance to Ivermectin: Candidate Genes, Pgps, and NHR-8

Resistance to ivermectin and its analogs in parasitic nematodes is of increasing concern; the mechanisms of this resistance has not been explained satisfactorily. We do have information on ivermectin resistance in the model nematode, *C. elegans*, where it appears that simultaneous mutations of several genes are required for very high levels (>100×) of resistance. Dent *et al.* [13] observed that three GluCl channel genes – *glc-1*, *avr-14*, and *avr-15* – were required to produce strong ivermectin …

Concluding Remarks

We have seen that ivermectin and analogs are remarkable anthelmintics and insecticides. Despite their wide spectrum of action on many species of parasite they have limited effects on adult filarial nematodes. Future research should seek to determine the explanation for

this (see Outstanding Questions). If it is found that the GluCl channels of adult filaria are less sensitive to the existing macrocyclic lactones, a second generation of ivermectin analogs, or a combination with other …

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Glossary

Allosteric site

a binding site on the GluCl receptor channel that is not the same site on the receptor as the glutamate agonist. Ivermectin binds to the allosteric site to increase the opening of the channel.

EC_{50}

the concentration of a drug that produces 50% of the maximum response.

Excretory/secretory (ES)

nematodes have an esophageal gland near the head region that releases ES substances; they include a range of active substances that, in animal parasitic nematodes, have immune-suppressant

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> …It shows activity against a broad spectrum of parasitic nematodes after both oral and parenteral administration, but not against cestodes or trematodes. In addition, it has activity against different arthropods like fleas, lice, mites and some tick species (McKellar and Benchaoui, 1996; Martin et al., 2020). While it is effective against microfilariae, L3 and L4 stages, it is not efficacious against adult but does reduce fertility (Martin et al., 2020).…

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