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CYCLIC NUCLEOTIDE SPECIFIC PHOSPHODIESTERASES OF T. BRUCEI – POTENTIAL NEW TARGETS FOR TRYPANOCIDAL DRUGS?

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Signal transduction through cAMP is one of the most conserved concepts in biology. cAMP signalling is found in all organisms, from bacteria to humans. Nevertheless, the comparative analysis of cAMP signalling in T. brucei and in mammals has revealed significant differences in the molecular details of adenylyl cyclases and phosphodiesterases between the two groups of organisms. These findings suggested that cAMP signalling might be exploited as a target for selective drug development. We are currently exploring the phosphodiesterases of T. brucei for their potential as novel targets for chemotherapy. Phosphodiesterase inhibitors are currently in widespread clinical and experimental use for conditions such as congestive heart failure, asthma, allergy, impotency and others. The effectiveness of such compounds as trypanocides remains to be investigated.

We have identified and characterized several phosphodiesterases in T. brucei. TbPDE-1 and TbPDE-3 are single-copy genes, while TbPDE-2 is coded for by a gene family containing several members. The catalytic domains of all PDEs share significant sequence homology with those of mammalian PDEs, but they are clearly distinct from all of the eleven PDE families identified in mammals. Genetic knock-outs of PDE-1 were constructed both in procyclic and in bloodstream forms of T. brucei. Procyclic PDE-1 knock-outs show no discernible phenotype in culture, except that their generation time is increased by about 1 h. Transmission experiments in tsetse flies demonstrated that midgut infection rates and intensities are not affected by the deletion of PDE-1. Deleting the PDE-1 gene in bloodstream forms also does not produce a discernible phenotype in culture. RNAi knockdown of TbPDE2 family members were invariably lethal for booldstream forms, and caused severe distortions of nuclear division in procyclic forms. The biological functions and the potiental as drug targets of these enzymes are currently under investigation.

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LOWERED ECHINOCOCCUS MULTILOCULARIS EGG CONTAMINATION IN URBAN AREAS DUE TO ANTHELMINTIC BAITING OF FOXES

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Previous studies have shown, that the urban cycle of E. multilocularis depends mainly on the highly infected intermediate host populations of arvicolids living in the border area of the city of Zurich where the prevalence in foxes exceeds 60%. Ecological investigations have demonstrated small home ranges and low immigration rate for urban foxes. Therefore, we hypothesised that a reduction of the infection pressure with E. multilocularis eggs in small distinct risk areas should be feasible. We distributed praziquantel-containing baits in six areas of 1km^2 in the border area of the city of Zurich at monthly intervals from April 2000 to October 2001. Another six 1km^2 areas , arranged alternately with the bait areas, were defined as control areas. We collected 1078 fox faeces and trapped 1000 Arvicola terrestris during the course of the experiment to evaluate the effect of baiting. The portion of coproantigen-positive faeces decreased significantly from 24.6% (+/-5.8%SE) during the initial period of baiting to 5.5% (+/-1.4%SE) during the last sampling period ($P<0.001$). The proportion of coproantigen-positive faeces remained unchanged in the control areas. The anthelmintic treatment was only effective in the close vicinity of the baited area. At a distance of 250 to 750 m from the baited area, the portion of coproantigen-positive faeces sampled was nearly the same as for to fox faeces collected at a greater distance. Initially, the prevalence of E. multilocularis in A. terrestris was similar in baited and control areas (8.4% +/-2.3%SE vs. 8.9% +/-2.6%SE), but was significant lower in baited areas at the end of the experiment (1.0% +/-0.7%SE vs. 5.7% +/-1.5%SE $P<0.01$). This controlled field experiment clearly shows, that control of the environmental contamination with E. multilocularis eggs is feasible in restricted areas by continuous treatment of the fox population.

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TREATMENT OF CUTANEOUS LEISHMANIASIS IN VISITORS TO ENDEMIC AREAS – AN OVERVIEW

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Leishmaniasis is endemic in 88 countries in 5 continents. 1–1.5 million cases of cutaneous leishmaniasis are yearly reported worldwide. There is a sharp increase in recorded cases over the last ten years. Leishmaniasis is transmitted by the bite of various types of phlebotomine sand flies. Travellers with outdoor activities are mainly at risk.

Based on their geographical distribution cutaneous leishmaniasis is divided into the Old world and the New world leishmaniasis. In the past time consuming culture and isoenzyme analysis were performed to determine the species. The recently developed and now routinely available PCR technology allows a rapid diagnosis with determination of the species and thus a species oriented treatment. While the Old world species mostly cause benign and often self limiting cutaneous disease, the American species cause a broad spectrum from benign to severe manifestations including mucosal involvement. The clinical spectrum of the disease and its response to treatment vary according to the species. Therefore a species related approach is proposed. Drug for systemic and topical treatment are presented and discussed with regard to their use and adverse effects. An overview of the treatment options for the most important species is given. The level of evidence of the studies behind these recommendations is given.