

Chronic treatment with ivermectin changes drug disposition in mice through modulation of metabolism gene expression

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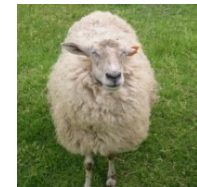
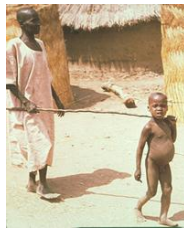
SCIENTIFIC CONTEXT

Macrocyclic Lactone Anthelmintics Ivermectin



Human medicine

Veterinary medicine

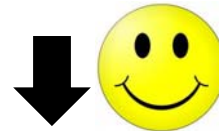


Filarial nematode
Onchocerca volvulus

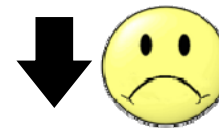
Gastro intestinal nematodes

Very efficient

low dose (0,2 mg/kg) + broad spectrum of activity

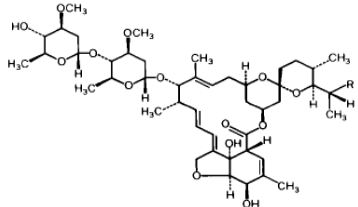


Extensive use (...repeated dose)



Emergence of resistant parasites

IVERMECTIN AND METABOLISM



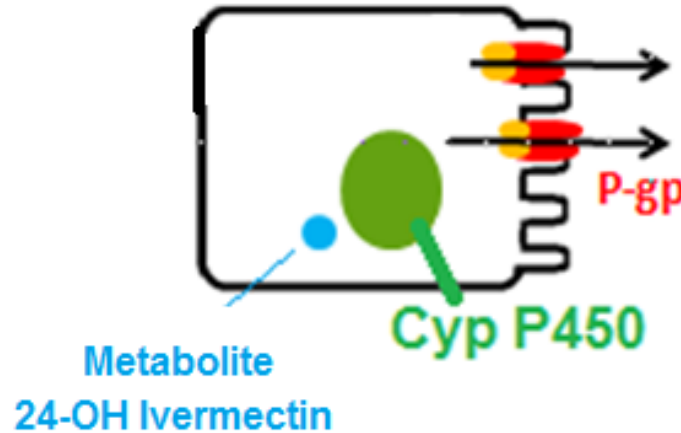
Ivermectin

Substrate of ABC transporter P-glycoprotein (P-gp)

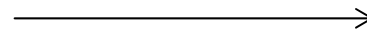
(Shinckel et al, 1994)

Metabolised by cytochromes P450 (Cyp)

Human (Cyp3A), Rat (Cyp3A + 1A1) (Skalova et al, 2001)

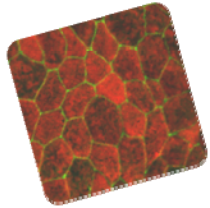


Drug concentration
in the organism



Drug efficacy

IVERMECTIN AND GENE EXPRESSION



In mammalian
cells

Ivermectin induces Pgp gene expression (Menez et al, 2012)



In nematodes

Ivermectin-resistance increases ABC transporter genes expression

- Ppgs and MRPs in *Caenorhabditis elegans* (James and Davey, 2009)
(Yan et al, 2012)
- Ppg9 in *Teladorsagia circumcincta* (J.Dicker et al, 2011)
- Ppg1 and Ppg9 in *Haemonchus contortus* (Williamson et al, 2011)

OBJECTIVES

Ivermectin exposure of the host whole organism?

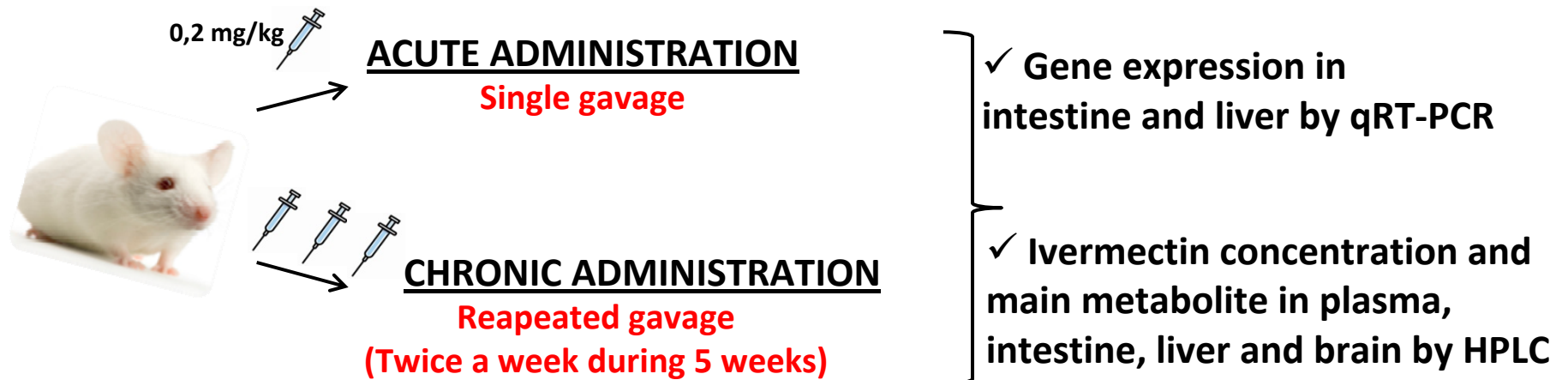
➔ Effect on the transport and biotransformation genes:

ABC Transporter genes = *abcb1a*, *abcb1b*, *abcc1*, *abcc2*, *abcc3*, *abcg2*

Cytochrome P450 genes = *Cyp1a2*, *Cyp2b10*, *Cyp3a11*

➔ Impact on drug disposition?

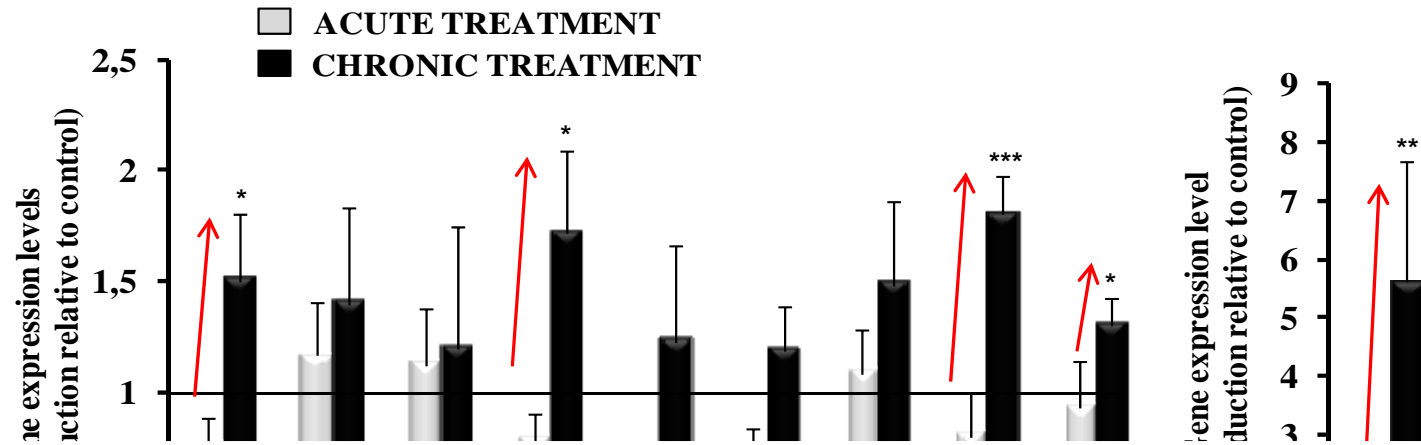
MATERIAL AND METHODS



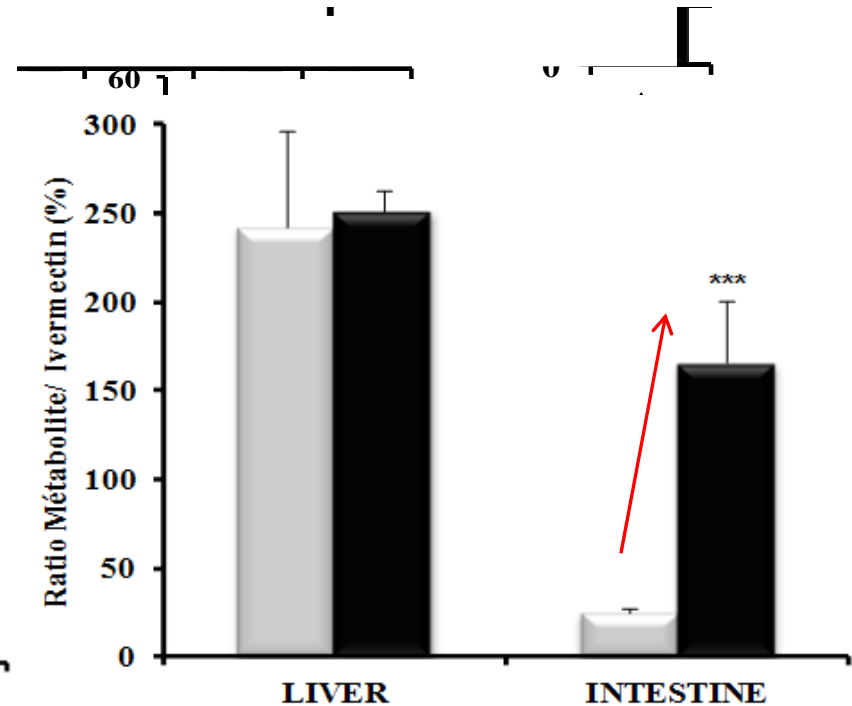
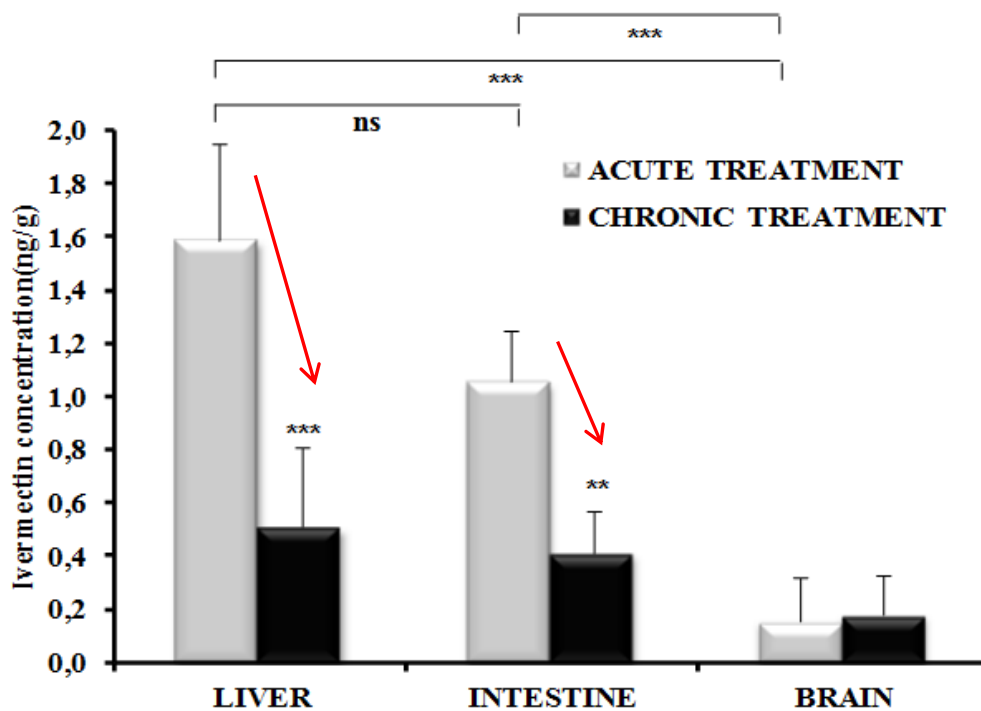
MAIN RESULTS



Gene expression in the intestine after ivermectin exposure



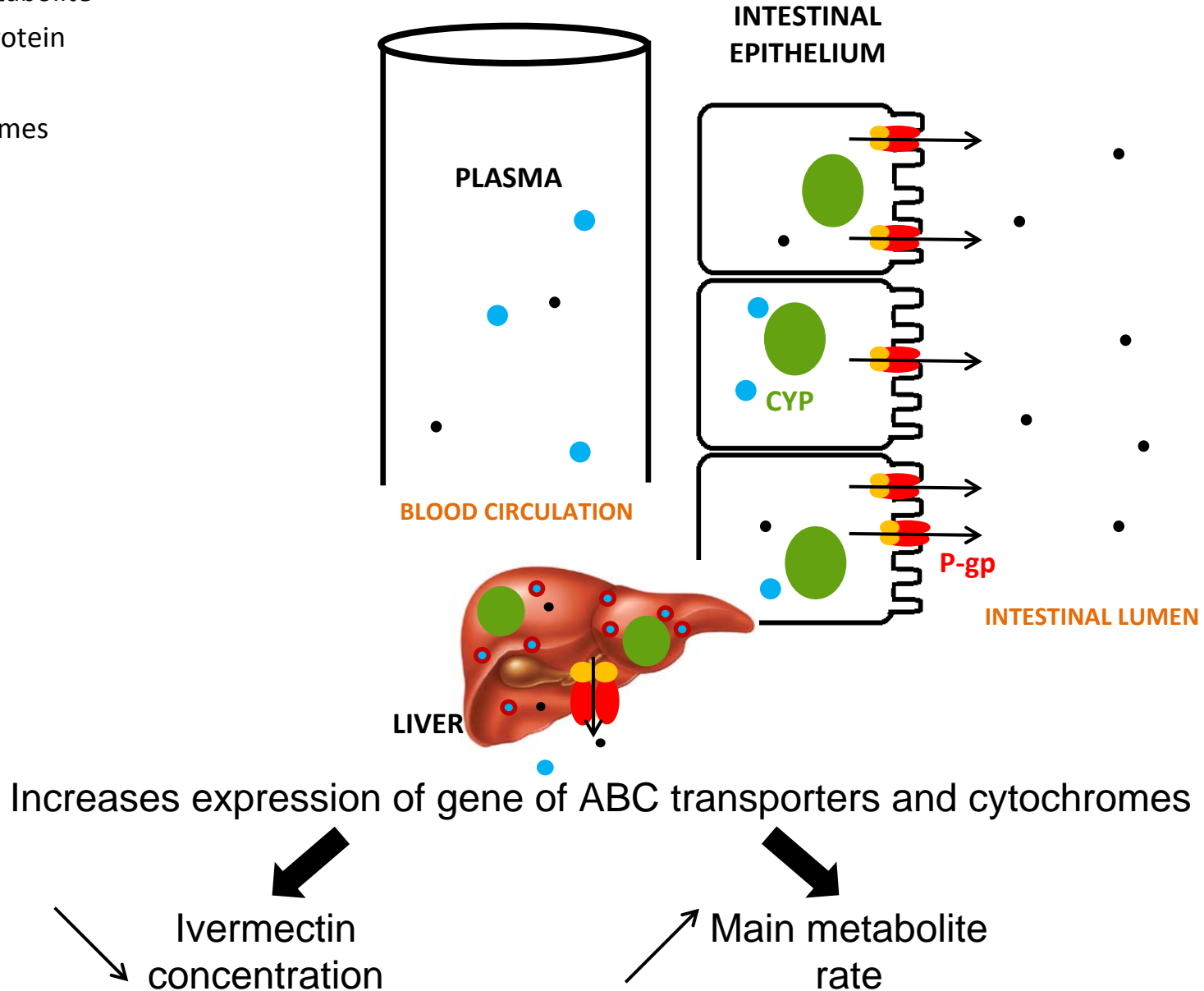
Ivermectin and its main metabolite in organs



SUMMARY

- Ivermectin
- Main metabolite
- P-glycoprotein
- MRPs
- Cytochromes

Chronic administration of ivermectin



CONCLUSION

Long term exposure to ivermectin decreases ivermectin concentration in the host through regulation of metabolism gene

?

Sub-lethal concentrations

?



?

Selection of resistant parasites

Decrease efficacy of other drug

PROSPECTS



- Relates gene expression and protein (western, activity, Pgp inhibitors)
- Study the synergism between Pgp and cytochrom: single and double KO



- Impact of a long acting treatment with ivermectin in sheep

THANK YOU FOR LISTENNING

Membrane transporters and Resistance team

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