We have previously reported that extracellular cAMP induced a reversible shift, from apparent $M_1 = 40,000$ to $43,000$, in the electrophoretic mobility of a polypeptide identified by photofinity labeling with $^{32}$P-$N$-$	ext{cAMP}$ as the cAMP receptor of Dictyostelium (Klein, P., Theibert, A., Fontana, D., and Devreotes, P. (1985) J. Biol. Chem. 260, 1757-1764). In this report, we examine the kinetics and concentration dependence of this stimulus-induced receptor modification. Prior to stimulation, 90% of the receptors migrated as the higher mobility form ($M_1 = 40,000$) and 10% as the lower mobility form ($M_2 = 43,000$). Following 15 min of persistent stimulation with 1 mM cAMP, the percent of receptors migrating as the lower mobility form rose to 85%. This transition occurred with a half-time of 2.5 min. Removal of the stimulus initiated a return to the basal state which occurred with a half-time of about 6 min at 22 °C. No reversal occurred at 0 °C. Addition and removal of a 50 nM cAMP stimulus induced transitions with similar kinetics, but the final plateau value reached was only 40% lower mobility form. The stimulus concentration which induced transitions with similar kinetics, but the final concentration was 0.222, $k_2 = 0.104$, $k_3 = 0.222$, and $k_4 = 0.055$. The unoccupied higher and lower mobility forms of the receptor, designated R and D, are considered to be in rapid equilibrium with liganded forms, designated RL and DL. The rate constants for interconversion of the receptor forms R $\rightarrow$ D and RL $\rightarrow$ DL were calculated from the kinetic data: $k_1 = 0.012$, $k_2 = 0.104$, $k_3 = 0.222$, and $k_4 = 0.055$. The interconversion steps are not at equilibrium, suggesting that an energy expenditure occurs during the receptor modification. The pattern of modulation of the cAMP-induced receptor modification suggests that it may be the biochemical mechanism of adaptation.

In Dictyostelium, starvation initiates a developmental program characterized by a spontaneous cell aggregation and the differentiation into two cell types (2). The aggregation is mediated by extracellular cAMP which functions both as a chemostattractant and as a cell–cell signal relay molecule (3–5). The periodic release of cAMP at centers of aggregation triggers the propagation of waves of cAMP through the cell monolayer (6). The waves provide gradients which orient cell movements toward the center and also control the rate of early gene expression (see Ref. 7 for review).

Responses to cAMP are mediated by high affinity surface receptors. Many of the responses triggered by cAMP stimulation such as activation of adenylate and guanylate cyclases (8, 9), cell shape changes (10), and myosin heavy and light chain kinase activation are characterized by adaptation. Adaptation refers to an adjustment of cellular sensitivity that occurs during persistent occupancy of the surface receptors by cAMP. Cells respond only when the fractional occupancy of surface receptors is increased. When occupancy is held constant, the responses elicited by cAMP subside within 10–20 min. Dictyostelium provides a convenient model system for the study of adaptation, a process which occurs in a wide variety of receptor-mediated responses. Other systems which have been shown to adapt on a similar time scale are bacterial chemotaxis (11), leucocyte chemotaxis (12), hormone-activated adenylate cyclases (13), and the light-stimulated cyclic nucleotide cascade in vision (14).

We have recently identified and characterized the surface cAMP receptor of Dictyostelium (1, 15). It was noted that cAMP induced a reversible modification in the electrophoretic mobility of the receptor (1). The kinetics and concentration dependence of the cAMP-induced mobility shift are presented here. The pattern of modulation of the receptor modification by cAMP suggests that it may be the biochemical mechanism of adaptation in Dictyostelium.

**MATERIALS AND METHODS**

**Cell Growth and Development—Ax-3 cells were grown in HL-5 medium (16) and harvested at a density of less than 5 x 10$^7$/ml. Cells were washed twice and resuspended in DB (5 mM Na$_2$HPO$_4$, 5 mM KH$_2$PO$_4$, 2 mM MgSO$_4$, 0.2 mM CaCl$_2$) at 2 x 10$^7$/ml and shaken at 100 rpm for 5 h at 22 °C (17).

Quantitation of Autoradiographs—The low bisacrylamide gels (see below) separated the two bands of the receptor doublet by about 8 mm. The higher mobility form (apparent $M_1 = 40,000$) was designated R, and the lower mobility form (apparent $M_2 = 43,000$) was designated D. Autoradiographs were scanned, and the height (in centimeters) of the R and D peaks was determined. Data in Figs. 2-4 are presented as Fraction in D Form, that is, the fraction of optical density in the lower mobility form, D, divided by the sum of that in the two forms (Fraction in D Form = (height of D)/(height of D + height of R)). To test the effectiveness of this procedure, samples were prepared in which receptors were predominantly in the R or D forms as presented below in Fig. 2. These were mixed in known proportions and analyzed for Fraction in D Form in the mixtures. As shown in Table I, the

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† American Heart Association Established Investigator.
and Methods.” Known volumes (in microliters) of each preparation were either loaded directly on low bisacrylamide gels (L1–L6 and U1–U6) or first mixed with known volumes of the other preparation (M1–M6). Autoradiographs were scanned, and the amount of R or D forms of the receptor present in each sample was determined (presented here as centimeter deflection of chart recorder). From the L1–L6 and U1–U6 data, the predicted Fraction in D Form in the mixtures (M1–M6) could be calculated and compared to the measured values.

**Table 1. Fraction of Receptors in D Form**

<table>
<thead>
<tr>
<th>Volume added</th>
<th>Amount measured</th>
<th>R PREP</th>
<th>D PREP</th>
<th>R</th>
<th>D</th>
<th>Calculated</th>
<th>Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>30.0</td>
<td>3.5</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>L2</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>16.8</td>
<td>2.0</td>
<td>0.37</td>
<td>0.33</td>
</tr>
<tr>
<td>L3</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>9.5</td>
<td>0.5</td>
<td>0.56</td>
<td>0.55</td>
</tr>
<tr>
<td>L4</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>4.0</td>
<td>0.0</td>
<td>0.72</td>
<td>0.66</td>
</tr>
<tr>
<td>L5</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1.8</td>
<td>0.0</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>L6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>M1</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>34.5</td>
<td>3.8</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>M2</td>
<td>60</td>
<td>40</td>
<td>0</td>
<td>19.3</td>
<td>6.0</td>
<td>0.25</td>
<td>0.23</td>
</tr>
<tr>
<td>M3</td>
<td>40</td>
<td>60</td>
<td>0</td>
<td>13.0</td>
<td>6.3</td>
<td>0.37</td>
<td>0.33</td>
</tr>
<tr>
<td>M4</td>
<td>20</td>
<td>80</td>
<td>0</td>
<td>7.5</td>
<td>7.5</td>
<td>0.56</td>
<td>0.55</td>
</tr>
<tr>
<td>M5</td>
<td>10</td>
<td>90</td>
<td>0</td>
<td>4.3</td>
<td>8.3</td>
<td>0.67</td>
<td>0.66</td>
</tr>
<tr>
<td>M6</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>2.5</td>
<td>10.0</td>
<td>0.78</td>
<td>0.80</td>
</tr>
</tbody>
</table>

measured fractions in the mixtures agreed with the calculated fractions over a wide range.

**Kinetic Experiments**—Cells were washed once in DB, resuspended at 4 × 10⁷ cells/ml, and shaken at 100 rpm. Cells were treated with 5 mM caffeine for 30 min. To measure the kinetics of redistribution of receptors from the R to D forms upon addition of CAMP, cells were stimulated with 10 mM DTT and cAMP. Samples were taken before stimulation and at intervals after addition of CAMP. To measure the kinetics of redistribution from the D to R forms of the receptor that occurs upon removal of CAMP, cells were stimulated with CAMP and DTT for 10 min, washed twice at 0 °C, and resuspended at a 5-fold higher density at 0 °C. The reversal reaction was initiated by dilution of the cells into 4 volumes of DB at 22 °C, and samples were taken at intervals thereafter. At each indicated time point, samples (0.5 ml) were added to 50 ml of PB (5 mM Na₂HPO₄, 5 mM K₂HPO₄, 5 mM KH₂PO₄) at 0 °C. This 100-fold dilution of the stimulus was required to stop the reaction. All subsequent steps were carried out at 0 °C. Cells were centrifuged 4 min at 2000 × g and resuspended in 0.5 ml of 500 µg/ml concanavalin A. After 10 min, 50 ml of PB was added, and cells were centrifuged and resuspended in 250 µl of PB containing 10 mM DTT. 200 µl of cells were added to 50 µl of [³²P]β-N₃-CAMP in PB/DTT, and 5 ml of saturated ammonium sulfate were added (18). Photolabeling was carried out as previously described (1, 15). Membranes were prepared and analyzed on low bisacrylamide gels (1).

**Test of Stop Procedures**—Two duplicate sets of cells were prepared to be stimulated with cAMP as described above. The first set was stimulated with 1 µM cAMP, and samples were taken immediately before and 15 s after stimulation and added to 50 ml of PB and held at 0 °C. After 30 min, the duplicate set of cells was stimulated and samples were taken in the same manner. Both sets were immediately carried through the rest of the procedure. In both sets, the Fraction in D Form was identical (0.21). Thus, even though the first set of cells had remained in the stop solution for 30 min longer than the second, no change in the distribution of receptor forms occurred. In other experiments, cells were added to the stop solution first and then 200 nM cAMP was added. No shift to the D form occurred in the stop solution. There was also a concern that a redistribution might occur during the photolabeling procedure. However, the same distribution of R and D forms was found whether the cells were incubated with [³²P]β-N₃-CAMP for 5 s or 5 min or whether the cells were incubated in ammonium sulfate for 1 or 15 min. The above experiments indicated that no cAMP-induced shift from the R to D forms occurred in the stop solution or subsequent procedures by SDS-PAGE, autoradiographs were scanned. The optical density in the R plus D forms is shown (O——O). Values are normalized to that observed for cells not pretreated with cAMP. This optical density corresponded to an efficiency of photoaffinity labeling of about 4–10% as previously reported (15). The data are from the same experiments as shown in Figs. 2 and 3.

**cAMP Stimulus Remains Constant**—It was important that the added cAMP stimulus remain constant during the course of the experiment. The strategy was to stimulate cells in the presence of caffeine and DTT. Caffeine blocks activation of the adenylate cyclase and cAMP production (19). DTT inhibits the phosphodiesterase (20). Thus, cells could neither increase nor decrease the added cAMP concentration. To test whether cAMP was stable under the standard conditions, cells were developed for 5 h at 2 × 10⁷ cells/ml and then washed and resuspended at 4 × 10⁷ cells/ml in DB. Cells were treated with 5 mM caffeine for 30 min and then with 10 mM DTT. Trace amounts of [³H]cAMP were added in the presence of cAMP ranging from 0.1 nM to 10 µM. After 15 min incubation, reactions were stopped and cAMP was purified by sequential Dowex/Alumina chromatography (21). In all cases, at least 80% of the added cAMP was recovered.

**Measurements of Receptor Losses**—It was noted that, in addition to the cAMP-induced shift in the electrophoretic mobility of the...
receptor, there was a cAMP-induced loss in the optical density of the receptor doublet. (This is apparent in the insets in Figs. 2-4.) In all experiments, aliquots of each sample were taken for measurements of noncovalent binding prior to photoaffinity labeling. As shown in Fig. 1, there was a slight apparent loss or down-regulation of binding sites during persistent stimulation with cAMP, as has been previously reported (22). The maximal loss in binding sites observed was about 20%. This loss, in part, accounted for the time-dependent decrease in optical density on the gel. However, the total loss in optical density was slightly greater than 50%, indicating that a loss in addition to the binding site loss occurred. It was reasoned that the additional 30% loss was due to either a lower efficiency of photoaffinity labeling or a loss during preparation of membranes for gel electrophoresis. In an effort to find the lost material, a crude subcellular fractionation was carried out. No additional receptor of either form was found in the supernatants of the standard membrane preparation. It appears that following treatment with cAMP, the efficiency of photoaffinity labeling decreases or the receptor polypeptide is more sensitive to proteolysis or a redistribution of the receptors occurs during the preparation of membranes. Since it could not be determined whether this loss was selective for the R or D form, no correction could be made. Note, however, that if the entire loss was of the R (or D) form, the final fraction in D Form in Figs. 2 and 4 would be corrected to 0.40 (or 0.90). The larger of these corrections would increase by only a factor of 2 the rate constants k_2 and k_d-2 calculated under "Discussion."

RESULTS

Kinetics of Receptor Modification—As previously reported, photoaffinity labeling of the surface cAMP receptor in Dictyostelium reveals a doublet band in SDS-PAGE. The higher mobility form (apparent M_r = 40,000) was designated R, and the lower mobility form (apparent M_r = 43,000) was designated D. The kinetics of the cAMP-induced shift in the relative intensity of the higher (R) and lower (D) mobility forms of the receptor doublet was examined at 1 μM cAMP, a concentration that saturates the surface receptors. In order to prevent spontaneous oscillations in cellular cAMP levels characteristic of aggregation stage Dictyostelium, cells were pretreated with caffeine which blocks activation of adenylate cyclase and, therefore, stops the oscillations (19). Samples were taken before and after addition of 1 μM cAMP (plus DTT to inhibit phosphodiesterase), washed twice at 0 °C, and photoaffinity-labeled with [32P]-8-N1-cAMP as described under "Materials and Methods." As shown in Fig. 2, prior to addition of cAMP the fraction of radioactivity in the D form of the doublet was about 0.1. (This basal level varied from 0.03 to 0.13 in 19 independent observations.) The addition of 1 μM cAMP triggered a time-dependent redistribution in the fraction of receptors in each of the receptor forms. By 15 min, the fraction of the radioactivity migrating as the D form had increased to a plateau value of 0.80. This ratio remained constant after 26 min of continuous stimulation. A detectable shift was observed within 15 s of addition of cAMP. The transition occurred with a half-time of about 2.5 min.

After 10 min of stimulation with 1 μM cAMP, a portion of the cells was removed, washed free of cAMP at 0 °C, and incubated at 0 or 22 °C. At intervals, aliquots were removed and the receptor doublet was photoaffinity-labeled. As shown in Fig. 2, at 22 °C, there was a time-dependent return toward the basal state until the fraction of radioactivity migrating as the D form was about 0.12 after 32 min. A detectable decrease in the fraction of receptors migrating as the D form was observed within 30 s of warming to 22 °C. The complete transition from D to R forms occurred with a half-time of 5–6 min. At 0 °C, no redistribution occurs and the fraction of radioactivity migrating as the D form remains at 0.8 for as long as 32 min.

**Fig. 2.** Kinetics of reversible modification of the receptor induced by a cAMP stimulus concentration that saturates binding. Cells were stimulated with 1 μM cAMP, and samples taken at the indicated intervals, photoaffinity-labeled, and analyzed by SDS-PAGE as described under "Materials and Methods." The results of four independent experiments are combined for kinetics of modification following addition of the stimulus (○—○). Inset at left shows a portion of a typical gel. (It has been previously demonstrated that 90% of the radioactivity in the gel is in the doublet bands shown here (15).) Sequential lanes show samples taken at 0, 0.25, 0.5, 1, 2, 4, 8, and 16 min after stimulus addition. The results of two independent experiments are combined for the kinetics of reversal following removal of the stimulus (C—C). Inset at right shows a portion of a typical gel. Sequential lanes are samples taken at 0.5, 2, 4, 8, 16, and 32 min after stimulus removal. In two experiments, cells were held at 0 °C for 32 min following the removal of cAMP (□).
The kinetics of cAMP-induced shift in the relative intensities of the R and D forms of the receptor was also examined at 50 nM cAMP, a concentration which occupies about 50% of the surface receptors. As before, spontaneous oscillations in cellular cAMP levels were blocked by caffeine. Samples were taken prior to and after addition of stimulus, washed twice at 0 °C, and photoaffinity-labeled. As shown in Fig. 3, the lower concentration of cAMP induced a rapid increase in the fraction of receptors in the D form which reached a value of 0.4 after about 10 min. No further increase occurred between 10 and 26 min. A detectable shift was observed within 15 s of addition of the stimulus. The transition occurred with a half-time of about 1.5 min. In order to compare the kinetics of the redistribution at high and low cAMP concentrations, the data from Fig. 2 have been replotted in Fig. 3. Note that about 2 min are required for the shift induced by 1 μM cAMP to reach a value of 0.4, the final plateau value attained after 10 min of persistent stimulation with 50 nM cAMP.

After 10 min of stimulation with 50 nM cAMP, a portion of the cells was removed, washed free of cAMP at 0 °C, and incubated at 22 °C. At intervals, aliquots were removed and the receptor doublet was photoaffinity-labeled. As shown in Fig. 3, there was a gradual return to the basal state in which the fraction of receptors in the D form was again about 0.10. A detectable decrease in the fraction of receptors in the D form was observed within 30 s of warming to 22 °C, and the half-time of the decline was about 5 min, similar to that which occurred upon removal of 1 μM cAMP (Fig. 2).

Concentration Dependence of Receptor Modification—The data in Figs. 2 and 3 indicate that a steady-state, fractional shift in the distribution of R and D forms of the receptor is attained after 15 min of persistent stimulation with 1 μM cAMP and 50 nM cAMP. (These concentrations correspond to about 100 and 50% occupancy of surface binding sites.) The steady-state distribution of R and D forms was examined as a function of the cAMP stimulus concentration. Again, spontaneous oscillations in cellular cAMP levels were blocked by addition of caffeine. Identical sets of cells were stimulated with 0.5 nM to 10 μM cAMP, and samples were taken after 15 min of continuous stimulation, washed twice at 0 °C, and photoaffinity-labeled. As shown in Fig. 4, a detectable increase in the fraction of receptors in the D form was observed with 0.5 nM cAMP. The maximal fraction in the D form, about 0.8, occurred with 1 μM cAMP. About 50% of the maximal shift occurred with 27 nM cAMP. After 15 min of persistent stimulation with these concentrations of cAMP, 10 μM cAMP was added to each set of cells. Thus, each set received an increment in the cAMP stimulus concentration from the indicated concentration to about 10 μM cAMP. Incubation was continued for an additional 15 min, and cells were washed twice at 0 °C and photoaffinity-labeled. As shown in Fig. 4, the fraction of receptors in the D form rose to about 0.8 in all cases.

Affinities of the Two Receptor Forms—As illustrated in Fig. 2, sets of cells could be prepared in which receptors were predominantly in the R or D form. The affinities of receptors in the two states were measured by binding of [3H]cAMP. As shown in Fig. 5, the two forms of the receptor have nearly identical affinities. The $K_D$ of the preparation predominantly in the R form was about 15 nM and that of the preparation predominantly in the D form was about 30 nM. The Scatchard analysis also illustrates the 20% loss in binding sites which occurs after 15 min of stimulation (see Fig. 1).

**DISCUSSION**

The simplest interpretation of these observations is that cAMP induces a reversible modification of surface cAMP receptors which alters electrophoretic mobility in SDS-PAGE. The kinetics and cAMP concentration dependence of this modification correlate closely with those of the adaptation process which gradually extinguishes the cAMP-induced activation of guanylate and adenylyl cyclases (8, 9), cell shape changes (10), and myosin heavy and light chain kinase activation. (11) Adaptation of the adenylyl cyclase during stimulation with cAMP has been extensively investigated (8, 23–25). It was shown that cells only respond to increases in the fractional occupancy of surface receptors. When occupancy is held constant, responses subside within 10–20 min. The magnitude of the elicited response is proportional to the fractional increase in receptor occupancy. This holds for the initial
Fig. 3. Concentration dependence of CAMP-induced receptor modification at steady state. Cells were prepared as described under "Materials and Methods" and stimulated with the indicated concentrations of CAMP. After 15 min of persistent stimulation, samples were taken, photoaffinity-labeled, and analyzed by SDS-PAGE as described under "Materials and Methods." Two independent experiments are combined for the initial challenge experiment ( ). Inset shows a portion of a typical gel. The first two lanes are controls not stimulated with CAMP. The remaining 14 lanes (sequentially from right to left) are for stimulation with a 2-fold dilution series starting at 10 μM CAMP. In one experiment, after aliquots were taken at 15 min, 10 μM CAMP was added to each set of cells. After an additional 15 min, aliquots were taken for analysis ( ).

Fig. 5. Scatchard analysis of [3H]CAMP binding to preparations predominantly in the R or D forms. Sets of cells were prepared in which receptors were predominantly in the R (>90%) or D (>80%) forms. The effectiveness of the method of preparation of the two forms is illustrated in Figs. 2 and 4. To maintain these distributions, cells were held at 0 °C throughout the binding assay (see Fig. 2). Binding assays were carried out with a range of CAMP concentrations from 0.5 nM to 10 μM as previously described (15). Scatchard analysis of the binding data to the R ( ) and D ( ) form preparations is shown.

challenge with CAMP or for any subsequent increment in the stimulus level. Several theoretical treatments have shown that receptor modification could account for these features of adaptation (26-30). The pattern of modulation of receptor modification theoretically required to bring about adaptation is consistent with the data presented here in Figs. 2-4.

The rate of adaptation has been investigated by determining the times at which cells become insensitive to increasing levels of test stimuli following pretreatment with an initial higher stimulus level (8, 23). Detectable adaptation occurs within 20 s of stimulation with 1 μM CAMP, and adaptation is nearly complete after 12 min. Complete adaptation occurs slightly sooner with lower concentrations of CAMP. This agrees closely with the kinetics of the CAMP-induced shifts in the distribution of the R and D forms of the receptor reported here in Figs. 2 and 3.

It was previously demonstrated (24) that the reversal in the receptor distribution which occurs with the same half-time (about 4 min) following removal of either a 10 nM or 10 μM CAMP stimulus. The data in Figs. 2 and 3 are consistent with this observation. The reversals in the distribution of receptors following removal of 1 μM or 50 nM CAMP occurred with similar half-times (6 and 5 min, respectively). It was noted (Fig. 2) that the reversal in the receptor distribution which

normally occurs when cells are freed of cAMP is blocked at 0 °C. This predicts that deadaptation will not occur at 0 °C, a possibility currently being tested. In contrast, we have observed that the upward shift in the receptor distribution did occur at 0 °C, albeit more slowly and to a lesser extent (data not shown). Consistent with this observation, it has been reported that cells do synthesize cAMP at 0 °C and that the total duration of synthesis is longer (31). In addition, activation of adenylate cyclase occurs at 0 °C and lasts several times longer than at 22 °C. However, at 0 °C, adaptation does not appear to be complete.4

To facilitate analysis of the data presented here, we assumed that the receptor could exist in two states. The lower band of the doublet is considered to be an unmodified state, R, and the upper band in a modified state, D. (Of course, since the observations are based on an electrophoretic mobility shift, the opposite designation is equally possible.) Consider that the formation of complexes with cAMP gives two more states designated RL and DL, where L represents covalent modification. Although none of these possibilities can currently be ruled out, the requirement for the expenditure of energy favors the last interpretation. Preliminary evidence suggests that cAMP induces a phosphorylation of the receptor on serine and threonine residues.6

The ω-adrenergic receptor of turkey erythrocytes, another receptor coupled to adenylate cyclase, has recently been shown to undergo a ligand-induced alteration in electrophoretic mobility from apparent M, = 40,000 to M, = 43,000 (35, 36). Rather than a shift in the distribution between two discrete forms, as observed here for the cAMP receptor, these investigators observed a progressive decrease in electrophoretic mobility over a 2-h period. We have noted a similar apparent effect, in experiments such as that in Fig. 2, when samples were heavily loaded on standard SDS-PAGE gels. The two discrete bands presented here are observed most clearly on low bisacrylamide gels when low concentrations of sample are loaded. These investigators have also demonstrated correlations among the decrease in electrophoretic mobility, increased phosphorylation of the receptor, and the “desensitization” process in turkey erythrocytes. We are currently testing whether the cAMP-induced phosphorylation of the cAMP receptor leads to its altered mobility and adaptation of the physiological responses.

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REFERENCES


4 A. Theibert, personal communication.

5 Prior to this point, the symbols R and D have designated the unmodified (R) and modified (D) forms of the receptor without specific reference to the state of occupancy of either form.

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