Regulation of β-Galactosidase Synthesis in Escherichia coli by Cyclic Adenosine 3',5'-Monophosphate

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SUMMARY

Cyclic adenosine 3',5'-monophosphate (cyclic AMP) increases the differential rate of synthesis of β-galactosidase in Escherichia coli made permeable by treatment with tris(hydroxymethyl)aminomethane and ethylenediaminetetraacetic acid. In normal, growing cells, cyclic AMP overcomes the transient repression of β-galactosidase by glucose. A half-maximal effect of cyclic AMP occurs at about 7 × 10^{-9} M.

Cyclic AMP overcomes the transient repression of β-galactosidase synthesis in two regulatory mutants which produce β-galactosidase constitutively, 3300 (i-) and O67. Cyclic AMP also acts in cells which are deficient in the lac permease.

Cyclic AMP overcomes the transient repression of β-galactosidase synthesis produced by α-methylglucoside in strain C600 which has normal regulatory genes. In mutant LA-12G, which is resistant to permanent repression, cyclic AMP also overcomes transient glucose repression.

In cells treated with chloramphenicol, isopropylthio-β-D-galactopyranoside promotes the accumulation of β-galactosidase-specific messenger RNA, glucose prevents its accumulation, and cyclic AMP overcomes this repression by glucose. Cyclic AMP also overcomes the glucose repression of mRNA production in a threonine-requiring mutant during threonine starvation. Cyclic AMP fails to stimulate β-galactosidase production in cells in which mRNA synthesis has been arrested by inducer removal or proflavine addition. Thus, cyclic AMP appears to participate in the regulation of β-galactosidase mRNA synthesis at the gene level.

Factors governing the synthesis of the enzyme β-galactosidase have been extensively investigated, and the mechanism by which inducers act at the genetic level to stimulate its synthesis serves as the best known model for the control of protein synthesis. The synthesis of β-galactosidase and various other catabolic enzymes is repressed when glucose is added to cultures synthesizing the enzyme (1). This phenomenon has been called the glucose effect (2), catabolite repression (3), or metabolic repression (4). Nakada and Magasanik (5) have investigated the mechanism of catabolite repression and found that glucose repressed the synthesis of messenger RNA specific for β-galactosidase. In a preliminary communication (6), we reported that the synthesis of β-galactosidase is stimulated and its repression by glucose prevented by cyclic AMP. This effect of cyclic AMP is specific inasmuch as ATP, ADP, 3'-AMP, 5'-AMP, adenosine, adenine, and fructose 1,6-diphosphate were inactive. Further, cyclic AMP failed to affect the over-all rate of protein or RNA synthesis; thus, it increased the differential rate of β-galactosidase synthesis.

Cyclic AMP acts at the level at which DNA is transcribed into RNA.

MATERIALS AND METHODS

Cyclic AMP was obtained from Calbiochem, IPTG and o-nitrophenyl-β-D-galactopyranoside from Mann and chloramphenicol from Parke, Davis and Company. Glucose-1-14C (1 mC per mmole) was obtained from New England Nuclear. Crooke's strain of Escherichia coli, ATCC 8739, was used in our initial experiments. In other experiments, the following strains of E. coli K12 have been used (relevant genotypes in parentheses): 3000 (lac i+ o+ y+), 3300 (i-), O67 (o+), all from Dr. E. Steers; C600 (y- leu- thr-), from Dr. I. Leder; and LA-12G ("catabolite repression" resistant (7)), from Dr. B. Magasanik. Organisms were grown aerobically at 37° in Medium A, containing 14.0 g of KH2PO4, 6.0 g of KH2PO4, 2.0 g of (NH4)2SO4, and 0.2 g of MgSO4 per liter, supplemented when necessary with specific nutritional requirements. Unless otherwise stated, 0.5% glycerol was the carbon and energy source.

The oxidation of glucose-1-14C was measured by the method of Macchia and Pastan (8). In some experiments, IPTG was removed by filtration, according to the method of Kaempfer and Magasanik (9). All other methods were as described pre-
RESULTS

Cyclic AMP stimulates β-galactosidase induction in E. coli made permeable by treatment with Tris-EDTA. Fig. 1 presents the results of a typical experiment with Crooke's strain of E. coli. In this experiment, cells were incubated from time 0 with IPTG, in the presence and absence of cyclic AMP. In the control culture, there is a lag period of about 4 min between the addition of inducer and the appearance of active enzyme. After this lag period, active enzyme accumulates at approximately a linear rate over the next 15 min. In the presence of 10^{-3} M cyclic AMP, the lag period is not detectably shortened, but after this lag period, the rate of enzyme production is greater than in the control. The magnitude of this stimulation is variable. In the experiment shown in Fig. 1, it is about 60%; in other experiments, the stimulation of β-galactosidase synthesis caused by cyclic AMP ranged between 30 and 100% of the control rate. We have previously shown that this stimulation of β-galactosidase synthesis by cyclic AMP is not accompanied by an increase in the rate of total RNA or protein synthesis (6). Rather, it represents an increase in the differential rate of enzyme synthesis.

In Crooke's strain, glucose represses β-galactosidase induction by about 50%. Cyclic AMP completely overcomes this glucose repression and restores enzyme synthesis to unrepressed levels. The effect of varying concentrations of cyclic AMP on β-galactosidase synthesis, in the presence and absence of glucose, is shown in Fig. 2. In the absence of glucose, 10^{-4} M cyclic AMP produces about a 40% stimulation in the rate of β-galactosidase synthesis. Glucose at 0.1 M represses enzyme synthesis by about 50%. However, in the presence of glucose, cyclic AMP more than doubles the rate of enzyme synthesis. In the presence of glucose, a maximal effect of cyclic AMP is seen at 3 × 10^{-4} M, and a half-maximal effect at about 7 × 10^{-5} M. Cyclic AMP concentrations as high as 2.4 × 10^{-4} M have been reported in E. coli.

We elected to conduct our subsequent studies on the action of cyclic AMP in glucose-repressed cells, in which the effects of cyclic AMP were much larger than in unrepressed cells. In the presence of glucose, cyclic AMP stimulated β-galactosidase synthesis in normal, growing cells as well as in Tris-EDTA-treated cells, although cyclic AMP did not stimulate β-galactosidase synthesis in untreated cells in the absence of glucose. These untreated cells were used in subsequent studies. Fig. 3 illustrates the results of an experiment in which E. coli 3000 grown in glycerol were induced from time 0 with IPTG, with and without the additions of glucose and cyclic AMP. In the control culture, active enzyme begins to accumulate after a lag period of 2 to 3 min. In the presence of 0.025 M glucose, this lag period is increased to about 20 min, after which the rate of enzyme accumulation is similar to that in the control. In the presence of 10^{-4} M cyclic AMP, this increased lag period is abolished, and the time course of enzyme synthesis is indis-

![Fig. 1](http://www.jbc.org/)

**Fig. 1.** Time course of β-galactosidase induction in Crooke's strain of E. coli. Bacteria were treated with Tris and EDTA and were then incubated from time 0 with 5 × 10^{-4} M IPTG, in the absence (○) and presence (●) of 10^{-4} M cyclic 3',5'-AMP.

![Fig. 2](http://www.jbc.org/)

**Fig. 2.** Effect of cyclic 3',5'-AMP concentration on the rate of β-galactosidase synthesis in Crooke's strain of E. coli. Bacteria were treated with Tris and EDTA, and were then incubated with 5 × 10^{-4} M IPTG and varying concentrations of cyclic 3',5'-AMP in the absence (○) and presence (●) of 0.1 M glucose. Rates of β-galactosidase synthesis were calculated from assays made 10 and 30 min after the start of induction.
AMP. Cyclic AMP did not inhibit the oxidation of glucose, as the amount of $^{14}C_2O_2$ produced in the presence and absence of cyclic AMP was indistinguishable by incubating cells with glucose-$^{14}C$ and determining the rate of glucone oxidation. This was investigated in cells made permeable by treatment with Tris and EDTA, in high concentrations of glucose used, and because cyclic AMP frequently has been observed and will be discussed in detail later. The important point is that this transient repression resulting from the addition of glucose to cells grown on a different carbon source is completely overcome by cyclic AMP. Because of the effect of cyclic AMP on $\beta$-galactosidase synthesis in the presence of glucose at various inducer concentrations in two strains of E. coli: Crooke's strain, which has an inducible galactosidase permease, and C-600, a permeaseless mutant. The results of these experiments are presented in Fig. 3. In Crooke's strain, $10^{-4} M$ IPTG induces a maximal rate of $\beta$-galactosidase synthesis. Increasing the IPTG concentration to $10^{-3} M$ has no further effect. In the presence of cyclic AMP, the synthesis of $\beta$-galactosidase is increased to almost three times the control rate, but again $10^{-4} M$ IPTG is required for maximal induction. If cyclic AMP was stimulating inducer uptake, lower concentrations of IPTG should produce maximal induction in the presence of the permeaseless mutant, C-600 (Fig. 4).

**Table I**

**Effect of cyclic AMP on glucose oxidation**

<table>
<thead>
<tr>
<th>Incubation (min)</th>
<th>$^{14}C_2O_2$ produced (nmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>15</td>
<td>42.5 ± 0.5</td>
</tr>
<tr>
<td>30</td>
<td>69.2 ± 0.1</td>
</tr>
</tbody>
</table>

Immunoassay of $\beta$-galactosidase in permeable, Tris-EDTA-treated cells, it also seemed unlikely that it acts by increasing the uptake of inducer into the cells. However, to investigate this possibility further, we examined the effect of cyclic AMP on $\beta$-galactosidase synthesis in permeable, Tris-EDTA-treated cells. Bacteria were grown in Medium A, containing glycerol and thiamine, and were incubated from time 0 with $5 \times 10^{-4} M$ IPTG and the following additions: $\triangle$, none; $\Delta$, $0.025 M$ glucose; $\bullet$, $0.025 M$ glucose; $10^{-4} M$ cyclic $3',5'$-AMP.

**TABLE I**

_E. coli_ C600 cells were incubated at a density of about $7 \times 10^8$ organisms per ml in Medium A containing glycerol, threonine, thiamine, and glucose-$^{14}C$ ($10^{-4} M$, $2 \mu$C per mmole), in the presence and absence of $10^{-3} M$ cyclic AMP. Incubation was carried out at $37^\circ$ in sealed flasks, after gassing with 95% O$_2$-5% CO$_2$. The results are the means of three samples ±S.E.

**Fig. 3.** Effect of glucose and cyclic $3',5'$-AMP on $\beta$-galactosidase synthesis in _E. coli_ 3000. This and all subsequent figures present the results of experiments in which Tris-EDTA treatment was not used. Bacteria were grown in Medium A, containing glycerol and thiamine, and were incubated from time 0 with $5 \times 10^{-4} M$ IPTG and the following additions: $\bigcirc$, none; $\triangle$, $0.025 M$ glucose; $\Delta$, $0.025 M$ glucose; $10^{-4} M$ cyclic $3',5'$-AMP.

**Fig. 4.** Effect of IPTG concentration on $\beta$-galactosidase synthesis. Bacteria were incubated with $0.1 M$ glucose and varying concentrations of IPTG, in the absence (○) and presence (●) of $10^{-3} M$ cyclic $3',5'$-AMP. Rates of $\beta$-galactosidase synthesis were calculated from assays made 10 and 20 min after the start of induction. ---, Crooke's strain; --, C-600.
and without cyclic AMP. At 9 min, IPTG, chloramphenicol, glucose, and cyclic AMP were removed by filtration, and the cells were incubated in a complete medium without these compounds. No β-galactosidase was formed during the 9-min induction period, with or without cyclic AMP. Evidently, cyclic AMP does not overcome the chloramphenicol-induced inhibition of protein synthesis. β-Galactosidase accumulates after the chloramphenicol is removed as a result of translation of pre-existent mRNA. Cells that were induced in the presence of cyclic AMP make about twice as much β-galactosidase after filtration as do the control cells. This finding suggests that cells induced in the presence of cyclic AMP accumulate more β-galactosidase mRNA than do cells induced in the absence of the nucleotide.

Cyclic AMP increases the accumulation of β-galactosidase mRNA in cells in which protein synthesis is decreased due to threonine starvation (Fig. 6). In this experiment, C-600 cells, which require threonine, were deprived of threonine for 15 min and were then induced with IPTG in a glucose-containing, threonine-free medium, in the presence and absence of cyclic AMP. After 5 min of induction, IPTG, glucose and cyclic AMP were removed by filtration, and the cells were incubated in a complete glucose-free, threonine-containing medium. Under these conditions, active enzyme is not formed during the 5-min induction period, but does accumulate when threonine is added after filtration due to translation of mRNA synthesized during induction. Cells induced in the presence of cyclic AMP produce more enzyme after filtration than do the control cells, again indicating that cyclic AMP causes an increased accumulation of β-galactosidase mRNA.

If E. coli C-600 cells are induced in a threonine-free medium in the absence of an energy source, they will make β-galacto-
β-Galactosidase synthesis (Fig. 7). Under these conditions, breakdown of preformed protein provides threonine for enzyme synthesis. However, as shown in Fig. 7, in a threonine-free, glucose-containing medium, virtually no enzyme is formed during a 50-min induction because of arrest of β-galactosidase mRNA synthesis (5). If induction is effected in a threonine-free, glucose-containing medium to which cyclic AMP has been added, a significant amount of β-galactosidase is produced, indicating that cyclic AMP stimulates the production of β-galactosidase mRNA.

A possible effect of cyclic AMP on a later step of β-galactosidase synthesis was also investigated. The experiment reported in Fig. 8 was performed in order to examine the effect of cyclic AMP on the translation or half-life of β-galactosidase mRNA. In this experiment, cells were induced with IPTG for 8 min, the inducer was removed by filtration, and the cells were then incubated in the presence and absence of glucose and cyclic AMP. As shown in Fig. 8, neither glucose nor cyclic AMP affect the amount of enzyme produced under these conditions, or the rate at which this enzyme appears. The lack of effect of glucose on the translation or half-life of β-galactosidase mRNA is in agreement with the findings of Nakada and Magasanik (5). The lack of effect of cyclic AMP under these conditions indicates that the increased accumulation of β-galactosidase mRNA which occurs in the presence of nucleotide is caused by a stimulation of β-galactosidase mRNA synthesis. In other experiments, cells were induced with IPTG, and then incubated with glucose and

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**Fig. 8.** β-Galactosidase synthesis after removal of inducer in *E. coli* C600. Cells were incubated from time 0 with 2.5 × 10⁻⁴ M IPTG. At 8 min, IPTG was removed by filtration, and incubation was continued with the following additions: O, none; ●, 10⁻³ M cyclic 3',5'-AMP; △, 0.1 M glucose; ▲, 0.1 M glucose + 10⁻³ M cyclic 3',5'-AMP. The jagged portion of the abscissa represents the time required for filtration and washing.

**Fig. 9.** β-Galactosidase synthesis in *E. coli* 3300. Bacteria were grown in Medium A, containing glycerol and thiamine. At 0 time, incubation was continued with the following additions: O, none; △, 0.025 M glucose; ▲, 0.025 M glucose + 10⁻⁴ M cyclic 3',5'-AMP.

**Fig. 10.** β-Galactosidase synthesis in *E. coli* O14. Protocol and legend are the same as in Fig. 9.
FIG. 11. β-Galactosidase synthesis in *E. coli* C600. Bacteria were grown in Medium A, containing glycerol, leucine, threonine, and thiamine, and were incubated from time 0 with $5 \times 10^{-4}$ M IPTG and the following additions: O, none; ●, $10^{-3}$ M cyclic 3',5'-AMP; □, $0.025$ M α-methylglucoside; ■, $0.025$ M α-methylglucoside + $10^{-3}$ M cyclic 3',5'-AMP.

Fig. 12. β-Galactosidase synthesis in *E. coli* LA-12G. Bacteria were grown in Medium A plus glycerol and thiamine, and were incubated from time 0 with $5 \times 10^{-4}$ M IPTG and the following additions: O, none; ●, $10^{-3}$ M cyclic 3',5'-AMP; Δ, $0.025$ M glucose; ▲, $0.025$ M glucose + $10^{-3}$ M cyclic 3',5'-AMP.

cyclic AMP after RNA synthesis was inhibited by proflavine. Under these conditions also, there was no effect of cyclic AMP on β-galactosidase accumulation.

Cyclic AMP thus appears to stimulate β-galactosidase synthesis at the level of mRNA synthesis. β-Galactosidase mRNA synthesis is also known to be controlled by an interaction between a protein repressor and the operator region of the lac operon. To study the relationship between the cyclic AMP effect and the operator-repressor system, we investigated the effect of cyclic AMP on β-galactosidase synthesis in two constitutive mutants of *E. coli*: 3300, which has a point mutation in the repressor gene, and 007, which is a deletion mutant of the operator region. Experiments with these mutants are presented in Figs. 9 and 10. In both mutants, glucose produces a transient repression of β-galactosidase synthesis, and this repression is overcome by cyclic AMP. Thus, the site at which cyclic AMP acts is not the repressor-recognition site.

Transient inhibition of β-galactosidase synthesis also occurs when the nonmetabolizable sugars, α-methylglucoside or 2-deoxyglucose, are added to *E. coli*. Cyclic AMP overcomes the transient repression caused by α-methylglucoside (Fig. 11) as well as that caused by 2-deoxyglucose. A mutant LA-12G has been isolated by Loomis and Magasanik which is sensitive to transient repression but does not display mild permanent repression of β-galactosidase synthesis. Cyclic AMP also overcomes the transient repression in this organism (Fig. 12).

**DISCUSSION**

We have found that cyclic AMP stimulates β-galactosidase induction in *E. coli*. In order to study the mechanism of this stimulation, we have used two different experimental approaches. The first approach involved the use of inducer removal to separate the process of enzyme induction from that of enzyme production. Pardee and Prestidge (13) have shown that *E. coli* cells incubated with IPTG accumulate β-galactosidase mRNA, and that this mRNA can be translated after the inducer is removed. We find that *E. coli* cells incubated with IPTG in the presence of cyclic AMP accumulate more of this mRNA than do cells induced in the absence of the nucleotide. Nakada and Magasanik (6) have shown that *E. coli* cells incubated with IPTG and chloramphenicol accumulate β-galactosidase mRNA and that this mRNA can be translated after the inducer and chloramphenicol are removed by filtration. They also found that glucose or glycerol repressed the formation of this mRNA. We find that cyclic AMP overcomes the glucose repression of mRNA synthesis in chloramphenicol-treated cells.

The increased accumulation of β-galactosidase mRNA caused by cyclic AMP might have been secondary to some other effect of the nucleotide. Indeed, Stent (14) has proposed that mRNA synthesis is regulated by its translation. A possible effect of cyclic AMP on the translation of β-galactosidase mRNA was investigated in an experiment in which cyclic AMP was added after inducer removal, and so was present only during the phase of enzyme production. Under these conditions, cyclic AMP has no effect on β-galactosidase synthesis. Thus, cyclic AMP does not increase the accumulation of β-galactosidase mRNA by stimulating its translation. However, our experiments do not rule out the possibility that mRNA synthesis is dependent on some other step, such as the attachment of ribosomes to nascent mRNA, and that cyclic AMP stimulates this other process. This experiment also showed that cyclic AMP does not prolong
the half life of β-galactosidase mRNA. Instead, cyclic AMP must stimulate the synthesis of β-galactosidase mRNA. This stimulation is specific, because cyclic AMP does not increase the rate of total RNA synthesis in E. coli (6). We have shown recently that cyclic AMP stimulates tryptophanase production in cells induced with tryptophan and that this effect occurs at the level of translation. Thus, cyclic AMP stimulates the synthesis of these two enzymes by two different mechanisms.

Our second experimental approach involved the use of various E. coli mutants. One mutant, C-600, lacks galactoside permease and does not actively transport β-galactosides. Since cyclic AMP stimulates β-galactosidase induction in this mutant, it is unlikely that it acts by stimulating inducer uptake. Conclusive evidence that cyclic AMP does not work in this manner was obtained in experiments with the constitutive mutants 3300 and 0γ. In these mutants, cyclic AMP stimulates β-galactosidase synthesis in the absence of inducer. The experiments with these mutants also help to clarify the relationship between the effect of cyclic AMP on β-galactosidase synthesis and the other factors which regulate the synthesis of this enzyme. The control of the lac operon has recently been reviewed by Beckwith (15). In wild-type E. coli, β-galactosidase synthesis is regulated by the interaction between the repressor, a protein product of the i gene, and the operator, a region on the E. coli chromosome. In the absence of inducer, the repressor binds to the operator and prevents mRNA synthesis. The inducer binds to the repressor, removing it from the operator and thus allowing mRNA synthesis to proceed. Strain 3300 is a point mutant of the i gene. This mutant makes an inactive repressor, which no longer recognizes the operator. Mutant 0γ carries a deletion of part of the operator region. The fact that cyclic AMP stimulates β-galactosidase synthesis in these two mutants suggests that cyclic AMP action does not involve the repressor-operator interaction. Ippen et al. (16) have identified another chromosomal site, the promotor, which controls the rate of β-galactosidase synthesis, and which they postulate to be the point of attachment of RNA polymerase. Cyclic AMP might act at the promotor region to stimulate RNA synthesis, or it might act at another, still undiscovered, chromosomal site. The study of promotor mutants will help to clarify the site and mechanism of cyclic AMP action.

In the experiments reported here, we studied the effect of cyclic AMP on β-galactosidase production under conditions in which the synthesis of this enzyme was repressed by glucose. The possibility that the stimulation of β-galactosidase synthesis by cyclic AMP was secondary to some effect of the nucleotide on glucose metabolism was considered unlikely for the following reasons. First, cyclic AMP has only a very small effect on glucose oxidation under our conditions. Second, cyclic AMP overcomes the repression of β-galactosidase synthesis produced by the nonmetabolized glucose analogues, α-methylglucoside and 2-deoxyglucose. Finally, in cells treated with Tris and EDTA, cyclic AMP stimulates β-galactosidase induction in the absence of glucose.

Glucose can affect β-galactosidase synthesis in several different ways. When glucose is added to cultures of E. coli growing on a different carbon source, a severe, transient repression of β-galactosidase synthesis ensues (10-12). In our experiments, we observed the acute effects of glucose on E. coli grown on glycerol; presumably, we have been observing the phenomenon of transient repression. We have shown that cyclic AMP overcomes the transient repression of β-galactosidase synthesis produced by glucose, and that the nucleotide can stimulate β-galactosidase synthesis in the absence of glucose. Makman and Sutherland (17) have shown that the addition of glucose to cultures of E. coli causes a rapid and pronounced decrease in their intracellular concentration of cyclic AMP. It seems likely that the transient inhibition of β-galactosidase synthesis produced by glucose is due at least in part to this lowered cyclic AMP concentration.

In addition to this transient severe repression, glucose also produces a prolonged, mild repression of β-galactosidase synthesis (13). The differential rate of β-galactosidase synthesis in cells growing on glucose is lower than in cells growing on other carbon sources. In E. coli 3000 used in our laboratory, permanent repression of β-galactosidase synthesis was less than observed by others (12, 18), perhaps because the organism was well adapted to glycerol and grew on it rapidly (19). The role of cyclic AMP in permanent repression is, as yet, unclear.

Finally, under some conditions, glucose can repress β-galactosidase induction by interfering with inducer uptake (19). However, for reasons given above, this phenomenon is not involved in our experiments.

We find that glucose produces a transient repression of β-galactosidase synthesis in the constitutive mutants 3300 and 0γ. Our results are in agreement with those of Tyler, Loomis, and Magasanik (12), who observed transient repression in mutant 3300 and in a different operator constitutive mutant, 2,000 Ω. On the other hand, Palmer and Moses (18) report that transient repression occurs in mutant 3300, but not in mutant 0γ. These authors postulate that transient repression is mediated via the repressor-operator interaction discussed above. A partial explanation of these differences lies in the different glucose concentrations used by various workers. In our studies and those of Tyler, Loomis, and Magasanik, glucose at 0.25 m was used, whereas Palmer and Moses used a concentration of 0.01 m. We have found that the duration of transient repression is decreased at 0.01 m glucose.

In 1960, Kunkee (20) reported the stimulation of β-galactosidase synthesis by a series of substituted pyrimidines. At that time, the mechanism of this stimulation was not known. These substituted pyrimidines may act as analogues of cyclic AMP or promote its intracellular accumulation.

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