Adenosine kinase of T. b. Rhodesiense identified as the putative target of 4-[5-(4-phenoxyphenyl)-2H-pyrazol-3-yl]morpholine using chemical proteomics

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 533201
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Year 2009
Title Adenosine kinase of T. b. Rhodesiense identified as the putative target of 4-[5-(4-phenoxyphenyl)-2H-pyrazol-3-yl]morpholine using chemical proteomics
Journal PLoS Neglected Tropical Diseases
Volume 3
Number 8
Pages / **Article-Number** e506
BACKGROUND: Human African trypanosomiasis (HAT), a major parasitic disease spread in Africa, urgently needs novel targets and new efficacious chemotherapeutic agents. Recently, we discovered that 4-[5-(4-phenoxyphenyl)-2H-pyrazol-3-yl]morpholine (compound 1) exhibits specific antitrypanosomal activity with an IC(50) of 1.0 microM on Trypanosoma brucei rhodesiense (T. b. rhodesiense), the causative agent of the acute form of HAT. METHODOLOGY/PRINCIPAL FINDINGS: In this work we show adenosine kinase of T. b. rhodesiense (TbrAK), a key enzyme of the parasite purine salvage pathway which is vital for parasite survival, to be the putative intracellular target of compound 1 using a chemical proteomics approach. This finding was confirmed by RNA interference experiments showing that down-regulation of adenosine kinase counteracts compound 1 activity. Further chemical validation demonstrated that compound 1 interacts specifically and tightly with TbrAK with nanomolar affinity, and in vitro activity measurements showed that compound 1 is an enhancer of TbrAK activity. The subsequent kinetic analysis provided strong evidence that the observed hyperactivation of TbrAK is due to the abolishment of the intrinsic substrate-inhibition. CONCLUSIONS/SIGNIFICANCE: The results suggest that TbrAK is the putative target of this compound, and that hyperactivation of TbrAK may represent a novel therapeutic strategy for the development of trypanocides
Publisher Library of Science
ISSN/ISBN 1935-2727
edoc-URL http://edoc.unibas.ch/dok/A5843129
Full Text on edoc No;
Digital Object Identifier DOI 10.1371/journal.pntd.0000506
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/19707572