Mechanism of Cyclization of Pyridine Nucleotides by Bovine Spleen NAD⁺ Glycohydrolase*

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We have shown that bovine spleen NAD⁺ glycohydrolase (EC 3.2.2.5), purified to homogeneity, is a multifunctional enzyme. A time-dependent formation of cADPR from NAD⁺ that did not exceed 1.5–2% of the reaction products was measurable. The cyclase activity of this enzyme was, however, best evidenced by its transformation of NGD⁺ into cyclic GDP-ribose (cGDP). The formation of the cyclic compound could be monitored spectrophotometrically (UV and fluorescence) and by high-performance liquid chromatography; the product ratio of cGDPR/GDP-ribose was 2:1. Bovine spleen NAD⁺ glycohydrolase is also able to hydrolyze cADPR (Muller-Steffer et al. (1994) Biochem. Biophys. Res. Commun. 204, 1279–1285); the kinetic parameters (V/Kₘ) measured exclude, however, the possibility that cADPR is a kinetically competent reaction intermediate in the transformation of NAD⁺ into ADP-ribose. Experimental data indicating that NAD⁺ glycohydrolase-catalyzed hydrolysis and methanolysis of NA(G)D⁺ occurred at the expense of the formation of the cyclic compounds are in favor of a reaction mechanism involving the partitioning of a common oxocarbenium reaction intermediate between the different acceptors. Thus E(A)(G)D-riboyl oxocarbenium intermediate can react according to i) intramolecular processes with the positions N-1 of adenine and N-7 of guanine to give cA(G)DPR as reaction products, and ii) intermolecular reactions with water (formation of A(G)DP-ribose) and methanol (formation of methyl A(G)DP-ribose). We attribute the marked difference in yield of cADPR and cGDPR to the intrinsic reactivity (nucleophilicity and positioning) of the purine N-positions that are involved in the cyclization reactions within the E(A)(G)D-riboyl oxocarbenium complexes.

Cyclic ADP-ribose, which was originally discovered in sea urchin eggs, is thought to be the endogenous regulator of the Ca²⁺-induced Ca²⁺-release process mediated by the ryanodine receptors (reviewed in Lee et al., 1994). In invertebrates, this new metabolite is the exclusive reaction product obtained from NAD⁺ by an ADP-riboyl cyclase (Lee and Aarhus, 1991; Hellmich and Strumwasser, 1991). In mammalian tissues no equivalent enzyme could be detected; however, a high sequence homology was found between the cyclase from Aplysia californica and CD38, a human lymphocyte cell surface antigen, for which no biological activity was hitherto known (States et al., 1992). CD38 revealed itself to be a multifunctional enzyme; i.e. in addition to catalyzing the hydrolytic cleavage of NAD⁺ into ADP-ribose, it was also able to produce cADPR, albeit in small amounts (less than 2–3% of reaction products), and to hydrolyze cADPR into ADP-ribose (Howard et al., 1993). Similar catalytic activity had previously been established for a canine spleen enzyme that had the characteristics of a NAD⁺ glycohydrolase (Kim et al., 1993a). The low yield of cADPR production by these mammalian systems was attributed to their multifunctionality: the cyclic metabolite does not accumulate because it is turned over by the same enzyme that produces it (Kim et al., 1993a; Lee, 1994; Lee et al., 1995). In apparent agreement with this hypothesis, it was established by Graeff et al. (1994) that NGD⁺, an analogue of NAD⁺, is converted in high yield by CD38 into cyclic GDP-ribose, a metabolite that cannot be further transformed.

Since the occurrence of CD38 was originally thought to be restricted to B and T lymphocytes (Malavasi et al., 1994; Lund et al., 1995) and erythrocytes (Zocchi et al., 1993), it was of interest to broaden the issue of the biosynthesis of cADPR in mammalian systems by investigating the possible contribution of the classical NAD(P)⁺ glycohydrolases (EC 3.2.2.5 and 3.2.2.6). These enzymes have been known for several decades and they have a wider tissular and cellular distribution than CD38 (Price and Pekala, 1987). We have been engaged for many years in the study of the molecular mechanism of bovine spleen NAD⁺ glycohydrolase and have shown conclusively that this enzyme catalyzes a dissociative mechanism; i.e. the nicotinamide-ribose bond is cleaved to generate an enzyme-stabilized oxocarbenium ion-type intermediate that reacts in a non-rate-limiting step with acceptors such as water (hydrolysis), methanol (methanolysis), or pyridines (transglycosidation) (Schuber et al., 1979; Tarnus and Schuber, 1987; Tarnus et al., 1988; Handlon et al., 1994). Recently we have also shown that this enzyme was able to hydrolyze cADPR into ADP-ribose; the measured kinetic parameters, however, excluded the possibility that cADPR is a kinetically competent reaction intermediate in the conversion of NAD⁺ into ADP-ribose (Muller-Steffer et al., 1994).

In the present study we provide evidence that bovine spleen NAD⁺ glycohydrolase can cyclize NGD⁺ into cGDP in high yields and that the low net conversion of NAD⁺ into cADPR is not due to a fast turnover that prevents it from accumulating but to a lesser reactivity of the adenine ring, compared to guanine, with the intermediary oxocarbenium ion.

EXPERIMENTAL PROCEDURES

Chemicals—NAD⁺, NGD⁺ and CHAPS were from Sigma. adenine-U-¹³C]NAD⁺ (604 Ci/mol) was from NEN DuPont (France). cADPR and cGDPR were prepared by incubating respectively NAD⁺ and NGD⁺ with Aplysia ADP-riboyl cyclase and were purified by HPLC.

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Enzymes—ADP-ribosyl cyclase from A. californica was from Sigma. NAD$^+$ glycohydrolase (with a specific activity of 180 U/mg protein) was solubilized from calf spleen microsomes and purified as described previously (Muller-Steffner et al., 1993).

Transformation of NGD$^+$ by NAD$^+$ Glycohydrolase—The conversion of NGD$^+$ into cGDP-ribose was followed by two continuous assays (Graeff et al., 1994): (i) spectrophotometrically, by monitoring the increase in absorbance at 300 nm, and (ii) fluorometrically, by monitoring the increase in fluorescence at 310 nm (excitation at 280 nm). To that end, NGD$^+$ (final concentration, 100 μM) was incubated at 37°C in a 10 mM potassium phosphate buffer, pH 7.4, containing 0.5% (w/v) CHAPS, in the presence of 50 milliunits of NAD$^+$ glycohydrolase, which, compared to NAD$^+$, is a better substrate for bovine spleen NAD$^+$ glycohydrolase. The enzyme (50 milliunits) was incubated at 37°C with NGD$^+$ (100 μM) in 10 mM potassium phosphate buffer (pH 7.4) containing 0.5% (w/v) CHAPS (final volume, 1 ml). The progress curve represents the increase in fluorescence emission measured at 310 nm (excitation at 290 nm). Inset, double-reciprocal representation of rate of NGD$^+$ transformation in the presence of 6 milliunits NAD$^+$ glycohydrolase versus substrate concentration (10–200 μM). Initial rates were calculated from progress curves obtained by HPLC analysis on aliquots of the reaction mixture (see “Experimental Procedures”).

Analysis of the Reaction Products by HPLC—Product analysis was performed on aliquots of the reaction medium by using a Waters HPLC system. Chromatography was carried out on a 3.9 mm × 30 cm Bondapak C$_{18}$ column (Waters) operated at ambient temperature, at a flow rate of 1 ml/min. The compounds were eluted isocratically with a 10 mM ammonium phosphate buffer, pH 5.5, containing 1.2% (v/v) acetonitrile and detected by their UV absorbance at 260 nm or by radiodetection (Flow-one, Packard Instruments). Peak areas were integrated and those obtained from UV recordings were normalized, using calibration curves, to take into account the differences in the molar extinction coefficients of the reaction products.

**Determination of the Kinetic Parameters of NGD$^+$**—NGD$^+$ (final concentrations, 10–200 μM) was incubated at 37°C in a 10 mM potassium phosphate buffer, pH 7.4, containing 0.5% (w/v) methanol (final concentration, 7.41%). In the enzymatic experiment, NGD$^+$ (100 μM; final volume, 1 ml) was incubated at 37°C in a 10 mM potassium phosphate buffer, pH 7.4, containing 0.5% (w/v) CHAPS and increasing concentrations of methanol (0, 1, 2, and 3%) in the presence of 50 milliunits of NAD$^+$ glycohydrolase. Reaction progress was followed spectrophotometrically at 300 nm. In both enzymatic and non-enzymatic reactions, product analysis was obtained on aliquots by HPLC as described above.

**Conversion of NAD$^+$ into cADPR by NAD$^+$ Glycohydrolase**—In the nonenzymatic experiment, NAD$^+$ (100 μM; final volume, 1 ml) was incubated at 80°C in 25 mM sodium phosphate buffer, pH 7.0, containing 30% (v/v) methanol (final concentration, 7.41%). In the enzymatic experiment, NAD$^+$ (100 μM; final volume, 1 ml) was incubated at 37°C in a 10 mM potassium phosphate buffer, pH 7.4, containing 0.5% (w/v) CHAPS and increasing concentrations of methanol (0, 1, 2, and 3%) in the presence of 50 milliunits of NAD$^+$ glycohydrolase. Reaction progress was followed spectrophotometrically at 300 nm. Initial rates were calculated from progress curves obtained by HPLC analysis on aliquots of the reaction mixture (see “Experimental Procedures”).

**RESULTS**

**Cyclization of NAD$^+$ Catalyzed by Calf Spleen NAD$^+$ Glycohydrolase**—NGD$^+$, which, compared to NAD$^+$, is a better substrate for bovine spleen NAD$^+$ glycohydrolase, was incubated at 37°C in a 10 mM potassium phosphate buffer, pH 7.4, containing 0.5% (w/v) CHAPS, in the presence of 50 milliunits of NAD$^+$ glycohydrolase. Reaction progress was followed spectrophotometrically at 300 nm. Initial rates were calculated from progress curves obtained by HPLC analysis on aliquots of the reaction mixture (see “Experimental Procedures”).

Kinetic parameters of the transformation of NGD$^+$ into cyclic ADP-ribose were calculated from the reaction rates obtained from the HPLC profiles (Fig. 1, inset). The $K_m$ of bovine NAD$^+$ glycohydrolase for NGD$^+$ was estimated to be 24 μM, which is equivalent to that of NAD$^+$ (26.2 ± 3.6 μM under the same experimental conditions). The $V_{max}$ of the enzyme for NGD$^+$ was 80 μmol/min/mg of protein. When considering NGD$^+$ and NAD$^+$ as competing substrates for the active site of calf spleen NAD$^+$ glycohydrolase, the ratio of their specificity constants $V/K_m$ (i.e. 3.3 and 6.9 liters/min/mg protein respectively) is about 2.1 in favor of NAD$^+$). It appears, therefore, that NGD$^+$ is an excellent substrate for bovine NAD$^+$ glycohydrolase and that the only difference between this dinucleotide and NAD$^+$ lies in the products generated during enzymatic catalysis.

**Conversion of NAD$^+$ into Cyclic ADP-ribose by Calf Spleen NAD$^+$ Glycohydrolase**—Because of the ability of NAD$^+$ glycohydrolase to catalyze the conversion of NGD$^+$ into cyclic GDP-
ribose, we have reassessed the formation of cADPR from NAD+, which we had previously estimated to be very low (Muller-Steffner et al., 1994). Thus [14C]NAD+ was incubated in the presence of the enzyme and the reaction products were analyzed by HPLC using on-line UV and radioactivity detectors. The main product was ADP-ribose, but we could establish the formation, albeit in low amounts, of a product presenting a slightly different retention time (Fig. 3). It amounted to about 1.5% ($\pm$ 0.3%; $n = 6$) of cADPR. HPLC analyses were obtained on a reverse-phase $\mu$Bondapak C18 column (see “Experimental Procedures”).

To verify this hypothesis, which implies that these different acceptors compete for the same oxocarbenium ion, we decided to perform the reaction in presence of methanol. We have previously demonstrated that the oxocarbenium intermediate formed during the NAD+ glycohydrolase-catalyzed transformation of NAD+ reacts about 50-fold faster with methanol than with water (Tarnus et al., 1988). Methyl ADP-ribose is formed with retention of configuration, and in the presence of high enough concentrations of methanol, it becomes the preponderant reaction product. Thus, if a similar water/methanol partitioning ratio is found in the transformation of NGD+, one should observe the formation of methyl GDP-ribose at the expense of cGDPR.

**TABLE I**

| Methanol | (cGDP-ribose)/(GDP-ribose) + (methyl GDP-ribose) |
|----------|-------------------------------------------------|
| 0        | 2.10                                            |
| 0.5      | 1.34                                            |
| 1        | 1.12                                            |
| 2        | 0.59                                            |
| 3        | 0.36                                            |

**Fig. 2.** HPLC elution profile of the products obtained by incubation of NGD+ with NAD+ glycohydrolase. NGD+ (100 $\mu$M) was incubated for different time periods at 37 °C in a 10 mM potassium phosphate buffer (pH 7.4) containing 0.5% (w/v) CHAPS and 6 milliunits of enzyme, in the absence (A) or presence (B) of 3 M methanol. HPLC analyses were obtained on a reverse-phase $\mu$Bondapak C18 column (see “Experimental Procedures”). a, cGDP-ribose; b, GDP-ribose; c, methyl GDP-ribose; d, NGD+; e, nicotinamide.

**Fig. 3.** Formation of ADP-ribose and cyclic ADP-ribose from NAD+ catalyzed by bovine spleen NAD+ glycohydrolase. NAD+ (50 $\mu$M) and 106 dpm [adenine-$U$-14C]NAD+ were incubated at 37 °C in a 10 mM potassium phosphate buffer (pH 7.4) containing 0.5% (w/v) CHAPS in the presence of 5 milliunits of enzyme. Aliquots were removed at given time intervals and analyzed by HPLC as described under “Experimental Procedures.” Quantitative estimates (given as percentage of total radioactivity) for the formation of ADP-ribose (○) and cADPR (■) were obtained from the radiochromatograms. Note the difference in scale for the formation of cADPR.
glycohydrolase in the presence of increasing concentrations of methanol was analyzed by HPLC. In the presence of this acceptor, a new reaction product was formed (Fig. 2B) whose retention time was identical to one of the methyl GDR-ribose isomers obtained by spontaneous solvolysis of NAD⁺ in presence of 30% (v/v) methanol. Analysis of the data indicated that, similarly to NAD⁺, the partitioning ratio² was 52.4 (± 4.6; n = 6) in favor of methanolysis. As indicated in Table I, increasing concentrations of methanol led to increased formation of methyl GDP-ribose, at the expense of cGDPR; this demonstrates that methanolysis, as expected from our hypothesis, competes with the cyclization process. It was also found that addition of methanol did not increase the turnover of NAD⁺, confirming that the reaction of the oxocarbenium ion with acceptors is a fast step in the catalytic process of NAD⁺ glycohydrolase relative to the formation of this intermediate (Schuber et al., 1976). Importantly, in control experiments performed with the same concentration of enzyme and using a continuous flurometric assay, NAD⁺ glycohydrolase was found to be unable to transform cGDPR even in the presence of the highest concentrations of methanol used above.

Nonenzymatic Hydrolysis of cADPR and cGDPR—The nonenzymatic hydrolysis of cADPR and cGDPR was studied in phosphate buffer at pH 6.0. Under these experimental conditions, where pyridinium analogues of NAD⁺ are hydrolyzed according to a monomolecular mechanism (Tarnus and Schuber, 1987), the N-1-position of the adenosine moiety of cADPR should be fully positively charged (Kimber, 1987), the N-1-position of the adenosine moiety of cADPR according to a monomolecular mechanism (Tarnus and Schuber, 1987), thus favoring the formation of cyclic ADP-ribose by mammalian systems and its relevance to the mobilization of intracellular Ca²⁺ is still under intense study (Lee et al., 1994). In this communication, we have shown that the “classical” bovine spleen NAD⁺ glycohydrolase is able to catalyze the transformation of NAD⁺ into ADP-ribose (its classical hydrolytic reaction) and into a small fraction of cADPR (less than 2%). The cyclase activity of this enzyme was much better evidenced when using NAD⁺ as substrate, where cGDPR represented the major reaction product. Moreover, as shown previously, this NAD⁺ glycohydrolase is also able to hydrolyze cADPR into ADP-ribose ( Muller-Steffner et al., 1994), but in contrast does not readily convert cGDPR into GDP-ribose. Altogether, bovine spleen NAD⁺ glycohydrolase shares with CD38 (Howard et al., 1993) and a recently described canine spleen NAD⁺ glycohydrolase (Kim et al., 1993a) the different catalytic activities that are involved in the metabolism of cADPR. Such a result, of course, raises the question of the identity and/or the differences in tissular localization and functions between CD38 and NAD⁺ glycohydrolases. Although it recently became apparent that the distribution of CD38 is somewhat wider than was previously believed (Funaro et al., 1995), it should be emphasized that NAD⁺ glycohydrolases are found associated with cells such as Kupffer cells in liver (Amar-Costescu et al., 1985) and microglial cells (Bocchini et al., 1988) and with organelles such as mitochondria (Masmoudi and Mandel, 1987), where no CD38 has been reported so far.

An important issue is the very low production of cADPR by the mammalian enzymes, as compared to the invertebrate enzymes. The reaction conditions were similar to those that were used for the nonenzymatic solvolysis of NAD⁺ and that yield a mixture of α- and β-methyl ADP-ribose (Tarnus et al., 1988). In analogy with NAD⁺, the enzymatic methanolysis of NAD⁺ presumably yields the β-methyl GDP-ribose isomer; this point remains, however, to be verified.

The partitioning ratio is defined (Tarnus et al., 1988) by the ratio:

\[ K = \frac{\text{methyl GDP-ribose}}{\text{GDP-ribose}} \times \frac{\text{H}_2\text{O}}{\text{CH}_3\text{OH}} \]  

(Eq. 1)

² Formally, the positive charge is delocalized over the N-7 and N-9 positions. Analysis by HPLC of the hydrolytic product(s) revealed a single peak, but we have not determined the nature of the bond, i.e. N(7)-C(1)′ or N(9)-C(1)′, that is prevalently hydrolyzed.

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\[ \frac{\text{methyl GDP-ribose}}{\text{GDP-ribose}} \times \frac{\text{H}_2\text{O}}{\text{CH}_3\text{OH}} \]  

⁴ It should be noted that within the active site of the enzyme, the ADP-riboyl oxocarbenium ion might not be a single species with regard to the configuration of the adenine-ribose bond. Thus, when generated from NAD⁺, its methanol/water partitioning ratio is 50 (which might be an average value for the different conformers), whereas when generated from cADPR, this ratio drops to 30 (Muller-Steffner et al., 1994), indicating that an oxocarbenium ion generated from a species where the adenine has exclusively a syn configuration is less stabilized by the active site.

Fig. 4. Partitioning of the oxocarbenium intermediate occurring in the reaction catalyzed by bovine spleen NAD⁺ glycohydrolase. The enzyme-stabilized oxocarbenium intermediates generated from NADGD⁺ during the rate-limiting step undergo intramolecular cyclization reactions involving the attack by the positions N-1 of adenine and N-7 of guanine. The formation of cADPR (minor pathway) and cGDPR are in competition with the intermolecular reaction of the intermediate with water (formation of A(G)DPR) and methanol (formation of methyl A(G)DPR), respectively. The low amount of cADPR formed by the enzyme, compared to cGDPR, is proposed to be related to a lower rate of intramolecular reaction, which might be ascribed to a combination of a lower nucleophility of the N-1 of adenine, compared to N-7 of guanine, and/or a less favorable configuration of the adenine ring for cyclization.⁵
ADP-ribosyl cyclases. This was attributed to the absence of accumulation of the cyclic metabolite because of its fast hydrolysis by the very same enzyme that produces it. Several mechanisms have been published to explain that point (Kim et al., 1993a; Lee et al., 1995; Graeff et al., 1996), and since the outcome of the reaction catalyzed by NAD\(^+\) glycohydrolases is that of an ADP-ribosyl cyclase coupled to an ADPR hydrolase, it has been proposed that these enzymes, for which no physiological roles had been found so far, were similar to CD38; i.e. enzymes whose multifunctionality had been overlooked. If from our studies it seems obvious that classical mammalian NAD\(^+\) glycohydrolases are indeed multifunctional, their very low production of cADPR from NAD\(^+\) cannot be attributed to a fast hydrolysis of this cyclic metabolite into ADP-ribose. On the contrary, as shown in this study, the very limited capacity of calf spleen NAD\(^+\) glycohydrolase to generate cADPR is a direct consequence of the reaction mechanism of the enzyme. We have conclusively demonstrated that the cyclization reactions, which involve the N-1-position of adenine and the N-7-position of guanine in NAD\(^+\) and NGD\(^+\), respectively, are in competition with the nucleophilic attack of a common intermediary oxocarbonium ion by a water molecule that yields (A)(G)DP-ribose (Fig. 4). A question is raised about the origin of such a marked difference in the extent of cADPR and cGDPR formation. It is well known that in adenine the most nucleophilic position is N-1, whereas in guanine it is N-7 (Jones and Robins, 1963; Singer, 1975); it is therefore probably not a coincidence that the cyclic compounds that are formed are precisely the ones that involve these nucleophilic centers in the purine rings. Moreover, the fact that 1,N\(^{6}\)-etheno-NAD\(^+\), whose N-1 is masked, is also cyclized at position N-7 (Zhang and Sih, 1995; Graeff et al., 1996) indicates that in the active site of these enzymes, the purine rings do not have a fixed binding pattern. It appears therefore that the differences in the formation in cADPR and cGDPR in this intramolecular cyclization reaction might reflect the differences in nucleophilicity of the two nitrogens in the active site of the enzyme; indeed, it is well known that in many reactions involving the alkylation of bases, N-7 of the guanine ring is more nucleophilic than N-1 of adenine (Brown, 1974; Singer, 1975; Beranek et al., 1980). Interestingly, a high sensitivity of NAD\(^+\) glycohydrolases to the nucleophilicity of attacking pyridines, which yield by transglycosidation pyridinium analogues of NAD\(^+\), has been noted before (Yost and Anderson, 1983; Tarnus and Schuber, 1987).

Since the hydrolysis of the cyclic compounds by NAD\(^+\) glycohydrolase is also expected to yield an intermediary oxocarbonium ion (Muller-Steffner et al., 1994), the observation that cADPR is hydrolyzed much better than cGDPR is, on the first analysis, in good agreement with our previous studies, which demonstrated a very high dependence of the rate of such reactions on the pH of the leaving group (\(\rho_H = -0.9\)) and an excellent correlation with the chemical stability of the pyridinium-ribose bond (Tarnus and Schuber, 1987). Under unimolecular hydrolysis conditions (pH 6.0), however, the half-life of cGDPR is only about 5-fold higher than that of cADPR, indicating that the difference in energy of their scissile bonds is not as important as anticipated from their behavior as substrates of NAD\(^+\) glycohydrolase. It seems, therefore, that other factors are of importance in explaining such differences, which might be related to the mode of binding of cADPR and cGDPR to the active site of the enzyme. Moreover, since the energy of the ribose-nitrogen bonds in cA(G)DP also reflects the nucleophilicity of the N-1 and N-7 positions in the adenine and guanine moieties during the enzyme-catalyzed cyclization reactions, the much favored formation of cGDPR might also indicate the occurrence of additional factors, such as e.g. a better position-
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