氏　　名	Nagwa Shaban Mohamed ALY
授与した学位	博　士
専攻分野の名称	学　術
学位授与番号	博甲第３４０３号
学位授与の日付	平成１９年　３月２３日
学位授与の要件	自然科学研究科生体機能科学専攻 （学位規則第４条第１項該当）
学位論文の題目	New Antimalarial Endoperoxides: Action and Resistance Analysis Against *Plasmodium falciparum* Malaria Parasites （新規環状過酸化抗マラリア薬：熱帯熱マラリア原虫(*Plasmodium falciparum*)に対する作用機序の解析研究）
論文審査委員	教授　綿矢　有佑　　教授　三好　伸一　　教授　佐々木健二

学位論文内容の要旨

The main objectives of the present study are to investigate the activity of new antimalarial endoperoxide compounds and development of resistant strain to study the possible mechanism of action.

With the emergence and spread of malaria parasites that are resistant to most of the antimalarial drugs presently available, there is an urgent need for the identification of new drug targets and the development of novel antimalarial strategies. Synthesized endoperoxide 1,2,6,7-Tetraoxaspiro [7.11] nonadecane (N-89) and its derivative N-251 exhibited significant antimalarial activity *in vitro* (EC_{50} 2.5 and 2.3 $X10^{-8}$M respectively on FCR-3 strain), and *In vivo* (ED_{50} value of N-89 and N-251 were 12 and 10 mg/ kg on intraperitoneal (ip), ED_{50} value 20 and 15 mg/ kg on oral (po) administration respectively). N-89 resistant strains were obtained after 2 years of intermittent drug pressure and single erythrocyte micro dilution technique. The most resistant strain, NRC10 showed 10 folds increase in N-89 EC_{50} value. No cross-resistance was obtained to other structurally related or unrelated antimalarial compounds. The proteomic techniques were used to identify the mode of action of novel antimalarial agent. On two-dimensional gels, we generally observed quite a number of proteins with levels that are differentially altered by exposure of parasite to N-89 application and resistance. Mass spectrometry identified them as proteins having different functions for parasitic cells (e.g. glycolytic pathway, protein and lipid metabolism, hemoglobin digestion and calcium related proteins), indicative of the likely complexity of parasite response to interference with its metabolism, which may extend beyond the immediate targets of the drug. Our results suggest that aspartic proteases and MSP7 precursor are valuable N-89 targets.

論文審査結果の要旨

The main objectives of the present study are to investigate the activity of new antimalarial endoperoxide compounds and development of resistant strain to study the possible mechanism of action.

With the emergence and spread of malaria parasites that are resistant to most of the antimalarial drugs presently available, there is an urgent need for the identification of new drug targets and the development of novel antimalarial strategies. Synthesized endoperoxide 1,2,6,7-Tetraoxaspiro [7.11] nonadecane (N-89) and its derivative N-251 exhibited significant antimalarial activity *in vitro* (EC_{50} 2.5 and 2.3 $X10^{-8}M$ respectively on FCR-3 strain), and *In vivo* (ED_{50} value of N-89 and N-251 were 12 and 10 mg/ kg on intraperitoneal (ip), ED_{50} value 20 and 15 mg/ kg on oral (po) administration respectively). N-89 resistant strains were obtained after 2 years of intermittent drug pressure and single erythrocyte micro dilution technique. The most resistant strain, NRC10 showed 10 folds increase in N-89 EC_{50} value. No cross-resistance was obtained to other structurally related or unrelated antimalarial compounds. The proteomic techniques were used to identify the mode of action of novel antimalarial agent. On two-dimensional gels, we generally observed quite a number of proteins with levels that are differentially altered by exposure of parasite to N-89 application and resistance. Mass spectrometry identified them as proteins having different functions for parasitic cells (e.g. glycolytic pathway, protein and lipid metabolism, hemoglobin digestion and calcium related proteins), indicative of the likely complexity of parasite response to interference with its metabolism, which may extend beyond the immediate targets of the drug. Our results suggest that aspartic proteases and MSP7 precursor are valuable N-89 targets.

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