Disparities in drug sensitivity of *T. congolense* and brucei group trypanosomes is related to differences in adenosine transporters and aquagyceroporins

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Control of African Animal Trypanosomiasis (AAT) is seriously undermined by the challenge of drug resistance. *Trypanosoma brucei*, one of the three species that cause AAT, has been extensively studied, and the mechanism of drug resistance in this species depend mostly on mutations in transmembrane transporters that import the drugs. However, advances in molecular parasitology have revealed enormous genetic differences between *T. brucei* and other animal trypanosomes especially *T. congolense*. Thus, there is need to understand the genetic and molecular basis of drug resistance in *T. congolense* in order to aid rational drug design and development and verify whether the *brucei* models apply. Drug sensitivity assays showed that the EC_{50s} of diminazene aceturate and melarsomine in *T. congolense* were 3 and 20 times higher than in *T. brucei,* respectively. In addition, *T. congolense* was 151 times less sensitive to pentamidine and 296 times resistant to suramin relative to *T. brucei*. It is hypothesised that lack of authentic orthologues of some *T. brucei* transporters (TbAQP2, TbAT1, and a lysosomal MFST) is responsible for low sensitivity to these drugs in *T. congolense*. Expression of *T. brucei* AQP2 (TbAQP2) in *T. congolense* resulted in an approximately 8-fold increase in sensitivity to pentamidine and 6-fold increase in sensitivity to melarsomine compared to wild type. The *T. congolense* + TbAQP2 also displayed a higher rate of uptake of [^{3}H]-pentamidine, as well as faster lysis when exposed to melarsomine. On the other hand, *T. congolense* clones expressing *T. brucei* P2 adenosine transporter (TbAT1) show a 30-fold increased sensitivity to melarsomine and a 12-fold increase in sensitivity to diminazene, pentamidine and isometamidium. In addition, there is a higher uptake of [^{3}H]-diminazene and [^{3}H]-pentamidine in *T. congolense* clones expressing TbAT1 compared to the wild type. This indicates that differences in transporters between *Trypanosoma* species play important role in differential sensitivity and should be considered in the development of new drugs for AAT.