Calcium-dependent Dephosphorylation Mediates the Hyperosmotic and Lysophosphatidic Acid-dependent Inhibition of Natriuretic Peptide Receptor-B/Guanylyl Cyclase-B*

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C-type natriuretic peptide binding to natriuretic peptide receptor-B (NPR-B) stimulates cGMP synthesis, which regulates vasorelaxation, cell proliferation, and bone growth. Here, we investigated the mechanistic basis for hyperosmotic and lysophosphatidic acid-dependent inhibition of NPR-B. Whole cell cGMP measurements and guanylyl cyclase assays indicated that acute hyperosmolarity decreased NPR-B activity in a reversible, concentration- and time-dependent manner, whereas chronic exposure had no effect. Acute hyperosmolarity elevated intracellular calcium in concentration-dependent fashion that paralleled NPR-B desensitization. A calcium chelator, but not a protein kinase C inhibitor, blocked both calcium elevations and desensitization. Hyperosmotic medium stimulated NPR-B dephosphorylation, and the receptor was rapidly rephosphorylated and resensitized when the hypertonic media was removed. Lysophosphatidic acid also inhibited NPR-B in a calcium- and phosphorylation-dependent process, consistent with calcium being a universal regulator of NPR-B. The absolute requirement of dephosphorylation in this process was demonstrated by showing that a receptor with glutamates substituted at all known NPR-B phosphorylation sites is unresponsive to hyperosmotic stimuli. This is the first study to measure the phosphorylation state of an endogenous guanylyl cyclase and to link intracellular calcium elevations with its dephosphorylation.

The mammalian natriuretic peptide family consists of three members: atrial natriuretic peptide (ANP),¹ brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) (1). ANP and BNP are produced in atrial and ventricular myocytes, respectively. ANP reduces blood pressure by stimulating sodium and water excretion, by stimulating vasorelaxation, and by inhibiting renin and aldosterone secretion. CNP is most highly expressed in the brain (2), endothelial cells (3), and chondrocytes (4, 5). It relaxes vascular smooth muscle cells (6) and inhibits their proliferation (7), a process that has been exploited to inhibit vascular restenosis and to stimulate vascular regeneration (8). In addition, CNP stimulates the proliferation of chondrocytes, which promotes the growth of long bones (4, 5).

Natriuretic peptide receptors are structurally related cell surface guanylyl cyclases called natriuretic peptide receptor-A (NPR-A) and natriuretic peptide receptor-B (NPR-B) or guanylyl cyclase-A and guanylyl cyclase-B (9–11). They consist of an extracellular ligand binding domain, a single membrane-spanning region and intracellular kinase homology, dimerization, and carboxyl-terminal guanylyl cyclase domains. ANP and BNP activate NPR-A, whereas CNP activates NPR-B. Binding of these receptors by their respective ligands stimulates the synthesis of the intracellular second messenger, cGMP.

The mechanisms regulating NPR-A and NPR-B activity are incompletely understood. It is known, however, that receptor phosphorylation is required for natriuretic peptide activation and that prolonged exposure to natriuretic peptides or acute exposure to activators of protein kinase C causes receptor dephosphorylation and desensitization (12, 13). NPR-A and NPR-B are also inhibited by hormones (arginine, vasopressin, angiotensin II, and lysophosphatidic acid) or growth factors (platelet-derived and fibroblast growth factors) that antagonize the actions of natriuretic peptides (14–18). Protein kinase C was initially implicated in this so-called heterologous desensitization, but recent studies indicate that it is dispensable for this response (17, 18).

While characterizing how hyperosmotic medium inhibits NPR-B, we found that agents or conditions that elevate intracellular calcium stimulate the dephosphorylation of NPR-B and that both calcium elevations and dephosphorylation are required for the inhibition. We suggest that this is a universal mechanism by which environmental conditions and antagonistic hormones inhibit natriuretic peptide signaling. This mechanism may underlie the desensitization of NPR-A and NPR-B that accompanies pathological conditions such as diabetes and congestive heart failure (19–21).

EXPERIMENTAL PROCEDURES

Materials—Rat CNP, GF-109203X, and BAPTA-AM were purchased from Sigma-Aldrich. Lysophosphatidic acid (LPA) was acquired from Sigma-Aldrich. LPA was acquired from Sigma-Aldrich. Rat CNP, GF-109203X, and BAPTA-AM were purchased from Sigma-Aldrich.
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RESULTS

Hyperosmolarity Acutely Inhibits NPR-B in NIH3T3 Cells—To examine the effect of hyperosmolarity on the activity of NPR-B, we incubated NIH3T3 cells with medium alone or medium containing 10 or 100 mM final concentrations of Tri-HCl or HEPES buffers to increase the extracellular osmotic pressure. After 30 min, we prepared crude membranes from these cells and assayed them for CNP-dependent and Triton X-100-dependent guanylyl cyclase activities. The former treatment measures the physiologic activation of NPR-B, whereas the latter artificial conditions indicate the total amount of guanylyl cyclase present in any given membrane preparation. CNP-dependent but not Triton X-100-dependent cyclase activity was markedly reduced in membranes from cells exposed to 100 mM concentrations of either buffer, whereas activities measured in membranes from cells exposed to 10 mM concentrations were only slightly decreased (Fig. 1A).

To determine whether other general osmolytes inhibit NPR-B, we incubated serum-starved cells with 100 mM NaCl, 200 mM sorbitol, or 200 mM urea so that 200 mg of each osmolyte were added per treatment. As shown in Fig. 1B, membranes prepared from cells exposed to either NaCl or sorbitol had similarly reduced CNP-dependent guanylyl cyclase activities. In contrast, no significant reductions were observed in membranes prepared from cells incubated with the same number of milliosmoles of urea. The lack of effect of urea is because of its high cell membrane permeability (22). Hence, its osmotic gradient is short lived. In further support of a general osmotic inhibitory mechanism, we found that the effects of submaximal concentrations of NaCl (50 mM) and sorbitol (100 mM) were additive, whereas incubations with 50 mM NaCl and 100 mM urea resulted in an inhibitory response that was about half that observed with 100 mM NaCl alone.

To further examine the sensitivity of the NPR-B receptor to hyperosmolarity, we conducted guanylyl cyclase assays on membranes derived from NIH3T3 cells that were incubated for 30 min with 0, 10, 25, 50, 100, and 150 mM NaCl in addition to the normal 110 mM NaCl contained in the medium. We found that the additional NaCl inhibited CNP-dependent activity in a concentration-dependent manner (Fig. 1C). Slight reductions were observed with NaCl incubations of 25 mM, and marked desensitization was detectable after exposure of cells to 50 mM or higher additional NaCl concentrations. The maximum concentration tested, 150 mM, reduced hormone-dependent but not detergent-dependent cyclase activity to about half of the amount detected in untreated cells.

To characterize the time course of the inhibition, cells were serum-starved overnight and then incubated for 0, 5, 10, 20, 30, or 60 min with 100 mM additional NaCl. Membranes were prepared from these cells and assayed for hormone-dependent or detergent-dependent guanylyl cyclase activities (Fig. 1D). The effect of NaCl on hormone-dependent activity was rapid, having a \( t_{1/2} \) of \(-15 \) min. Again, the hyperosmotic conditions had no effect on cyclase activity measured in the presence of detergent.

Chronic Hyperosmolarity Does Not Increase NPR-B Activity—Because previous studies have shown that the ANP-dependent activity of NPR-A is enhanced after long term exposure to hyperosmotic medium (23), we investigated the effect of a long term (days) NaCl incubation on NPR-B activity in the NIH3T3 fibroblasts. In these experiments, cells were exposed to 25 mM, 50 mM, or 75 mM additional NaCl for 2 days. However, neither CNP-dependent nor detergent-dependent NPR-B guanylyl cyclase activities were affected by these treatments.
Acute Hyperosmolarity Inhibits NPR-B in NIH3T3 Cells—

We next asked whether the osmotic regulation of NPR-B is specific to NIH3T3 cells or is a general characteristic of this receptor by investigating the osmotic regulation of NPR-B in the A10 vascular smooth muscle cell line. We have shown previously that NPR-B is expressed and regulated appropriately in these cells (17). As with the NIH3T3 fibroblasts, we found that acute but not chronic exposure to hyperosmotic medium inhibited CNP-dependent NPR-B activity in vascular smooth muscle cells (Fig. 1, A–D). Hence, both the acute osmotic effect and the lack of a chronic osmotic effect are general characteristics of this receptor.

Hyperosmolarity Inhibits CNP-dependent cGMP Elevations—

Because the previous experiments were conducted by directly measuring the guanylyl cyclase activity of NPR-B in broken cell preparations, we examined the hyperosmotic effect in the more physiologic environment of an intact cell. Whole cells were incubated with 50, 100, or 150 mM additional NaCl for 30 min as shown in Fig. 1A, but instead of measuring cyclase activity in crude membrane preparations, we treated the cells with 20 nM CNP and measured intracellular cGMP concentrations. CNP-dependent eGMP elevations in the whole cells were markedly inhibited by NaCl exposure in a concentration-dependent manner (IC50 ~50 mM) (Fig. 2, top panel). Remarkably, the maximal concentration tested, 150 mM, suppressed CNP-dependent cGMP production to less than 15% of control values.

The Hypersomotic Effect Is Reversible—

To confirm that the acute suppression of the CNP-dependent activity was not because of irreversible cellular damage, we incubated whole cells with hypertonic medium and measured the CNP-dependent cGMP response after an additional 30-min incubation. In this “washout” experiment, we found that removal of the hypertonic medium resulted in a marked recovery of the CNP-dependent cGMP response (Fig. 2, middle panel). In a similar experiment, we incubated cells in hypertonic medium for 30 min and then replaced it with medium lacking additional salt for 5, 10, 15, or 30 min. After the indicated times, we prepared membranes from these cells and assayed them for guanylyl cyclase activity (Fig. 2, bottom panel). CNP-dependent guanylyl cyclase activity increased from the inhibited levels as early as 5 min after the removal of the hypertonic medium and was completely recovered by 30 min. Detergent-dependent cyclase activity was unaffected by the presence or absence of exogenous NaCl. These data indicate that the hyperosmotic inhibition of NPR-B is reversible. It also suggests that the reductions in cyclase activity do not result from receptor degradation as was reported for the osmotic inhibition of NPR-A (24).

Calcium Elevations Are Required for Hyperosmotic and LPA-dependent Inhibition of NPR-B—

We recently demonstrated that the arginine-, vasopressin-, and sphingosine-1-phosphate-dependent desensitization of NPR-B requires elevated calcium concentrations (17, 25). Therefore, we asked whether calcium also mediates the hyperosmotic effect. To determine whether hyperosmotic medium elevates intracellular calcium, we employed a confocal imaging approach based on the calcium indicator fluo-4-AM. As shown in the top panel of Fig. 3, superfusion of the NIH3T3 cells with modified HEPES buffer containing 150 mM additional NaCl caused a sustained increase in intracellular calcium as evidenced by increased fluo-4-AM fluorescence at the calcium-bound wavelength. We also performed parallel experiments with GFP-transfected fibroblasts to confirm that changes in fluorescence represented bona fide calcium signals rather than simply a change in fluorophore distribution resulting from altered cell morphology. We exam-
ined the concentration dependence of the response by incubating the cells with 25, 50, 100, or 150 mM additional NaCl. In all cells the -fold change in fluo-4-AM fluorescence was greater than that observed with GFP (Fig. 3, middle panel). The net difference between these curves (% change in fluo-4-AM fluorescence /% change in GFP fluorescence) is displayed in the bottom panel of Fig. 3, along with the concentration response curve for CNP-evoked guanylyl cyclase activity to highlight the correlation between calcium levels and desensitization. Small elevations in media osmolarity (25 mM NaCl) did not cause significant cytoplasmic calcium elevations or NPR-B desensitization. However, over the higher range of 50 to 150 mM supplemental NaCl, the amplitude of the calcium signals and NPR-B desensitization were generally correlated.

To examine the absolute requirement of intracellular calcium elevations in the osmotic and LPA-dependent desensitization of NPR-B, we tested whether the cell-permeable calcium chelator, BAPTA-AM, could prevent either process. Consistent with a common calcium-dependent mechanism, pretreatment of the cells with 50 mM BAPTA-AM completely blocked the ability of LPA and hyperosmolarity to inhibit NPR-B (Fig. 4, top panel). In contrast, the protein kinase C inhibitor, GF-109203X, was ineffective, although it blocked the PMA-dependent inhibition (Fig. 4, bottom panel). These data indicate that elevated intracellular calcium but not protein kinase C activation is required for these inhibitory processes.

Hyperosmolarity and LPA Cause NPR-B Dephosphorylation—Because the hormone responsiveness of NPR-B is di-

**Fig. 2. Hyperosmolarity decreases CNP-dependent NPR-B activity in NIH3T3 cells.** Top panel, cells were incubated with increasing amounts of NaCl for 30 min. The medium was aspirated, and the cells were stimulated with 20 nM CNP for 3 min. Cyclic GMP concentrations were estimated by radioimmunoassay. Values are the mean of six separate determinations. Vertical bars within symbols represent the S.E. Middle panel, cells were incubated with 100 mM additional NaCl for 30 min. The hypertonic medium was replaced with normotonic medium, and the cells were incubated for an additional 30 min and then stimulated with 20 nM CNP for 3 min. Bottom panel, cells were incubated with 100 mM additional NaCl for 30 min. Then the hyperosmotic medium was removed and replaced by a normotonic medium for 5, 10, 15, and 30 min. Crude membranes were prepared at the indicated time points and assayed for CNP-dependent (squares) and Triton X-100-dependent (circles) guanylyl cyclase activities. Values are the mean of five separate experiments that were assayed in duplicate (n = 10). The vertical bars within each column represent the S.E.

**Fig. 3. Hypertonic medium increases cytoplasmic calcium in concert with NPR-B desensitization.** Top panel, NIH3T3 cells loaded with fluo-4-AM (black) or transiently transfected with GFP (gray) were superfused with modified HEPES buffer containing 150 mM additional NaCl. The resulting changes in fluorescence emission were monitored from single cells as a function of time. Middle panel, additional extracellular NaCl increases intracellular calcium concentrations in a concentration-dependent manner. Cumulative data are from the fluorescence traces of fluo-4-AM-loaded NIH3T3 and GFP-transfected NIH3T3 cells expressed as a ratio of fluorescence intensity (F) versus initial fluorescence intensity (F0) at any time. Bottom panel, the lower curve (triangles) represents the net fluorescence change evoked by NaCl obtained by subtracting the mean amplitudes of the GFP signal from the fluo-4-AM signal at each point (triangles). The upper curve (squares) represents the CNP-dependent NPR-B desensitization after treatment of NIH3T3 cells with the indicated additional NaCl concentrations.
directly proportional to its phosphorylation state (26), we tested whether the calcium-elevating treatments stimulate NPR-B dephosphorylation. The phosphate content of NPR-B was determined by immunoprecipitating the receptor, fractionating the immunocomplex by SDS-PAGE, and staining the gel with a phosphoprotein-specific dye. In control experiments, we found that this staining closely paralleled the $^{32}$P content of NPR-B isolated from metabolically labeled cells. The intensity of the phosphoprotein stain was quantitated on a phosphorimaging device, and then the gel was washed and incubated with SYPRO ruby stain to determine protein levels.

To demonstrate the selectivity of this method, we immunoprecipitated NPR-B from HEK 293T cells that were transfected with or without NPR-B, fractionated the immunocomplexes by SDS-PAGE, and incubated the gel with a phosphoprotein-specific dye. In control experiments, we found that this staining closely paralleled the $^{32}$P content of NPR-B isolated from metabolically labeled cells. The intensity of the phosphoprotein stain was quantitated on a phosphorimaging device, and then the gel was washed and incubated with SYPRO ruby stain to determine protein levels.

To definitively determine whether hyperosmotic medium was removed, the phosphorylation state of NPR-B returned to untreated levels. The dephosphorylation/rephosphorylation is strikingly reminiscent of the desensitization/sensitization scenario observed in Fig. 2, middle and bottom panels.

Because LPA also inhibited NPR-B in a calcium-dependent manner, we asked whether this process was associated with NPR-B dephosphorylation as well. NPR-B isolated from LPA-treated cells contained less phosphate than NPR-B isolated from untreated cells. In all cases, the decreased phosphoprotein staining was not due to reduced amounts of immunoprecipitated receptor because subsequent staining of the same gel with a protein-specific dye indicated that equal amounts of NPR-B were being precipitated (Fig. 5, middle panel). The phosphorylation state of NPR-B was consistently reduced a statistically significant amount by LPA or hyperosmotic medium but was unaffected when the hyperosmotic medium was replaced with regular Dulbecco’s modified Eagle’s medium (washout) (Fig. 5, bottom panel). These data directly demonstrate that hyperosmotic media and LPA exposure induce NPR-B dephosphorylation in whole cells. Importantly, although we and others have shown that the $^{32}$P content of NPR-A and NPR-B is reduced in response to various desensitizing agents in metabolically labeled highly overexpressing cells (10, 27), this is the first report to document changes in the phosphorylation state of an endogenous guanylyl cyclase.

Hyperosmolarity Does Not Inhibit a “Constitutively Phosphorylated” Form of NPR-B—To definitively determine whether the dephosphorylation of NPR-B is required for hyperosmotic

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2 D. Smirnov and L. R. Potter, unpublished data.
desensitization, we employed a mutant version of NPR-B containing glutamate substitutions at all five known phosphorylation sites (NPR-B-5E) to mimic the normal negative charge of a phosphoserine or phosphothreonine. Unlike an inactive mutant that contains alanines at these positions, the cyclase activity of this glutamate-substituted receptor is stimulated by CNP, although to a lesser extent than the wild type receptor (13). We reasoned that if the hyperosmotic desensitization of NPR-B is mediated by receptor dephosphorylation, then the cyclase activity of a receptor that cannot be dephosphorylated should be unaffected by these treatments. Because the NIH3T3 and A10 cells endogenously express wild type NPR-B, which would complicate the interpretation of guanyl cyclase results from cells transfected with NPR-B-5E, we performed these experiments in HEK 293T cells, which do not express detectable levels of any natriuretic peptide receptor.

Hyperosmotic conditions dose-dependently inhibited wild type NPR-B stably expressed in the HEK 293T cells (Fig. 6, top panel). As a control for dephosphorylation-dependent desensitization of NPR-B, we treated cells with PMA and observed marked inhibition of CNP-dependent but not detergent-dependent guanylyl cyclase activity. Next, we examined the effect of hyperosmolarity on the phosphorylation state of NPR-B in the HEK 293T cells (Fig. 6, middle panel). Again, we found that NPR-B was dephosphorylated in cells exposed to high salt conditions and was rapidly rephosphorylated upon removal of the hypertonic medium. As shown previously in metabolically labeled HEK 293 cells, PMA exposure also causes NPR-B dephosphorylation (13). To determine whether the phosphoprotein staining was specific for phosphorylation and not highly negatively charged regions within NPR-B, we stained NPR-B-5E with phosphoprotein. Consistent with phosphate-specific staining, NPR-B-5E was only visualized with the protein-binding dye.

Finally, we investigated whether hyperosmotic medium and PMA exposure inhibit CNP-dependent guanylyl cyclase activity in membranes from cells transfected with NPR-B-5E. In striking contrast to wild type NPR-B, the so-called constitutively phosphorylated receptor was totally unaffected by either treatment (Fig. 6, bottom panel). Together, these data strongly suggest that dephosphorylation of NPR-B is the mechanism by which hyperosmolarity inhibits its cyclase activity.

DISCUSSION

Natriuretic peptide receptors have been studied for almost 20 years, yet we remain surprisingly ignorant of the mechanisms involved in their activation and desensitization. In this report, we present the first characterization of hyperosmolarity on the activity of NPR-B. This may be important physiologically because studies have shown that increased osmolarity resulting from uncontrolled diabetes is an important factor in causing the vascular complications associated with this disease. In fact, NPR-A is desensitized in animal models (19) as well as in human subjects (20) with uncontrolled insulin-dependent diabetes. It is therefore quite possible that a mechanism similar to the one we described for NPR-B may explain this process.

During the course of these studies, we made several key observations. First, we found that short term exposure of NIH3T3 fibroblasts or A10 smooth muscle cells to medium made hypertonic by a variety of osmolytes decreased the ability of CNP to activate NPR-B. However, unlike the results obtained for NPR-A in renal epithelial cells, chronic exposure to hyperosmotic conditions failed to increase NPR-B activity in either cell line, suggesting that the long term hypertonic responses of these two natriuretic peptide receptors differ. It is interesting that chronic hyperosmotic exposure elicits differential responses from NPR-A and NPR-B because their intracellular domains are 78% identical at the amino acid level. This difference could be explained if the increased NPR-A activity is mediated through elevated gene expression. On the other hand, if the increased activity results from mechanisms that are independent from NPR-A protein levels as was demonstrated in primary endothelial cells (23), then this implies a previously unappreciated regulatory mechanism for NPR-A that is not shared with NPR-B. In contrast, the acute regulatory mechanism appears to be conserved between the two receptors. These properties may indicate that only NPR-A plays a significant role in adaptation to chronic hyperosmotic conditions, whereas both receptors are needed to respond adequately to acute situations.

A second important finding from our studies was that acute
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In conclusion, we have shown that NPR-B is acutely inhibited by hyperosmotic stress in a reversible manner. Moreover, we found that the hyperosmotic and LPA-induced NPR-B desensitization require calcium-dependent receptor dephosphorylation. We propose that calcium-dependent receptor dephosphorylation is a universal mechanism for inhibiting natriuretic peptide signaling.

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