The effect of flucytosine on the germination of Candida albicans

WILLIAM H. WAIN
Ph.D.

ANNEMARIE POLAK*
Dr sc. nat.

National Heart Hospital, Westmoreland Street, London, and Cardiothoracic Institute, Beaumont Street, London, and *Pharmaceutical Research Division, Hoffmann-La Roche Ltd, Basle

Summary

The effect of flucytosine on the germination of 3 strains of Candida albicans in serum was tested. No inhibition of germination was observed and it was concluded that germination did not require the synthesis of DNA.

Introduction

Recent studies with Candida albicans have revealed that there are at least 2 fundamentally different modes of action for flucytosine (Arai et al., 1977; Polak and Wain, 1977, 1978; Diasio, Myers and Bennett, 1978). The incorporation of the deaminated metabolite 5-fluorouracil (5-FU) into RNA was investigated by Giege and Weil (1970), and the implications of different malfunctionings in the pathways of uptake and incorporation have been described by Polak and Scholer (1975). Another metabolite of flucytosine, 5-fluorodeoxyuridine monophosphate has been detected by Diasio, Bennett and Myers (1978) and they also demonstrated an inhibition of thymidylate kinase. Arai et al. (1977) ascribed the morphological changes induced by flucytosine to an inhibitor of DNA synthesis and germination during the first few hours after inoculation into serum have therefore been investigated.

Materials and methods

Three strains of C. albicans sensitive to flucytosine (MIC 0.5 mg/l) and selected for their consistent ability to form hyphae in serum were maintained on Sabouraud's malt agar. Overnight cultures, termed early stationary phase cultures, were inoculated into pooled human serum at 37°C. The serum had been filtered through 0.45 μm pore size membrane filter (Millipore) and contained either flucytosine or cytosine to a concentration of 100 μg/ml. The non-budding cells were inoculated to a concentration of 1.5 × 10⁶/ml and cultured at 37°C with shaking. Samples were taken at intervals to measure germination, hyphal elongation rates and DNA, RNA, protein and carbohydrate amounts (Polak and Wain, 1977, 1979). All experiments were repeated at least twice with all 3 strains.

FIG. 1. The germination of Candida albicans in serum in the presence of flucytosine.

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Results

It was very clear from Fig. 1 that flucytosine did not affect the germination of C. albicans in serum. Moreover, the only immediate effect of flucytosine was on the increase in DNA (Fig. 2). Unlike the exponentially growing hyphae used by Polak and Wain (1977, 1978, 1979) there was not a parallel inhibition of RNA increase in the germinating cells. The effect on the RNA was seen several hours later in the growing, germinated hyphae.

Discussion

Although flucytosine is an inhibitor of both RNA and DNA synthesis in exponentially growing cells, it does not influence the germination in serum.

Investigations with synchronous cultures of both yeast and hyphal phases of C. albicans have shown that yeast budding follows the first period of DNA synthesis whereas hyphal germination precedes it (Wain et al., 1976). The slower manifestation of abnormal carbohydrate synthesis produced by flucytosine is unlikely to affect germination, which occurs within the first 2 hr of inoculation into serum. Similarly, although DNA synthesis is more rapidly affected than carbohydrate synthesis, since germination precedes DNA synthesis, any inhibition of DNA synthesis, however rapid, should not affect germination.

Germination is thus seen to be an event which does not require the synthesis of DNA and which can proceed in the presence of an RNA inhibitor. The lack of similarity between RNA and DNA in response to flucytosine during germination lends further support to the idea that the influence of flucytosine on RNA synthesis is also mediated by the action on DNA. The information for germination is immediately available from the existing DNA in response to some factor or factors which induce germination.

Fig. 2. Rate of hyphal elongation and increase in DNA, RNA, protein and carbohydrate content of Candida albicans in the presence of flucytosine (5-FC).

\[\text{Control}; \quad \text{5-FC added at 2 hr}; \quad \text{5-FC added at 0 hr.}\]

References


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W. H. Wain and A. Polak

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