Bacterial exopolysaccharides provide protection against phagocytosis, opsonization, and dehydration and act as a major structural component of the extracellular matrix in biofilms. They contribute to biofilm-related resistance by acting as a diffusion barrier to positively charged antimicrobial agents including cationic antimicrobial peptides (CAPs). We previously created novel CAPs consisting of a nonamphipathic hydrophobic core flanked by Lys residues and containing a Trp residue in the hydrophobic segment as a fluorescent probe. Peptides of this type above a specific hydrophobicity threshold insert spontaneously into membranes and have antimicrobial activity against Gram-positive and Gram-negative bacteria at micromolar concentrations. Here we show that alginate, a polymer of β-D-mannurionate and α-L-gulurionate secreted by the cystic fibrosis pathogen Pseudomonas aeruginosa, induces an α-helical conformation detected by circular dichroism spectroscopy and blue shifts in Trp fluorescence maxima in peptides above the hydrophobicity threshold, changes typically observed upon association of such peptides with nonpolar (membrane) environments. Parallel effects were observed in the archetypical CAPs magainin II amide and cecropin P1. Fluorescence resonance energy transfer studies indicated that alginate induces peptide-peptide association only in peptides above the hydrophobicity threshold, suggesting that the hydrophilic alginate polymer behaves as an “auxiliary membrane” for the bacteria, demonstrating a unique protective role for biofilm matrices against CAPs.

Pseudomonas aeruginosa is the predominant respiratory tract pathogen in cystic fibrosis (CF) patients, where chronic infection is due to the bacteria growing as a mucoid biofilm, a state characterized by overproduction of alginate (1–3). Alginate is a secreted extracellular polysaccharide composed of the uronic acid β-D-mannurionate and its C-5 epimer α-L-gulurionate (4), which is partially O-acetylated at the second and/or third position(s) of the D-mannuronate residues. The chronicity of P. aeruginosa infections in CF; its high level intrinsic antimicrobial resistance, a result of the low permeability of its outer membrane to antibiotics and multidrug efflux systems; and its propensity to develop resistance during prolonged antimicrobial therapy have all presented major therapeutic challenges to CF caregivers.

Our laboratory has developed a new category of cationic antimicrobial peptides that display antibacterial activity (5). The peptides consist of a nonamphipathic hydrophobic core sequence (11–19 residues) flanked at one or both termini by a number of Lys or Arg residues. These peptides, which were originally designed as transmembrane mimetic model peptides (6, 7), have the prototypic sequence KKAAAAXAX-AAXAXAXXKX- NH₃ with several key features: (i) Ala is the preferred background residue because of its mid-range hydrophobicity and frequent occurrence in membrane protein transmembrane domains; (ii) a Trp residue is inserted into the hydrophobic segment as a fluorescent probe; and (iii) N- and C-terminal hydrophilic Lys residues act to solubilize the otherwise hydrophobic peptides in aqueous media to facilitate purification and characterization. These peptides have been shown to spontaneously insert into membranes when the average hydrophobicity of their core segment is above an experimentally determined “threshold” value based on the Liu-Deber hydrophobicity scale (see Table I), approximately above where Xaa = Ala (7). We have previously shown that peptides in this general category containing sequences above the hydrophobicity threshold have antimicrobial activity against both planktonic Gram-positive and Gram-negative bacteria at μg/ml concentrations (5).

However, many antimicrobial compounds become considerably less effective against bacteria in biofilms. More specifically, alginate has been shown to act as a penetration barrier to conventional positively charged antibiotics through binding based on electrostatic interactions with the anionic sugars (8, 9). However, the peptide-alginate interaction per se has not been widely studied. In this study, we investigated the effects of alginate on the structure of the 25-residue transmembrane mimic peptides. This set of model peptides allows us to vary the “guest” residue Xaa to any of the 20 commonly occurring amino acids individually and correlate the effects observed with the properties of the specific amino acid. By investigating the primary mode of interaction of these model peptides and the alginate polymers within biofilms, we can increase our understanding of the mechanism by which alginate may “trap” cationic antibiotics and ultimately progress toward optimizing the antimicrobial activity of this cationic antimicrobial peptide family against the P. aeruginosa biofilms in CF patients.

EXPERIMENTAL PROCEDURES

Peptide Synthesis—The reagents for peptide synthesis, cleavage, and purification were Fmoc-protected amino acids (Novabiochem), Fmoc, 9-(fluorenylmethoxycarbonyl), HPLC, high pressure liquid chromatography; TAMRA, carboxytetramethylrhodamine.

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Purified peptides were characterized by analytical HPLC and mass spectrometry. Concentrations of peptides were determined in triplicate by a spectropolarimeter using a 1-mm path-length quartz cell at 25 °C. Peptide interactions with alginate were performed as previously described (11). 5-Dimethylaminonaphthalene-1-sulfonyl chloride (dabsyl chloride), and 5-(and-6)-carboxytetramethylrhodamine (TAMRA) were obtained from Molecular Probes.

**RESULTS**

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**Fluorophore Labeling**—Fluorophore labeling of peptides was performed as previously described (11). 5-Dimethylaminonaphthalene-1-sulfonyl chloride (dabsyl chloride), 4-dimethylaminoazobenzene-4'-sulfonyl chloride (dabsyl chloride), and 5-(and-6)-carboxytetramethylrhodamine (5/6-TAMRA), succinimidyl ester mixed isomers were obtained from Molecular Probes.

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**Fluorescence Resonance Energy Transfer (FRET) Measurements**—Separate populations of peptides were labeled with dabsyl chloride as the donor chromophore and dabsyl chloride as the acceptor chromophore to observe association. The samples were prepared with 3 μM donor chromophore-labeled peptide solutions (20 mM Tris-HCl, pH 7.0) with or without the addition of variable concentrations of dabsyl chloride-labeled peptide in the presence of 0.02 mg/ml alginate. Excitation wavelength was 341 nm. Emission spectra of the donor chromophore and dabsyl chloride-labeled peptide were recorded from 450 to 600 nm at 25 °C with Tris-HCl. The spectra were recorded from 300 to 400 nm.

**Penetration of Peptides into Alginate Beads**—Alginate beads (0.5 mm in diameter) were made by the “dripping method” (12). Where droplets (1 μl) of a 1 mg/ml solution of alginate were added to a solution containing 1 M CaCl₂. Following dialysis performed to remove excess CaCl₂, 20 μl of 0.50 mM of TAMRA-labeled peptides were allowed to incubate with the alginate beads for 10 min. Unbound peptides were removed by washing with H₂O. Examination of the interaction of TAMRA-labeled peptides with alginate beads was performed using a LSM 510 confocal laser scanning microscope (Zeiss). The images were recorded with an excitation wavelength of 543 nm and an emission wavelength of 635 nm for TAMRA-labeled peptides at the mid-cross-section of the beads using the LSM 510 positioning software.

**Alginate Induces Helical Conformations in Peptides above the Hydrophobicity Threshold**—In aqueous solution, the peptide with the guest residue Xaa = Phe displayed a partially helical CD spectrum (Fig. 1a) consistent with residue preferences on the Chou-Fasman (Pα) scale (7, 13). However, upon the addition of alginate, the peptide adopted an essentially fully α-helical conformation. Peptide interactions with alginate were seen to vary with peptide/alginate ratios, with CD spectra displaying a nonmonotonic progression of curves before progressing toward final helical patterns. Similar to the Xaa = Phe peptide (Fig. 1a), we found that peptides above the hydrophobicity threshold of the Liu-Deber scale (7) (Xaa = Trp, Leu, Ile, Met, Val, Tyr, and Ala) demonstrated similar properties, i.e. alginate induced α-helical formation in each of these peptides (spectra not shown). In contrast, although the spectra of peptides below the threshold similarly display nonmonotonic progression of CD curves, the final spectra at highest alginate/peptide ratios showed little or no net conformational change; as an example, the model peptide with guest residue Xaa = Pro is shown in Fig. 1b. As well, some peptides with guest residues having polar and/or charged side chains (such as Xaa = Arg, Asp, Glu, Lys, and His) similarly displayed a variable pattern (shown for Xaa = Glu in Fig. 1c), where alginate induced intermediate conformational changes other than helical induction but little net conformational alteration. The observation that only peptides above the hydrophobicity threshold undergo
Table I
Core segment hydrophobicity of transmembrane mimic peptides and alginate-induced changes in tryptophan fluorescence emission maxima ($\Delta \lambda_{\text{max}}$)

| Peptide Xaa residue | Core segment hydrophobicity $^a$ | Alginate-induced blue shift ($\Delta \lambda_{\text{max}}$) $^b$ |
|---------------------|---------------------------------|--------------------------------------------------|
| Phe                 | 1.12                            | 10                                               |
| Trp                 | 1.11                            | 7                                                |
| Leu                 | 1.09                            | 12                                               |
| Ile                 | 1.05                            | 11                                               |
| Met                 | 0.86                            | 8                                                |
| Val                 | 0.83                            | 3                                                |
| Cys                 | 0.75                            | 9                                                |
| Tyr                 | 0.68                            | 9                                                |
| Ala                 | 0.42                            | 5                                                |
| Ser, Gly, Asp, Gln, Arg, Pro, and Lys | 0.21 to –0.37 | All = 0 |

$^a$ Peptides have sequence $\text{KK}X\text{AAK}X\text{AAA}XX\text{AA}X\text{A}X\text{A}X\text{AK}X\text{AAK}X\text{NN}$$\text{H}_{3}$, where each contains three copies of a given Xaa residue. $X$ indicates each of the 20 commonly occurring amino acids.

$^b$ Average hydrophobicity of the core 19-residue segment based on Xaa residue relative hydrophobicity values on the Liu-Deber hydrophobicity scale (5). Peptides with average core hydrophobicity above 0.42 ($X = \text{Ala}$) are above the “threshold hydrophobicity” for membrane insertion (18).

The blue shift is the shift in Trp emission maximum in a given peptide upon addition of alginate, given in nanometers as $\Delta \lambda_{\text{max}} = \lambda_{\text{max}}(\text{aqueous}) - \lambda_{\text{max}}(\text{alginate})$.

Table I lists the blue shift values of the peptides in a buffered alginate solution. Blue shifts of 3–10 nm were observed for all peptides above the hydrophobicity threshold (i.e., all the antimicrobially active peptides); alginate had no effect on spectra of peptides below the threshold (Table I). Consistent with previous data showing that alginate can absorb pyrene molecules from bulk aqueous media (16), these results support the notion that alginate contains hydrophobic microdomains that may induce $\alpha$-helicity and blue shifting effects in peptides above the hydrophobicity threshold.

Molecular Modeling of Alginate—A previous study on lipid-alginate interactions suggested that alginate could insert into the lipid bilayer by broad analogy to insertion of membrane proteins (17), an observation providing further indication that alginate possesses some discrete hydrophobic character. Because the alginate-induced blue shifts observed in fluorescence studies correlate with formation of $\alpha$-helix in CD spectra of the same set of peptides (Table I and Fig. 1), hydrophobic peptide–alginate interactions are implicated as a potential contributor to the observed spectroscopic effects. To identify a molecular origin for a hydrophobic compartment in alginate, we considered the chemical nature of the faces of its monomeric components (Fig. 2, a and b) (Sweet Program; www.dkf-heidelberg.de/spec/sweet2/doc/index.html). Although $\alpha$-l-guluronate (~30% of alginate composition in P. aeruginosa) projects two axially oriented C–H protons on its more hydrophobic face, we noted that $\beta$-D-mannurionate (70% composition) contains a highly hydrophobic face with a total of four C–H protons (three axial + one equatorial) in similar orientation (Fig. 2b). A composite of such structures among alginate strands, particularly in $\beta$-D-mannurionate-rich segments, could readily form a localized hydrophobic compartment.

Fluorescence Resonance Energy Transfer Studies of Peptide-Alginate Interactions—To show that the anionic alginate can not only bind to cationic peptides through electrostatic and hydrophobic interactions but also can promote peptide-peptide interactions, we used FRET to measure the distance-dependent interaction between the excited electronic states of donor-acceptor pairs of dye molecules covalently attached to the N termini of selected peptides. This technique has been widely used to study interactions between subunits in protein complexes (19, 20), e.g., where dansyl-chloride-labeled and dabsyl-chloride-labeled glycolporin A peptides in lipid vesicles were used to demonstrate that the protein exists in a dimeric form (11). Thus, two cationic antimicrobial peptides with guest res-
were created: one labeled with dansyl chloride (as a donor) and the other labeled with dansyl chloride (as an acceptor). As shown in Fig. 3a, the emission maximum is quenched when the dabsyl-labeled Phe peptide was added to the dansyl-labeled peptide in alginate solution. Similar to results with the glycophorin dimer, quenching was not affected over a range of 5-fold increase in the amount of alginate present but decreased upon the addition of unlabeled Phe peptide (results not shown), indicating that the FRET signal is not simply the result of nearby but noninteracting peptides (11). A nonlinear curve fit to the observed energy transfer for a number of donor-to-acceptor ratios indicated that the peptide likely forms dimers and/or higher oligomers in alginate solutions (results not shown). A further indication of the intimate interaction of the Phe peptide with alginate is the observation of a significant blue shift in the dansyl emission maximum, from ∼550 nm in aqueous phases to ∼525 nm in the presence of added alginate. In contrast, when the same studies were performed with peptide with Xaa = Asp, no quenching of the dansyl chloride emission was observed when dabsyl-chloride-labeled peptide was added in alginate solution (Fig. 3b), and no blue shift occurred in dansyl emission maxima.

Studies of Peptide-Alginate Interactions by Confocal Laser Scanning Microscopy—To correlate the helical induction properties of the peptides in alginate to their ability to permeate the alginate matrix, we investigated the penetration of the peptides in alginate beads. Peptides with Xaa = Trp and Phe (both above the hydrophobicity threshold) and with Xaa = Glu and Ser (both below the threshold) were labeled with TAMRA. Consistent with studies on fluorescently labeled magainin (21), TAMRA-labeled peptides used in the present experiments displayed the same antimicrobial activity against *P. aeruginosa* as their unlabelled counterparts (data not shown). As seen in Fig. 4, both the Trp and Phe peptides (Fig. 4, a and b) were largely concentrated on the surface of the beads, whereas the Glu and Ser peptides (Fig. 4, c and d) diffused nonspecifically into the center of the beads.

CD of Other Antimicrobial Peptides in Alginate—To examine the generality of the ability of alginate to induce α-helical character in peptides with antimicrobial activity, we performed parallel experiments on two commercially available antimicro-
brial peptides. As shown in the CD spectra in Fig. 5, both cecropin P1 (SWLSKTAKLENSAKKRISEGIAIQGGPR) (22) and magainin-II-amide (GIGKFLHSAKKFKAFVGE-IMNS-NH₂) (23) adopt α-helical conformations in the presence of alginate.

**CD and Fluorescence Spectroscopy of Model Peptides in Other Carbohydrates**—To address whether alginate can induce α-helical conformations in the presence of neutral polysaccharide amylose (composed of glucose), of the negatively charged polymer hyaluronate (a polymer composed of glucuronate and N-acetyl glucosamine), and of the monomeric uronic acid sugar glucuronate. We found that amylose did not evoke any helix induction effects (spectra not shown). Hyaluronate was able to induce α-helical structure but only in the peptide with Xaa = Trp (results not shown; spectra with the Xaa = Trp peptide similar to Fig. 1a). Monomeric glucuronate was also able to induce helical structure, indicating that a polymer is not required to induce peptide helicity, but again, only in the peptide Xaa = Trp. Note that a hydrophobic “face” is available in the glucuronate molecule, as formed by three co-oriented C-H protons (Fig. 2c). However, distinct from alginate, no blue shift in Trp emission maxima was observed for any peptide studied under all of the conditions in amylose, hyaluronate, or glucuronate solutions.

**DISCUSSION**

Helix induction in peptides by sugars may be fundamentally a consequence of the fact that the addition of saccharides lowers the dielectric constant of the pure aqueous medium, in effect creating a less polar medium in which competition by solvent for peptide backbone H-bonds is reduced. An accompanying phenomenon is the ability of anionic sugars to “neutralize” Lys side chain amino acids by serving as organic counte-

rions, with the consequence that the already hydrophobic peptides become significantly less soluble in the presence of alginate. This latter effect could also promote peptide aggregation. However, in contrast to the observation that basic polylysines form precipitates in pectate solutions, likely because of Lys-promoted “cross-linking” of pectate strands (24–26), the current FRET experiments confirm the presence of peptide-peptide interactions that likely originate from the intrinsic hydrophobic character of the peptides. Although the oligomeric state of hydrophobic peptides can explain, in part, the blue shifts in Trp fluorescence indicating the burial of the Trp residue within the peptide oligomers, it is important to note that the alginate-induced blue shift is accompanied by a concomitant increase in fluorescence intensity, whereas Trp fluorescence would usually be quenched in peptide aggregates (27).

Therefore, the hydrophobic “compartment” presented to the peptides by alginate, in concert with the hydrophobic character of the peptides, apparently act synergistically to produce the observed structured helical monomeric and/or oligomeric peptide species. Along with the confocal laser scanning microscopy images, these data lead us to postulate that alginate, by promoting peptide-peptide association, could play a protective role by inhibiting the antimicrobially active peptides from reaching the target bacterial membrane in biofilms.

Among the peptides tested in the present work, only the peptide with Xaa = Trp, which contains a total of four Trp residues, adopts an α-helical conformation in the presence of carbohydrates other than alginate, suggesting a degree of specificity of Trp binding to carbohydrates. A crystal structure of the alginate-binding protein AlgQ2 complexed with the alginate tetrasaccharide MMGM suggested that the nonpolar/non-

topic protein-sugar contacts occur mainly through aromatic (mainly Trp) side chains (14). Indeed, the proximity of aromatic side chains to bound carbohydrates is a feature of carbohydrate binding to many proteins and/or enzymes, as exemplified by Trp-galactopyranosyl ring stacking interactions within the lactose permease LacY membrane domain (28), where interactions between the π electrons of aromatic side chains and the C–H bonds present in hexopyranoses are a common motif (28–32). The carbohydrate and OH groups of the alginate sugars render the protons of the C–H bonds δ-positive, which enhances their capacity for interaction with electron-rich aromatic rings (33). However, the fact that alginate induced both α-helical conformation and blue shifting of Trp emission maximum only in peptides above the hydrophobicity threshold (viz., the anti-

microbially active subset) indicates that alginate possesses some unique characteristics possibly related to its biological function in biofilms. As well, the Trp residue is not in itself sufficient to mediate the effects observed, because peptides below the threshold (Table I), all of which contain Trp, do not interact substantively with the polysaccharides. Thus, the alginate matrix, which contains both equatorial-axial and axial-equatorial monomer-monomer linkages, may offer local strand-strand interactions to produce hydrophobic “pockets” that can effectively sequester added peptides. As mentioned above, such pockets could be formed largely from β-β-mannuronate-rich alginate segments (Fig. 2b).

Although structural details of the macromolecular complexes formed by peptide-alginate interactions remain to be elucidated, we have shown here that alginate can induce α-helical structure in antimicrobially active peptides whose average core sequence hydrophobicity exceeds a “hydrophobicity threshold.” In addition to the nonpolar/nonpolar interactions between hydrophobic residues and suitably positioned carbohydrate C–H protons, the neutralizing effects by the anionic sugars on Lys play a significant role in helix induction in peptides above the hydrophobicity threshold (as demonstrated by amylose, a neutral polysaccharide). Because peptides of this category are antimicrobially active only when above the hydrophobicity threshold, we postulate that alginate exhibits membrane-mi-

metic properties. The fact that α-helical induction of membraneeactive peptides is typically observed upon peptide association with micelles or membrane bilayers (7, 34–35) leads us to suggest that alginate behaves as an “auxiliary membrane” for the bacteria. Furthermore, just as nonpolar clusters present in alginate are likely tracked with aromatic residues (14), ar-

omatic residues are correspondingly responsible for anchoring protein transmembrane segments at the membrane/water interface (36). Alginate thus forms complexes with peptides competitively with the bacterial membrane and probably entraps the peptide by promoting peptide oligomerization before the peptide can reach the bacterial membrane, consistent with the decreased effectiveness of these antibiotics in biofilm-situated bacteria. As such, these results provide, in part, a novel molec-

ular basis for the protection mechanism afforded the bacteria by alginate. One may speculate that anionic oligosaccharides on mammalian cell surfaces could perform an analogous scav-

enger function. As further details of peptide interactions with polysaccharides emerge, suitable manipulation of peptide hydrophobicity, charge, and length can potentially produce pep-

ptides, which more effectively penetrate the biofilm matrix and kill P. aeruginosa.

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J. Biol. Chem. 2004, 279:38749-38754.
doi: 10.1074/jbc.M406044200 originally published online July 9, 2004

Access the most updated version of this article at doi: 10.1074/jbc.M406044200

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