Topoisomerase II Site-directed Alkylation of DNA by Psorospermin and Its Effect on Topoisomerase II-mediated DNA Cleavage*

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Yan Kwok and Laurence H. Hurley‡
From the Drug Dynamics Institute, College of Pharmacy, The University of Texas, Austin, Texas 78712-1074

Psorospermin, a plant-derived antitumor agent, has been shown to selectively alkylate a guanine at the topoisomerase II cleavage site to trap the topoisomerase II-DNA cleaved complex. The results of this study provide further important insight into the mechanism of the topoisomerase II site-directed alkylation of DNA by psorospermin and its subsequent effects on the topoisomerase II-induced DNA cleavage. First, we demonstrate that the topoisomerase II-induced alkylation of DNA by psorospermin occurs at a time preceding the topoisomerase II-mediated strand cleavage event, because it occurs in the absence of Mg$^{2+}$. We confirm that the alkylation of DNA by psorospermin takes place at N-7 of guanine in the presence of topoisomerase II, because substitution of the target guanine by 7-deazaguanine prevents alkylation. Because the stimulation of the topoisomerase II-induced DNA cleavage by psorospermin can be slowly reversed by the addition of excess salt, this indicates that alkylation of DNA by psorospermin traps a reversible topoisomerase II-DNA complex. Both the DNA alkylation by psorospermin in the presence of topoisomerase II and the enzyme-mediated DNA cleavage elevated by psorospermin are more enhanced at acidic pH values, in accordance with the increased stability of the topoisomerase II-DNA complex at acidic pH values. Finally, our results suggest that it is the psorospermin-DNA adducts, not the abasic sites resulting from depurination, that are responsible for the stimulation of the topoisomerase II-mediated cleavage. Because the precise location of the psorospermin within the topoisomerase II cleavage site is known, together with the covalent DNA linkage chemistry and the conformation of the psorospermin-DNA adduct, this structural insight provides an excellent opportunity for the design and synthesis of new, more effective topoisomerase II poisons.

Psorospermin (Fig. 1), a natural product isolated from the roots and stem bark of the African plant Psorospermum febrifugum (1, 2), has been shown to intercalate into the DNA helix and to covalently modify guanine at the N-7 position in the major groove through an epoxide-mediated electrophilic attack (3). It is active against drug-resistant human leukemia lines and AIDS-related lymphoma.1 In the initial mechanistic studies using recovered SV40 DNA from psorospermin-treated cells, it was found that numerous abasic sites were generated on the DNA. The extensive loss of DNA bases was proposed to lead to DNA strand breaks and protein-DNA cross-links, which might be responsible for the cytotoxicity and antitumor activity of this compound (5). Furthermore, although topoisomerase I and II can form cross-links to DNA in the presence of psorospermin, it was suggested that these cross-links are not specific (5). However, we have recently demonstrated that psorospermin alkylation at specific sites on DNA was greatly enhanced in the presence of topoisomerase II, indicating that the antitumor activity of psorospermin might be related to its specific interaction with the topoisomerase II-DNA complex.

Type II topoisomerases are essential nuclear enzymes that regulate the topological status of DNA (7). The topoisomerase II catalytic cycle consists of several discrete steps. First, topoisomerase II forms a noncovalent complex with duplex DNA. In the presence of Mg$^{2+}$, a double-stranded DNA cleavage and re-ligation equilibrium is then established at the prestrand passage stage, with a topoisomerase II tyrosine residue attached to the 5’-phosphate of the broken DNA. Next, after the binding of ATP, an intact DNA duplex is passed through the transient double-stranded break site (or “gate site”). A post-strand passage equilibrium involving DNA breakage and re-ligation is then established. Finally, after the re-ligation, ATP is hydrolyzed to facilitate enzyme turnover and the initiation of a subsequent cycle (8–10).

A number of clinically important anticancer drugs have been shown to kill tumor cells by targeting topoisomerase II (11–13). On the basis of their mechanism of action, the topoisomerase II inhibitors are classified into two groups: topoisomerase II poisons, which interfere with the breakage-rejoining reaction of the enzyme by trapping the covalent reaction intermediate, the cleaved complex; and topoisomerase II suppressors, or catalytic inhibitors, which prevent the cleaved complex formation (12).

In this study, the mechanism of topoisomerase II-mediated site-directed alkylation of DNA by psorospermin and the effect of the psorospermin-DNA adduct on topoisomerase II-mediated DNA cleavage are investigated. Our results show that the enhanced DNA alkylation by psorospermin in the presence of topoisomerase II is dependent on pH but is independent of Mg$^{2+}$ or ATP. This suggests that topoisomerase II-mediated psorospermin alkylation occurs in the initial noncovalent binding step in the topoisomerase II catalytic cycle. We also demonstrate that N-7 of guanine is still the alkylation site for psorospermin in the presence of topoisomerase II. Furthermore, the topoisomerase II-DNA complex trapped by psorospermin is slowly reversible with the addition of excess salt. Last, the psorospermin-DNA adducts, rather than abasic sites from depurination, seem to contribute to the topoisomerase II poison effect.

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‡ To whom correspondence should be addressed: Drug Dynamics Institute, College of Pharmacy, The University of Texas, Austin, TX 78712-1074. Tel.: 512-471-4841; Fax: 512-471-2746; E-mail: dig-dna@mail.utexas.edu.

1 Drug Development Branch, NCI, National Institutes of Health, personal communication to J. Cassady.

2 Kwok, Y., Zeng, Q., and Hurley, L. H. (1998) Proc. Natl. Acad. Sci. U. S. A., in press.
Psorospermin was a generous gift from Dr. John M. Cassidy (The Ohio State University). Electrophoretic reagents (acrylamide, N,N'-methylenebisacrylamide, and ammonium persulfate) were from J. T. Baker, Inc., and N,N,N',N'-tetramethylethylenediamine was from Fisher Scientific. T4 polynucleotide kinase, *Drosophila* topoisomerase II, and [γ-32P]ATP were purchased from Amersham Pharmacia Biotech.

Preparation and End Labeling of Oligonucleotides—The 60- and 80-base oligonucleotides were synthesized on an Expedite 8900 nucleic acid synthesis system (PerSeptive Biosystems) using the phosphoramidite method. The oligonucleotides were eluted out of the column by aqueous ammonia and deprotected by heating at 75 °C for 1 h, followed by 12% denaturing polyacrylamide gel purification. Because the DNA synthesizer is incapable of placing N-7-deazaguanine into the DNA, the oligonucleotides were end-labeled with [γ-32P]ATP using T4 polynucleotide kinase.

Sample Preparation for the Denaturing Gel Retardation Assay—The 5'-end-labeled single-stranded oligonucleotides were obtained by incubating the DNA with T4 polynucleotide kinase and [γ-32P]ATP at 37 °C for 1 h. The labeled strands were then annealed with the complementary strands and purified on an 8% native polyacrylamide gel.

**RESULTS**

Effects of Mg2+ and ATP, and App(NH)p on Psorospermin Alkylation in the Presence of Topoisomerase II—In our previous study, we demonstrated that the alkylation reactivity of psorospermin at the +4′ position (see Fig. 2 for the nomenclature of the position relative to the gate) within the cleavage gate at site B (Fig. 2, oligo J) was enhanced more than 25-fold in the presence of topoisomerase II. It was proposed that a topoisomerase II-mediated structural distortion in DNA creates the high-affinity DNA binding site for psorospermin. However, it was not determined at which stage during the topoisomerase II catalytic cycle this proposed distortion takes place.

The roles of Mg2+ and the high-energy cofactor ATP in the topoisomerase II catalytic cycle have been previously determined (14, 15). The Mg2+ ion is required for the topoisomerase II-mediated DNA cleavage but not for the DNA binding (15). ATP, or its nonhydrolyzable analog App(NH)p, can induce DNA strand passage, but only hydrolyzable ATP can support the enzyme turnover (14, 16). Therefore, by excluding Mg2+ or ATP one at a time, or by substituting App(NH)p for ATP in the reaction buffer, the different steps in the catalytic cycle of topoisomerase II can be studied. Using this method, the step (or steps) at which the site-directed DNA alkylation by psorospermin takes place can be determined.

The DNA substrate used in this study (Fig. 2, oligo J) contains two topoisomerase II cleavage sites, sites A and B in the enlarged region. In the absence of drug, the intensity of the DNA cleavage induced by topoisomerase II is much less at site B than at site A (see below). To examine the psorospermin alkylation in the presence of topoisomerase II, a strand breakage assay was used in which the 5′-end-labeled DNA was incubated with *Drosophila* topoisomerase II to form the topoisomerase II-DNA complex. Psorospermin was then added to the reaction mixture followed by piperidine-heat treatment to generate the strand breakage products from the psorospermin-(N7-guanine) DNA adduct (3). Psorospermin alkylation of the guanine at the +4′ position within cleavage site B (Fig. 2, oligo I) was enhanced dramatically in the presence of topoisomerase II (Fig. 3, compare lanes 4 and 8; the guanine with enhanced alkylation is indicated by an asterisk), as described elsewhere. This enhancement was not affected if either ATP alone (Fig. 3, lane 6) or Mg2+ and ATP (Fig. 3, lane 5) were omitted in the reaction buffer. In addition, substituting ATP with App(NH)p (Fig. 3, lane 7) has no effect on the site-directed alkylation of DNA by psorospermin in the presence of topoisomerase II. These results demonstrate that the enhanced alkylation of DNA by psorospermin in the presence of topoisomerase II is independent of the divalent cation Mg2+, or the high energy cofactor ATP, suggesting that the DNA conformational change that creates a favorable alkylation site for psorospermin is induced by topoisomerase II before the strand cleavage event.

Finally, the effect of order of addition of topoisomerase II and psorospermin on the topoisomerase II site-directed psorospermin alkylation was determined. In Fig. 3, a comparison of lanes 7 and 8 with lanes 9 and 10 shows that there was no difference when topoisomerase II was allowed to incubate with DNA for 5 min before the addition of psorospermin (Fig. 3, lanes 7 and 8), compared with when psorospermin was incubated with DNA for 5 min before the addition of topoisomerase II (Fig. 3, lanes 9 and 10). This result suggests that in the absence of topoisomerase II, psorospermin interacts with DNA predominantly in a noncovalent binding mode, which is reversible, whereas in the presence of topoisomerase II, the DNA distortion produced by the enzyme accelerates the forward psorospermin alkylation reaction by creating a favorable binding and subsequent binding site for the drug.
strand breakage assay (3). Because N-3 and N-7 alkylation of guanine by psorospermin would both produce the DNA strand breakage that is observed, we set out to determine whether psorospermin still alkylates N-7 of guanine in the presence of topoisomerase II, as it does with DNA alone (3). Oligomers containing either guanine (Fig. 2, oligo II) or N-7-deazaguanine (Fig. 2, oligo III) at the 149 position of the cleavage gate B were designed. Strand breakage assays were performed on oligos II and III in the absence (Fig. 4, lane 3) and in the presence (Fig. 4, lane 4) of topoisomerase II. Whereas partial duplex oligo II behaves the same as duplex oligo I, in which psorospermin alkylation was greatly enhanced in the presence of topoisomerase II (Fig. 4A, compare lanes 3 and 4), the partial duplex oligo III containing N-7-deazaguanine was unreactive in both the absence and presence of topoisomerase II (Fig. 4B, compare lanes 3 and 4). These results confirm that N-7 of guanine is also the alkylation site for psorospermin in the presence of topoisomerase II.

The Magnitude of Topoisomerase II-directed Enhanced Psorospermin DNA Alkylation Is pH-dependent—The enhanced DNA alkylation by psorospermin in the presence of topoisomerase II was pH-dependent (Fig. 3). MgCl₂, ATP, and App(NH)p were added to the reaction buffer to test their effects on the topoisomerase II site-directed alkylation of DNA by psorospermin. Lanes 1 and 2 are control DNA without and with heat treatment, respectively. Lanes AG and TC contain the Maxam-Gilbert sequencing reactions. Lanes 3 and 4 contain DNA and 10 μM psorospermin in a reaction buffer of 10 mM imidazole-HCl (pH 6.0) and 50 mM KCl without and with 10 mM MgCl₂ and 1 mM ATP, respectively. Lanes 5–10 contain DNA, 10 μM psorospermin, and 10 units of topoisomerase II in the same buffer as lanes 3 and 4. To this mixture was added 10 mM MgCl₂ (lane 6), 10 mM MgCl₂ and 1 mM App(NH)p (lanes 7 and 9), and 10 mM MgCl₂ and 1 mM ATP (lanes 8 and 10). In lanes 5–8, topoisomerase II was allowed to incubate with DNA for 5 min before the addition of psorospermin. In lanes 9 and 10, psorospermin was incubated with DNA for 5 min before the addition of topoisomerase II.
Cleavage at Site B at pH 6 and 7—It has been demonstrated that psorospermin enhances topoisomerase II-DNA cleavage at site B but reduces it at site A, suggesting that the alkylation of DNA by psorospermin at the cleavage site traps the topoisomerase II-DNA complex. Because the magnitude of this enhancement is pH-dependent, experiments were designed to determine the effect of pH on the psorospermin-stimulated DNA cleavage produced by topoisomerase II. In the absence of drug, the topoisomerase II-DNA cleavage is much less at site B than at site A, regardless of the pH that was used (Fig. 6, lanes 2 (pH 6), 8 (pH 7), and 14 (pH 8)). As the concentration of psorospermin was increased, the topoisomerase II-mediated cleavage at site A was decreased at all the tested pHs (see the quantitation in Fig. 6B; the gel in Fig. 6A was overexposed to detect the small amount of cleavage at pH 8), whereas the cleavage at site B was enhanced at pH 6 and 7 (Fig. 6A, lanes 3–7 and 9–13). At pH 6 and 7 (Fig. 6B), psorospermin (100 μM) enhanced the topoisomerase II-mediated cleavage at site B by 3- and 2-fold, respectively. However, at pH 8 (Fig. 6B), the enhancement was insignificant. This result, together with the experiment described before, demonstrates that both the enhancement of topoisomerase II-mediated DNA cleavage stimulated by psorospermin at site B and the topoisomerase II-directed DNA alkylation by psorospermin at site B are pH-dependent, suggesting that there is a linkage between these two events.

The Topoisomerase II-DNA Cleavage Stimulated by Psorospermin Is Reversible—Topoisomerase II-mediated DNA cleavage induced by many topoisomerase II poisons is reversible either by addition of excess NaCl or at elevated temperatures (17–19). Raising the ion strength or temperature affects the topoisomerase II-DNA dissociation by shifting the equilibrium to the direction of re-ligation. The reversibility of the topoisomerase II-DNA cleavage stimulated by psorospermin was examined by the addition of 0.5 M NaCl to the topoisomerase II cleavage reaction (Fig. 7). In the presence of psorospermin (Fig. 7, lane 2), the DNA cleavage produced by topoisomerase II at site B was enhanced (Fig. 7, compare lanes 2 and 1), as shown in the previous experiments. Addition of 0.5 M NaCl to the reaction mixture led to a time-dependent reversal of the DNA cleavage at sites A and B (Fig. 7, lanes 3–5). The reversal of the cleavage at site B was close to completion after a 60-min incubation (Fig. 7, lane 5), although the rate of reversal at site B appeared slower than at site A. This result indicates that psorospermin alkylation at site B slows the re-ligation process of the enzyme; however, it does not produce an irreversible topoisomerase II-DNA-cleavable complex.

The Psorospermin-(N-7-Guanine) DNA Adduct, Rather Than the Abasic Site, Is Most Likely to Contribute to the Enhancement of Topoisomerase II-mediated Cleavage—Abasic sites have been shown to stimulate DNA cleavage by topoisomerase II when the lesions are located within the 4-base cleavage overhang (20–22). In the case of psorospermin, both psorospermin-DNA adducts and the abasic sites resulting from depurination could contribute to the enhanced topoisomerase II-me-
diated cleavage. To distinguish between these two possibilities, the psorospermin-DNA adduct was separated from unmodified DNA and DNA with abasic sites resulting from depurination of psorospermin-(N-7-guanine) DNA adducts using denaturing gel electrophoresis (Fig. 8). Because the molecular weight of the psorospermin-DNA adduct is greater than that of free DNA, and the molecular weight of unmodified DNA is greater than that of DNA with abasic sites, the psorospermin-(N-7-guanine) DNA adduct should migrate the slowest, and the DNA with abasic sites should migrate the fastest. Using this denaturing gel retardation assay, it should be possible to determine whether there is any depurination during the 60-min period, which is the normal length of time required to produce the topoisomerase II cleavage. In Fig. 8, compared with lanes 1 and
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The DNA Conformational Change Induced by Topoisomerase II, Which Is Responsible for the Enhanced Psorospermin Alkylation, Occurs Preceding the Topoisomerase II Strand Cleavage Event—Although Mg$^{2+}$ is essential to the topoisomerase II-mediated cleavage reaction and the ATPase reaction, it is not required for the binding of the enzyme to DNA (15). Therefore, excluding Mg$^{2+}$ and ATP in the reaction buffer should trap the topoisomerase II-DNA complex in its initial noncovalent complex form. Our results demonstrate that the enhanced psorospermin alkylation at the topoisomerase II cleavage site is independent of Mg$^{2+}$ and ATP. This strongly suggests that the DNA conformational change produced by topoisomerase II that is required for the enhanced psorospermin alkylation takes place at the noncovalent topoisomerase II-DNA complex formation step that occurs before the strand cleavage event. It is therefore the helix distortion induced by the binding of topoisomerase II to DNA that creates the favorable covalent bonding site for psorospermin.

This is not the first case showing that topoisomerase II-induced DNA cleavage is not required for the binding of drugs to the topoisomerase II-DNA complex. A recent study on gyrase, a bacterial topoisomerase II, has demonstrated that the quinolone drugs can still bind to a mutant gyrase-DNA complex when the active site tyrosine in the A subunit of gyrase is replaced by phenylalanine or serine (23). These mutant enzymes can form a complex with DNA but cannot carry out the strand cleavage. In addition, the structural perturbation produced by topoisomerase IV, the other type II bacterial topoisomerase, was observed with both wild-type and mutant topoisomerase IV (which lacks the strand cleavage activity) and was exacerbated by binding of the quinolones (24). Together with our results, these data suggest that type II topoisomerases produce a DNA distortion at the initial noncovalent binding stage, creating high affinity binding sites for drugs. Because this distortion for psorospermin is inferred to be an unwinding of duplex DNA within the gate site, it is likely that this is also the case for the quinolones. This is in accord with a 2:2 quinolone:Mg$^{2+}$ model that we have proposed for the quinolones based on the interaction of the related quinobenzoxazines with topoisomerase II (29).4

Psorospermin Alkylation Traps a Reversible Topoisomerase II-DNA Complex—Several topoisomerase poisons with potential alkylating moieties have been shown to irreversibly trap the enzyme-DNA covalent complexes (25–28). Topoisomerase II-mediated DNA cleavage stimulated by an alkylating camptothecin derivative is unable to reseal in the presence of high salt or proteinase K at 50°C (25). It has been demonstrated that camptothecin interferes with the re-ligation step of the enzyme (28); therefore, an alkylating camptothecin derivative that cannot dissociate from the enzyme-DNA complex may irreversibly trap the topoisomerase I-DNA complex. In contrast to camptothecin, and despite its alkylating nature, psorospermin slows the re-ligation step of topoisomerase II without completely shutting down the process, suggesting that it traps a reversible topoisomerase II-DNA complex.

Acidic pH Increases the Binding Affinity of Topoisomerase II to DNA, Which Enhances Psorospermin Alkylation—It has been demonstrated by DNase I footprinting experiments that...

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there is a stronger binding of Drosophila topoisomerase II to DNA at lower pH (31). At pH 6, the relative intensity of the protection by Drosophila topoisomerase II against DNase I is more than 2 times greater than that at pH 8.2 Therefore, we propose that the stronger binding of topoisomerase II to DNA at pH 6 is probably responsible for the enhanced alkylation of DNA by neutral or alkaline pHs. Presumably the tighter binding of topoisomerase II to DNA extends the duration of complex formation, which in turn increases the opportunity for psorospermin alkylation.

The Psorospermin-DNA Adduct Induces Topoisomerase II-Mediated DNA Cleavage at Site B—in accordance with the instability of (N7-guanine) DNA adducts (30), psorospermin-DNA adducts can undergo a slow depurination over several days at room temperature and neutral pH (3). Because it has been demonstrated that apurinic sites can stimulate topoisomerase II-mediated DNA cleavage when the lesions are located within the 4-base cleavage sites (21), the enhanced topoisomerase II-mediated DNA cleavage by psorospermin at cleavage site B could be produced either directly by the psorospermin-DNA adducts or indirectly by the depurination products, or both. However, under the experimental conditions normally required for the topoisomerase cleavage reaction, we have demonstrated that depurination is unlikely to occur. Therefore, our results suggest that psorospermin-DNA adduct formation is most likely the cause of the topoisomerase II poisoning at cleavage site B, although we cannot completely exclude the possibility that depurination can occur in vivo.

Psorospermin is not the first example of a DNA alkylating agent that can enhance the cleaved complex formation by topoisomerase II. Additionally, some of the chrysophanol derivatives with DNA alkylating potential have been shown to induce the topoisomerase II-mediated DNA cleavage and have more potent antitumor activity in vitro (26). Recently, it has also been reported that covalent attachment of ethidium bromide to DNA converts ethidium bromide from a catalytic inhibitor of topoisomerase II, which prevents the formation of topoisomerase II-mediated DNA cleavage, into a topoisomerase II poison, which enhances the cleaved complex formation (4). However, in previous studies, neither the positions of drug alkylation on DNA nor the conformations of the drug-DNA adduct were determined (4, 26). Thus, to our knowledge psorospermin is the first example of a DNA-alkylating topoisomerase II poison for which the precise location of the drug within the topoisomerase II cleavage site, the chemistry of alkylation, and the conformation of drug-DNA adduct have been determined (3).2 This structural insight provides an excellent opportunity for the design and synthesis of new, perhaps more effective, topoisomerase II poisons for cancer chemotherapy.

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