Zeitschrift: Acta Tropica
Herausgeber: Schweizerisches Tropeninstitut (Basel)
Band: 39 (1982)
Heft: 3

Artikel: Antimalarial activity of inhibitors of ADP-ribosyl transferase against "Plasmodium yoelii" infection in mice. Part 1, Preliminary data : short communication

Autor: Okolie, E.E. / Adewunmi, A.I. / Enwonwu, C.O.

DOI: https://doi.org/10.5169/seals-312987

Acta Tropica *39*, 285–287 (1982)

National Institute for Medical Research, Yaba, Lagos State, Nigeria

Antimalarial activity of inhibitors of ADP-ribosyl transferase against *Plasmodium yoelii* infection in mice. 1. Preliminary data

Short communication

E. E. Okolie, A. I. Adewunmi, C. O. Enwonwu

Introduction

One of the major objectives of the WHO Special Programme for Research and Training in Tropical Diseases is the development of effective chemotherapy for malaria. However, drug resistance in the malaria parasites of man as well as lack of efficient and safer drugs developed on a more rational basis, is increasingly causing serious clinical and public health problems. Consequently, a massive search has been undertaken in recent years to find new and safe compounds that are effective for both the prevention and the treatment of human malaria.

The aim of the present study, therefore, is to investigate the therapeutic potential of inhibitors of a new enzyme, ADP-ribosyl transferase (poly [ADP-ribose]polymerase), against malaria infection in mice. The enzyme has been reported to be present in the nuclei of malaria parasites (Okolie, 1980) and its properties have been studied (Okolie et al., 1982). The possible physiological functions of this enzyme have been extensively reviewed (Hilz and Stone, 1976; Hayaishi and Ueda, 1977; Shall et al., 1977; Smulson and Sugimura, 1980).

Materials and Methods

The antimalarial activity of the inhibitors was screened using the "4-day Suppressive Test" (WHO, 1973). Groups of five young male Swiss albino mice (28 days old) were injected, intraperitoneally, with 1×10^6 donor erythrocytes infected with *Plasmodium yoelii nigeriensis*. Each inhibitor or drug (100 mg/kg body weight) was suspended with the aid of ultrasonicator in physiological saline to which was added a suitable amount of Tween 20. The inhibitors were nicotinamide, 5-methylnicotinamide, 3-aminobenzamide, m-methoxybenzamide, theophylline, and theobromine. Chloroquine sulphate was included for comparison.

Correspondence: Dr. E. E. Okolie, National Institute for Medical Research, PMB 2013, Yaba, Lagos State, Nigeria

Table 1. Antimalarial activity of inhibitors of ADP-ribosyl transferase and chloroquine against *P. yoelii* infection in mice

Inhibitor/drug (100 mg/kg body weight)	Total PD* 'score' inhibitor/drug	Total PD* 'score' saline control	Inhibitor (drug)/saline ratio
Nicotinamide	34	35	0.97
5-methylonicotinamide	26	35	0.74
3-aminobenzamide	36	35	1.03
m-methoxybenzamide	18	35	0.51
Theophylline	24	35	0.69
Theobromine	22	35	0.63
Chloroquine sulphate	5	35	0.14

* PD = Parasite density

The suspensions were then administered intraperitoneally into the appropriate groups of mice daily for four consecutive days starting from the day of infection. On the fourth day, thin blood films were made from the tail of each mouse and stained with Giemsa. Parasite densities were determined by counting the parasites against 400 leucocytes in the same fields as the parasitized red blood cells. They were then 'scored' from 0 to 7 according to the classification of Bruce-Chwatt (1958). The total 'score' of the parasite densities for each inhibitor or drug was compared with that of control, infected mice treated with saline and Tween 20 only.

Results and Discussion

The result of the primary screening of inhibtors of ADP-ribosyl transferase is given in Table 1. It shows that at a concentration of 100 mg/kg body weight, 5-methylnicotinamide, theophylline, theobromine and m-methoxybenzamide are active against *Plasmodium yoelii* infection in mice. Nicotinamide and 3-aminobenzamide are inactive at this concentration. The results indicate that ADP-ribosyl transferase can be used as a target for chemotherapeutic attack in malaria parasites.

The therapeutic potential of the inhibitors of this enzyme in the treatment of cancer has been suggested by Nduka et al. (1980). In a recent study this group of workers found that the combination of inhibtors of ADP-ribosyl transferase with anticancer drugs was much more powerful in killing the leukaemic cancer cells than the anticancer drugs used alone. More recently it has been observed that some of these compounds inhibited the differentiation of *Trypanosoma cruzi* in mammalian cells, in vitro (Williams, 1982). Work is in progress to determine the dose-activity relationships of the active compounds as well as their toxicity and tolerability.

Acknowledgments

This work was supported financially by the Federal Ministry of Science and Technology, Lagos, Nigeria, and WHO (TDR) Re-entry Grant. The technical assistance of Messrs Emmanuel Osho and Samuel Umobong is acknowledged.

Bruce-Chwatt L. J.: Parasite density index in malaria. Trans. roy. Soc. trop. Med. Hyg. *52*, 389 (1958).

Hayaishi O., Uedo K.: Poly (ADP-ribose) and ADP-ribosylation of proteins. Ann. Rev. Biochem. *46*, 95–116 (1977).

Hilz H., Stone P.: Poly (ADP-ribose) and ADP-ribosylation of proteins. Rev. Physiol. Biochem. Pharmacol. *76*, 1–58 (1976).

Nduka N., Skidmore C. J., Shall S.: The enhancement of cytotoxicity of N-methyl-N-nitrosourea and of gamma radiation by inhibitors of Poly (ADP-ribose) polymerase. Europ. J. Biochem. *105*, 525–530 (1980).

Okolie E. E.: Isolation of malaria parasite nuclei and evidence for the existence of poly (ADP-ribose) polymerase activity in parasitic protozoa. In: Proceedings of the 3rd European Multicolloquium of Parasitology, Cambridge, p. 19 (1980).

Okolie E. E., Adewunmi A. I., Onyezili N. I.: ADP-ribosyl transferase in *Plasmodium* (Malaria Parasites) (1982). In preparation.

Shall S., Goodwim P., Halldorson H., Khan G., Skidmore C., Tsopanakis C.: Post-synthetic modifications of nuclear macromolecules. Biochem. Soc. Symp. *42*, 103–116 (1977).

Smulson M. E., Sugimura T. (eds.): Novel ADP-ribosylations of regulatory enzymes and proteins. Elsevier/North Holland Inc., New York 1980.

World Health Organization: Chemotherapy of malaria and resistance to antimalarials. WHO Techn. Rep. Ser. No. 529, 93–121 (1973).

Williams G. T.: The effect of inhibitors of nuclear ADP-ribosyl transferase on the infection cycle of *Trypanosoma cruzi* in mammalian cells, in vitro (1982). In preparation.