

Suramin, a key trypanosomiasis drug developed over a century ago, remains in the clinic for treatment of early stage disease, while its mode of action is elusive. Recent studies suggest a prominent role of endocytosis for suramin uptake and an apparent receptor function of invariant surface protein 75 (ISG75). We demonstrate here that suramin is taken up rapidly and accumulates to high intracellular concentrations, dependent on ISG75 abundance. Furthermore, we investigated how suramin impacts the global proteome and metabolome at various timepoints. Suramin treatment perturbs the mitochondrial membrane potential within hours, preceding a drop of cellular ATP-levels and a build-up of intracellular pyruvate. Global proteomics analysis of suramin treated cells revealed significant upregulation of enzymes of the tricarboxylic acid cycle, proline dehydrogenase, glutamate dehydrogenase, pyruvate dehydrogenase and mitochondrial metabolite transporters, suggesting a dramatic switch of mitochondrial metabolism. Also among the upregulated cohort are proteins involved in differentiation to stumpy form, including PAD isoforms and PIP39. Notably, the vast majority (>90%) of upregulated (>2 fold) proteins were previously described to be more abundant in the procyclic form when compared to the bloodstream form proteome. Our results demonstrate that suramin accumulation by endocytotic uptake is highly efficient, amounting to higher intracellular concentrations than previously assumed, indeed likely sufficient to act as micromolar inhibitor. The observed metabolic switching indicates the possibility that the suramin mode of action relies on trapping the parasite between life cycle stages.