Induction of Nonmuscle Myosin Heavy Chain II-C by Butyrate in RAW 264.7 Mouse Macrophages*

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RAW 264.7 macrophages express nonmuscle myosin heavy chain II-A as the only significant nonmuscle myosin heavy chain isoform, with expression of nonmuscle myosin heavy chain II-B and II-C low or absent. Treatment of the cells with sodium butyrate, an inhibitor of histone deacetylase, led to the dose-dependent induction of nonmuscle myosin heavy chain II-C. Trichostatin A, another inhibitor of histone deacetylase, also induced nonmuscle myosin heavy chain II-C. Induction of nonmuscle myosin heavy chain II-C in response to these histone deacetylase inhibitors was attenuated by mithramycin, an inhibitor of Sp1 binding to GC-rich DNA sequences. Bacterial lipopolysaccharide alone had no effect on basal nonmuscle myosin heavy chain II-C expression, but attenuated butyrate-mediated induction of nonmuscle myosin heavy chain II-C. The effects of lipopolysaccharide were mimicked by the nitric oxide donors sodium nitroprusside and spermine NONOate, suggesting a role for nitric oxide in the lipopolysaccharide-mediated down-regulation of nonmuscle myosin heavy chain II-C induction. This was supported by experiments with the inducible nitric-oxide synthase inhibitor 1400W, which partially blocked the lipopolysaccharide-mediated attenuation of nonmuscle myosin heavy chain induction. 8-Bromo-cGMP had no effect on nonmuscle myosin heavy chain induction, consistent with a cGMP-independent mechanism for nitric oxide-mediated induction of nonmuscle myosin heavy chain II-C.

Vertebrate nonmuscle myosin II represents a branch of the myosin superfamily, closely related to skeletal and smooth muscle myosin II isoforms. This ubiquitously distributed class of myosins has been shown to be present in all vertebrate cells including smooth muscle, cardiac muscle, and skeletal muscle cells where, similar to the more highly expressed isoforms of myosin II, they consist of a hexamer containing two heavy chains (200 kDa) and two pairs of light chains (20 and 17 kDa). Two isoforms of the nonmuscle myosin heavy chain (NMHC),1,2 the abbreviations used are: NMHC, nonmuscle myosin heavy chain; LPS, lipopolysaccharide; TSA, trichostatin A, (4,6-dimethyl-7-[p-dimethylaminophenyl]-7-oxohepta-2,4-dienohydroxamic acid); NO, nitric oxide; 1400W, N-[2-(aminoethyl)-N-(2-hydroxy-2-nitrosohydrazino)-2,5-ethylenediamine] NONOate, inducible nitric-oxide synthase; HDAC, histone deacetylase; RT, reverse transcriptase.

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The abbreviations used are: NMHC, nonmuscle myosin heavy chain; LPS, lipopolysaccharide; TSA, trichostatin A, (4,6-dimethyl-7-p-dimethylaminophenyl)-7-oxohepta-2,4-dienohydroxamic acid); NO, nitric oxide; 1400W, N-[2-(aminoethyl)-N-(2-hydroxy-2-nitrosohydrazino)-2,5-ethylenediamine] NONOate, inducible nitric-oxide synthase; HDAC, histone deacetylase; RT, reverse transcriptase.
A time course of induction of NMHC II-C protein in response to 10 mM sodium butyrate. Cells were treated for 3 days in the presence or absence of butyrate, 2 mM. They were then lysed (lanes 1 and 2) or subjected to a change of buffer. Cells that had been incubated with butyrate were then incubated for a further 3 days with (lane 4) or without (lane 5) butyrate. Control cells were incubated without butyrate for a further 3 days (lane 3). N/A, not applicable. E, immunoblotting of lysates from control and butyrate-treated lysates with a second antibody recognizing an epitope close to the amino terminus of NMHC II-C showed a similar induction pattern, supporting the identity of the induced band as NMHC II-C.

RESULTS

We first investigated whether NMHC II-C was expressed in RAW 264.7 macrophages. Immunoblotting of RAW 264.7 cell lysate with an antibody specific for NMHC II-C demonstrated the myosin isoform to be present at a very low concentration in the macrophages (Fig. 1A). In contrast, NMHC II-C was expressed more abundantly in PC12 and COS cells. Treatment of the RAW 264.7 cells with sodium butyrate for 24 h led to the dose-dependent induction of NMHC II-C expression (Fig. 1B). A time course of NMHC II-C induction using 10 mM butyrate is shown in Fig. 1C; significant induction of NMHC II-C was detectable by 10 h of stimulation. Induction of NMHC II-C was reversible, because removal of butyrate after 3 days of induction led to a decline in NMHC II-C levels (Fig. 1D). To confirm the identity of the 225-kDa band identified by the antibody to the COOH terminus of NMHC II-C, immunoblotting was performed with a second antibody that recognizes a different epitope, close to the amino terminus of NMHC II-C (see Experimental Procedures). A similar induction of the 225-kDa band was observed (Fig. 1E), supporting the identity of the induced band as NMHC II-C.

Analysis of NMHC II-C mRNA expression by RT-PCR demonstrated that the mRNA level was very low in untreated cells, but was increased at 6 h and maximal at 10–16 h butyrate treatment (Fig. 2A). RT-PCR of HPRT mRNA was used as a control, showing that similar mRNA amounts were used. Induction of NMHC II-C mRNA was not dependent on de novo protein synthesis, because cycloheximide in the presence of butyrate did not inhibit induction (Fig. 2B, lanes 5 and 6). In fact, cycloheximide alone induced NMHC II-C mRNA expression (lanes 3 and 4) and appeared to enhance butyrate-mediated induction (lanes 5 and 6). Cycloheximide was, however, effective at preventing induction of NMHC II-C protein expression, as demonstrated by immunoblot analysis (Fig. 2C).

Sodium butyrate has been shown to inhibit HDAC and the resultant histone hyperacetylation and chromatin rearrangement have been proposed as the mechanism by which butyrate activates transcription (9). To assess the role of HDAC inhibition in NMHC II-C induction, cells were treated with trichostatin A (TSA), which is also known to inhibit HDAC. TSA stimulation led to the induction of NMHC II-C and the extent of induction was similar to that obtained with butyrate (Fig. 3).

To determine whether the effects of butyrate on induction of NMHC II-C were specific for RAW 264.7 cells, the RBL-2H3 rat mast cell line and HeLa cells were stimulated with butyrate. Non-stimulated RBL-2H3 cells do not express NMHC II-B (7) and NMHC II-C is also undetectable (Fig. 4A). However, treatment with butyrate led to a robust induction of expression of NMHC II-C (Fig. 4A). Expression of NMHC II-C is also absent in non-stimulated HeLa cells (Fig. 4B). Extended treatment for
72 h with high dose butyrate (10 mM) led to a very modest induction of NMHC II-C, much lower than that found in the hemopoietic macrophage and mast cell lines. A second slower

**FIG. 2.** Induction of NMHC II-C mRNA in response to butyrate. A, time course of induction of NMHC II-C mRNA. Total RNA was subjected to reverse transcription and the cDNA used for PCR using primers specific for NMHC II-C (top) or for the housekeeping gene HPRT (bottom). The left lanes contain DNA markers. B, effect of cycloheximide on induction of NMHC II-C mRNA. Cells were treated with cycloheximide, 3.6 or 36 μM, for 30 min and then incubated with or without sodium butyrate, 10 mM, for 16 h before preparation of RNA and RT-PCR as above. C, effect of cycloheximide on induction of NMHC II-C protein. Cells were incubated with or without cycloheximide, 36 μM, for 30 min before incubating in the presence or absence of butyrate, 10 mM, for 24 h. Cells were then lysed and lysates were subjected to immunoblotting for NMHC II-C. Note the absence of signal in lane 4 compared with lane 2.

**FIG. 3.** Treatment of RAW 264.7 cells with trichostatin A induces NMHC II-C. A, time course of NMHC II-C induction in response to TSA, 100 ng/ml (lanes 1–5). Induction in response to 10 mM butyrate for 24 h is shown in lane 6. B, dose response for induction of NMHC II-C in response to TSA. Cells were incubated for 24 h with the indicated concentrations of TSA before lysis and immunoblotting for NMHC II-C.

**FIG. 4.** Butyrate induces NMHC II-C in RBL-2H3 but only marginally in HeLa cells. RBL-2H3 (A) and HeLa cells (B) were treated with the indicated concentrations of butyrate for 72 h before preparation of cell lysates and immunoblotting for NMHC II-C. An equal loading of lysate from RAW 264.7 macrophages treated with butyrate (10 mM) was loaded in the right-hand lane for comparison. For RBL-2H3 cells, detached cells were collected by centrifugation, washed, and lysed after pooling with attached cells. An additional band migrating more slowly than NMHC II-C was observed in the HeLa experiments. C, immunoprecipitation of lysates prepared from HeLa cells treated with or without butyrate, 10 mM, for 72 h was performed using the carboxyl terminus NMHC II-C antibody. Immunoprecipitated proteins were then subjected to SDS-PAGE followed by immunoblotting with a second NMHC II-C antibody to an amino terminus epitope. A single band at 225 kDa was observed, consistent with the slower migrating band in panel B being nonspecific.

**FIG. 5.** NMHC II-C induction is attenuated by the SP1 inhibitor mithramycin. A, cells were pretreated with mithramycin, 10 nM to 10 μM, for 30 min before incubation with sodium butyrate, 10 mM, for 20 h. B, cells were pretreated with mithramycin, 1 μM, for 30 min before incubation with sodium butyrate, 2 or 10 μM, for 20 h. Cell lysates were then prepared and subjected to immunoblotting for NMHC II-C. C, cells were treated with mithramycin for 30 min following by sodium butyrate for 16 h before preparation of RNA and RT-PCR using primers for NMHC II-C (top) or HPRT (bottom).
The transcription factor Sp1 has been implicated in butyrate-mediated gene regulation (10–13). To address the possible role of Sp1 in butyrate-mediated induction of NMHC II-C, RAW 264.7 cells were preincubated with the antibiotic mithramycin, which binds to GC-rich DNA and inhibits Sp1 binding (14). Mithramycin inhibited induction of NMHC II-C in a dose-dependent manner (Fig. 5, A and B), consistent with a role for Sp1 in butyrate-mediated NMHC II-C induction. A similar mithramycin-mediated inhibition was observed when TSA was used to induce NMHC II-C (results not shown). Measurement of NMHC II-C mRNA by RT-PCR demonstrated a similar pattern of inhibition by mithramycin (Fig. 5C), indicating that the inhibitor was acting at the transcriptional level.

Butyrate has been shown to modulate the effects of bacterial LPS on macrophages and endothelial cells, inhibiting iNOS expression (15), but enhancing expression of interleukin-8 (16) and alkaline phosphatase (17). It was, therefore, of interest to determine whether there was any interaction between butyrate and LPS in modulating NMHC II-C isoform expression. Treatment of naive RAW 264.7 cells with LPS induced expression of iNOS as expected (Fig. 6A, lower blot, lane 2), but had no effect on expression of NMHC II-C (upper blot). However, when LPS was added in combination with butyrate, 2 or 10 mM, induction of NMHC II-C (upper blot, lanes 4 and 6) was attenuated. The effects of LPS on NMHC II-C induction are summarized in Fig. 6B. As reported previously (15), butyrate attenuated iNOS induction in response to LPS (Fig. 6A, lanes 4 and 6, lower blot). The inhibition of NMHC II-C induction in response to LPS raised the possibility that the NO produced in response to the induction of iNOS played a role in regulation of NMHC II-C expression. This was confirmed by induction of NMHC II-C with butyrate in the presence or absence of nitric oxide donors. Sodium nitroprusside, 0.25 mM (Fig. 7A), and spermine NONOate, 0.2 mM (Fig. 7B), attenuated NMHC II-C expression in response to butyrate. The results are summarized in Fig. 7C. Conversely, the inhibition of butyrate-mediated NMHC II-C induction by LPS was attenuated by inhibition of iNOS with the specific inhibitor 1400W (Fig. 8). Inhibition of iNOS was confirmed by measurement of the stable products of NO breakdown, nitrate and nitrite; 1400W inhibited nitrite/nitrate production in response to LPS by 90% (results not shown).

NO mediates its effects on vasodilation via activation of guanylate cyclase and elevation of cGMP, but it can also act in a cGMP-independent fashion. To address the role of cGMP in
the inhibitory action of NO, induction of NMHC II-C with butyrate was performed in the presence or absence of a cell-permeable cGMP analog. 8-Bromo-cGMP, 0.1 to 1 mM, had no effect on NMHC II-C induction in response to butyrate (Fig. 9), arguing against a role for cGMP elevation in the attenuation of NMHC II-C induction by NO and LPS.

**DISCUSSION**

NMHC-II isoforms differ in their tissue distributions, indicating that expression of the genes is regulated in a cell-specific manner. Evidence has been obtained previously for transcriptional regulation of both NMHC II-A and II-B expression. A 100-bp region in intron 1 of **MYH9**, the gene encoding human NMHC II-A, located 23 kb downstream from the transcriptional start site, has been shown to activate transcription in a cell-type and differentiation-specific manner (18). This region contains a binding site for Sp1 or Sp3, a site for USF1 or USF2, and a novel site (18). Induction of NMHC II-A was demonstrated during differentiation of HL-60 myeloid cells and U-937 promonocytic cells to a more monocytic phenotype (19). For NMHC II-B, the homeobox protein Hex has been demonstrated to induce transcription in a cAMP-response element-dependent manner, although Hex binds to a specific homeodomain-binding sequence rather than cAMP-response element (20). NMHC II-B is also down-regulated in cells transformed by a variety of oncogenes (21).

Here we demonstrate using mouse macrophages that expression of NMHC II-C can be regulated by a physiologically relevant stimulus, sodium butyrate. In contrast, this treatment had no effect on the expression of II-A, which is abundant in these cells. NMHC II-B, which is not expressed in these cells, similar to RBL-2H3 cells, was only minimally up-regulated (data not shown). Butyrate is produced in large quantities by bacterial fermentation of fiber and its intracolonic concentration is typically in the 5–15 mM range (22). Stimulation with this short chain fatty acid has been shown to lead to differentiation in a wide range of cell types and, in many cases, can also cause apoptosis. A diverse range of gene products have been shown to be induced by butyrate, including the G-protein G_{i2} (13), cell-cycle related proteins such as p21^{Waf1} (10, 23) and p27^{Kip1} (23), γ-globin (24), and alkaline phosphatase (25). Induction of NMHC II-C was found both in hematopoietic cell lines, the macrophage line RAW 264.7 and basophilic leukemia line RBL-2H3, and in non-hematopoietic HeLa fibroblasts. However, HeLa cells were much less sensitive to butyrate than the hematopoietic lines.

The induction of NMHC II-C mRNA expression does not require de novo protein synthesis, because cycloheximide, at concentrations that abolished induction of NMHC II-C protein expression, tended to increase butyrate-mediated NMHC II-C mRNA expression. Induction of specific mRNAs in response to cycloheximide treatment is often interpreted to indicate regulation of mRNA expression by a labile regulatory protein (26). However, other mechanisms by which cycloheximide can act include stabilization of mRNA (27, 28) and direct transcriptional activation (29, 30). Cooper-
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Butyrate causes differentiation and cell cycle arrest in a wide range of cell types (9) and, in many cases, butyrate stimulation also induces apoptosis. Butyrate inhibits HDAC and the resultant histone hyperacetylation and chromatin rearrangement have been proposed as the mechanism by which butyrate activates transcription (9). However, there is increasing evidence that other mechanisms contribute to the actions of butyrate. Butyrate stimulation of transcription of several genes, including p21\textsuperscript{Waf1} (10), ferritin H (31), galectin-1 (32), and G\textsubscript{S2} (13), involves Sp1 binding sites. HDAC1 can form a complex with Sp1 and inhibit transcription through Sp1 binding sites (33). The transactivating factor E2F1 competes with HDAC1 for binding to Sp1 and abolishes HDAC1-mediated transcriptional repression (33). Here we show that mithramycin, an antibiotic that binds to GC-rich sequences and blocks binding of Sp1 to DNA (14), inhibited the induction of NMHC II-C in response to butyrate. Inhibition of induction of NMHC II-C occurred both at the mRNA and protein levels at 1 and 10 \(\mu\)M mithramycin.

The normal condition of the gut has been described as a state of controlled inflammation (34). Typically, cells of the colon and liver will be exposed to both butyrate and LPS and the balance of interactions between these two mediators is likely to play a role in inflammatory diseases such as irritable bowel syndrome. NMHC II-C induction is attenuated by LPS in RAW 264.7 cells, an interaction that could be important in regulating NMHC II-C levels in cells of the colon and liver. The inhibition of NMHC II-C induction appears to be mediated by NO, produced in response to the LPS-mediated induction of iNOS, because the NO donors spermine NONOate and sodium nitroprusside attenuated NMHC II-C induction in a similar fashion. Conversely, inhibition of iNOS with the specific inhibitor 1400W attenuated the LPS-mediated inhibition of NMHC II-C induction. There is, thus, a mutual antagonism between butyrate and LPS, with butyrate inhibiting iNOS induction while the product of iNOS, NO, inhibits NMHC II-C induction.

Whereas NO regulates vascular tone via soluble guanylate cyclase (35), it has been shown to have cGMP-independent effects on gene transcription. Nitric oxide donors increased tumor necrosis factor-\(\alpha\) expression in response to phorbol ester in U937 cells, which lack soluble guanylate cyclase (11). NO increased tumor necrosis factor-\(\alpha\) promoter activity and this increase was associated with decreased Sp1 binding. Insertion of Sp1 sites also conferred NO responsiveness to a minimal cytomegalovirus promoter (11). NO also inhibited interleukin-2 expression in response to interleukin-1\(\beta\) in murine lymphocytes (36). NO was shown to abrogate the DNA binding activities of the zinc finger transcription factors Sp1 and EGR-1, and native Sp1 derived from NO-treated nuclear extracts and NO-treated lymphocytes lacked DNA binding activity (36). LPS was found to down-regulate Sp1 binding activity by promoting Sp1 protein dephosphorylation and degradation (37); whereas the mechanism of LPS action was not determined, NO would clearly be a candidate effector. The inhibitory effects of NO on NMHC II-C induction appear to be cGMP-independent, because the cGMP analog 8-bromo-cGMP had no effect on butyrate-mediated induction of NMHC II-C. NO regulates NF-\(\kappa\)B activity by nitrosylation of the transcription factor (38), and this has been proposed as a potential regulatory mechanism for Sp1, perhaps interfering with the zinc finger structure (39).

It is, thus, tempting to speculate that Sp1 may play a role in both the induction of NMHC II-C in response to butyrate and in its suppression by NO. However, confirmation of this hypothesis will require the isolation of the NMHC II-C promoter, permitting mechanistic studies on the transcriptional regulation of NMHC II-C.

At higher butyrate concentrations (>2 mM), treatment of RAW 264.7 cells resulted in the induction of apoptosis, as indicated by membrane blebbing and poly(ADP-ribose) polymerase cleavage, and the time course of induction of NMHC II-C paralleled the onset of apoptosis in response to these relatively high amounts of butyrate (results not shown). However, induction of NMHC II-C is not required for apoptosis, because sodium nitroprusside treatment at concentrations >0.25 mM also caused apoptosis, but did not induce NMHC II-C protein expression (data not shown). Conversely, induction of NMHC II-C at lower butyrate concentrations was not accompanied by apoptosis. Thus, the function of NMHC II-C isoform induction is currently unknown. Whereas there is overlap between the tissue distributions and intracellular localizations of NMHC isoforms, it is clear that the isoforms are not redundant. Ablation of NMHC II-B expression has been shown to lead to cardiaco (40) and brain abnormalities (41), leading to embryonic or neonatal lethality, whereas ablation of NMHC II-A leads to lethality at an early (E6.0) embryonic stage.\(^2\) The II-A and II-B isoforms also differ in their physical properties; NMHC II-A from Xenopus had a 2.6-fold greater actin-activated Mg\textsuperscript{2+}-ATPase activity relative to NMHC II-B and moved actin filaments 3.3-fold faster (42). Further experiments to assess the physical properties of expressed NMHC II-C and its subcellular localization may give insight into the role of NMHC II-C and the functional significance of its induction in response to butyrate.

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