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# Evidence for Mannose-Mediated Adherence of *Candida albicans* to Human Buccal Cells In Vitro†

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Various lectins and sugars were used to study the possible role of saccharide-containing moieties on the surface of *Candida albicans* and human buccal cells in the adherence of this yeast to mucosal surfaces. The lectins possessed affinities for several different sugar moieties and were used to pretreat *C. albicans* or buccal cells before mixing and incubating in the adherence assay. It was found that concanavalin A, a lectin that recognizes mannose and glucose, inhibited adherence of the pretreated yeasts to buccal cells and also inhibited adherence of pretreated buccal cells to nonpretreated yeast cells. Adherence was restored by preincubating the concanavalin A with a mannose derivative, but preincubation of concanavalin A with other sugars did not produce this effect. Lectins that do not recognize mannose had no effect on adherence. The presence of α-D-methyl mannopyranoside in the incubation medium during the assay inhibited adherence, whereas other sugars did not. Germinated yeasts adhered to buccal cells more effectively than nongerminated cells and were more susceptible to adherence inhibition by concanavalin A than were nongerminated yeasts. Thus, mannose-containing moieties on the surface of *C. albicans* and buccal cells could mediate the adherence of this yeast to human epithelium.

The adherence of microorganisms to epithelial cell surfaces is now recognized as an important first step in the colonization and infection of mammalian membranes (7). *Escherichia coli* (18, 20), *Klebsiella pneumoniae* (6), *Pseudomonas aeruginosa* (27), and other gram-negative bacteria attach to epithelial cells by means of pili on their surfaces. A mannose-specific lectin on the pili of *E. coli* (18, 20) and mannose residues on buccal cell surfaces help mediate the adherence of this organism. The lipoteichoic acid on the surface of group A streptococci (1, 19) is believed to be involved in the adherence of these bacteria to epithelial cells presumably by the intercalation of this substance into the lipid bilayer of the host cell membrane.

*Candida albicans* adheres to buccal cells (10–12), vaginal cells (12), and fibrin-platelet matrixes (14) in vitro. The germ tube, an intermediate stage between the blastospore and the filamentous form of the fungus, has been implicated (10, 11, 25) in the adherence process since germinated yeasts adhere in vitro in greater numbers than nongerminated yeasts. *C. albicans* adheres in greater numbers than other species of *Candida* to vaginal cells (12) and to fibrin-platelet matrixes formed in vitro (14).

Little is known about the molecular structure of the surface receptors that mediate the adherence of *C. albicans*. Recently, Lee and King reported the extraction of a soluble, biologically active compound of a mannoprotein nature that was involved in the adherence of *C. albicans* to epithelial cells (J. C. Lee and R. D. King, Abstr. Annu. Meet. Am. Soc. Microbiol. 1981, F1, p. 313). This study identifies the general nature of the surface receptors on *C. albicans* and on human buccal cells involved in in vitro adherence.

## MATERIALS AND METHODS

**Buccal cells.** Buccal cells were collected by gently rubbing the inside cheek area of one of the authors (R.L.S.) with sterile swabs and swirling the swabs in phosphate-buffered saline (PBS), pH 7.2. The cells were washed three times in PBS and then suspended to concentrations of $2 \times 10^5$ cells per ml of PBS.

**Yeasts.** *C. albicans* MSU-1, a clinical isolate, was grown on Sabouraud dextrose agar slants for 48 h at 37°C. A loop of cells was transferred to 100 ml of Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.) plus 4% glucose and incubated at 37°C on a rotary shaker (180 rpm) for approximately 15

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h to develop the stationary phase. A sample was removed, washed three times in PBS, and then resuspended in tissue culture medium M199 (GIBCO Laboratories, Santa Clara, Calif.) adjusted to a pH of 7.2. The suspension was incubated for 1 h at 37°C for the development of germ tubes and resuspended in 0.5% formaldehyde in PBS for 30 min at 4°C to kill the cells. The majority of the yeast cells possessed germ tubes after the treatment. Unless otherwise indicated, all experiments were performed with germinated yeast cells. The yeast cells were killed to prevent further growth of germ tubes during experimentation involving sugars and lectins. After removal of the formaldehyde by washing with PBS the yeasts were resuspended at $10^6$ cells per ml of PBS.

**Adherence test.** Adherence of *C. albicans* was studied by a modification of a previously described adherence test (10). Briefly, 0.2-ml samples of buccal and yeast cells (ratio of yeast to buccal cells, 5:1) were pipetted into tubes (12 by 75 mm) and incubated on a shaker at 180 rpm for 1 h at 37°C. Three tubes were used for each control and for each experimental test followed by repetitions of each experiment. Polycarbonate filters (12-μm pore size; Nuclepore Corp., Pleasanton, Calif.) were used for collection of the adherence mixtures from each tube and washed with 100 ml of PBS under continual agitation. Filters of this pore size allowed the nonadhering yeasts to pass through while retaining those adhering to buccal cells. The filters were stained with Gram crystal violet, and the number of yeasts adhering to 200 buccal cells was determined by light microscopy at ×430. Double-blind conditions were used in all studies.

**Lectin pretreatment of yeasts.** All lectins were used at a concentration of 10 μg/ml of PBS containing added cations (0.002 M magnesium, calcium, and manganese salts). Concanavalin A (ConA) was obtained from ICN Pharmaceuticals, Cleveland, Ohio; phytohemagglutinin was obtained from Wellcome Reagents, Beckenham, England; and the other lectins (soybean agglutinin, wheat germ agglutinin, *Dolichos biflorus* agglutinin, *Ulex europaeus* agglutinin 1, peanut agglutinin, and *Ricinus communis* agglutinin 1) were from a lectin screening kit from Vector Laboratories, Burlingame, Calif. The lectins were supplied in crystallized or salt-free and lyophilized form. Samples (2 ml) of the yeasts were pelleted, suspended in 5 ml of the lectin solution, and incubated for 45 min at room temperature on a shaker. The cells were washed, resuspended in PBS to 2 ml, and mixed with buccal cells for the adherence assay. Although ConA can agglutinate yeast cells, as observed in slide agglutination tests, we never observed yeast agglutination in our system during either cell pretreatment with lectins or the 1-h adherence test. All steps were carried out under conditions of continual agitation. Washing the cells that had been collected on filters was also performed under continuous agitation.

**Saccharide pretreatment of ConA.** Solutions of 2, 4, and 6% α-D-methylmannopyranoside (α-D-mM) (Sigma Chemical Co., St. Louis, Mo.) and 6% solutions of D-galactose, D-ribose, and D-raffinose (Nutrition Biochemicals, Cleveland, Ohio) were prepared by adding the appropriate amounts of carbohydrate to 5 ml of PBS containing added cations and the lectin at 10 μg/ml. The solutions were incubated at 24°C on a shaker at 180 rpm for 2 h, after which 2-ml samples of the standardized yeast suspension were resuspended in each of the sugar solutions and incubated at 24°C on a shaker for 45 min. After washing the yeast cells and resuspending in 2 ml of PBS, buccal cells were added for the adherence assay.

**Saccharide inhibition of adherence.** A 200-mg amount of α-D-mM, D-ribose, D-galactose, D-xylose, *N*-acetyl-D-glucosamine, or α-D-methylglucopyranoside was dissolved in 0.5 ml of PBS and added to tubes that already contained a total of 0.4 ml of the standardized yeast and buccal cell suspensions. The contents of each tube were mixed in a Vortex mixer and were immediately set on a shaker at 180 rpm to proceed with the adherence test as described earlier.

## RESULTS

**Adherence of *C. albicans* to buccal cells.** Every experiment included a control(s) that showed the number of *C. albicans* adhering to buccal cells in nontreated systems. Each table or graph includes these controls. For instance, 440 ± 19 yeast cells adhered to 200 buccal cells in the control shown in Table 2.

**Effect of various lectins on the adherence of treated *C. albicans* to buccal cells.** Preincubation of the yeast cells with various concentrations of ConA before mixing with buccal cells reduced adherence significantly. Since there was no significant difference between the results obtained using different concentrations of ConA, we decided to use 10 μg of ConA per ml in PBS for all of our assays. Seven other lectins were used at this same concentration. Included in this group of lectins were some specific for L-fucose, *N*-acetylgalactosamines, *N*-acetyl-D-glucosamine, and others and not specific for mannose or glucose. None of these lectins produced significant inhibition of adherence when compared to the untreated controls. (Table 1).

**Suppression of the inhibitory effect of ConA on the adherence of pretreated *C. albicans* to buccal cells.** The specificity of the observed inhibitory effect by ConA on pretreated yeasts was examined. A hapten inhibition test was performed in which increasing concentrations of a sugar hapten with affinity for ConA, i.e., α-D-mM (24), were used to pretreat the lectin before pretreatment of the yeast. Figure 1 shows that increasing concentrations of α-D-mM diminished significantly the inhibitory effect of the ConA, prompting the number of adhering yeasts to increase within the range of the control.

Further proof of the specificity of the inhibitory effect of ConA on the yeast cells was acquired by pretreating the lectin with various other sugars for which it is not known to have affinity. The data in Fig. 2 compare the effect of D-ribose, D-galactose, and D-raffinose on the lectin with that of α-D-mM. The only sugar that significantly abolished the inhibitory effect of the ConA was α-D-mM.

TABLE 1. Effect of pretreatment of *C. albicans* with various lectins on adherence to buccal cells

| Treatment | % Adherence[a] | Probability[b] |
|---|---|---|
| Control[c] | 100 | |
| ConA[d] | 18.4 | <0.001 |
| Soybean agglutinin | 92.6 | |
| *U. europaeus* agglutinin 1 | 103.4 | >0.05 |
| *D. biflorus* agglutinin | 112.6 | |
| Wheat germ agglutinin | 98.9 | |
| Peanut agglutinin | 84.8 | |
| *R. communis* agglutinin 1 | 74.5 | |
| Phytohemagglutinin | 92.8 | |

[a] Treated/control × 100.

[b] All probabilities, except the one indicated from ConA, were greater than 5% according to the Student's *t* test as compared with the control. Probabilities reported in subsequent tables, if not otherwise specified, were based on this same test.

[c] For the controls, yeasts were pretreated with PBS; the control value was taken as 100% adherence. A typical control in these experiments represented approximately 150 adhering yeasts per 200 buccal cells.

[d] All lectins were used at 10 μg/ml as described in the text.

**Inhibition of adherence of *C. albicans* to ConA-pretreated buccal cells.** Preincubation of the buccal cells with ConA before mixing with *C. albicans* reduced the number of yeasts adhering to their surfaces significantly (Table 2). When the lectin was incubated with α-D-mM before being used to pretreat the buccal cells, its inhibitory effect on adherence was suppressed and adherence of yeasts increased significantly. Other sugars such as D-ribose, D-raffinose, and D-galactose used to pretreat the ConA did not suppress the inhibitory effect of the lectin.

**Effect of germination on adherence.** The adherence of nongerminated yeasts to buccal cells at concentrations higher than $10^6$ cells per ml used for germinating yeasts was always lower than the adherence of the latter (Table 3). These results suggest the importance of germination in the process of adherence. ConA pretreatment of nongerminated yeasts ($10^6$ cells per ml) before the adherence test produced no significant additional diminution in already markedly low adherence values (data not shown).

**Effect on adherence of incorporation of saccharides into the medium before the adherence assay.** Including α-D-mM in the incubation medium immediately before the assay resulted in a significant inhibition (Table 4) of adherence. Inclusion of another sugar (D-ribose, D-galactose, D-xylose, *N*-acetyl-D-glucosamine, or α-D-methyl glucopyranoside) in the incubation medium at the same concentrations produced a nonsignificant or smaller decrease in adherence than did α-D-mM. The latter two monomeric sugars are found in chitin and glucan, polymers found in the cell wall of *C. albicans*.

## DISCUSSION

*C. albicans* is an opportunistic yeast known to reside in the gastrointestinal and urogenital tracts of many individuals (17). It can remain as a saprophyte or cause mucocutaneous infections (23) like thrush in children or vaginitis in women. In debilitated individuals or in compromised hosts, such as recipients of organ transplants or patients undergoing intensive antibiotic therapy, this organism may spread systemically and even lead to death (23). Miles et al. (17) have suggested that the continuous presence of the organism in the gastrointestinal tract of the host may serve

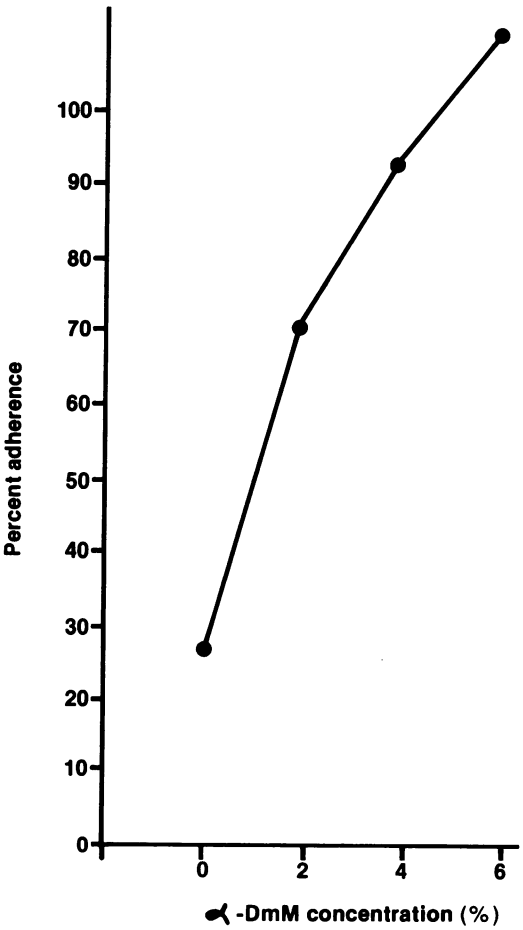


FIG. 1. Effect of incubation of ConA with various concentrations of α-D-mM before pretreatment of *C. albicans*. All groups were treated with either ConA (10 μg/ml) or ConA pretreated with the indicated concentration of α-D-mM. The percent adherence = treated/control × 100; the control is taken to be 100% adherence. Controls had approximately 150 yeasts adhering per 200 buccal cells.

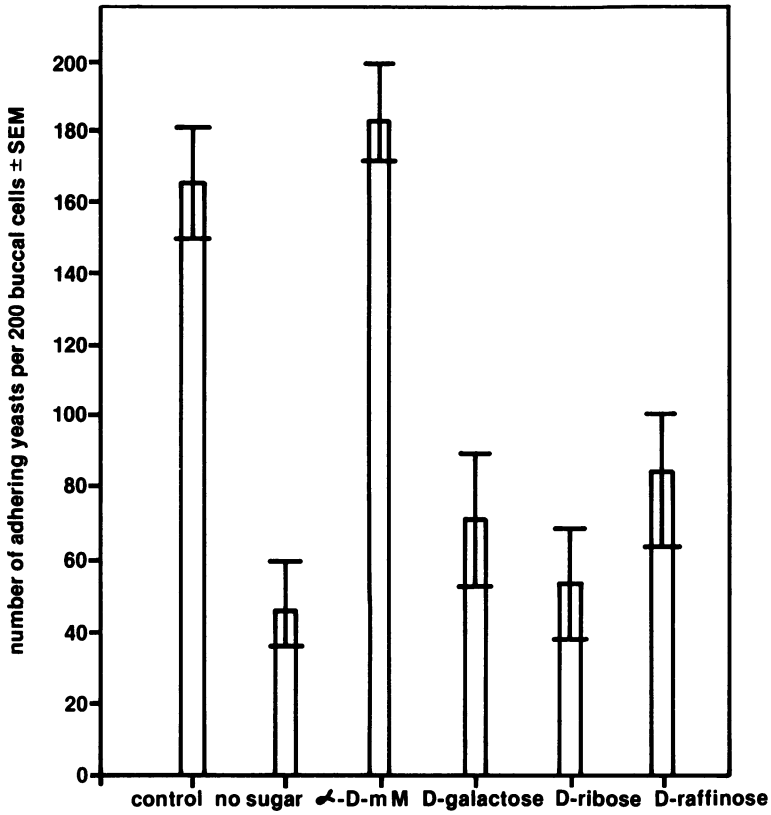


FIG. 2. Effect of various sugars on the ability of ConA to inhibit adherence of *C. albicans* to buccal cells. Control = PBS − treated yeasts. All other groups were treated with either ConA (10 μg/ml) or ConA pretreated with a 6% solution of the indicated sugar. The results are the means of triplicate determinations.

as a reservoir from which this yeast can reinfect the vagina anew in cases of recurrent vaginitis. To persist as part of the gastrointestinal microflora it is likely that this yeast possesses a means of attachment and anchorage to the substrate epithelium. If not, secretions, movement of food products, and defecation might be expected to dislodge the organism from its substratum.

Studies defining the parameters of adherence of *C. albicans* to epithelial cells have been

TABLE 2. Inhibition of adherence of *C. albicans* to ConA-pretreated buccal cells and the effect of sugars on the inhibitory effect of lectin

| Treatment | No. of adhering yeasts per 200 buccal cells + SEM | % Adherence | Probability[a] |
|---|---|---|---|
| None (control)[b] | 440 ± 19 | 100 | |
| ConA[c] | 77 ± 10 | 17.5 | <0.001 |
| ConA pretreated with: | | | |
| α-D-mM[d] | 293 ± 29 | 66.6 | <0.01 |
| D-Galactose | 81 ± 22 | 18.3 | >0.8 |
| D-Ribose | 49 ± 8 | 11.1 | >0.05 |
| D-Raffinose | 79 ± 22 | 17.9 | >0.9 |

[a] The first probability is that between the control and the ConA-pretreated cells; all others are between the ConA-treated cells and those pretreated with the lectin that had undergone pretreatment with the individual sugars.

[b] PBS-treated buccal cells.

[c] ConA (100 μg/ml) with added cations.

[d] Solutions (20%) of the sugars were prepared by adding the appropriate amounts of sugar to 5 ml of PBS containing added cations and ConA dissolved at 100 μg/ml of PBS. All other procedures are identical to those used in the saccharide pretreatment of the ConA used to pretreat yeasts as described in the text.

TABLE 3. Adherence of germinated and nongerminated yeast cells to buccal cells

| *C. albicans* cells/ml | % Adherence | Probability[a] |
|---|---|---|
| Germinated[b] | | |
| $10^6$ | 100 | |
| Nongerminated[c] | | |
| $10^6$ | 1.9 | <0.001 |
| $10^7$ | 3.4 | <0.001 |
| $10^8$ | 63.6 | <0.001 |
| $10^9$ | 91.3 | >0.2 |

[a] As compared with germinated yeasts.
[b] Control. Cells were germinated in M199 medium as described. Samples of the yeast suspensions were mixed with buccal cells, and the standard adherence test with $2 \times 10^5$ buccal cells per ml was performed.
[c] Cells remained in PBS during the development of germ tubes in M199.

published in recent years. There appears to be a direct relationship between those species of *Candida* that adhere to epithelial cells or fibrin platelet matrixes in vitro (12, 14) and those that are known to colonize host tissues or cause disease. *C. albicans* ranks first in both phenomena; thus, this species was used for our studies. The form of this dimorphic organism used here, the yeast with germ tube, is an intermediate stage between the blastospore and the filamentous form. Numerous reasons prompted this decision. Our experiments with the germinated stage demonstrated significantly greater adherence to buccal cells than those conducted with the blastospore stage, a fact previously reported in the literature (10, 11). Aside from this, germ tubes can be produced in vitro from blastospores in relatively short periods of time, which validates our utilization of this form even though the blastospore has been reported to be an important stage in the colonization of the host (26). Finally, the fact that mycelial elements are usually found in infected tissue further supports our use of this form for experimentation. Buccal cells are ideal due to their ease of collection and because they are a natural mucocutaneous substrate, as in thrush. Histologically, they are similar to vaginal cells that serve as the substrate for vaginitis infections.

The experiments with ConA reported here indicate that pretreatment of *C. albicans* with this lectin inhibits adherence of the yeast to human buccal cells by binding to mannose-containing moieties on the yeast surface. This process is specific and could occur because these moieties are saturated by the ConA and thus are made less available for binding. Previous studies on the structure of the cell wall of *C. albicans* and on the carbohydrate-binding properties of ConA further support this conclusion. Cassone et al. (3) found that the outer wall portion of this yeast is a capsule-like component with spiky protrusions consisting essentially of mannan. Extraction of the yeast mannan by acid or alkali resulted in loss of yeast agglutinability by ConA. These studies on the wall of *C. albicans* also minimize the possibility that ConA inhibits yeast adherence by binding to glucan or to glucan-protein complexes on the cell wall since the glucan was only found in the inner layers of the cell wall forming part of a rigid and alkali-insoluble glucan-chitin matrix. Furthermore, for a polysaccharide to be bound by ConA it must be ramified and contain terminal, nonreducing α-D-mannopyranosyl or α-D-glucopyranosyl units (8, 9). Of the three main polysaccharides found in the cell wall of *C. albicans* (α-mannan, chitin, and β-glycan) only the mannan is α-linked (2). None of the other lectins used in our study to pretreat yeast cells had predilection for mannose residues. Consequently, none resulted in significant inhibition of adherence, including those with an affinity for *N*-acetyl-D-glucosamine, the monomeric sugar that forms the polymer chitin that is part of the inner cell wall portion of *C. albicans*.

Recent findings by Maisch and Calderone (15) also point to the involvement of α-mannan in the adherence of *C. albicans* to fibrin-platelet matrixes formed in vitro. An alkali-soluble cell wall extract of *C. albicans*, when conjugated to sheep erythrocytes, caused these cells to adhere to clots formed in vitro in greater numbers than nonconjugated sheep erythrocytes. The effect could be abolished by pretreating the alkali extract with α-mannosidiase or acetolysis before conjugation to sheep erythrocytes. McCourtie and Douglas (16) have found that *C. albicans*

TABLE 4. Effect of incorporation of saccharides in the medium on adherence of *C. albicans* to buccal cells

| Treatment | % Adherence | Probability[a] |
|---|---|---|
| Control[b] | 100 | |
| α-D-mM | 47 | <0.01 |
| *N*-Acetyl-D-glucosamine | 88 | |
| D-Ribose | 79 | |
| α-D-Methylglucopyranoside | 100 | >0.05 |
| D-Galactose | 82 | |
| D-Xylose | 85 | |

[a] The first probability is that of the system containing α-D-methylmannoside as compared with the control. The >0.05 represents the probability of occurrence of any of the other systems as compared to the control.
[b] PBS was added instead of sugar solution. Controls in these experiments represent approximately 250 adhering yeasts per 200 buccal cells.

also adheres to acrylic, found in dentures, and that growth of *C. albicans* in media that contain high amounts of individual sugars as the sole carbon source resulted in increased adherence.

We have observed that ConA inhibits adherence of germinated *C. albicans* to buccal cells to a greater extent that it does nongerminated yeasts. The chemical entity on the yeast cell responsible for adherence may be concentrated on the germ tube surface since it is the lack of a germ tube that distinguishes a nongerminated yeast from a germinated one. Previous studies have identified antigens present on the germ tube surface that are not found on the yeast forms (5).

We have inhibited adherence significantly by adding α-D-mM, a mannose derivative, to the adherence medium during the incubation to act as a competitor for the binding sites on the cell surfaces. This inhibition could not be reproduced using other sugars like D-galactose, D-xylose, D-ribose, *N*-acetyl-D-glucosamine, or α-D-methylglucopyranoside. It is interesting to mention that the recent work by Lee and King (Abstr. Annu. Meet. Am. Soc. Microbiol. 1981, F1, p. 313) also points to the involvement of a mannose-containing compound, a mannoprotein, on the cell wall of *C. albicans* in the adherence of this organism to epithelial cells. Our results are in partial disagreement with those of Sobel et al. (25), who found that pretreating *C. albicans* with L- or D-fucose, but not with mannose, mannoside, or galactose, inhibited adherence.

Observations concerning the receptor sites for *C. albicans* on the epithelial cell surfaces show that there is a great variation in the number of these receptors from person to person (12, 25) and from day to day in the same person (12). We have also found great variations in the number of yeasts adhering per buccal cell from swabbings of the mouth done for each single experiment, a fact also observed with streptococci (1). We found that a majority of the cells had little or no *C. albicans* attached to their surfaces (data not shown), whereas a minority of them had greater numbers of attached yeasts, which was responsible for the elevation in adherence. The discrete number of receptor sites for *C. albicans* on epithelial cells has also been studied by saturating those cell surfaces with lactobacilli (25) and streptococci (13) and finding that adherence of *C. Albicans* is inhibited.

We hypothesize that ConA inhibition of adherence of pretreated yeasts to nonpretreated buccal cells may occur as a result of binding to and blocking mannose-containing receptors on the yeast surface or mannose moieties of an indigenous lectin associated with the yeast cell surface (or both). Our model is a reasonable one if we consider that there is recent evidence for the involvement of surface mannoproteins in adherence of *C. albicans* to epithelial cells and that in most, if not all, microbial systems the lectin is found on the surface of the microorganism (6, 18, 20).

Additionally, mannose-containing moieties on the buccal cell surface could be acting as receptors for the *C. albicans*. Pretreatment of the buccal cells with ConA inhibited the adherence of nontreated *C. albicans*, an effect that was specific and a possible consequence of the blockage of receptors. Previous studies with this lectin have shown that mannose-containing compounds are widely distributed on the membranes of mammalian cells (24). Similar models have been proposed to explain the adherence of other microorganisms. A lectin on the pili of *E. coli* has affinity for the mannose residues on the surface of buccal cells (18, 20). Identical residues of 2-deoxyglucose on the surface of root hair cells of the white clover plant and on the surface of *Rhizobium trifolii* function as cross-reactive antigens to a lectin that recognizes and binds each of them, joining together both cell types (4).

Novel mechanisms of adherence of cells to surfaces have been proposed (21, 22). We are presently extracting the cell wall components of *C. albicans* and doing experiments with the extracted cells. A procedure which extracts preferentially the α-mannan from the cell wall of *C. albicans* renders the cells unable to adhere to buccal cells (unpublished data).

The knowledge that we have gained by the use of ConA and other lectins and sugars is a contribution to the field of fungal adherence. Understanding the mechanism of adherence of *C. albicans* to human mucosal surfaces might permit us to prevent the process and prevent subsequent infections, thus shedding light on fungal pathogenesis.

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