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Studies on the Trypanocidal activities of cysteine proteinase and proteasome inhibitors

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The protozoan parasite *Trypanosoma brucei* causes sleeping sickness in sub-Saharan Africa and exerts significant morbidity and mortality in man. For chemotherapy of sleeping sickness only four drugs, with serious side effects, are available. Therefore, the development of new anti-trypanosomal drugs is urgently required.

Peptidyl, peptidomimetic and non-peptidyl inhibitors of brucipain, the major lysosomal cysteine proteinase of *T. brucei*, have proved trypanocidal. In the present study, potent and selective peptidyl inhibitors of cathepsin-L, and non-peptidyl acyl hydrazides have been investigated for their trypanocidal activities *in vitro* using culture-adapted bloodstream forms of *T. brucei*. The anti-trypanosomal activities of the cathepsin L inhibitors and of the most effective acyl hydrazides were comparable with those of commercial anti-sleeping sickness drugs. Whereas the cathepsin-L inhibitors exhibited promising ratios of cytotoxic to trypanocidal activity, acyl hydrazides showed less favourable selectivity indices. Compared to other cysteine proteinase inhibitors, the cathepsin-L inhibitors were found to be the most trypanocidal compounds tested so far. In conclusion, the data support the potential of cathepsin-L and acyl hydrazide inhibitors for rational anti-trypanosomal drug development.

Proteasome inhibitors are a novel class of anti-tumour agents and currently in clinical trails for treatment of multiple cancers. However, anti-tumour agents could also be of use against sleeping sickness. In the present study, seven peptidyl proteasome inhibitors were tested for trypanocidal activity against bloodstream forms of *T. brucei*. Two compounds showed promising activity in the nanomolar range. In addition, one proteasome inhibitor was also shown to exert anti-trypanosomal activity *in vivo*. In general, trypanosomes were more susceptible to the compounds than were human cells. The trypanocidal effects of the proteasome inhibitors may be attributed in part to induction of apoptosis. The data support the potential of proteasome inhibitors as rational choice for the development of future anti-sleeping sickness drugs.

As the alkyldiguanide synthalin has been shown to exhibit prolific anti-trypanosomal activity, the effect of two related biguanides, metformin and phenformin, on the growth of *T. brucei* bloodstream forms was studied *in vitro*. However, both compounds showed very little or no trypanocidal activities. Thus, biguanides are disqualified as lead compound for rational anti-trypanosomal drug development.