We have reconstituted nucleosomes containing the Xenopus borealis 5 S RNA gene, a single histone octamer, and 1 or 2 molecules of histone H1. We determine that the 1st molecule of histone H1 to associate with the 5 S nucleosome binds with high affinity (KD = 2 nM), and the 2nd molecule of H1 binds with a reduced affinity (KD = 10 nM). This latter binding is comparable with the association of histone H1 with naked DNA. Neither molecule of histone H1 alters the helical periodicity of DNA in the nucleosome as revealed by hydroxyl radical cleavage. We conclude that although multiple molecules of histone H1 can associate with nucleosomal DNA, there is only a single high affinity binding site for histone H1 within the 5 S nucleosome.

In vivo during the maturation of the chromatin of chicken erythrocytes, multiple molecules of linker histones have been shown to become associated with a single nucleosomal repeat length of DNA containing a single histone octamer (1-4). In contrast, the chromatin of mammalian tissue culture cells contains on average a single molecule of histone H1 per histone octamer (5, 6). In vitro deconstruction and reconstruction experiments indicate that two H1-binding sites exist within each nucleosome and that the presence of 2 molecules of H1 per nucleosome generates a more compact structure than native chromatin (7). The biological and structural significance of chromatin potentially consisting of a mixture of nucleosomes containing 0, 1, or 2 molecules of histone H1 has not been resolved.

More recently several investigators have made use of Xenopus or Drosophila chromatin assembly extracts to investigate the influence of chromatin structure on transcriptional regulation. These extracts are deficient in the normal somatic form of histone H1 (8-12) and at least for Xenopus contain maternal H1 variants (13, 14). Deficiency in the normal somatic form of histone H1 should have allowed these extracts to prove useful in determining the influence of this variant of histone H1 on transcription. However, the results of such experiments are controversial. Histone H1 has been variously reported to act as a general inhibitor of transcription within chromatin (10, 12, 15) or not to influence the transcription process (11, 16) or to selectively inhibit the transcription of particular genes (9, 17). In vivo the selective inhibition of particular genes by the normal somatic variant of histone H1 is observed (18).

One possible explanation for the discrepancy in results is that chromatin templates with different structural properties are being assembled as a consequence of including histone H1 in varying stoichiometries. The standard assay for the assembly of histone H1 into chromatin in the Xenopus and Drosophila assembly systems requires measurement of the change in nucleosome spacing (19). The nucleosomal spacing increases from 180 bp without addition of exogenous H1, to a repeat of 205 bp when 2 molecules of histone H1 are present per nucleosome, to a repeat of 220 bp when an excess of 5 molecules of histone H1 per nucleosome is present (19). Without histone H1, transcription in the Xenopus extract is repressed by histone octamers alone only at very high densities (one per 160 bp), but with histone H1 transcription was repressed at a ratio of 1.5 molecules of H1 per nucleosome, at a nucleosomal repeat length of 205 bp (10, 19). Comparable results in which exogenous histone H1 increases the spacing of nucleosomes were reported in Drosophila extracts; 1 molecule of histone H1 per nucleosome increased nucleosome spacing from 190 to 210 bp, and 3 molecules per nucleosome increased spacing to 220 bp (15, 16). However, transcription results were very different; Kamakaka and colleagues (15) find that 3 molecules of H1 per nucleosome are necessary to repress transcription, whereas Sandaltzopoulos and colleagues (16) find that histone H1 makes a negligible contribution to transcriptional repression.

A concern with these studies is whether an unusual or atypical chromatin structure is being assembled as a consequence of including much higher stoichiometries of histone H1 than are normally present in chromatin. The spacing of nucleosomes in a normal somatic cell is typically 180-200 bp (20). Thus multiple molecules of histone H1 must be physically associated per nucleosome to generate the increase in nucleosome spacing to 220 bp. How might these additional molecules bind to nucleosomal DNA? We have investigated this issue using a positioned nucleosome containing a fragment of the Xenopus 5 S rRNA gene (21-26). We establish conditions under which a 2nd molecule of histone H1 can be stably incorporated into a 5 S nucleosome protecting additional linker DNA from micrococcal nuclease digestion. We find that the association of this 2nd molecule of histone H1 with nucleosomal DNA occurs with comparable affinity to the association of H1 with naked DNA. Thus, only a single high affinity histone H1 binding site exists on the 5 S nucleosome.

MATERIALS AND METHODS

DNA Fragments—Radiolabeled DNA fragments contained the Xenopus borealis 5 S rRNA gene. A 237-bp HpaII-DdeI fragment derived from plasmid pJHX1 (27) was used for nucleosome reconstitution after radiolabeling, either at the HpaII site 102 bp upstream from the initiation site for transcription of the 5 S gene (+1) or at the DdeI site 137 bp downstream from the start of transcription.

Nucleosome Reconstitution and Footprinting—Histone H1 was prepared from calf thymus as described previously (21). Nucleosome cores were reconstituted onto radiolabeled DNA fragments either by ex-
change with chicken erythrocyte core particles (28, 29) or by dialysis using purified histone octamers (30). The original 20 μl of exchange reaction containing 3.0 μg of donor chromatin, 0.5 μg of naked nonspecific DNA, and 10–100 ng of labeled 5 S fragment was incubated for 1 h (all incubations at room temperature). This was then diluted from 1 m NaCl with two 5-μl additions of TE (to 0.8 and 0.66 NaCl, respectively, where TE is 10 mM Tris, pH 8.0, 1 mM EDTA), each for 1 h. The salt concentration was then diluted to 0.2 μl with 170 μl of TE for 15 min and later finally diluted to 100 mM NaCl with 200 μl of TE. About 50–60% of the labeled 5 S fragment was assembled into mononucleosome cores without detectable dinucleosome complexes with this procedure as monitored by electrophoresis. Cleavage of DNA in the reconstituted nucleosome with hydroxyl radical was as described (31). All footprinting was accomplished by gel isolation of the nucleoprotein products of digestion, followed by deproteinization and denaturing gel electrophoresis.

Linker Histone Binding Experiments—Unless indicated otherwise in the figure legends, approximately 5 ng of labeled 5 S DNA, either naked in the presence of 50 ng of unlabeled calf thymus DNA or reconstituted with a single histone octamer in the presence of 50 ng of unlabeled “nonspecific” chromatin, were incubated with various amounts of linker histone H1 (see figure legends) in 10 μl of binding buffer (10 mM Tris-HCl, pH 8.0, 50 mM NaCl, 0.1 mM EDTA, 5% (v/v) glycerol). Samples were incubated at room temperature for 15 min and loaded directly onto a 0.7% agarose gel in 0.5 × TBE (1 × TBE is 90 mM Tris base, 90 mM boric acid, 2.5 mM EDTA). After electrophoresis, the gels were dried and autoradiographed.

Micrococcal Nuclease Digestion Analysis—Digestions were for 5 min with 0.01–0.5 unit of enzyme/sample at 22°C. Samples contained 100 ng of reconstituted chromatin, and the incubation with H1 was as described (21). Ca2+ was adjusted to 0.5 mM concomitantly with addition of micrococcal nuclease. Digestion was terminated by the addition of EDTA (5 mM), SDS (0.25% w/v), and proteinase K (1 μg/ml). The DNA was recovered and 5′-end labeled with polynucleotide kinase, and fragments were separated by electrophoresis in nondenaturing 8% polyacrylamide gels (21). Restriction endonuclease cleavage to determine the exact position of micrococcal nucleosome cleavage sites was as described (21, 32, 33).

Radiolabeling of Linker and Core Histones—For these experiments purified histones were used to reconstitute nucleosomes (30). Nucleoprotein-containing bands were excised from the gel, and proteins were electroeluted in 2 × TE, 0.1% SDS, 0.5 mM disopropropyl fluorophosphate for 25 min at about 5 V/cm and dialyzed thoroughly to 0.01% SDS, freeze-dried, and dissolved in 5 μl of 5 mM HEPES-Na, pH 7.4, 1 mM EDTA. The eluted proteins (or the reference protein mixtures) were radiolabeled by adding an aliquot of the protein solution to a test tube with 10–40 μCi of Bolton-Hunter reagent (Amersham Corp., freshly dried by a stream of dry nitrogen). The reaction was allowed to proceed for 20 min at room temperature, stopped by 10 μl of Tris/glycine, pH 8.0, incubated at 95°C for 1 min, and adjusted to 60 μl of 0.2% SDS. The labeled proteins were precipitated by 27 μl of 5 × NaCl on ice, redissolved in 30 μl of TE containing 1% β-mercaptoethanol on 0.1 μg/ml protein carrier (see below), adjusted to 0.3 × NaCl and precipitated by 6 volumes of acetone, dissolved in the appropriate sample buffer, and resolved by gel electrophoresis. We used a mixture of peptides derived from histone H5 by prolonged hydrolysis in 2.5% acetic acid at 105°C as a carrier protein. The advantage of this carrier is that although the component polypeptides closely resemble the histones by molecule size and composition, none of them match the histones by electrophoretic mobility.

RESULTS

Histone H1 Forms Two Distinct Complexes with 5 S DNA Associated with a Histone Octamer—Earlier work has examined the structure of a nucleosome in which a single molecule of histone H1 associates with the X. borealis 5 S RNA gene wrapped around an octamer of core histones (21, 24). Association of histone H1 is dependent on the length of linker DNA available for binding; removal of linker DNA eliminated the selective association of histone H1 with nucleosomal DNA compared with naked DNA (21). The association of histone H1 with DNA in the 5 S nucleosome is asymmetric (21, 24). Since one model of asymmetric histone H1 association with nucleosomal DNA would potentially leave a second histone H1 binding site exposed (26), we examined whether we could bind a 2nd mol-
Naked DNA—We made use of the gel retardation assay to determine the affinity with which histone H1 interacts with naked and nucleosomal DNA (Figs. 2 and 3). The 1st molecule of histone H1 binds to nucleosomal DNA with a $K_D$ of ~10 nM (Figs. 2B and 3). The binding of histone H1 to naked DNA was also with a $K_D$ of ~10 nM (Figs. 2C and 3). The initial association of histone H1 with the naked 5S DNA fragment leads to the appearance of specifically retarded nucleoprotein species (Fig. 2A, lane 9; Fig. 2C, lanes 2-5). This may reflect the stable association of linker histone at a single site before additional molecules of linker histones associate. Note that the binding curve for H1 association with naked DNA (Fig. 3) is consistent with cooperative binding (34). The binding constants obtained in these assays are consistent with the preferential association of the 1st molecule of histone H1 with DNA wrapped around a histone octamer and the disappearance of naked DNA only at high H1 excess (Fig. 2A). The ability of histone H1 to bind naked DNA and form aggregates is unaffected by the presence of octamer-bound DNA (Fig. 2, compare B with C). Dissociation experiments yield the same relative affinities (Fig. 4), and the 2nd molecule of histone H1 is displaced from nucleosomal DNA at the same level of competitor DNA required to release naked DNA from association with histone H1 (Fig. 4, compare lanes 4 and 12). These results lead to the conclusion that a single high affinity site exists on each nucleosome for the binding of histone H1. Importantly the additional molecules of histone H1 that bind to the nucleosome do so with comparable affinity to the binding of H1 to naked DNA.

Structural Consequences of Binding 2 Molecules of Histone H1 per Nucleosome—The original assay for the stable inclusion of histone H1 into a nucleosome is the generation of a “chromatosome stop” (35). In this assay, histone H1 association leads to the appearance of a new kinetic intermediate during the digestion of chromatin by micrococcal nuclease. Typically for nucleosomes containing a mixture of a large number of DNA sequences, 1 molecule of histone H1 will protect a total of 20 bp of linker DNA immediately contiguous to the 146 bp in the nucleosome core (35, 36). In earlier work, we have documented that the histone octamer adopts a single translational position on the 5S RNA gene and that the association of histone H1 extends this protection into the linker DNA (21, 24, 37, 38). We repeated this analysis for nucleosomal structures containing 1 and 2 molecules of histone H1. A 5S nucleosome core without histone H1 protects approximately 149 bp of DNA from micrococcal nuclease whereas a 5S nucleosome containing a single molecule of histone H1 protects approximately 175 bp of DNA (21) and a 5S nucleosome containing 2 molecules of histone H1 protects both 175 and 200 bp of DNA from micrococcal nuclease (not shown). The variation in the size of fragments protected between 5S nucleosomes (149 bp) and 5S chromatosomes (175 bp) suggests that the association of histone H1 with the 5S DNA fragment is more stable

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H1 Binding to Naked and Nucleosomal DNA

FIG. 2. Gel retardation assays for the measurement of the binding affinity of histone H1 to DNA when associated with a histone octamer (A) or when associated with a histone octamer and a single molecule of histone H1 (B) or when naked (C) (see “Materials and Methods”). A, gel retardation assays for H1 binding to a mixture of naked and octamer-associated DNA (see “Materials and Methods” and note that carrier chromatin is present). Final histone H1 concentrations were 0, 0.19, 0.39, 1.0, 2.0, 3.0, 6.0, 13.0, 26.0, and 52.0 nM in lanes 1-10, respectively. B, gel retardation assays for H1 binding to DNA already associated with a histone octamer and a single molecule of H1 (see “Materials and Methods” and note that carrier chromatin is present). Lane 1 shows naked DNA; lane 2 shows DNA associated with a histone octamer; lanes 3-9 contain DNA associated with a histone octamer and final histone H1 concentrations of 10, 11, 13, 14, 17, 20, and 25 nM, respectively. C, gel retardation assays for H1 binding to naked DNA (see “Materials and Methods” and note that carrier DNA is present). Lane 1 shows naked DNA; lanes 2-9 contain histone H1 at concentrations of 11, 13, 14, 17, 20, 25, 33, and 50 nM, respectively.
defined sequence nucleosome containing 1 or more molecules of

compare alter the wrapping of DNA within the nucleosome (Fig. 5, compare 9 and 10 molecules of histone H1 (Fig. 5, compare 9 and 10). Neither does addition of a 2nd molecule of histone H1 alter the wrapping of DNA within the nucleosome (Fig. 5, compare lanes 3 and 5, and lanes 8 and 10). We conclude that the incorporation of a 2nd molecule of histone H1 into the nucleosome does not significantly alter pre-existing contacts made by the core histones and histone H1 with DNA.

DISCUSSION

These experiments were designed to examine the nature of a defined sequence nucleosome containing 1 or more molecules of histone H1. The major conclusion is that although multiple molecules of histone H1 can bind to DNA wrapped around a single histone octamer, only a single preferential high affinity binding site exists for histone H1 (Figs. 1-4). Structural changes to this defined sequence nucleosome following inclusion of more than one histone H1 molecule are minor (Fig. 5). Although these results are obtained with a particular nucleosome they have general implications for studies interrelating the influence of histone H1 on chromatin structure and

FIG. 4. Dissociation of histone H1 from nucleoprotein complexes. Left panel, dissociation of histone H1 from nucleosomal DNA. A mixture of naked and octamer-bound 5 S DNA (10 ng) (shown in lane 1) was incubated with 100 ng of histone H1 for 15 min before the addition of increasing amounts of linearized competitor DNA. Lanes 2-8 contain 0, 5, 10, 16, 32, 63, 125, and 250 ng of competitor DNA, respectively. Right panel, as in left panel except 10 ng of naked 5 S DNA was used.

bp from those of mixed sequence nucleosomes (146 bp) and chromatosomes (166 bp) is due to sequence-specific variation in micrococcal nuclease cleavage of a defined sequence DNA fragment (24). The ~200-bp DNA fragment derived from the 5 S nucleosome is much less abundant than the 175-bp DNA fragment (not shown). This may reflect the necessity of 2 molecules of histone H1 binding to nucleosomal DNA to protect 200 bp and the reduced binding affinity of the 2nd molecule of histone H1 to the nucleosome (Figs. 2-4). Weaker association of histone H1 with DNA is less likely to impede the digestion of DNA by micrococcal nuclease.

A feature of histone H1 association with 5 S nucleosomal DNA is that the additional linker DNA protected from micrococcal nuclease digestion is asymmetrically distributed with respect to the nucleosome core (21). We next mapped the micrococcal nuclease digestion boundaries of the 175- and 200-bp DNA fragment using denaturing gel electrophoresis. We found the boundaries of histone-DNA interactions in the 175-bp DNA fragment to be tightly distributed as previously determined (Ref. 21, not shown). However, the boundaries of the 200-bp fragment were much more diffuse and weaker than those obtained with the 175-bp fragment (not shown). The variation in the position of the boundaries of the 200-bp fragment indicates that either significant heterogeneity in the position of histone H1-DNA contacts exists or that these additional histone-DNA contacts are easily displaced during digestion.

Finally we examined the influence of incorporating 2 molecules of histone H1 into the nucleosome for the wrapping of DNA around the core histones. Previous work with 5 S monosomes and dinucleosomes had not detected any change in DNA structure on the surface of the histone octamer following inclusion of histone H1 (21, 37, 38). Hydroxyl cleavage of the 5 S nucleosome does not reveal any change in the helical periodicity of DNA on the surface of the histone octamer or in the extent of histone DNA interactions following inclusion of a single molecule of histone H1 (Fig. 5, compare lanes 3 and 4, and 8 and 9). Neither does addition of a 2nd molecule of histone H1 alter the wrapping of DNA within the nucleosome (Fig. 5, compare lanes 3 and 5, and lanes 8 and 10). We conclude that the incorporation of a 2nd molecule of histone H1 into the nucleosome does not significantly alter pre-existing contacts made by the core histones and histone H1 with DNA.

FIG. 5. Structure of DNA in the 5 S nucleosome is not changed significantly by conclusion of multiple histone H1 molecules. Hydroxyl radical footprinting is shown. Reconstitution reactions as shown in Fig. 1, lanes 2, 3, and 5, were cleaved with hydroxyl radical (see "Materials and Methods") before resolution on a non-denaturing gel, excision of the appropriate complex, deproteinization, denaturation of DNA, and resolution on a denaturing gel (see "Materials and Methods"). Lanes 1-5 and lanes 6-10 show the same samples subjected to electrophoresis for different times. Lanes 1 and 6 show a Maxam-Gilbert G reaction for markers (G); lanes 2 and 7 show hydroxyl radical cleavage of naked DNA (N); lanes 3 and 8 show cleavage of octamer-bound DNA (C); lanes 4 and 9 of H1-octamer show cleavage of bound DNA (A); and lanes 5 and 10 show cleavage of 2H1-octamer-bound DNA (B). The ellipsoids show the position of core (shaded) and chromatosome (open) boundaries for lanes 6-10. The asterisks mark the dyad position for the nucleosome core.
transcription.

A Single High Affinity Binding Site for Histone H1 in the Nucleosome—We have determined that a single molecule of histone H1 prefers to bind to nucleosomal DNA with a 5-fold higher affinity than the affinity for nucleosomes already containing H1 or for naked DNA (Figs. 1–4). This increased affinity of histone H1 for nucleosomal compared with naked DNA may depend on contacts the linker histone makes with the core histones (39, 40) or a preference for DNA that is curved through interaction with the core histones (24) or that contains two DNA helices that are juxtaposed in space (41–43). The preferential binding of a single molecule of histone H1 in a nucleosomal context indicates that studies examining the binding of histone H1 to naked DNA as a model for chromatin structure (34, 44) might not recapitulate the same quality of histone H1 association with DNA as seen within the nucleosome (21). This might account in part for the failure of histone H1 complexes with naked DNA to repress transcription, under conditions where histone H1 incorporated into a nucleosome will repress transcription (12, 45). A weaker association of histone H1 with DNA will make the repressive “chromatin” complex more accessible to the transcriptional machinery.

The binding of a 2nd molecule of histone H1 to nucleosomes may occur in vivo (4) and has been documented in vitro (Refs. 7, 15, 16, and 19, and this work). The association of additional molecules of basic protein with nucleosomal DNA is not surprising, since additional histone octamers can also bind to the nucleosome (46). The association of additional molecules of histone H1 during chromatin assembly does, however, lead to a decreased density of nucleosomes on the DNA molecule and an increased length of DNA bound by H1 away from core histone-DNA contacts (15, 16, 19). The additional molecules of histone H1 bound to nucleosomal DNA under these conditions are likely to be bound more weakly than the 1st molecule to bind to the nucleosome (Figs. 1–4). Thus it is possible that the repressive character of chromatin will decrease as more histone H1 is reconstituted into chromatin. This result is in fact observed by Sandaltzopoulos et al. (16).

The Structure of Nucleosome Containing 2 Molecules of Histone H1—We make use of two established assays to demonstrate the association of the mixture of multiple molecules of histone H1 with nucleosomal DNA. The first is the gel retardation assay, which clearly resolves a second nucleoprotein complex that migrates more slowly than nucleosomal DNA containing a single molecule of H1 (Figs. 1, 2, and 4). The second assay is the protection of linker DNA from digestion with micrococcal nuclease. Each molecule of histone H1 protects an additional ~25 bp of linker DNA from digestion by micrococcal nuclease. Each basis for this protection is not known; it could derive from direct contacts made between histone H1 and DNA, or it could derive from allosteric changes in contacts made between the core histones and DNA (25). Mapping the boundaries of histone DNA contacts in the nucleosome containing at least 2 molecules of histone H1 reveals that strong histone-DNA contacts are not apparent (data not shown). Moreover, inclusion of 1 or more molecules of histone H1 has no apparent influence on the wrapping of DNA on the surface of the histone octamer (Fig. 5) (21). Thus major changes in chromatin structure attributed to the incorporation of multiple molecules of linker histone per nucleosome repeat (7) are unlikely to derive from structural changes at the level of the single nucleosome.

Conclusion—Chromatin templates containing either histone H1 bound to naked DNA, a single molecule of histone H1 bound per nucleosome, or 2 molecules of histone H1 bound per nucleosome will differ significantly in the quality and stability of histone H1 association. It is probable that these differences will contribute to variation in the transcriptional properties of these chromatin templates (15, 16, 19).

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