Induction of Catecholamine-responsive Adenylate Cyclase in HeLa Cells by Sodium Butyrate

EVIDENCE FOR A MORE EFFICIENT STIMULATORY REGULATORY COMPONENT*

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HeLa cells, when exposed to 5 mM sodium butyrate, increased their responsiveness to isoproterenol and their number of β-receptors. As untreated HeLa cells have a substantial number of receptors but respond poorly to isoproterenol, the effect of butyrate could be due to quantitative or qualitative changes in β-receptors or other components of the adenylate cyclase system. Receptors were analyzed by membrane/membrane and membrane/cell fusion techniques. HeLa donor membranes, treated to inactivate regulatory and catalytic components of adenylate cyclase, were fused with Fc cells, which lack β-receptors. Isoproterenol-stimulated adenylate cyclase activity in the fusates was proportional to the number of receptors present. There appeared to be only quantitative but not qualitative differences in β-receptors from control and butyrate-treated HeLa. Prostaglandin E1 receptors from neuroblastoma cell membranes were similarly coupled to HeLa adenylate cyclase. The hybrid prostaglandin E1-stimulated activity was lower when acceptor membranes were from control HeLa than when they were from butyrate-treated HeLa cells. These results suggested that butyrate was altering the ability of the regulatory component to interact with receptors. HeLa membranes were extracted with sodium cholate and the extracts used to reconstitute effector-stimulated adenylate cyclase activity in S49 cyc- membranes, which lack a functional regulatory component. Whereas extracts from control and butyrate-treated HeLa were equally effective in restoring NaF-stimulated activity in cyc- membranes, extracts from control HeLa were less efficient in reconstituting isoproterenol- and prostaglandin E1-stimulated activities. We conclude that the poor response of control HeLa to β-agonists is due to a limited activity of the regulatory component but not the receptor. Butyrate induces quantitative changes in the receptor and quantitative changes in the regulatory component that facilitate its ability to couple to receptors but do not alter its ability to interact with the catalytic component of adenylate cyclase.

EXPERIMENTAL PROCEDURES

Materials—(-)-Isoproterenol hydrochloride, (+)-propranolol, PGEl, nucleotides, creatine phosphokinase, phosphocreatine, polyethylene glycol 8000, sodium cholate, and sodium butyrate were purchased from Sigma. Cholera toxin was obtained from Schwarz/Mann. (±)-[3H]Iodocyanopindolol and (α-32P)NAD were from New England Nuclear and (α-32P)ATP was from ICN.

Cell Culture—HeLa cells, strain 30002 (14), were grown as monolayers in Dulbecco’s modified Eagle’s medium containing 0.45% glucose, 10% fetal bovine serum, and 50 μg/ml of gentamicin in 175-cm² flasks at 37 °C in a humidified atmosphere of 95% air/5% CO2. Cells used for experiments were seeded at a density of 15–25 × 10^6 cells/cm² and fed daily. Cells were incubated in growth medium containing sodium butyrate for 20–24 h before being used for experiments. Neuroblastoma cells (clone NB41A from the American Type Culture Collection) were grown in monolayers in the above medium containing 5% fetal bovine serum. The cyc- variant of S49 mouse lymphoma (16) was grown in suspension in the above medium containing 10% horse serum. Friend erythroleukemic cells (clone TS-C12; GM0279 from the Institute of Medical Research, Camden, NJ) were grown in suspension in Eagle’s minimal essential medium supplemented with 10% fetal bovine serum and 50 μg/ml of gentamicin.

Membrane Preparation—Monolayers of HeLa and NB cells were

The catecholamine-responsive adenylate cyclase system is known to contain at least three components: a specific β-

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Butyrate Adenylate cyclase activity

| Butyrate treatment | Adenylate cyclase activity* |
|--------------------|-----------------------------|
| mM                 | pmol/10 min/mg protein      | fmoI/mg protein |
| 0                  | 54 ± 6                      | 134 ± 4        | 316 ± 21 |
| 0.6                | 55 ± 4                      | 128 ± 14       | 359 ± 17 |
| 5.0                | 72 ± 8                      | 145 ± 15       | 1424 ± 141 |
| 10                 | 112 ± 8                     | 145 ± 15       | 1424 ± 141 |

* Similar results were obtained in at least four additional experiments with 5 mM butyrate and two with 0.6 mM butyrate.

RESULTS

Effect of Butyrate on Adenylate Cyclase and $\beta$-Receptors

HeLa Cells—HeLa cells were cultured for 20 h in medium supplemented with 0, 0.6, and 5 mM sodium butyrate. Then membranes were prepared and assayed for $\beta$-receptors and adenylate cyclase activity (Table I). Specific binding of the antagonist ICP increased 2.4- and 3.5-fold after treatment with low and high butyrate, respectively.† Similar fold increases were observed in several additional experiments including those using the antagonist iodohydroxybenzylpidol (data not shown). These results confirm previous reports that low butyrate increased the number of $\beta$-receptors (12-14, 25) as such an effect had not been observed in another study (15). These differences may be due to varying effects of butyrate on different strains of HeLa.$^3$ The affinity of ICP for receptors from control and 5 mM butyrate-treated HeLa cells was similar; the $K_d$ values were 84 and 94 pm, respectively.

Adenylate cyclase activity in HeLa membranes was increased 2-fold by GTP regardless of the butyrate treatment (Table I). In the presence of GTP and isoproterenol, there was only a further 2.4- and 2.8-fold increase in activity in membranes from control and low butyrate-treated cells. In contrast, membranes from high butyrate-treated cells exhibited a 9.8-fold response to isoproterenol compared to GTP alone. Thus, while either concentration of butyrate induced a significant increase in $\beta$-receptor number, only 5 mM butyrate enhanced the response of adenylate cyclase to the agonist.

The response of adenylate cyclase to other effectors also was determined (Table II). Although basal, Gpp(NH)p-, and NaF-stimulated activities were slightly higher in membranes from 5 mM butyrate-treated cells, the fold increases to these effectors was similar in the three membrane preparations. To determine whether butyrate treatment has an effect on C, Mn²⁺-, and forskolin-stimulated activities were measured (Table III). Adenylate cyclase activity in membranes from control and 5 mM butyrate-treated cells appeared to respond similarly to Mn²⁺ and to forskolin.

Functional Analysis of $\beta$-Receptors—In order to determine whether there were qualitative differences in $\beta$-receptors after

† HeLa cells grown in Eagle's minimal essential medium (12-14) have more $\beta$-receptors than cells grown in Dulbecco's medium as described here. The fold increase due to butyrate treatment, however, is similar.

Table:<ref>

| Butyrate treatment | Adenylate cyclase activity | $\beta$-Receptors |
|--------------------|-----------------------------|-------------------|
| mM                 | pmol/10 min/mg protein | fmoI/mg protein |
| 0                  | 54 ± 6                      | 134 ± 4        | 316 ± 21 |
| 0.6                | 55 ± 4                      | 128 ± 14       | 359 ± 17 |
| 5.0                | 72 ± 8                      | 145 ± 15       | 1424 ± 141 |
| 10                 | 112 ± 8                     | 145 ± 15       | 1424 ± 141 |

* Similar results were obtained in at least four additional experiments with 5 mM butyrate and two with 0.6 mM butyrate.

† Similar results were obtained in two additional experiments with 0.6 mM butyrate and three with 5 mM butyrate.

2 HeLa cells grown in Eagle's minimal essential medium (12-14) have more $\beta$-receptors than cells grown in Dulbecco's medium as described here. The fold increase due to butyrate treatment, however, is similar.

3 Other strains of HeLa vary in their response to butyrate. HeLa cells (ATTC CCL 2) obtained from Flow Laboratories behaved similarly to the HeLa cells (strain S3) described by Lin et al. (15) whereas HeLa, strain Stone (25), was similar to strain 3005 used in the present study.

Effect of butyrate on adenylate cyclase activity and number of $\beta$-adrenergic receptors in HeLa cells

HeLa cells were treated with the indicated concentration of sodium butyrate for 20 h. Membranes were prepared and assayed for adenylate cyclase activities and specific ICP binding as described under "Experimental Procedures."
butyrate treatment, HeLa receptors were coupled to a different adenylate cyclase system by membrane/membrane fusion techniques. HeLa membranes treated with NEM (19–21) were fused with Fc membranes, which had no detectable isoproterenol-stimulated adenylate cyclase activity; the fusates then were assayed for this activity (Fig. 1A). As the ratio of HeLa to Fc membranes was increased, the activity increased until a plateau was reached at 1 mg/mg. Irrespective of the ratio used, a higher isoproterenol-stimulated activity was obtained with membranes from butyrate-treated than from control membranes. 

HeLa cells. HeLa membranes treated with NEM still retained a small amount of cyclase activity which was stimulated by Mn

"Experimental Procedures." The binding of ICP to the fusion products has been corrected for any binding to Fc membranes alone. 

"(−)-isopropenol.

Fusates made with alkali-treated donor membranes had lower isoproterenol-stimulated adenylate cyclase activity than was observed with NEM-treated donor membranes (Fig. 1B). Again, the donor membranes from 5 mM butyrate-treated cells were more effective than those from control cells. A plateau, however, was not reached even at a ratio of 2 mg of control HeLa per mg of Fc membrane protein. Similar results were obtained when NB membranes, which also lack isoproterenol-stimulated adenylate cyclase activity, were used as the acceptor (data not shown).

These latter results suggested that the difference in donor activity may only be due to differences in β-receptor number. To test this possibility, HeLa membranes were fused with intact Fc cells, and the fusates were separated from the remaining membranes by low speed centrifugation. After lysis, the fusates were assayed for ICP binding and isoproterenol-stimulated adenylate cyclase activity (Fig. 2). Donor membranes from HeLa cells treated with 5 mM butyrate were more effective than those from control HeLa in both parameters (Fig. 2A and B). When binding was plotted as a function of cyclase activity, however, the data from both membrane preparations gave almost parallel plots (Fig. 2C). The slopes were 17.3 pmol of cAMP produced per fmol of receptor (r = 0.998) for membranes from control cells and 14.6 (r = 0.997) for membranes from butyrate-treated cells. Thus, the intrinsic activity of β-receptors in HeLa cells before and after butyrate treatment appeared to be similar. As the data points using butyrate-treated membranes did not extrapolate through the origin, control HeLa receptors, if anything, may be slightly lower in activity than the corresponding HeLa membranes.
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Fig. 2. Transfer of HeLa β-receptors to Fc adenylate cyclase by membrane/cell fusion. Membranes from control (○) and 5 mM butyrate-treated (●) HeLa cells were exposed to pH 10.9 and were fused with intact Fc cells. After fusion, the fusates were separated from the remaining membranes by low speed centrifugation, lysed, and assayed for (A) isoproterenol (ISO)-stimulated adenylate cyclase activity (picomoles per 10 min per 5 × 10⁶ Fc cells and (B) specific ICP binding (femtomoles per 5 × 10⁶ Fc cells). C, activity as a function of binding. Similar results were obtained in a second experiment.

more efficient in coupling to the acceptor adenylate cyclase.

Transfer of PGE₁ Receptors to HeLa Adenylate Cyclase—To explore the possibility that control HeLa cells were defective in components required for efficient coupling of receptors to adenylate cyclase, another receptor was introduced into HeLa by membrane/membrane fusion. As both Fc and NB cells have a PGE₁-sensitive adenylate cyclase, membranes from these cells were used as donors. Using the exact procedure described by Citri and Schramm (26), very little PGE₁-stimulated activity was detected. When the modified procedure described under “Experimental Procedures,” a significant response was observed (Fig. 3). Without fusion, HeLa membrane adenylate cyclase did not respond to PGE₁ (<20% above GTP alone). When NEM-treated NB membranes were used as the donor, membranes from both control and butyrate-treated HeLa were very efficient as acceptors; the control membranes actually were more effective (Fig. 3A). When alkali-treated membranes were used, membranes from butyrate-treated HeLa were more effective than those from control HeLa in forming the hybrid PGE₁-stimulated adenylate cyclase activity (Fig. 3B). As had been observed above with HeLa donor membranes, alkali treatment gave lower hybrid activity than NEM treatment. Similar results were obtained when Fc membranes were used as the donor (data not shown). As alkali, but not NEM treatment completely inactivates G/F, these results suggested that G/F was the locus for the butyrate effect.

ADP-ribosylation of HeLa Membranes—HeLa membranes were incubated with [α-²³P]NAD and activated cholera in order to ADP-ribosylate G/F subunits. When analyzed by SDS-polyacrylamide gel electrophoresis, two polypeptides of 42 and 47 kDa were specifically labeled by the toxin (Fig. 4). The amount of ²³P incorporated into each of these peptides was almost twice as much in membranes from butyrate-treated HeLa cells compared to those from control cells (Fig. 4A). As increased labeling of nontoxin substrates was not observed (Fig. 4, A and B), the increased ADP-ribosylation of the 42 and 47 kDa peptides appears to be specific. Labeling of these toxin substrates increased in proportion to the amount of HeLa membranes present, and the difference between control and butyrate-treated cells was evident at all membrane concentrations assayed (Fig. 4C). The difference was also observed when the NAD concentration was varied (data not shown). Thus, the increased labeling of toxin substrates in membranes from butyrate-treated HeLa cells appears to be intrinsic to the membranes and not to the ADP-ribosylation assay conditions.

The increase in ADP-ribosylation of toxin substrates in membranes from butyrate-treated HeLa cells was unexpected as cholera activated adenylate cyclase the same in both types of membranes (see Table II). We varied the NAD concentration between 1 μM and 2 mM in the cyclase activation assay. The activation of the enzyme by the toxin increased with increasing NAD concentrations up to 2 mM, and the activity in membranes from butyrate-treated cells was similar or slightly higher (<20% at all NAD concentrations tested) than that in membranes from control cells (data not shown).

Reconstitution of Cyc⁻ Membranes—We directly assayed the functional activity of G/F by reconstituting effector-stimulated adenylate cyclase activity in cyc⁻ membranes with G/F extracted from HeLa membranes. As shown in Fig. 5, NaF-
stimulated activity in the reconstituted cyc⁻ membranes increased equally with increasing amounts of cholate extracts from control or butyrate-treated HeLa until the same maximum activity was reached. In contrast, when isoproterenol-stimulated activity was reconstituted, extracts from control HeLa were less effective at all concentrations assayed, and the maximum activity was 45% lower than that obtained with extracts from butyrate-treated cells. In addition, PGE₁-stimulated activity in cyc⁻ membranes was restored to a lesser extent by the control extract (Table V). Thus, G/F of control HeLa cells appears to be less effective than G/F of 5 mM butyrate-treated HeLa in interacting with the receptors but equally effective in interacting with C.

**DISCUSSION**

HeLa cells contain a substantial number of β-adrenergic receptors, more than avian myoblasts (27) and human fibroblasts (17) and similar to rat (28) and human (29) astrocytoma cells. In contrast to these latter cells, HeLa cells respond poorly to β-agonists. As 0.6 mM butyrate induced a several-fold increase in receptor number but no increase in agonist-stimulated adenylyl cyclase activity, it appears unlikely that receptor number alone is responsible for the inefficient catecholamine-sensitive adenylyl cyclase system in HeLa cells. When exposed to 5 mM butyrate, the cells acquired not only more receptors but also an enhanced responsiveness to the agonist. As butyrate treatment does not affect the responsiveness of adenylyl cyclase to other effectors such as Mn²⁺, forskolin, NaF, guanine nucleotides, and choleragen, it is unlikely that C or its interaction with G/F is involved. The most probable explanations for the induction of catechol-
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Butyrate sensitivity by high concentrations of butyrate are either a qualitative change in the induced β-receptors or a change in components involved in the coupling of the receptors to adenylate cyclase.

We explored the first possibility by transferring HeLa β-receptors to membranes and cells which lacked these receptors using the fusion techniques developed by Schramm and co-workers (19-21, 26). Our modified procedure gave better results than theirs; we found that phospholipids were not required and that fusion at 25 °C for 5 min resulted in higher recoveries of cyclase activity. This may be due to the fact that we were using mammalian cells as both donor and acceptor whereas they used turkey erythrocytes in many of their studies. We also found that NEM treatment did not completely inactivate C and partially inactivated G/F; the latter effect had been reported by others (26, 30). Thus, the receptors in the fuses were capable of interacting with both donor and acceptor cyclase components. By treating the donor membranes at pH 10.9, we were able to completely inactivate both C and G/F and directly examine the ability of the HeLa β-receptors to couple with a foreign adenylate cyclase. Based on membrane/membrane fusion experiments, it appeared that the only difference between control and butyrate-treated HeLa α and δ of β-receptors was the difference in receptor number. This was directly confirmed by fusing HeLa membranes with Fa cells and separating the fusion products from the remaining membranes. In this way, the number of β-receptors transferred was determined and correlated with agonist-stimulated adenylate cyclase activity. From these experiments, it was clear that the β-receptors in control HeLa cells were not less effective in coupling to adenylate cyclase than the receptors in butyrate-treated cells.

We next explored the second possibility, namely a change in the ability of HeLa receptors to couple to G/F. To assay directly G/F function, G/F from HeLa was used to reconstitute effector-stimulated adenylate cyclase activity in cycr membranes. G/F from control HeLa was less effective than G/F from butyrate-treated HeLa in restoring isoproterenol- and PGF-stimulated activities but was equally effective in reconstituting NaF-stimulated activity. The latter result indicated that the reduced response to the hormones in the reconstituted system was not due to differences in extraction of G/F from control and butyrate-treated HeLa. PGF receptors from other cells were transferred to HeLa membranes using the fusion procedure. When the acceptor membranes were from control HeLa, the response of the hybrid adenylate cyclase to PGF was less than when they were from butyrate-treated cells. Based on these results, it appears that coupling of G/F with the receptor but not with C is poor in control HeLa cells and is enhanced by butyrate treatment.

G/F has been purified from different sources and appears to consist of two subunits: one of 45 or 54 kilodaltons, which can be ADP-ribosylated by cholerae; and one of 35 kilodaltons, which is not a toxin substrate (8-11). We were also able to detect cholerae substrates of 42 and 47 kilodaltons in both control and butyrate-treated HeLa cells. The increased level of ADP-ribosylation observed in membranes from the latter cells does not appear to be due to an increase in the amount of these G/F subunits. Reconstitution of NaF-stimulated activity in cycr membranes indicated equal amounts of G/F activity in control and butyrate-treated HeLa cells; and, the A1 subunit is a (mono)ADP-ribosyltransferase (31) and the extent of ADP-ribosylation does not correlate directly with its activation by the toxin (7, 17, 32-34); these results suggest that additional sites on the G/F subunits are more accessible to A1 in membranes from butyrate-treated cells. This increased access may be due to a change in their conformation or interaction with other membrane components, which in turn may be related to the enhanced coupling efficiency observed between G/F and the receptors.

Control HeLa cells appear to be similar to the UNC variant of S49 lymphoma cells (35-38). The latter cells respond to nonhormonal effectors of adenylate cyclase but not to β-agonists or PGF, even though they have the required receptors. Based on reconstitution assays, G/F in the UNC variant is unable to couple to the receptors (36, 37). Insel et al. (38) reported that treatment of UNC cells with choleragen restored their ability to respond to hormones. In contrast, we observed that toxin-treated HeLa cells remained insensitive to isoproterenol. Furthermore, UNC β-receptors have a lower affinity for isoproterenol compared to receptors from wild type S49 cells and the affinity is not modulated by guanine nucleotides (35-37). β-Receptors from control and butyrate-treated HeLa have nearly the same high affinity for isoproterenol, and GTP does cause some modulation of agonist affinity for control receptors. Finally, UNC cells are completely unresponsive to isoproterenol (35-38) whereas control HeLa cells exhibit a small but significant response to the agonist. Thus, the poor coupling observed in UNC and in control HeLa cells may be due to different causes.

Our results clearly indicate that 5 mM sodium butyrate induces only quantitative changes in HeLa β-receptors and qualitative changes in the functional activity of G/F. The changes in G/F may be due to a direct modification of this component or indirectly caused by a change in another membrane component that modulates G/F activity. The latter possibility appears less likely as the enhanced coupling activity of G/F from butyrate-treated HeLa is still detected after extraction and insertion into cycr membranes. Although additional experiments will be required to elucidate the exact nature of these changes, the ability of butyrate to induce increased coupling between receptors and G/F may be a potent tool in understanding the coupling process.

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