

Bacterial Adhesion: Modulation by Antibiotics with Primary Targets Other Than Protein Synthesis

DIETER M. SCHIFFERLI^{1,2*} AND EDWIN H. BEACHEY^{1,2,3}

Departments of Microbiology and Immunology¹ and Medicine,³ University of Tennessee Center for the Health Sciences, and Veterans Administration Medical Center,^{2*} Memphis, Tennessee 38104

INTRODUCTION

Antibiotics are best known for inhibiting bacterial multiplication and survival. Under certain circumstances, these agents may also interfere with microbial attachment to freely circulating macromolecules or cells of mammalian hosts. We have reviewed data in the literature on the action of protein synthesis inhibitors on bacterial adhesion (50). In this article, we refer to studies describing the antiadhesive effects of inhibitors of the synthesis of folate coenzymes, nucleic acids, and peptidoglycan, as well as of antibiotics which disorganize bacterial membrane structures.

MODULATION OF ADHESION BY ANTIMICROBIAL AGENTS THAT PERTURB THE FOLATE PATHWAY

By inhibiting dihydropteroate synthetase and dihydrofolate reductase, sulfonamides and trimethoprim inhibit the synthesis of folate coenzymes and thereby affect the central pathway of the metabolism of C₁ compounds (25). The sub-MIC of trimethoprim was shown to reduce the fimbriation, hemagglutination, and epithelial cell adhesion of several *Escherichia coli* strains (49, 55, 61) through the inhibition of fimbrial subunit synthesis (49). Trimethoprim, which is known to regulate RNA synthesis in *E. coli* (53), may act similarly on bacterial regulatory mechanisms at low doses, giving priority to the synthesis of proteins that are indispensable for growth and division. It is therefore plausible that other components of the bacterial surface are affected by trimethoprim. The altered membrane structure of *E. coli* probably reflects the pleiotropic effects of sub-MICs of trimethoprim (53, 61). Sulfonamides had similar effects on hemagglutination and epithelial cell adhesion (49, 55, 61). Sulfamethoxazole and trimethoprim used together acted synergistically on type 1 fimbrial subunit synthesis (49). How sulfamethoxazole alone affected hemagglutination but not fimbriation and fimbrial subunit synthesis remains unclear (49). It is possible that this drug is more effective in inhibiting the synthesis of the adhesin, a minor protein of type 1 fimbriae, than that of the major structural subunit (29, 32, 33).

MODULATION OF ADHESION BY ANTIBIOTICS THAT PERTURB NUCLEIC ACID SYNTHESIS

Rifampin binds to and inhibits DNA-dependent RNA polymerase (19). Hirashima et al. observed that rifampin was more inhibitory to the overall synthesis of cytoplasmic proteins of *E. coli* than to that of envelope proteins and suggested that mRNAs for envelope proteins were more stable than were those for cytoplasmic proteins (26). No study as yet has indicated an effect of this antibiotic on fimbria-mediated hemagglutination or adhesion of *E. coli*

(13, 17), but the rapid appearance of resistant mutants may have hampered such studies (13). Sub-MICs of rifampin did, however, reduce the surface hydrophobicity and adhesion of *Streptococcus pyogenes* to pharyngeal cells (60). The experimental protocol used in the latter study maximized the antibiotic effect through the addition of the drug during the early log phase of growth and may have been responsible for the observed massive increase in negative charges at the bacterial surface (60). The effect on surface hydrophobicity was probably responsible for the decreased adhesion of *S. pyogenes*. A similar effect was observed with penicillin (see below), which interferes specifically with bacterial cell wall synthesis.

In *E. coli*, quinolones like nalidixic acid inhibit DNA synthesis by acting primarily on the two alpha subunits of topoisomerase II and preventing the resealing of double-stranded DNA (52). The rapid emergence of resistant strains hampered the evaluation of these drugs in one study (13). Curiously, however, nalidixic acid was reported to enhance the hemagglutination and adhesion of various strains of *E. coli* in another study (63). More recently, sub-MICs of pefloxacin, a new quinolone, were shown to inhibit the adhesion of *E. coli* and *Staphylococcus aureus* to epithelial cells (10). The mechanisms, however, remain to be elucidated.

MODULATION OF ADHESION BY ANTIBIOTICS THAT PERTURB PEPTIDOGLYCAN SYNTHESIS

β -Lactam antibiotics are targeted against enzymes involved in peptidoglycan metabolism. These enzymes, which are probably anchored to the cytoplasmic membrane, projecting their active site to the outside, are inactivated by the formation of covalent linkages with β -lactam antibiotics (43, 58). β -Lactam antibiotics reach the periplasmic space in seconds by traversing through porins of the outer membranes of gram-negative bacteria (7, 43). Each β -lactam antibiotic displays a specific affinity for the various penicillin-binding proteins. In *E. coli*, β -lactam antibiotics having a high affinity for a particular penicillin-binding protein cause that protein to resemble mutants of the same protein (58). Ofek et al. observed that a carboxypeptidase-defective mutant strain of *E. coli* formed nonseptate filaments when grown at 39°C and that both fimbrial expression and the adhesive properties of this strain were lost at the restrictive temperature (37). These authors obtained the same phenotype by growing the strain with a sub-MIC of penicillin at 37°C, suggesting a link between the functional inactivation of the carboxypeptidase and the absence of fimbriae on the bacterial surface. It remains unclear, however, whether the formation of nonseptate filaments (34) was directly coupled to inhibition of the processing, export, or assembly of fimbrial subunits. Studying 15 adhesive strains of *E. coli* isolated from the urine of patients with acute pyelonephritis, Sandbert et al. showed that all strains became less adhesive

* Corresponding author.

to urinary tract epithelial cells when grown for 4 h in one-fourth the MIC of ampicillin (46). These authors observed consistent bacterial elongation after ampicillin treatment and a preferential adhesion of nonelongated bacteria to epithelial cells, supporting a possible connection between peptidoglycan processing and active fimbrial expression.

In a clinical trial, low doses of ampicillin (10 mg/day for 3 days) cured 16 of 20 patients with acute urinary tract infections, whereas 18 control patients were still bacteriuric and pyuric after 4 days (5). The concentrations of ampicillin in the urine specimens of the treated patients corresponded to one-fifth to one-half the MIC for the isolated *E. coli* strain (5). Although inhibition of bacterial adhesion was invoked in this study, the exact mechanism was not elucidated.

Recent studies dealing with the binding properties of type 1 fimbriae provided strong evidence for a hydrophobic domain near the mannose-binding site (14, 15). This hydrophobic domain played a role in the mechanism of attachment of type 1-fimbriated *E. coli* to epithelial cells but not to erythrocytes (14). It was not surprising, therefore, that Klein et al. failed to find a correlation between the surface hydrophobicity and hemagglutinating activities of various strains of *E. coli* grown with 11 different inhibitors of peptidoglycan synthesis (28). Only vancomycin and fosfomycin, which interfere with peptidoglycan synthesis at earlier steps than do β -lactams, were reported to diminish consistently the hemagglutination and fimbrial expression of the seven strains tested (28).

In an elegant study with *Neisseria gonorrhoeae* and *Neisseria meningitidis*, Stephens et al. demonstrated that a penicillin-induced reduction in bacterial fimbriation paralleled a decrease in bacterial adhesion to epithelial cells (56). Because fimbrial subunit synthesis was unaffected by penicillin, as attested by sodium dodecyl sulfate-polyacrylamide gel electrophoresis of outer membranes, these authors proposed that penicillin disorganized the membrane-bound machinery responsible for fimbrial assembly and anchorage.

The adhesion of four mucoid and two nonmucoid strains of *Pseudomonas aeruginosa* to tracheobronchial mucin was inhibited by sub-MICs of ceftazidime; three nonmucoid strains remained unaffected. This effect correlated with reduced amounts of exopolysaccharides on the bacterial surfaces after growth with the antibiotic (62). Similarly, the adhesion of several slime-producing coagulase-negative staphylococci to plastic tissue culture plates was inhibited by β -lactam antibiotics (47). In this case, bacterial adhesion and surface hydrophobicity were both diminished.

Lipoteichoic acid (LTA) of gram-positive organisms plays a central role in inhibiting bacterial autolysis (8, 21) and in promoting the binding of streptococci to epithelial cells and fibronectin (2, 4, 9, 51). Exposure of certain streptococci and *S. aureus* to β -lactam antibiotics caused the release of LTA into the medium (1, 27, 35). Moreover, the penicillin-induced LTA release from stationary-phase cultures of *S. pyogenes* was paralleled by a reduction in the number of bacteria attaching to oral epithelial cells (1). The decrease in the surface hydrophobicity of penicillin-treated streptococci observed by Tylewska et al. most probably was due to LTA release (60). This interpretation is consistent with the proposed model of hydrophobic interactions of the lipid ends of LTA with host proteins and receptors (38). An example of such interactions is the complexing of fibronectin with cell surface LTA on intact *S. pyogenes* cells. Fibronectin-coated *S. pyogenes* cells released fibronectin-LTA complexes upon penicillin treatment, whereas fibronectin-coated *S. aureus* cells released LTA without fibronectin (3, 35). These results

not only confirm the major role of LTA as a group A streptococcal adhesin but also suggest that LTA does not function as an important receptor for fibronectin on *S. aureus* cells. A protein or a carbohydrate appears to bind fibronectin on the surfaces of these cells (16, 41, 42).

Scheld et al. studied the attachment of *Streptococcus sanguis* and *Streptococcus (Enterococcus) faecalis* to a fibrin-platelet matrix and showed that adhesion was reduced when the organisms were grown in the presence of one-fourth the MIC of penicillin or vancomycin (48). Although LTA was released in both species after such treatments (27, 59) and pretreatment of platelet-fibrin surfaces with LTA reduced the adhesion of *S. sanguis* (31), the role of surface components other than LTA in the adhesive processes of these organisms remains to be clarified.

Results of antibiotic treatment of experimental endocarditis in rats and rabbits have provided supportive evidence for an vivo effect of peptidoglycan inhibitors on bacterial adhesion (12). For example, *S. sanguis* exposed to sub-MICs of vancomycin lost not only its adhesive ability in an in vitro model but also the ability to induce endocarditis of traumatized aortic valves in rabbits (48). A vancomycin-tolerant strain of *S. sanguis* colonized traumatized aortic valves significantly less frequently in rats when the organisms were preincubated with vancomycin before injection (6). Control rabbits injected with untreated *S. sanguis* had a similar magnitude of bacteremia, indicating that reduced colonization of vegetations was not due to increased blood clearance of bacteria (6). Moreover, neutropenia did not abolish the vancomycin effect (6). Similar results were obtained with amoxicillin (22) and penicillin (18, 31).

MODULATION OF ADHESION BY ANTIBIOTICS THAT DISORGANIZE MEMBRANE STRUCTURES

Some antibiotics, including aminoglycosides, used at high concentrations may affect the physicochemical integrity of bacterial membranes. Polymyxins act primarily on bacterial membranes of gram-negative organisms. These polycationic antibiotics permeabilize the outer membrane by binding to lipopolysaccharide and displacing divalent cations, thereby perturbing the normal bacterial surface architecture (24, 36). K88- and K99-fimbriated *E. coli* grown to the stationary phase in drug-free medium and then incubated with erythrocytes in the presence of high concentrations of polymyxins had reduced hemagglutinating activity (54). Polymyxin B induces the release of blebs from the outer membranes of gram-negative bacteria (24). It is possible that fimbriated blebs compete with bacteria for receptors on erythrocytes.

CONCLUSIONS

Recent progress in the understanding of bacterial adhesion mechanisms at the molecular level permits unresolved questions concerning antibiotic modulation of adhesion to be readdressed. The specificity of the attachment process is defined by unique molecules on the bacterial surface and their complementary receptors in host tissues. Antibiotics modulate these surface structures in a variety of ways such that the models used are of importance and the results obtained must be interpreted with caution. Some of the variable effects observed by different investigators using the same models (Table 1) may be due to differences in experimental design such as the following: for bacteria, adhesin type and bacterial strain and species (surface hydrophobicity and autoagglutination), growth conditions, and growth

TABLE 1. Effects of antimicrobial agents on bacterial adhesion^a

Antibiotic and organism	Epithelial cell adhesion	Other effects	Reference(s)
Trimethoprim and sulfonamides			
<i>Escherichia coli</i>	-, ±	-, ± (HA)	23, 49, 55, 61, 63
<i>Proteus vulgaris</i>		-, ± (HA)	23
<i>Haemophilus influenzae</i>	-		20
<i>Streptococcus faecalis</i>		+ (FPM)	48
<i>Streptococcus sanguis</i>		+ (FPM)	48
Rifampin			
<i>Escherichia coli</i>	±	± (HA)	13, 17
<i>Haemophilus influenzae</i>	±		20
<i>Streptococcus pyogenes</i>	-	-(H)	60
Quinolones			
<i>Escherichia coli</i>	+, -	+, ± (HA)	10, 23, 63
<i>Staphylococcus aureus</i>	-		10
β-Lactams			
<i>Escherichia coli</i>	-	-, +, ± (HA)	17, 23, 28, 37, 44, 46, 54
Other <i>Enterobacteriaceae</i>	-, ±	± (HA)	23, 57
<i>Haemophilus influenzae</i>	-		20
<i>Neisseria</i> spp.	-	-(HA)	45, 56
<i>Pseudomonas aeruginosa</i>	-	-, ± (M)	39, 62
Odontopathic bacteria		-, +, ± (SHA, HA)	40
<i>Staphylococcus aureus</i>		+, ± (F)	3, 11, 35, 42
<i>Staphylococcus epidermidis</i>		-(TCP, H)	47
<i>Streptococcus pyogenes</i>	-, ±	-(F, H)	1, 3, 35, 60
<i>Streptococcus faecalis</i>		-(FPM)	48
<i>Streptococcus sanguis</i>		-(FPM)	31, 48
Vancomycin and fosfomycin			
<i>Escherichia coli</i>		-(HA)	28
<i>Neisseria meningitidis</i>		-(HA)	45
Odontopathic bacteria		-, +, ± (SHA, HA)	40
<i>Streptococcus faecalis</i>		-(FPM)	48
<i>Streptococcus sanguis</i>		-(FPM)	48
Polymyxins and <i>Escherichia coli</i>			
		-, ± (HA)	17, 54

^a -, Inhibited; +, enhanced; ±, no significant effect. HA, hemagglutination; SHA, saliva-treated hydroxyapatite; F, fibronectin binding; M, mucin binding; FPM, fibrin-platelet matrix binding; TCP, tissue culture plate binding; H, hydrophobicity.

phase; for receptors, degree of purification and stability, isolated or aggregated molecules and whole cells (monovalency or multivalency), animal species and cell type, and animal and cell ages; for antibiotics, physicochemical and biological properties, concentration and duration of application, and time of application (during bacterial growth [sub-MIC], after bacterial growth and during the adhesion assay, or after the adhesion assay); for the adhesion assay, buffers, time, and temperature conditions, separation procedure for bound and unbound bacteria (receptor fixation, filtration or centrifugation, and washing stringency), and evaluation method (bacterial counting, agglutination titer, and use of radioactive or enzymatic labels). Detailed characterization of the binding of host receptors to bacterial ligands should help to define which adhesive mechanism is acting in which model. For example, which molecule(s) and which cell are relevant for a particular strain of bacteria under study? Are the receptors loosely adherent macromolecules on cell surfaces? Do they belong to the membrane structure of juvenile, middle-aged, or desquamating epithelial cells? Are they found in the intercellular matrix or in the blood compartment? Idiosyncrasy is a trait not only of receptors but also of ligands and ligand inhibitors, which may appear on the bacterial surface and disappear at different times during growth. Therefore, future studies on antibiotic effects on

bacterial adhesion will need to address the dynamic properties of the host and bacterial surfaces. In general, antibiotics inhibit the adhesive properties of bacteria (Table 1). In certain cases, however, they may actually enhance adhesion (Table 1). The latter phenomenon needs more attention in future studies. Several experimental animal models were used to demonstrate the effects of antibiotics on adhesion in vivo (6, 12, 18, 22, 31, 48). Some clinical data suggest bacterial elimination and clinical cure after the application of antibiotics at sub-MICs (5, 30). Although these results are quite promising, for the time being, the accumulated results on the effect of antibiotics on bacterial adhesion remain insufficient to generate therapeutic recommendations.

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