Biological Activity of Restricted Peptides in the Erythrocytic Cycle

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Introduction

The anti-plasmodial activity of conformationally restricted analogs of angiotensin II against *Plasmodium gallinaceum* has been described[1,2]. To observe activity against another *Plasmodium* species, invasion of red blood cells by *Plasmodium falciparum* was analyzed. Analogs restricted with lactam or disulfide bridges were synthesized to determine their effects and constraints in the peptide-parasite interaction. The analogs were synthesized using *tert*-butoxycarbonyl and fluoromethoxycarbonyl solid phase methods, purified by liquid chromatography, and characterized by mass spectrometry.

Resultados e Discussão

Results indicated that the lactam bridge restricted analogs 1 (Glu-Asp-Arg-Orn-Val-Tyr-Ile-His-Pro-Phe) and 3 (Asp-Glu-Arg-Val-Orn-Tyr-Ile-His-Pro-Phe) showed activity toward inhibition of ring formation stage of *Plasmodium falciparum* erythrocytic cycle, preventing invasion in about 40% of the erythrocytes (Figure 1A). The disulfide-bridged analog 10 (Cys-Asp-Arg-Cys-Val-Tyr-Ile-His-Pro-Phe) was less effective yet significant, showing a 25% decrease in infection of new erythrocytes (Figure 1B). In all cases, the peptides presented no pressor activity, and hydrophobic interactions between the aromatic and alkyl amino acid side chains were preserved, a factor proven important in efficacy against *Plasmodium gallinaceum*. In contrast, hydrophilic interactions between the Asp[1] carboxyl and Arg[2] guanidyl groups proved not to be as important as they were in the case of *Plasmodium gallinaceum,* while interactions between the Arg[2] guanidyl and Tyr[4] hydroxyl groups were not important in either case. The β-turn conformation was predominant in all of the active peptides, proving importance in anti-plasmodial activity. This approach provides insight for understanding the importance of each amino acid residue on the native angiotensin II structure and a new direction for the design of potential chemotherapeutic agents.

Table 1. Characterization data of the tested peptides.

Entry	Sequence	HPLC Purity	Calculated Mass (Da)	Observed Mass (Da)
1	EDROVYIHPF	99%	1272.4	1271.4
2	EDRKVYIHPF	98%	1284.4	1286.1
3	DERVOYIHPF	99%	1272.4	1272.4
4	DERVKYIHPF	99%	1284.4	1286.4
5	eDROVYIHPF	98%	1272.4	1272.4
6	EDRoVYIHPF	98%	1272.4	1272.4
7	DRCVCYIHPF	99%	1249.4	1250.4
8	CDRVCYIHPF	98%	1249.4	1250.4
9	DCRCVYIHPF	99%	1249.4	1250.4
10	CDRCVYIHPF	99%	1249.4	1249.4

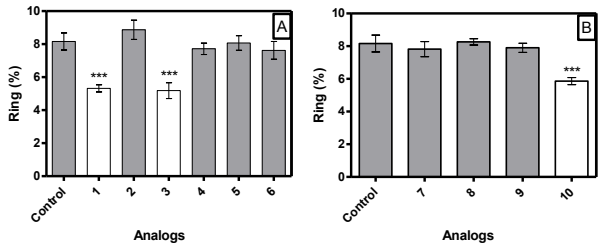

Figure 1. Effect of synthetic peptides in erythrocyte invasion by *Plasmodium falciparum*. Erythrocyte culture infected with *P. falciparum* schizonts was incubated for 24 h in the absence (control) or in the presence of 10^{-8} mol L^{-1} (A) Lactam Bridge or (B) Disulfide Bridge restricted peptides. ***Statistically significant compared with control value $p<0.05$.

Conclusões

Results showed that the restricted AII analogs could be used as templates for new and more potent antiplasmodial peptides. The interesting versatility of these peptides allow their use as preventive agents against malaria, acting against sporozoites in the infection stage and, simultaneously, as a drug during the erythrocyte invasion by merozoites.

Agradecimentos

FAPESP.

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