Effects of Acridine Derivatives on Ca2+ Uptake by Candida albicans

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Abstract:

The effects of several acridine derivatives, and chloroquine, which has a similar lateral chain to quinacrine, but with a quinoline nucleus, were studied on a strain of Candida albicans. Parameters estimated were: a) dichloromethane/water partition coefficients; b) uptake by cells; c) effects on respiration, d) effects on the acidification of the medium; e) efflux of K+ ; f) uptake of 86Rb+ and 45Ca2+, and d) effects on growth of cells. Results obtained in general: a) most of them showed a low hydrophobicity; b) most of them were significantly taken up by cells; c) acridine orange, acridine yellow, quinacrine and nonyl acridine orange inhibited respiration; d) acridine orange, quinacrine and nonyl acridine orange inhibited acidification of the medium. The most significant finding was that acridine orange, quinacrine and nonyl acridine orange at 60 µM or 120 µM, and acriflavine at 120 µM produced an efflux of K+ , an inhibition of 86Rb+ uptake, and a remarkable many fold increase of 45Ca2+ uptake. Acridine orange and acridine yellow produced only a decrease of duplication time; with the concentrations used, only nonyl acridine orange inhibited growth. It is suggested that quinacrine may be used as an adjuvant or topical agent against candidiasis. Chemical derivatives of some of the dyes might also be used against pathogenic fungi.

Keywords:

Acridine derivatives; Ca2+ uptake; Candida albicans

Introduction:

He diversity of organic molecules synthesized for more than one century is enormous; many of them are dyes with most varied industrial uses to stain all kinds of materials. Due to large-scale production and extensive application, synthetic dyes can cause considerable environmental pollution and are serious health-risk factors [1]. Hey may potentially generate ROS (reactive oxygen species), leading to oxidative stress (OS) and toxicity [2]. Methylene blue, for instance, at concentrations above 5 µM increases intracellular ROS and OS as evidenced by oxidation of glutathione (GSH), vitamin C and dihydrofluorescein [3], but in earlier studies almost a century ago [4], or more [5], treated several patients with malaria, using methylene blue.

Whether the increased Ca2+ uptake can induce apoptosis and death of cells is not clear. Gamarra et al. [26] have proposed use of amiodarone, which stimulates Ca2+ uptake, combined with fluconazole as a possible antifungal treatment against Candida albicans, even for a strain resistant to the antifungal. A similar therapeutic approach was also suggested for methylene blue by Schirmer et al. [27,28]. According to a general mechanism proposal, it was decided to evaluate a group of acridine derivatives, to verify whether it can or cannot be applied. Expecting them to inhibit yeast growth, we used the pathogenic yeast C. albicans as an experimental subject. Besides amiodarone, among the acridine derivatives tested, three of them had the most interesting e ́ects, producing a remarkable increase of Ca2+ uptake by cells, and three of them which either retarded or inhibited growth at the concentrations used.

Relating structure to activity:

Hree of the acridine derivatives increased Ca2+ uptake; however, some facts have to be taken in account about the chemical structure of the dyes (Figure 6): a) auramine, not an acridine, did not show any e ́ect- b) acriflavin, with two amino groups, but not methylated, showed some minor e ́ect- c) acridine yellow, also with two not methylated amino groups, was ine ́ective- d) the nonyl derivative of acridine orange, with a hydrophobic chain, at 120 µM became somewhat less e ́ective, as compared to the original dye; e) acridine orange deserves special mention because it was without any doubt the most e ́ective, mainly in stimulating Ca2+ uptake, and has the basic structure of 9-aminoacridine, but the first with a 5 C chain ending in a dimethylated amino group, and the second is a simple dimethyldiamino acridine; f) the lack of an e ́ect of chloroquine has to be noticed as well, because it has practically the same structure of quinacrine, but a quinoline nucleus instead of the acridine one. Hen, in general, it appears that some factors are important: a) the acridine nucleus, b) the existence of methylated amino groups, and c) the addition of an aliphatic chain increases the potency of the dyes. Hese characteristics may be at least considered as interesting for the possible synthesis of new compounds.

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