Ionic Inhibition of Catalytic Phosphorylation of Histone by Bovine Brain Protein Kinase

(Received for publication, October 21, 1976)

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The effects of various ions commonly found in protein kinase assays upon the rate of histone phosphorylation catalyzed by the highly purified bovine brain enzyme, protein kinase I, have been investigated. Sodium, potassium, and magnesium were found to inhibit histone phosphorylation by protein kinase I in a similar manner. The degree of inhibition by any of these cations was demonstrated to be directly proportional to the square root of the ionic strength of the assay medium. The relationship between the ionic strength of the assay medium and the rate of histone phosphorylation catalyzed by protein kinase I was employed to correct for the rate of histone phosphorylation at various magnesium acetate concentrations to a standard ionic strength. When this was done an analysis of the previously postulated rate law for histone phosphorylation catalyzed by protein kinase I gave a binding constant for the magnesium-ATP complex which was in agreement with that expected for this complex on the basis of various binding constants available in the literature.

These results demonstrate that it is unnecessary to postulate a specific ion inhibition process for protein kinase I by the ions employed in this study. They also support the reasonable assumption that magnesium ion binds to ATP at or prior to the rate-determining step in histone phosphorylation catalyzed by protein kinase I. The expression developed in this paper for the effect of ionic strength upon protein kinase I activity can now be used to correct activity measurements made under various assay conditions to a standard assay state, allowing facile comparisons of kinetic data. It should be possible to develop similar expressions for other protein kinases and substrates to permit useful interpretation of kinetic data.

Divalent metal ions are required for the catalytic activity of most protein kinases (for a review, see Ref. 1). It is generally believed that the metal ion interacts primarily with the nucleotide triphosphate substrates of these enzymes. The interaction of divalent cations with nucleotide triphosphates and their involvement in nucleotide bridged complexes with enzymes has been recently reviewed by Mildvan (2).

A divalent cation requirement has been reported for partially purified cyclic AMP-dependent bovine brain protein kinase (3). Also, at high metal ion concentrations, significant inhibition of histone phosphorylation was found, and specific inhibition by magnesium ion was suggested to occur for this enzyme. Other investigations of skeletal muscle protein kinases have led to the suggestion of regulatory functions for Ca$^{2+}$ and the ATP-Mg$^{2+}$ complex (4, 5). The observation of these regulatory or inhibitory effects poses a significant problem for any investigation of the kinetic mechanism of action of protein kinases. As far as we are aware, no attempts to quantitate such effects for cyclic AMP-dependent protein kinases have been described. In a previous publication we presented an analysis of the catalytic phosphorylation of histone by a highly purified cyclic AMP-dependent bovine brain protein kinase (protein kinase I) under conditions of constant ionic strength, and we developed a steady state rate equation which could describe this reaction (6).

In the present paper we wish to report the results of an investigation of the effects of magnesium ion and a number of salts commonly found in protein kinase assays upon the catalytic activity of protein kinase I. We have found that the influence of the various ions employed is most simply described as an ionic strength effect. As will be discussed, we have developed an equation which can be used to correct for the observed inhibition due to changes in ionic strength, and we have employed this correction and the previously described steady state rate equation (6) to obtain an association constant for the magnesium-adenosine triphosphate complex which is in agreement with that expected under the assay conditions.

EXPERIMENTAL PROCEDURES

Materials—Histone type II (calf thymus mixture) was obtained from Sigma. This calf thymus histone mixture was isolated by extraction with 1 M NaCl, precipitation in water, acid extraction, reprecipitation with ethanol, and drying of the final product. Histones isolated by this approach have been found to be of good purity, relatively free of nonhistone protein and DNA (7). The commercial product was analysed by gel electrophoresis to assure qualitatively its content of all undegraded histone subfractions. Two different lots of Sigma histone type II were employed, and both lots gave similar results in the studies reported here. Buffer chemicals were all of the highest grade commercially available. A small volume glass electrode (less than 100 μl volume requirement) was employed for pH measurements of selected assay samples.

1 The abbreviations used are: cyclic AMP, adenosine 3',5'-monophosphate; Mes, 2-(N-morpholino)ethanesulfonic acid; [γ-32P]ATP, adenosine 5'-[pyro-(γ-32P)]triphosphate.

2 Personal communication from the Sigma Chemical Co., St. Louis, Mo.
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model DR pH meter. High specific activity (1 to 4 mCi/mmol) [γ-32P]ATP was prepared according to the method of Glynn and Chappell (8), and the product was greater than 97% radiochemically pure by polyethyleneimine cellulose chromatography as described by Casbel et al. (9). Scintillation chemicals were obtained from Packard, Triton X-100 was purchased from Amersham/Searle.

Methods—The enzymatic phosphorylation of histone was performed in 50 mM sodium acetate or 50 mM Mes buffers, pH 6.0. The 200-μl incubation volume also contained 40 μg of histone, 5 mM [γ-32P]ATP, and the enzyme concentration was such that initial rate conditions were readily maintained. Assays were performed with or without 5 μM cyclic AMP, as indicated. Stock solutions (2 M) of the various salts employed were prepared in distilled, deionized water. Then, depending upon the salt and the buffer, the pH was adjusted to 6.0 with 13 N NaOH and either concentrated HCl or glacial acetic acid. The resultant stock solutions were appropriately diluted in the assay buffer so that the desired final concentration of salt could be added in a volume of 15 μl to the incubation mixture. For the measurements from which the apparent association constant of Mg2+ with ATP was determined, a 40 mM magnesium acetate (80 mg eq of acetate) stock solution was prepared in deionized, distilled water and titrated to pH 6.0 with glacial acetic acid to give a final acetate concentration of about 50 mM. This solution was stored at 5°C prior to use (40 μl per assay). Repetitive standard assays with the same final acetate concentration were performed every 2 weeks yielded the original specific activity for protein kinase I after 2 to 3 weeks of storage of the histone stock solution. Fresh stock solution of histone for assays was prepared as a 1 mg/ml solution in deionized, distilled water and titrated to pH 6.0 with glacial acetic acid. Appropriate amounts of this stock solution (0 to 100 μl) were added to the incubation mixture. For the measurements from which the apparent association constant of Mg2+ with ATP was determined, a 40 mM magnesium acetate (80 mg eq of acetate) stock solution was prepared in deionized, distilled water and titrated to pH 6.0 with glacial acetic acid to give a final acetate concentration of about 50 mM. This solution was stored at 5°C prior to use (40 μl per assay). Repetitive standard assays with the same final acetate concentration were performed every 2 weeks yielded the original specific activity for protein kinase I after 2 to 3 weeks of storage of the histone stock solution. Fresh stock solution prepared every 2 weeks yielded the original specific activity for protein kinase I in the standard assay. All components of the assay except [γ-32P]ATP were added to 5-ml conical glass test tubes at 4°C over a 15-min period. Additions were always made in the following order, as required: buffer, salt, histone, protein kinase I, and cyclic AMP. The mixture was allowed to stand on ice for 30 min, and the reactions were then initiated by the addition of [γ-32P]ATP and terminated and analyzed as described before (6).

The ionic strength was calculated with the standard equation, ionic strength = (r/z) 2 (concentration) (ionic charge) 2, employing the known pKₐ values for acetate, phosphate, Mes and the stability constant for the Mg²⁺(CH₃COO⁻) complex. The Mg²⁺(CH₃COO⁻) complex has a stability constant of about 10²· M⁻¹ (10), and its formation was assumed not to interfere with ATP-Mg²⁺ substrate complex formation. It was known that within an acetate concentration range of 0.002 to 0.05 M formation of the ternary complex Mg²⁺(CH₃COO⁻)₂⁻ was not significant (11), and the formation of the ternary complex was ignored in the ionic strength calculations. The resulting total magnesium concentration in the final assay mixture. The variation in pH at the extreme concentrations of all salts employed in both Mes and sodium acetate buffers was found to be negligible.

RESULTS AND DISCUSSION

Various sodium, potassium, and magnesium salts were found to inhibit protein kinase I catalytic activity in both Mes and sodium acetate buffer systems with an initial 10 mM magnesium acetate concentration. At a given salt concentration the inhibition of the catalytic activity of protein kinase I due to the presence of divalent magnesium was consistently greater than that due to the monovalent cations. This observation suggested the operation of a simple ionic strength effect, and plots of enzyme activity against ionic strength were constructed as shown in Fig. 1. Within experimental error, there is no significant difference in the response to increasing ionic strength for all of the salts employed.

A quantitative description of this ionic strength effect was derived as follows. A very simple formulation of the steady state rate law is given in Equation 1 where ES is the enzyme-substrate complex which breaks down to give products (6); then, the simplest assumption is that the ionic strength effect is primarily upon the activity of ES as expressed in Equation 2, where α is the activity coefficient of ES. If α is treated in a straightforward fashion according to Debye-Hückel theory (see Ref. 12 and Equation 5), Equation 4 is obtained.

\[ v = k \langle ES \rangle \]

\[ v = k_0 \langle ES \rangle \]

\[ \log v = \log k \langle ES \rangle - \text{constant} \sqrt{\mu} \]

The linear least squares slopes for each specific salt in Mes buffer and sodium acetate buffer are presented in Table I. All of the slopes are within the range of 4.5 ± 1.5. Ionic strengths from 0.06 to 0.5 were employed. Considering the limitations of the application of Debye-Hückel theory to complex enzymatic reactions, the data obtained in the present work fit the mathematical description of Equation 4 to within experimental er-

![FIG. 1. Dependence of rate of histone phosphorylation upon ionic strength. Protein kinase I concentration = 1.8 × 10⁻⁵ M. Initial magnesium acetate concentration = 10 mM. Added salts: ↓, NaCl; →, sodium acetate; ↓, sodium phosphate; ○, potassium phosphate; ▲, MgCl₂; A, Mes. The solid line represents (rate of histone phosphorylation) = (150 activity units)/(10⁻² μM) where μ is the ionic strength calculated as described in the text.](http://www.jbc.org/)

| Salt       | Mes buffer | Sodium acetate buffer |
|------------|------------|-----------------------|
| MgCl₂      | 4 4.2 ± 0.1 1.0  | 6 3.4 ± 0.3 0.99 |
| Mg-acetate | 4 4.5 ± 0.2 1.0  | 4 3.3 ± 0.2 0.99 |
| Na-acetate | 4 5.2 ± 0.2 1.0  | 4 5.0 ± 0.5 0.98 |
| NaCl       | 4 3.1 ± 0.5 0.95 | 5 4.7 ± 0.1 1.0  |
| Na-phosphate | 4 5.6 ± 0.5 0.99 | 5 4.7 ± 0.1 1.0  |
| K-phosphate | 4 5.8 ± 0.6 0.98 | 4 4.9 ± 0.4 0.98 |
| MgCl₂      | 4 4.1 ± 0.3 0.99 | 4 4.1 ± 0.3 0.99 |

| Salt       | Mes buffer | Sodium acetate buffer |
|------------|------------|-----------------------|
| MgCl₂      | 4 3.6 ± 0.1 1.0  | 5 3.3 ± 0.2 0.99 |
| Mg-acetate | 7 5.1 ± 0.5 0.99 | 4 5.5 ± 0.2 1.0  |
| Na-phosphate | 4 5.9 ± 0.1 1.0  | 5 5.9 ± 0.1 0.93 |
| K-phosphate | 5 3.9 ± 0.5 0.98 | 5 3.9 ± 0.5 0.98 |

a Slope ± standard deviation of the slope of least squares line.

b Square of correlation coefficient of least squares line.
The inhibition due to increasing ionic strength may result from an effect upon the histone, protein kinase I or both. It is well known that various histone fractions tend to form aggregates of increasing molecular weight with increasing ionic strength (7, 13). The ionic strengths employed in the present study are well within the range of ionic strength shown to affect histone aggregation. Lysine-rich histone subfraction f, Sigma type V, is considered to be the only subfraction which does not undergo self-aggregation with increasing ionic strength (7). However, this subfraction was phosphorylated to the same extent in our standard protein kinase I assay as the other subfractions which are expected to form aggregates under the conditions of this assay (6, 7). Lyophilized or aged histone preparations such as commercial preparations are known to have increased amounts of β structure when compared with fresh histone preparations, and this is considered to be an indication of partial denaturation of the histone (7). Alterations in histone secondary structure with changes in ionic strength may also affect the rate of histone phosphorylation. Although the chemical basis of the inhibition resulting from increasing ionic strength must be considered in any investigation of the mechanism of action of protein kinase I catalytic activity, it is now assumed that the enzyme employs the complexes (ATP·Mg)2+ and (ATP·MgH+) equally well as substrates and that no other significant forms of ATP and its complexes are utilized.

The marked inhibition of protein kinase I catalytic activity with increasing ionic strength must be considered in any investigation of the mechanism of action of protein kinase I involving varying ionic strengths. Equation 4 provides a means of correcting the data obtained at varying ATP and Mg2+ concentrations to a common ionic strength. Such a correction is required for an investigation of the interaction of ATP, magnesium ion, and protein kinase I. From data for the rate of histone phosphorylation determined over a range of Mg2+ and ATP concentrations corrected for the ionic strength effect, it might be feasible to estimate the association constant for the ATP·Mg2+ substrate complex, if this complex is involved prior to or in the rate-determining step. The system chosen for this analysis contained 50 mM sodium acetate, pH 6.0, 40 μg of histone (0.2 μg/μl), 0.3 to 0.6 μg of protein kinase I (9.3 × 10-9 to 1.9 × 10-8 M) with or without 5 μM cyclic AMP. The concentration of magnesium acetate present was varied over a range of total ionic strength from 0.05 to 0.08. It was not necessary to add magnesium acetate beyond this range of total ionic strength, since further addition made a much greater contribution to ionic strength than to ATP·Mg2+ substrate complex formation. The data obtained near 0.08 total ionic strength were employed in the determination of the intercept in Equation 4 represented by the term log K(ES).

Given the steady state equation developed previously (6) and employing initial rate conditions, the rate equation at constant histone concentration may be written as shown in Equation 5.

\[ v = \frac{V_{\text{ATP-Mg}}}{K_{n,\text{histone}}} \] (histone)

At constant histone concentration, Equation 5 can be transformed into Equation 6 where

\[ v = \frac{V^*}{K^* + (ATP-Mg)} \] (histone)

and

\[ V^* = \frac{V}{K_{n,\text{histone}}} + 1 \]

\[ K^* = \frac{K_{n,\text{histone}}}{K_{n,\text{histone}}} + 1 \]

Equation 7 can be written where A = (ATP·Mg)2+ + (ATP·MgH+)2+. T = (ATP·MgH+)2+ + A, and M = (Mg2+)2+ + (Mg2+·(CH3COO)2+). The above species are considered to be the only significant ones present in the assay system on the basis of the published equilibrium constants for the possible equilibria which must be considered (14). Since the magnesium concentration is always in excess of the ATP concentration by at least 20-fold, M is taken to be equal to the total concentration of magnesium added as magnesium acetate. T is equal to the total ATP concentration. From Equations 6 and 7, Equation 8 can readily be obtained.

\[ v = \frac{V^* T}{K^* + T} \]

All of the data were corrected to an ionic strength of 0.05 (the ionic strength of the 50 mM sodium acetate standard assay system without magnesium) by the use of Equation 4 with the intercept calculated from data points measured at magnesium acetate concentrations in excess of 10 mM where the changes in the protein kinase I catalytic activity are primarily influenced by changes in ionic strength. The corrected rates were fitted to Equation 8 by the method of Cleland (15) to obtain values where Y is defined as shown in Equation 9.

\[ Y = \frac{K(T^* + T)}{K^*} \]

The Y values measured at several different total ATP concentrations, T, were then plotted to obtain values for K and K*, the apparent association constant for magnesium ion·ATP complex formation and the apparent K m for ATP, respectively.

Fig. 2 is a plot illustrating the dependence of the rate of histone phosphorylation upon the magnesium acetate concentration over the ionic strength range 0.05 to 0.5. Data obtained in the absence of cyclic AMP indicated that cyclic AMP stimulation remains similar throughout this ionic strength range (10 ± 3 fold). The smooth line is the computer generated curve derived from Equations 4 and 5 with the experimentally determined values of K, K*, and V*.

The region actually required for the determination of K and K* involves only magnesium acetate concentrations of 1 to 20 μM where both changes in the degree of magnesium·ATP complex formation and changes in ionic strength have significant effects upon protein kinase I catalytic activity. In Fig. 3 at...
**Fig. 2.** Dependence of rate of histone phosphorylation upon magnesium acetate concentration. Total cyclic AMP and ATP concentrations equal 5 μM.

The top a plot of data treated according to Equation 9 is shown from which values of $K$ and $K^*$ were calculated. A linear least squares fit of the data, which are presented in Table II, gave a value of $190 \pm 20 \text{ M}^{-1}$ for $K$ and a value of $19 \pm 3 \text{ μM}$ for $K^*$ (errors are 1 S.D.).

Fig. 3 at the bottom shows a plot according to Equation 9 of data measured in the absence of cyclic AMP. There is a great deal of scatter which was expected, as discussed previously, but the plot still yields a value for $K$ within experimental error of that obtained in the presence of cyclic AMP. The apparent association constant $K$ (obtained from data corrected as described above for an assay system containing 50 meq of acetate) can be converted to a function of equilibrium constants which are available in the literature (14). This may be done as follows.

$$K = \frac{A}{M_{\text{ATP}}^{3-}}$$

$$K_1 = \frac{(\text{Mg}^{2+})(\text{CH}_3\text{COO}^-)}{(\text{Mg}^{2+})(\text{CH}_3\text{COO}^-)} = 10^{22}$$

$$K_2 = \frac{\text{(ATP-Mg)}^{-}}{\text{(ATP)}^{2-}(\text{Mg}^{2+})} = 10^{24}$$

$$K_3 = \frac{\text{(ATP-Mg)}^{-}}{\text{(ATP-Mg)}^{2-}(\text{H}^+)} = 10^{34}$$

$$M = (\text{Mg}^{2+}) (1 + K_1(\text{CH}_3\text{COO}^-))$$

$$= (\text{Mg}^{2+}) (1 + K_1(0.05)) = f(\text{Mg}^{2+})$$

$$K = \frac{1}{f(\text{K}_1(\text{H}^+))} \times 400 \text{ M}^{-1}$$

$$\log K = 2.6$$

If (ATP·Mg)$^{3-}$ were the only phosphate donor in the system, the apparent association constant $K'$ would be estimated as follows.

$$K' = \frac{1}{f(\text{K}_2(\text{H}^+))} = 300 \text{ M}^{-1}$$

$$\log K' = 2.5$$

If (ATP·Mg)$^-$ were the only phosphate donor in the system, the apparent association constant $K''$ would be estimated as follows.

$K'' = \frac{1}{f(\text{K}_1(\text{H}^+))} = 90 \text{ M}^{-1}$

$\log K'' = 2.0$

A correction can be made for the differences between the ionic strengths at which the equilibrium constants $K_1$, $K_2$, and $K_3$ were measured and the ionic strength of 0.05 for the standard assay system. In order to do this, activity coefficients were calculated according to Kicke (16) with Mg$^{2+}$ and hydrogen ion classified as inorganic ions. With this correction, the approximate values of the log of the apparent association constants are as follows.

$$\log K = 2.3$$

$$\log K' = 2.0$$

$$\log K'' = 1.8$$

The calculated value of log $K$ is in excellent agreement with the experimentally determined value for $\log K$ of $2.28 \pm 0.05$. The calculated values of log $K'$ and log $K''$ differ by more than 3 standard deviations from the experimentally determined value.

These results support the use of the steady state rate Equation 5 for a double displacement mechanism (6), the empirical ionic strength correction Equation 4 and the assumption that (ATP·Mg)$^{3-}$ and (ATP·Mg)$^-$ are the only significant phosphate donating substrates in the assay system (at pH 6.0, (ATP·Mg)$^-$ $\approx (0.16)$ (ATP·Mg)$^{2-}$). In particular, it is not

**Table II**

| ATP* | Number of points | $K(K^* + T)$ | S.D. |
|------|------------------|----------------|------|
| 2.9  | 6                | 210            | 20   |
| 4.9  | 3                | 240            | 30   |
| 5.0  | 5                | 320            | 40   |
| 5.9  | 6                | 280            | 70   |
| 32.0 | 6                | 520            | 100  |
| 45.4 | 6                | 710            | 50   |

* a Protein kinase I concentration was $2 \times 10^{-5}$ M in all studies except those with 4.9 μM ATP where it was $9 \times 10^{-5}$ M.

* b Standard deviations were obtained as described by Cleland (15).

**Fig. 3.** Plots of data according to Equation 9 for the determination of $K$ and $K^*$. Top, data obtained from assays performed in the presence of 5 μM cyclic AMP. Bottom, data obtained from assays performed in the absence of 5 μM cyclic AMP.
necessary to invoke substrate inhibition specifically to explain the dependency of the rate upon magnesium under the conditions employed here (magnesium concentrations of 1 to 20 mM and uncomplexed ATP concentrations of 4 to 32 μM). The data presented in this paper is insufficient to rule out all possible schemes for substrate and product inhibition, but a classical type of inhibition of histone phosphorylation by uncomplexed ATP would be expected to add a term of the form (((ATP)K1 + 1) to the denominator of the rate expression, Equation 5, where K1 is the association constant for the binding of the inhibitor. This term would be significantly greater than 1 for values of K1 greater than 10^4 M^-1 under the conditions employed here. It should also be noted that classical enzyme inhibition plots of the reciprocal of the rate against magnesium concentration or the concentrations of the other salts are nonlinear.

The K* value of about 20 μM is on the same order of magnitude as the estimated K* for Mg·ATP of about 10 μM (6). The factor (((K_m,histone)/(histone)) + 1) relating K* to K_m,ATP·Mg is difficult to determine since it depends upon the concentration of sites available for phosphorylation within the histone substrate. From earlier studies, the amount of histone substrate. From earlier studies, the amount of histone been reported by Miyamoto et al. (3) for their assay system. and indicated a significant increase in the apparent ATP concentration of sites available for phosphorylation in the absence of cyclic AMP were scattered and indicated a significant increase in the apparent K_m for ATP. The value of the measured association constant K, however, was still centered about the value obtained in the presence of cyclic AMP, as would be expected if K referred only to the association of magnesium with ATP.

The reasonable association constant for the complexation of magnesium ion with ATP obtained from our kinetic analysis is consistent with the hypothesis that the nucleotide-metal complex is formed at or prior to the rate-determining step for the action of bovine brain protein kinase I. Although this aspect of protein kinase action had not been investigated at the time of his review, in Mildvan’s discussion (2) of enzyme-nucleotide-metal (E·S·M) complexes he presented an analysis of the literature which also supports the postulate that binding to various other kinases occurs after the initial formation of the nucleotide-metal complex. We are continuing studies on the mechanism of action of protein kinase I with the aid of the quantitative treatment of the effect of changes in ionic strength developed in this paper.

Acknowledgments — We would like to express our appreciation for the generous assistance by Frank Ventimiglia in the laboratory of Professor I. Wool in the preparation of [γ-^32P]ATP. We also thank Dr. Y. Nakagawa for performing amino acid analyses and Professor F. J. Kézdy for his advice and help.

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Ionic inhibition of catalytic phosphorylation of histone by bovine brain protein kinase.
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J. Biol. Chem. 1977, 252:3007-3011.

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