The Conformation of the Chromatin Core Particle Is Ionic Strength-dependent

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We have examined the susceptibilities of the histones within the HeLa chromatin core particle to covalent modification by a diol-epoxide derivative of the carcinogenic polycyclic aromatic hydrocarbon benzo(a)pyrene. Core-particle histones exhibit substantial variation in their relative susceptibilities to modification, depending upon the ionic strength of the environment. In contrast, the relative susceptibilities of either purified histones or histones in urea-denatured core particles are insensitive to changes in ionic strength. The variations in the pattern of modification of core particle histones occur primarily at ionic strengths at which the histones remain associated with core-particle DNA (0 to 0.6 M NaCl). Non-histone proteins influence the ionic strength-dependent variations in histone modification. The results imply that the ionic strength of the environment affects the conformation of the core particle and that the nucleoprotein has a flexible structure.

In eukaryotic cells, chromosomal DNA is organized into a nucleoprotein complex termed chromatin. Biochemical, physical, and morphological evidence supports the proposal (1) that chromatin has a repetitive subunit structure and, at its primary level of organization, consists of nucleoprotein particles linked by flexible segments of relatively protein-free DNA, generating an overall structure which resembles a string of beads (for review, see Refs. 2 and 3). These nucleoprotein "beads" (chromatin core particles) can be isolated as rather homogeneous populations and are useful to study because they retain some of the important structural properties of intact chromatin.

Much of our current knowledge of chromatin structure stems from the use of enzymes (e.g. nucleases and proteases) to degrade the nucleoprotein in a controlled fashion. The pattern of fragments generated during the digestion is used to draw inferences about the organization of the intact nucleoprotein. Such experiments have been extremely valuable in elucidating not only the subunit structure of chromatin but also the internal architecture of the chromatin subunit (2, 3, and references therein).

More recently, we have become interested in the ways in which compounds of relatively low molecular weight interact with the nucleoprotein. Many such compounds are capable of inducing marked changes in the phenotype of the cell; perhaps the most obvious and widespread example is the production of neoplastic disease by chemical carcinogens. Presumably, a foreign compound must interact with a component(s) of the genome in order to induce an alteration in phenotype. In the case of neoplastic transformation, covalent binding is thought to be involved, primarily because virtually every carcinogen which has been studied in detail exhibits such binding (for review, see Refs. 4 to 8). We have been studying the covalent binding between a diol-epoxide of benzo(a)pyrene and the HeLa core particle, for the following reasons. First, we have previously described the protein DNA interactions within the HeLa core particle in some detail (9-11). Second, polycyclic aromatic hydrocarbons, such as the carcinogen benzo(a)pyrene, are important environmental contaminants to which virtually everyone is exposed (12, 13). Third, the chemistry and metabolism of benzo(a)pyrene has been studied extensively; several steps in its metabolic processing by the cell involve the formation of epoxides, which are chemically reactive and bind covalently to cellular macromolecules (14, 15); the current evidence indicates that the diol-epoxide 7,12-dihydroxy-1,2-oxo-7,12,9,10-tetrahydrobenzo(a)pyrene is an important "ultimate" carcinogen (16-21, and references therein).

We show here that BPDE can be a useful tool to study the protein-DNA interactions within the core particle. Our experiments show that the histones within the core particle exhibit substantial variability in their relative susceptibilities to modification by BPDE, depending upon the ionic strength of the environment. The variations in the pattern of modification occur largely at ionic strengths at which the histones remain associated with core particle DNA (0 to 0.6 M NaCl). These variations cannot be explained simply in terms of a nonspecific weakening of histone-DNA interactions, leading to an overall increase in the modification of all the histones. In contrast to the situation for core particles, the relative susceptibilities to modification of purified histones or of histones in urea-denatured core particles are not ionic strength-dependent. These findings imply that the ionic strength of the environment influences the conformation of the core particle and that the nucleoprotein is a flexible, rather than rigid, structure.

MATERIALS AND METHODS

The 4°C-labeled diol-epoxide derivative of benzo(a)pyrene (specific activity, 33.7 mCi/mmol) was obtained through the courtesy of the Carcinogenesis Research Program of the National Cancer Institute, Bethesda, Md. 20205. It was stored as a stock solution at a concentration of about 2 mM in tetrahydrofuran at −20°C.

Cell culture, preparation of nuclei, and preparation of core particles were as previously described (22). HeLa core particles prepared in this way contain a 140-base-pair segment of DNA, 2 molecules each of histones H2A, H2B, H3, and H4, and about 0.4 mg of non-histone

The abbreviations used are: BPDE, benzo(a)pyrene diol-epoxide (structure and formula shown in Fig. 1); SDS, sodium dodecyl sulfate.
Non-histone proteins were removed by making the core particles 0.6 M in NaCl and centrifuging them through a sucrose density gradient containing 0.6 M NaCl. The fraction containing the core particles was collected, dialyzed against 0.2 mM EDTA, pH 8, concentrated by dialysis against dry Sephadex G-100, redialyzed against 0.2 mM EDTA, and frozen until use.

Purified histones were prepared by dissociating the salt-washed core particles in 2.5 M NaCl, adsorbing the DNA to hydroxyapatite, and removing the DNA-hydroxyapatite complexes by centrifugation. The supernatant containing the histones was dialyzed against 0.2 mM EDTA, pH 8, concentrated by dialysis against dry Sephadex G-100, redialyzed against EDTA, and frozen until use.

Core particles, at a final concentration of 10 A\textsubscript{260} units/ml, or purified histones, at a final concentration of 0.6 mg/ml in 50 mM Tris/Cl, pH 8, and various concentrations of NaCl (see “Results”), were incubated with a 1/10 volume of [\textsuperscript{14}C]BPDE for 60 min at 20°C in the dark. Tetrahydrofuran at a concentration of 10% had no detectable effect on core particle structure, as measured by the pattern of DNA or protein fragments produced during digestion with DNase I or trypsin, respectively. In addition, modification of the nucleoprotein produced no detectable change in core particle structure, by the same criteria.

The modification reaction was terminated by making the mixture 1% in SDS, 100 mM in Tris/Cl, pH 8.2, and 10 mM in EDTA, followed immediately by extraction with 2 to 3 volumes of ethyl acetate, to remove unbound polycyclic hydrocarbon. The organic layer was removed, and the aqueous layer was extracted with an equal volume of phenol. The aqueous layer was removed, and the phenol phase was re-extracted three times with equal volumes of 1% SDS, 10 mM EDTA, 100 mM Tris/Cl, pH 8.2. The proteins were precipitated overnight at -20°C by the addition of 4 volumes of ethanol to the phenol phase. Protein recovery was 95 to 100%, as measured in total counts, 10 to 15% are associated with the histones (i.e. 10 to 20 molecules of covalently bound \textsuperscript{14}C]BPDE. Of the total covalently bound counts, 10 to 15% are associated with the histones (i.e. can be extracted from modified core particles with 0.4 M H\textsubscript{2}SO\textsubscript{4}); the remaining counts are associated either with DNA alone (in core particles from which the non-histone proteins have been removed) or with both DNA and non-hist protein (in core particles which contain nonhistones). Thus, in the experiments described here, the components of the nucleoprotein are modified to very limited extents, minimizing potential artifacts which might arise as a result of extensive chemical modification of the nucleoprotein.

RESULTS

The diol-epoxide (Fig. 1) used in these experiments is a chemically reactive, electrophilic compound which would be expected to react relatively nonspecifically with any available nucleophilic acceptor group within the nucleoprotein. The amino acid sequences of the four smaller histones reveal that each contains potential acceptor residues (methionine, cysteine, tyrosine, histidine) (25); therefore, we expected that each core particle histone would be more or less equally susceptible to covalent modification by BPDE. Yet, our initial experiments revealed that the histones in native core particles exhibited markedly different relative susceptibilities to modification by BPDE. In contrast, following denaturation of the nucleoprotein in either urea or SDS, the core-particle histones were more equally susceptible to modification, as would have been expected from their amino acid compositions (data not shown). Thus, these early experiments suggested that the organization of the histones within the core-particle complex influenced their relative susceptibilities to chemical modification. We, therefore, examined in more detail the potential usefulness of BPDE as a tool to study the protein-DNA interactions within the core particle.

Electrostatic forces between the histones and chromosomal DNA play an important role in the formation of the nucleoprotein complex. As the ionic strength of the environment increases, histone-DNA interactions progressively decrease, until, at about 2 M NaCl, the histones are completely dissociated from the DNA (26). We, therefore, asked whether alterations in electrostatic histone-DNA interactions produced changes in the relative susceptibilities of the core-particle histones towards chemical modification by BPDE. We covalently modified core particles with the radioactive diol-epoxide under conditions of increasing ionic strength and determined which histones were modified, using polyacrylamide gel electrophoresis and fluorography. In these experiments, we used core particles from which non-histone proteins had been removed, in order to minimize the potential influence of the nonhistones on the modification of the histones.

The fluorogram in Fig. 2 reveals that, as the NaCl concentration is raised from 0 to 1.2 M, there are substantial changes in the relative extents to which the four core-particle histones are modified. At low ionic strength (no NaCl), H2A is modified to a greater degree than H2B and H3, and there is no detectable modification of H4. As the NaCl concentration is progressively increased, there is a marked change in the pattern of histone modification. For example, in 1.2 M NaCl, H2A is much less susceptible to modification than it is in low salt, whereas H4 is more susceptible. Thus, the relative susceptibilities of the four core particle histones to modification by the polycyclic hydrocarbon vary as a function of the ionic strength of the environment. The stained gel in Fig. 2 indicates that these changes cannot be attributed to variations in the amounts of protein analyzed. Two aspects of this experiment are noteworthy. First, most of the changes in the relative susceptibilities of the histones to modification by BPDE occur at NaCl concentrations below 0.6 M, under these conditions, the histones remain associated with the DNA (as measured by the sedimentation properties of the nucleoprotein). Second,

![Fig. 1. r-7-t,8-dihydroxy-t-9,10-oxy-7,8,9,10-tetrahydrobenzo(a)pyrene.](http://www.jbc.org/)

![Fig. 2. Effect of [NaCl] on the modification of core-particle histones by [\textsuperscript{14}C]BPDE. Core particles were modified with BPDE in the presence of the indicated concentration of NaCl. Proteins were purified and analyzed by electrophoresis and fluorography. Migration was from top to bottom. Only that portion of the gel containing the histones is shown. The positions of the histones are indicated. Top panel, stained gel; bottom panel, fluorogram.](http://www.jbc.org/)
the changes in histone susceptibility cannot simply be attributed to a general, nonspecific weakening of electrostatic histone-DNA interactions, producing an overall increase in histone accessibility; the susceptibility of H2A to modification clearly decreases with increasing NaCl concentration. Thus, this experiment suggests that altering the ionic environment of the core particle produces a change(s) in the conformation of its histones; furthermore, such conformational changes occur within the physiologic range of ionic strength.

We, therefore, examined in more detail the modification of core-particle histones at NaCl concentrations below 0.6 M, in order to determine whether their relative susceptibilities changed abruptly or varied gradually, as the ionic strength increased through a physiologic range. Fig. 3 indicates that, as the NaCl concentration is increased in small increments from 0 to 0.6 M, the relative susceptibilities of H2B and H4 gradually increase, whereas that of H2A gradually decreases. The extents of these changes and the smoothness of the transitions are demonstrated quantitatively in Fig. 4. These alterations in susceptibility to chemical modification imply that the core-particle histones undergo an orderly, continuous change in conformation as the concentration of NaCl is increased from 0 to 0.6 M.

We next asked whether the susceptibility of the core-particle histones to modification was sensitive to changes in the concentration of salts other than NaCl. We performed an experiment analogous to that shown in Fig. 3, using KCl (0 to 0.6 M) in place of NaCl, we obtained virtually identical results to those observed using NaCl (data not shown). Thus, the changes in the pattern of histone modification which occur as the ionic strength is varied do not require that NaCl be the ionic species. We also performed an analogous modification experiment, with MgCl₂ as the ionic species, within a (presumed) physiologic range of 0 to 3 mM. We observed no differences in the pattern of histone modification within this range of MgCl₂ concentrations (data not shown). Thus, the susceptibility of the core-particle histones to modification by BPDE apparently is influenced primarily by the overall ionic strength of the environment, rather than by factors unique to a particular ionic species.

In contrast to the case for core particles, the relative susceptibilities of purified histones to modification by BPDE exhibit little, if any, ionic strength dependence. The fluorogram in Fig. 5 shows that the relative susceptibilities of the purified histones to modification do not change substantially as the NaCl concentration is increased from 0 to 0.6 M. At each ionic strength, H2B exhibits the greatest susceptibility, H3 and H4 lesser susceptibilities, and H2A the least suscep-

Fig. 3. Effect of [NaCl] on the modification of core-particle histones by [³²P]BPDE. Core particles were modified with BPDE in the presence of the indicated concentration of NaCl. Proteins were purified and analyzed by electrophoresis and fluorography. Migration was from top to bottom. Only that portion of the gel containing the histones is shown. The positions of the histones are indicated. Top panel, stained gel; bottom panel, fluorogram.

Fig. 4. Effect of [NaCl] on the modification of core-particle histones by [³²P]BPDE. Densitometric scans of the fluorogram in Fig. 3. The positions of the histones are indicated. Ordinate is linear with optical density.

Fig. 5. Effect of [NaCl] on the modification of purified histones by [³²P]BPDE. Purified histones were modified with BPDE in the presence of the indicated concentration of NaCl. Proteins were purified and analyzed by electrophoresis and fluorography. Migration was from top to bottom. Only that portion of the gel containing the histones is shown. The positions of the histones are indicated. Top panel, stained gel; bottom panel, fluorogram.
tibility. Densitometric scans of the fluorogram (Fig. 6) document this observation more quantitatively. These results imply that the histones must be interacting with DNA in order to exhibit ionic strength-dependent variations in their susceptibilities to modification by BPDE. This is consistent with the experiment shown in Fig. 2 which shows that, at relatively high ionic strengths, where dissociation between histones and DNA occurs, core-particle histones no longer exhibit ionic strength-dependent changes in their susceptibilities toward modification; indeed, at these higher ionic strengths, the pattern of modification of core-particle histones is similar to that observed for purified histones at lower ionic strengths (compare Figs. 2 and 5).

As an additional control, we asked whether the relative susceptibilities of the core-particle histones towards BPDE remained ionic strength-dependent under conditions where histone-histone interactions were disrupted. Core particles were denatured in 7 M urea (16 h, 0°C) prior to modification with BPDE. Fig. 7 shows that, in 7 M urea, the relative susceptibilities of the core-particle histones towards modification by BPDE exhibit little dependence upon the ionic strength; at each ionic strength studied between 0 and 1.2 M NaCl, H2B is most susceptible to modification, H3 and H2A are less susceptible, and H4 is least susceptible. Thus, when in an unfolded state, the core-particle histones no longer exhibit ionic strength dependence in their pattern of modification by BPDE.

A third type of control experiment indicates that the pattern of modification of the core-particle histones is not dependent upon the duration of the modification reaction. Core particles in a given ionic environment (e.g. 0.2 M NaCl) were modified with BPDE for increasing times (1 to 64 min). The binding of BPDE to the nucleoprotein continued to increase throughout the course of the reaction; however, at each time point, the pattern of histone modification (i.e. the extent to which each individual histone was modified relative to the others) was very similar. Thus, our observations are not artifacts related to a time-dependent variable in the modification reaction (data not shown).

We also asked whether the presence of nonhistone proteins influences the ionic strength-dependent variability in the susceptibilities of the core-particle histones to modification by BPDE. Core particles containing non-histone proteins were

![Fig. 6. Effect of [NaCl] on the modification of purified histones by [14C]BPDE. Densitometric scans of the fluorogram in Fig. 5. The positions of the histones are indicated. Ordinate is linear with optical density.](image_url)

![Fig. 7. Effect of [NaCl] on the modification of urea-denatured core particles by [14C]BPDE. Core particles were denatured in 7 M urea (16 h, 0°C) and then modified with BPDE at 20°C in the presence of the indicated concentration of NaCl. Proteins were purified and analyzed by electrophoresis and fluorography. Densitometric scans of the fluorogram are shown. The positions of the histones are indicated. Ordinate is linear with optical density.](image_url)

![Fig. 8. Effect of non-histone proteins on the NaCl-dependent modification of core-particle histones by [14C]BPDE. Core particles containing nonhistone proteins were modified with BPDE in the presence of the indicated concentrations of NaCl. Proteins were purified and analyzed by electrophoresis and fluorography. Migration was from top to bottom. Left panel, stained gel; right panel, fluorogram.](image_url)
modified with the diol-epoxide at concentrations of NaCl ranging from 0 to 0.6 M. The results in Fig. 8 indicate that, in the presence of non-histone proteins, the pattern of histone modification remains ionic strength-dependent. The changes in histone susceptibilities which occur as the ionic strength is increased are qualitatively similar to the changes observed in the absence of non-histones; the relative susceptibilities of H2B and H4 increase, and that of H2A decreases (compare Figs. 8 and 3). However, densitometric scans (Fig. 9) suggest that the non-histones do, in fact, influence the susceptibilities of the histones to modification, especially at NaCl concentrations between 0 and 0.2 M; at these lower ionic strengths, the relative susceptibility of H2A remains high, and the changes in the susceptibilities of H2B and H4 are less marked (compare Figs. 9 and 4). At NaCl concentrations of 0.4 and 0.6 M, the non-histones influence histone modification to a lesser degree; presumably this is because, at these higher ionic strengths, the non-histones interact weakly with the other core particle components.

We have not yet identified the amino acid residues which become modified by BPDE and, therefore, we do not know which sites within the histones undergo changes in their relative susceptibilities to modification by the compound. Our evidence suggests that at least some of the residues which presumably this is because, at these higher ionic strengths, the non-histones interact weakly with the other core particle components.

We have not yet identified the amino acid residues which become modified by BPDE and, therefore, we do not know which sites within the histones undergo changes in their relative susceptibilities to modification by the compound. Our evidence suggests that at least some of the residues which are located in the central and COOH-terminal histone regions. Trypsin digestion of chromatin and core particles preferentially excises the NH-terminal histone regions (10, 27). Fig. 10 shows that following trypsin digestion of BPDE-modified core particles, a substantial amount of radioactivity remains associated with the trypsin-resistant polypeptides, which represent primarily the central and COOH-terminal histone segments.

DISCUSSION

The experiments described here indicate that a reactive small molecule differentially modifies the four core-particle histones in an ionic strength-dependent manner. Substantial variations in the relative susceptibilities of the core particle histones to modification occur under conditions in which they remain associated with core particle DNA. These variations cannot be explained simply in terms of an overall increase in histone susceptibility as the ionic strength increases. These observations imply that the conformation of the core particle varies as a function of the ionic strength of its environment and, therefore, that it has a rather flexible structure. We cannot formally rule out the possibility that the reactivity of BPDE varies in an ionic strength-dependent manner, leading to variations in the pattern of modification of the core particle histones. However, the relative susceptibilities of 1) non-histone proteins, 2) purified histones, and 3) histones in urea-denatured core particles do not depend upon the ionic strength; therefore, it seems very unlikely that our observations are artifacts related to ionic strength-dependent properties of BPDE.

We do not know in detail which component(s) of the core particle undergo conformational changes as the ionic strength is varied through a physiologic range. Our results suggest that at least some of the amino acid residues involved in the change are located within the relatively hydrophobic regions of the histones, regions with which the nonpolar polycyclic hydrocarbon would presumably preferentially interact. An estimation of the number of amino acid residues involved in the change will require the identification of the residues modified by BPDE as well as additional studies using compounds which modify specific amino acids within the nucleoprotein.

Presumably, the magnitude of a conformational change in chromatin need not be exceptionally great in order to affect chromatin function. For example, both transcribed and non-transcribed DNA sequences in chromatin are in the same
basic subunit structure (28), yet the transcribed sequences are substantially more susceptible to nuclease digestion (29-31). These observations have been interpreted in terms of a subtle conformational difference(s) between transcribed and nontranscribed chromatin. Studies of the circular dichroism of chromatin as a function of ionic strength suggest that the conformations of both the DNA and protein components of the nucleoprotein are ionic strength-dependent (32, 33); Cowman and Fasman have recently suggested that alterations in the molecular ellipticity of chromatin in the range 250 to 300 nm may reflect changes in the tertiary, rather than secondary, structure of DNA (34). Our results are consistent with these previous observations and suggest that the conformation of the nucleoprotein are ionic strength-dependent (32, 33); Cowman and Fasman by a foreign compound such as BPDE could interfere with its ability to form the correct interactions with DNA. These observations have been interpreted in terms of a subtle conformational difference(s) between transcribed and nontranscribed chromatin; our experiments imply that this assumption is invalid.

We do not know whether the chemical modification of a histone(s) by a foreign compound such as BPDE could interfere with its ability to form the correct interactions with DNA. However, since the amino acid sequences of the histones have been so highly conserved throughout evolution, it has been argued that the histone modifications which occur in vivo (acetylation, phosphorylation, methylation) will have important effects on chromatin function (25, 35–39). By the same reasoning, histone modification by a foreign compound such as BPDE would also have the potential to influence the structure and function of the nucleoprotein.

Our experiments illustrate both the usefulness of reactive small molecules and the potential value of protein modification techniques in studying the macromolecular interactions in chromatin. Studies using other reagents should yield more detailed information concerning the conformational changes which occur. In addition, such studies should give us a better understanding of the factors which influence the interactions between the histone and small molecules. Such knowledge would seem to be a prerequisite to an understanding of the molecular mechanisms whereby foreign compounds exert their biological effects upon the cell.

Acknowledgments These experiments were performed at the National Institutes of Health in the laboratory of Dr. Robert T. Simpson, to whom I am grateful for encouragement and constructive criticism. I thank Drs. D. Brutlag, S. Kalman, R. Kornberg, and G. Ringold for thoughtful comments on the manuscript. I thank Ms. K. Benight for secretarial assistance.

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J. Biol. Chem. 1979, 254:5684-5689.