Induction of Hepatic Tyrosine Aminotransferase in Vivo by Derivatives of Cyclic Adenosine 3':5'-Monophosphate

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SUMMARY

A number of 8- and N4-substituted derivatives of cyclic adenosine 3':5'-monophosphate and 6-substituted derivatives of cyclic 9 β-D ribofuranosylpurine 3':5'-monophosphate were compared as inducers of tyrosine 2-oxoglutarate aminotransferase in rat liver in vivo, as activators of rat liver cyclic adenosine 3':5'-monophosphate-dependent protein kinase, and as substrates for rat liver cyclic nucleotide phosphodiesterase. All of the analogs tested were able to induce the transaminase. The induction by the analogs was shown to be the result of an actual increase in the amount of enzyme, and the mechanism of induction was an increase in the rate of synthesis of the transaminase. The induced enzyme appeared to be immunologically similar to the non-induced enzyme. A good correlation was found to exist between the dose that produced 50% of maximal induction and a combination of the activation constant for cyclic adenosine 3':5'-monophosphate-dependent protein kinase by the analog and its susceptibility to hydrolysis by cyclic nucleotide phosphodiesterase. These data suggest that the phosphorylation of some site is involved in the mechanism by which cyclic adenosine 3':5'-monophosphate affects the rate of synthesis of tyrosine aminotransferase.

In the last few years a number of new analogs of cyclic adenosine 3':5'-monophosphate have been described (1-6) which offer certain advantages over N6,02'-dibutyryl cyclic adenosine 3':5'-monophosphate. Many of them are stable to enzymatic hydrolysis and at the same time are significantly more active than cAMP as activators of cAMP-dependent protein kinase. In addition, they do not require metabolic transformation for activity, as does BtCAMP (7-9).

These new analogs of cAMP contain a wide range of chemical modifications and vary over a 2-order of magnitude range in their ability to activate cAMP-dependent protein kinase (1-6). This presents a situation in which a possible correlation between two different biological parameters can be tested.

Tyrosine transaminase (L-tyrosine:2-oxoglutarate amino-
for measuring the rate of transaminase synthesis were the same as those used by Wicks et al. (10).

**Preparation and Assay of Enzymes**—Rat liver cAMP-dependent protein kinase, assayed as described previously for the calf brain enzyme (9), was partially purified by the method of Chen and Walsh (16) through the DEAE-Sephadex step. The protein eluting from the column between 0.05 and 0.35 M NaCl was pooled, dialyzed against 10 mM phosphate buffer (pH 7.2) containing 5 mM 2-mercaptoethanol, and used as the source of protein kinase. Rat liver phosphodiesterase was prepared and assayed as described previously for other tissues (9).

**RESULTS AND DISCUSSION**

**Time Course and Dose Response of Induction**

The studies of tyrosine transaminase induction in vivo by cAMP derivatives were designed to minimize differences in absorption and metabolism. The general approach was as follows: by using an arbitrary dose, the time course of transaminase induction was followed to determine the time at which the largest-fold increase in enzyme activity occurred. A dose-response study was then performed by using the time interval previously determined. From the dose-response study the optimal dose was determined. The time course study was then repeated with this dose. Thus, the time course studies were performed at the optimal dose for each derivative, and likewise the dose-response studies were performed by using a time in which the largest response was seen.

**Butyrylated Derivatives of cAMP**—The time-course and dose-response of tyrosine transaminase induction by the three butyrylated derivatives of cAMP are shown in Fig. 1, A and B. N'Bt-cAMP produced a more rapid, although no larger, response than did Bt-cAMP (Fig. 1A). With both N'Bt-cAMP and Bt-cAMP the transaminase activity rapidly decreased after maximal induction was seen. By comparison, O"Bt-cAMP
demonstrated only slight activity. N⁴Br-cAMP was also slightly more potent than Bt-cAMP (Fig. 1B), whereas O⁴Br-cAMP was much less active. These results indicate that N⁴Br-cAMP is the active metabolite of Bt-cAMP, a finding which is consistent with previous data (7-9).

8-Substituted Derivatives of cAMP—Similar studies performed on 8-substituted cAMP derivatives are summarized in Fig. 1, C to F. With the exception of 8H₂N-cAMP, all of these derivatives were able to cause as great an increase in transaminase activity as did Bt-cAMP (Fig. 1, C and E). The lower inducing activity of 8H₂N-cAMP may be related to its rapid rate of hydrolysis by phosphodiesterase (Table II). Another enzyme, tyrosine hydroxylase, has been shown to be similarly induced by Bt-cAMP and 8MeO-cAMP in cultured neuroblastoma cells (17). The three 8-substituted cAMP derivatives containing aromatic 8-substituents (8PhCH₂S-cAMP, 8pClH₂S-cAMP, and 8PhCH₂HN-cAMP) elicited a more rapid response than did the other 8-substituted cAMP derivatives. With all of these 8-substituted derivatives and many of the N⁴-substituted cAMP derivatives and the 6-substituted cRMP derivatives, the transaminase activity returned very rapidly to basal levels, in some cases in as little as 1.5 to 2 hours. Although the data presented here did not allow an accurate determination of the half-life of the transaminase after induction by the analogs, previous studies in vivo suggested that induction of the enzyme by Bt-cAMP had no significant effect on the rate of enzyme degradation (10).

The dose-response curves (Fig. 1, D and F) show clearly that many of the 8-substituted derivatives were significantly more potent than Bt-cAMP. SpClH₂S-cAMP, for example, was 40 times more active than Bt-cAMP in terms of Ind₅₀ values.

In general, the arylthio-substituted derivatives (8pClH₂S- and 8PhCH₂S-cAMP) were the most active, followed by 8Br-, 8HS-, 8MeS-, and 8H₂O-cAMP with intermediate activity; the 8HN derivatives and 8MeO-cAMP were the least active of the group. It was found that 8MeO-, 8MeHN-, and 8PhCH₂HN-cAMP were toxic to the animals at doses greater than 200 mg per kg. Therefore, the time course studies with these analogs were done at a dose of 200 mg per kg.

N⁴-Substituted Derivatives of cAMP—In this class of compounds, only N⁴Et-cAMP and N⁴EtOOCO-cAMP were able to produce the magnitude of response produced by the 8-substituted derivatives and Bt-cAMP (Fig. 1G). Although all of the N⁴-substituted derivatives were hydrolyzed by phosphodiesterase, the latter two compounds were hydrolyzed at a relatively slower rate than the others (Table II). N⁴Et-cAMP and N⁴PhH₂C-cAMP were intermediate in both their ability to induce the transaminase and to be hydrolyzed by phosphodiesterase. N⁴EtO-cAMP and N⁴PhCH₂O-cAMP were the poorest inducers and the most rapidly hydrolyzed compounds of this group. The rapid onset of induction (Fig. 1H) demonstrated by N⁴PhH₂C- and N⁴PhCH₂O-cAMP sustains the suggestion that cyclic nucleotide derivatives containing aromatic substituents are more rapidly absorbed. Other derivatives in this group required somewhat longer to elicit maximal induction of the transaminase. The dose-response studies on these derivatives (Fig. 1H) show that they all demonstrated similar Ind₅₀ values, with only approximately a 4-fold difference between the most and least active. N⁴PhH₂C-cAMP proved toxic at doses greater than 200 mg per kg; therefore, the time course study was performed at this dose.

6-Substituted Derivatives of cRMP—None of the compounds

Ind₅₀ is the dose that produces 50% of the maximally obtainable induction.

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6-Substituted Derivatives of cRMP—None of the compounds

Ind₅₀ is the dose that produces 50% of the maximally obtainable induction.
between the catalytic activity and the antigenicity of tyrosine transaminase was not changed as a result of the induction of the enzyme by these cAMP derivatives. The results, therefore, show that the increase in catalytic activity of the transaminase actually represents an increase in the amount of enzyme, and not just activation of preexisting enzyme.

Isotopic-Immunochemical Analysis of Rate of Tyrosine Transaminase Synthesis in Response to cAMP Derivatives—In these experiments the labeling of tyrosine transaminase was compared with that of other soluble proteins after a pulse of [14C]leucine given 20 min before killing. With all four cAMP derivatives tested (8pClPhS-cAMP, 8MeS-cAMP, and N'PhH2C-cAMP and 6PhCH2S-cRMP), the incorporation of [14C]leucine into both soluble protein and the transaminase was increased, but the increase for the transaminase was approximately twice that for the soluble protein (Table I). In addition, there was a comparable increase in the specific activity of tyrosine transaminase in the supernatant fluid was next determined. The radioactivity in the precipitate (A) and the supernatant fluid (B) was then determined. A second, identical immunoprecipitation was performed on the supernatant from the first precipitation; these control precipitates averaged 87 and 112 cpm in Experiments 1 and 2, respectively. These background values have been subtracted from the reported values.

| Derivative | Dose | Time of killing after dosing | Transaminase activity | Radioactivity in Tyrosine transaminase (A) | Relative radioactivity | Soluble proteins (B) | Soluble protein activity |
|------------|------|-----------------------------|-----------------------|------------------------------------------|-----------------------|----------------------|------------------------|
|            | mg/kg mL/hr | min | units/hr | mg protein | cpm | cpm X 10^-3 | A/B X 10^3 |
| Experiment 1 | None | 22 | 1200 | 295 | 7.7 |
| 8pClPhS-cAMP | 2 | 0.5 | 22 | 3760 | 490 |
| 8pClPhS-cAMP | 2 | 2 | 98 | 4360 | 498 |
| 8MeS-cAMP | 1 | 1 | 26 | 5450 | 415 |
| 8MeS-cAMP | 10 | 3 | 67 | 5800 | 447 |
| Experiment 2 | None | 31 | 1570 | 781 | 2.0 |
| N'PhH2C-cAMP | 100 | 2 | 87 | 4010 | 1080 |
| 6PhCH2S-cRMP | 100 | 1.5 | 64 | 3140 | 924 |

The results show that these analogs were able to effect an increase in the rate of synthesis of tyrosine transaminase. This is consistent with the data of Wicks et al. (10) on Bt6cAMP. Although this mechanism of action of cAMP derivatives in the induction of the transaminase has been rigorously demonstrated for only the few derivatives listed above, it is probably a valid assumption that all of these analogs are inducing the enzyme by a similar mechanism. Wicks' group has found that some of the cAMP derivatives studied here were able to induce tyrosine transaminase by increasing its rate of synthesis in cultured Reuber H35 hepatoma cells (19).

Studies with Rat Liver Enzymes in Vitro

Two enzymes in liver with which these cAMP derivatives might interact are cAMP-dependent protein kinase and cAMP phosphodiesterase. The first is important as a possible intermediary in the mechanism by which cAMP derivatives induce tyrosine transaminase, and the second is important because it can inactivate the analogs.

Rat Liver cAMP-dependent Protein Kinase The activation constants (Kₐ values) were determined for each of the cAMP derivatives with cAMP-dependent protein kinase from rat liver. The results (Table II) indicate that the 8-substituted cAMP derivatives were widely divergent in their ability to activate this enzyme. The most active of this group was 8pClPhS-cAMP, which was nearly 100 times more effective than cAMP.

The Kₐ values for each of the cAMP derivatives with rat liver cAMP-dependent protein kinase were of the same relative magnitude as the Kₐ values previously reported for these analogs with other cAMP-dependent kinases (1-6, 20-23).3

Rat Liver Phosphodiesterase—A comparison of the Kₐ values with the corresponding Indₐ values (Table II) indicated that, although some correlation appeared to exist between these two groups of data, many of the compounds demonstrated higher Indₐ values than would be predicted on the basis of their Kₐ values. One possible reason for this could be that some of the compounds were being hydrolyzed by phosphodiesterase. This was indeed the case, as seen by the results in Table II. Of the 8-substituted derivatives, only 8H₂N-cAMP was hydrolyzed at a very rapid rate, compared with that of cAMP. All of the N²-substituted cAMP derivatives and 6-substituted cRMP derivatives were hydrolyzed at significant rates. 6H₂S-cRMP was an even better substrate than cAMP for the rat liver phosphodiesterase preparation used. In general, these results indicate that many of the analogs which demonstrated higher Indₐ values than expected were hydrolyzed by the phosphodiesterase.

The relative rates of hydrolysis of the analogs were in the same relative ranges as those reported previously for enzyme preparations from other sources (1-6, 20-23).

Analysis of Correlation of Indₐ with Kₐ and Phosphodiesterase Hydrolysis Values

The Indₐ values of the cyclic nucleotides were examined for possible correlation with their Kₐ values and with both Kₐ and phosphodiesterase hydrolysis values (expressed as S, the ratio of the rate of hydrolysis of the analog to the rate of hydrolysis of cAMP) by regression analysis.

Although many other factors would be expected to influence the Indₐ of the cyclic nucleotides in vivo, S and Kₐ were chosen to construct a mathematical model of induction of the transaminase because of their accessibility and their reflection of two fundamental events in which cAMP participates.

| Derivative | Dose | Time of killing after dosing | Transaminase activity | Radioactivity in Tyrosine transaminase (A) | Relative radioactivity | Soluble proteins (B) | Soluble protein activity |
|------------|------|-----------------------------|-----------------------|------------------------------------------|-----------------------|----------------------|------------------------|
|            | mg/kg mL/hr | min | units/hr | mg protein | cpm | cpm X 10^-3 | A/B X 10^3 |
| Experiment 1 | None | 22 | 1200 | 295 | 7.7 |
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| 6PhCH2S-cRMP | 100 | 1.5 | 64 | 3140 | 924 |

3 J. F. Kuo, E. Miyamoto, P. Reyes, and P. Greengard, unpublished results.
The protein kinase and phosphodiesterase assays were performed as described under "Experimental Procedures." The \( K_a \) values were determined from Lineweaver-Burk plots. The \( S \) value is the rate of hydrolysis of cAMP, rate of hydrolysis of the analog. The rate for cAMP was 45 nmol per min per mg of protein. \( \text{Ind}_{50} \) refers to the dosage of compound that produces 50% of maximal tyrosine transaminase induction. The observed values were determined by inspection of Fig. 1, B, D, F, H, and J, whereas the calculated values were obtained by using Equation 6.

### Table II

Activities of \( 6 \)- and \( 8 \)-substituted derivatives of cAMP as activators of rat liver cAMP-dependent protein kinase, substrates for rat liver phosphodiesterase, and inducers of rat liver tyrosine aminotransferase

| Compound Number | cAMP Derivative | \( K_a \) for Rat Liver Protein Kinase (nm) | \( S \) Value for Rat Liver Phosphodiesterase (mg/kg) | \( \text{Ind}_{50} \) for Tyrosine Transaminase Induction (mg/kg) |
|-----------------|-----------------|------------------------------------------|---------------------------------|---------------------------------|
| 1               | CAMP            | 21                                        | 1.0                             | 12                              |
| 2               | \( N^6 \)-Bt-cAMP | 26                                        | 0.06                            | 11.8                            |
| 3               | \( -\text{NH}_2 \) | 12                                        | 0.90                            | 58                              |
| 4               | \( -\text{NHMe} \) | 11                                        | 0.07                            | 90                              |
| 5               | \( -\text{NCH}_2\text{Ph} \) | 240                                      | 0.06                            | 160                             |
| 6               | \( -\text{OH} \) | 9.6                                       | 0.09                            | 3.8                             |
| 7               | \( -\text{OEt} \) | 8.4                                       | 0.06                            | 37                              |
| 8               | \( -\text{SH} \) | 5.4                                       | 0.10                            | 2.1                             |
| 9               | \( -\text{SMe} \) | 10                                        | 0.08                            | 2.8                             |
| 10              | \( -\text{SCH}_2\text{Ph} \) | 9.1                                      | 0.06                            | 0.90                            |
| 11              | \( -\text{SPhCl} \) | 0.22                                      | 0.05                            | 0.45                            |
| 12              | \( -\text{Br} \) | 7.0                                       | 0.11                            | 1.6                             |

\[ \text{Ind}_{50} = \frac{1}{2} \left( K_a \right) \]

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### Table II (continued)

| Compound Number | cAMP Derivative | \( K_a \) for Rat Liver Protein Kinase (nm) | \( S \) Value for Rat Liver Phosphodiesterase (mg/kg) | \( \text{Ind}_{50} \) for Tyrosine Transaminase Induction (mg/kg) |
|-----------------|-----------------|------------------------------------------|---------------------------------|---------------------------------|
| 13              | \( -\text{Et} \) | 30                                       | 0.29                            | 13                              |
| 14              | \( -\text{EtO} \) | 13                                       | 0.14                            | 14                              |
| 15              | \( -\text{OEt} \) | 19                                       | 0.40                            | 22                              |
| 16              | \( -\text{OCH}_3\text{Ph} \) | 42                                      | 0.46                            | 46                              |
| 17              | \( -\text{OCH}_2\text{Ph} \) | 17                                      | 0.55                            | 25                              |
| 18              | \( -\text{OOEt} \) | 100                                      | 0.12                            | 56                              |

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The cyclic nucleotides were examined in three groups, the \( 8 \)-substituted compounds and the \( 6 \)-substituted compounds, and as a whole. Data in Table II were used in the regression analyses. The \( 8\text{MeHN} \)-, \( 8\text{PhCH}_2\text{S} \)-, and \( N^6\text{Et-cAMP} \) values were eliminated from the fit because their values were anomalous. Equations 1 to 6 give the results of the regression analysis. The values given in parenthesis are the 95% confidence intervals; \( n \) is the number of points, \( sd \) is the standard deviation, and \( r \) is the correlation coefficient. Table II gives the values of \( \text{Ind}_{50} \) calculated from the regression Equation \( 6 \). \( \text{Ind}_{50} \) was expressed in milligrams per kilogram and \( K_a \) in nanomoles per liter.

8-Substituted cAMP derivatives (Compounds 3, 5 to 9, 11, and 12):

\[ \log (\text{Ind}_{50}) = -0.059 + 0.89(\pm 0.50) \log (K_a) \]

\[ n = 8, sd = 0.48, r = 0.874 \]

\[ \log (\text{Ind}_{50}) = 0.57 + 0.63(\pm 1.1) \log (S) \]

\[ + 0.89(\pm 0.47) \log (K_a) \]

\[ n = 8, sd = 0.43, r = 0.917 \]

\[ \log (\text{Ind}_{50}) = 0.63 + 0.50(\pm 0.19) \log (K_a) \]

\[ n = 11, sd = 0.14, r = 0.911 \]

\[ \log (\text{Ind}_{50}) = 0.71 + 0.26(\pm 0.17) \log (S) \]

\[ + 0.58(\pm 0.13) \log (K_a) \]

\[ n = 11, sd = 0.062, r = 0.997 \]

\[ \log (\text{Ind}_{50}) = 0.16 + 0.33(\pm 0.25) \log (K_a) \]

\[ n = 19, sd = 0.35, r = 0.862 \]

\[ \log (\text{Ind}_{50}) = 0.30 + 0.45(\pm 0.29) \log (S) \]

\[ + 0.80(\pm 0.20) \log (K_a) \]

\[ n = 19, sd = 0.28, r = 0.920 \]

Examination of the equations generated by multiple regression analysis of the data in Table II indicated some obvious trends. Considering either the \( 8 \)- or \( 6 \)-substituted derivatives separately or all analogs together, a better fit was obtained in each case by incorporation of the phosphodiesterase hydrolysis term \( S \). The regression coefficient of \( S \) was not as significant in the two smaller groups of compounds (Equations 2 and 4) as it was in the analysis of all the compounds (Equation 6). This was perhaps because the values of \( S \) are fairly similar within each group, but the average \( S \) value of the \( 6 \)-substituted compounds was quite a bit greater than that of the \( 8 \)-substituted compounds.

A qualitative overview of the information derived from regression analysis of the data would strongly suggest, but by no means prove, a mechanism of tyrosine transaminase induction by the cyclic nucleotide analogs which involves activation of a protein kinase (hence subsequent phosphorylation of a protein). The significance of the coefficient of log\((S)\) in Equation 6 suggests that the better substrates for phosphodiesterase (with a greater negative log\((S)\)) require higher concentrations for transaminase induction than would be obtained from examination of the \( K_a \) values alone. A fair rank correlation \((r = 0.762)\) has been noted between tyrosine transaminase induction and \( K_a \) values for bovine brain cAMP-dependent protein kinase for a series of \( 8 \)-substituted cAMP derivatives (1, 3, 24).

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