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Potential role of the glyoxalase pathway as a drug target in *Leishmania infantum*: an exact steady-state model analysis

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Background

The glyoxalase system is the main catabolic pathway of methylglyoxal, a toxic 2-oxoaldehyde which occurs in all living cells as a by-product of glycolysis [1,2]. Trypanosomatids, such as *Leishmania infantum*, are pathogenic microbial parasites which have glycolytic enzymes located in a specific cell organelle, the glycosome [3]. In these organisms, the usual glyoxalase cofactor glutathione is functionally replaced by trypanothione [4,5]. Inhibition of the glyoxalase pathway might cause the accumulation of methylglyoxal in the glycosome, hampering glycolysis and killing the parasite.

Methods

An ODE model of the glyoxalase pathway was developed based on a kinetic characterization of the glyoxalase system in *L. infantum* [6]. As depicted in Figure 1, it is assumed that methylglyoxal is formed at a constant rate, v_{in}. Methylglyoxal reacts with one or both thiol groups of trypanothione forming mono- or bis-hemithioacetals in a reversible mass-action reaction. These hemithioacetals are the substrates of the glyoxalase system, forming D-lactate as final product and regenerating free trypanothione. v_{in} is the input flux of methylglyoxal in the pathway; v_1 and v_{-1} are mass-action reaction rates; v_2 and v_3 are Michaelis-Menten enzyme-catalysed reaction rates. Steady-state concentrations and their sensitivities were derived as functions of glyoxalase I and II activities, methylglyoxal influx and total thiol concentration [6]. Necessary mathematical relations for the existence of a steady state were also calculated from the asymptotic behavior of these functions. All mathematical relations are exact and were derived symbolically using Mathematica® 4.0, from Wolfram Research, Inc.

Results

Methylglyoxal concentration achieves a steady state only when parameters remain within certain boundaries. Outside these boundaries, the typical dynamic behaviour of the system is the depletion of free trypanothione, leading to the accumulation of methylglyoxal over time. Total cofactor concentration cannot be arbitrarily low, it must exist above a defined threshold, the so-called "catalytic amount". Enzyme activities must also be greater than a threshold value, which is higher than the flux of the pathway. Conversely, for constant enzyme activities, there is a limit for methylglyoxal formation flux above which the glyoxalase pathway can not prevent the accumulation of methylglyoxal. Variations of enzyme activity have virtually no effect on methylglyoxal steady-state concentration (sensitivity of approximately 0). The non-enzymatic hemithioacetal formation has a sensitivity of -1. Methylglyoxal concentration sensitivity to input flux and total cofactor concentration are approximately 1 and -1, respec-

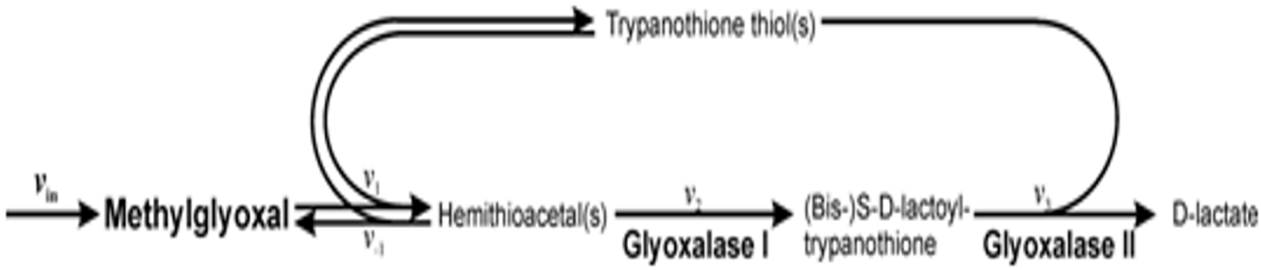

Figure 1
Glyoxalase pathway of *L. infantum*.

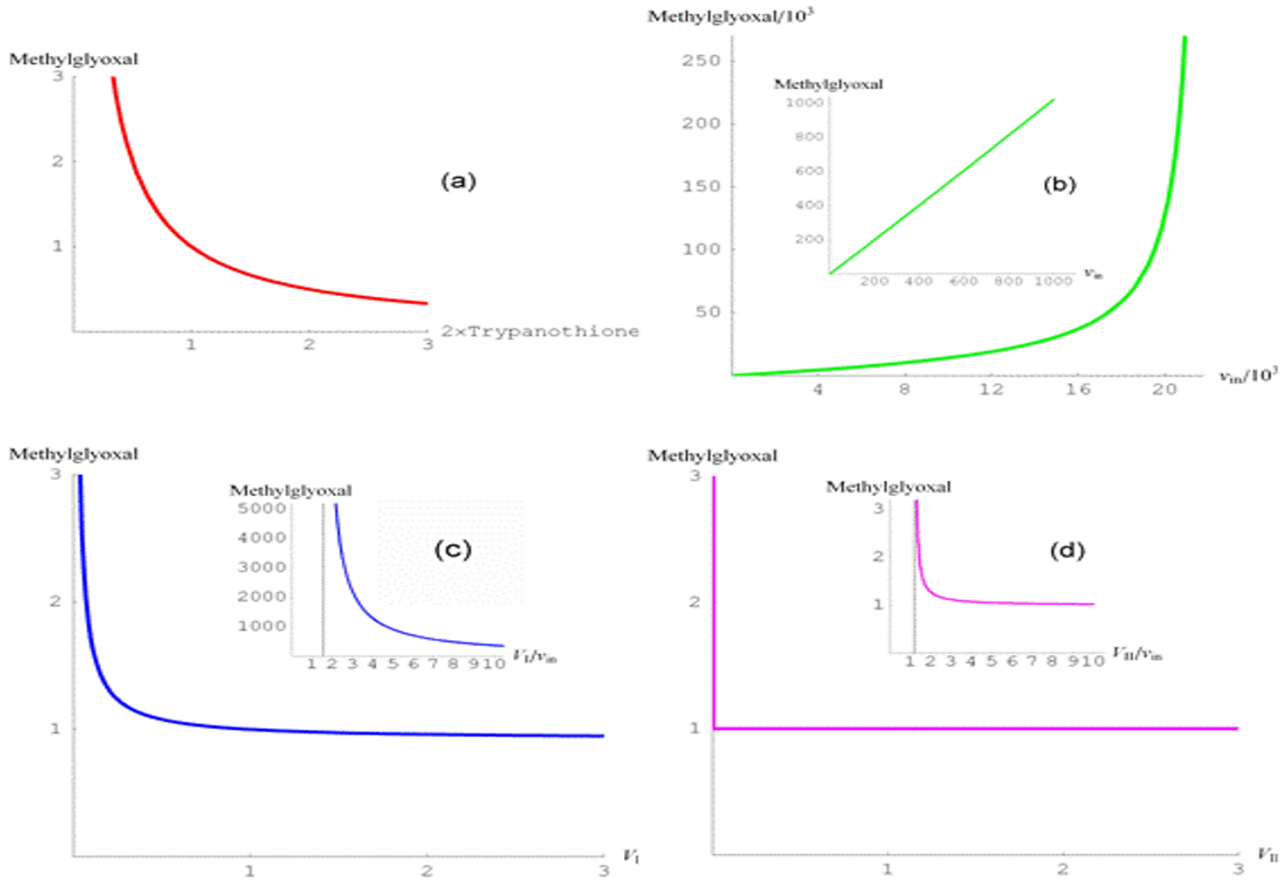

Figure 2
Methylglyoxal steady-state concentration as a function of (a) total trypanothione concentration, (b) methylglyoxal formation rate, (c) glyoxalase I activity and (d) glyoxalase II activity. Parameters are normalized to reference values.

tively. In the vicinity of the boundaries outside of which a steady state is not attained, the absolute values of all sensitivities rise to infinity. However, the reference parameter values, which correspond to the physiological state of *L. infantum* in exponential phase, are very far from the boundaries – compared to the minimum values required to attain a steady state, total cofactor is approximately 50,000 fold, glyoxalase I activity is approximately 23,000 fold, glyoxalase II activity is approximately 30,000 fold and input flux is approximately 25,000 fold.

Conclusion

Decreasing the activity of the glyoxalase enzymes is unsuitable to harm the parasite since no significant rise of methylglyoxal steady-state concentration is achieved. However, depletion of the cofactor trypanothione or the enhancement of methylglyoxal production leads to a significant increase of the concentration of this toxic compound. These results point to a possible strategy for treatment of leishmaniasis based on the interference with trypanothione metabolism or glycolysis. This study provides quantitative data which might be useful for future research on drug targeting this disease.

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