The Signal Transduction Pathway Underlying Ion Channel Gene Regulation by Sp1-c-Jun Interactions*

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During neuronal differentiation, an excellently controlled program of signal transduction events takes place, leading to the temporally and spatially regulated expression of genes associated with the differentiated phenotype. A critical class of genes involved in this phenomenon is that made up of genes encoding neurotransmitter-gated ion channels that play a central role in signal generation and propagation within the nervous system. We used the well-established PC12 cell line to investigate the molecular details underlying the expression of the neuronal nicotinic acetylcholine receptor class of ion channels. Neuronal differentiation of PC12 cells can be induced by nerve growth factor, leading to an increase in neuronal nicotinic acetylcholine receptor gene expression. Nerve growth factor initiates several signal transduction cascades. Here, we show that the Ras-dependent mitogen-activated protein kinase and phosphoinositide 3-kinase pathways are critical for the nerve growth factor-mediated increase in the transcriptional activity of a neuronal nicotinic acetylcholine receptor gene promoter. In addition, we show that a component of the Ras-dependent mitogen-activated protein kinase pathway, nerve growth factor-inducible c-Jun, exerts its effects on receptor gene promoter activity most likely through protein-protein interactions with Sp1. Finally, we demonstrate that the target for nerve growth factor signaling is an Sp1-binding site within the neuronal nicotinic acetylcholine receptor gene promoter. transduction cascades, including, among others, ras-dependent mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3-K), and the cAMP-dependent protein kinase pathways (3). Some of the downstream targets of the activated protein kinase pathways are transcription factors such as AP-1, cAMP responsive element-binding protein, and NF-xB.

Rat pheochromocytoma PC12 cells have been extensively used to study the molecular mechanisms involved in NGF signaling. PC12 cells are chromaffin-like cells that in response to NGF treatment withdraw from the cell cycle and differentiate into sympathetic-like neurons, a process accompanied by neurite outgrowth, increased electrical excitability, and changes in neurotransmitter synthesis (4–6). Among the signal transduction cascades activated by NGF in PC12 cells, the MAPK and the PI3-K pathways are thought to play a central role, although other pathways are clearly important (7–10). Activated TrkA promotes conversion of the membrane-anchored Ras-GDP into Ras-GTP. Ras then cooperates in activation of a serine/threonine kinase, Raf-1, which phosphorylates the dual specificity MAPK/extracellular signal-regulated kinase (ERK) kinase (MEK), which in turn phosphorylates and activates the ERKs, ERK1 and ERK2. Recently, it was demonstrated that activation of ERK in response to NGF in both primary sensory neurons and in PC12 cells also requires activation of the PI3-K pathway (11, 12). PI3-K is required for internalization of TrkA and for its signaling to ERK via a Ras family member, Rap 1 (11, 12). Rapid activation of ERK in response to NGF is mediated through Ras, whereas the sustained activation is Rap 1-dependent (11). Activation of ERK is thought to be required for PC12 responsiveness to NGF, because NGF-induced differentiation can be blocked by specific kinase inhibitors, by antibodies against Ras and MEK, or by expression of dominant negative mutants of Ras and MEK (13–16). In addition, constitutively active forms of Ras, Raf-1, and MEK1 can induce neuronal differentiation of PC12 cells (15, 17–19). Activated ERKs translocate to the nucleus, where they phosphorylate and activate the existing transcription factor c-Jun, as well as induce expression of c-Jun (20). Interestingly, overexpression of activated c-Jun in PC12 cells induces neurite outgrowth, suggesting that c-Jun plays an important role in promoting PC12 neural differentiation (20). Among the neuronal genes whose expression is up-regulated in response to NGF in PC12 cells are the genes encoding several subunits (α3, α5, α7, β2, and β4) of neuronal nicotinic acetylcholine receptors (nAChRs) (21–23). nAChRs are pentameric ligand-gated ion channels important for synaptic transmission in the nervous system (24). Previously, we demonstrated that the NGF-mediated increase in nAChR gene expression is independent of cAMP-dependent protein kinase signaling (21) and that NGF treatment of PC12 cells increases the transcriptional activity of the β4 gene promoter (25). In this study we investigated the involvement of the other NGF-sig-
naling pathways, namely MAPK, PI3-K, protein kinase C, and phospholipase C, in the regulation of nAChR gene expression. We show that in PC12 cells, activation of PI3-K and one of the components of the MAPK pathway, MEK, is important for up-regulation of β4 subunit gene promoter activity in response to NGF. We also show that NGF-inducible c-Jun can transactivate the promoter of the β4 gene through cooperation with Sp1 protein bound to the β4 promoter at a previously identified Sp1-binding site, a CA box. We further demonstrate that this Sp1-binding site is necessary for the responsiveness of the β4 promoter to NGF.

EXPERIMENTAL PROCEDURES

Cell Culture and Transfections—SN17 cells (26) and Drosophila melanogaster Schneider SL2 cells were maintained as described (27, 28). PC12 cells (29) were cultured and differentiated with NGF (Upstate Biotechnology, Lake Placid, NY) as previously described (25). Twenty-four h prior to transfections, SN17 cells were plated at a density of 250,000 cells per 35-mm dish. Transfections were performed by a calcium phosphate method using a commercially available kit (Eppendorf-5 Prime, Inc., Boulder, CO). The wild type rat β4-luciferase expression plasmid, pX1B4FH, containing a 226-bp PstI/HindIII fragment spanning nucleotides −89 to +137, relative to the β4 transcription initiation site, and the construct pX1B4FHmut4, containing a mutation in the CA box of the β4 promoter, were described previously (25, 30). Cells were transfected with 2.5 μg of test DNA (pX1B4FH or pX1B4FHmut4), 2.5 μg of effector DNA (the empty pCMV3 vector (Invitrogen, Carlsbad, CA) or pCMV-Jun constructs), and 2.5 μg of a β-galactosidase expression vector, RSV-βgal. In some cases, no effector DNA was included in the transfections. To ensure that the calcium phosphate/DNA precipitates had equal amounts of DNA, appropriate quantities of pBluescript II SK DNA (Stratagene, La Jolla, CA) were added to each sample. PC12 cells were transfected in 60-mm dishes at a density of 105 cells/ml using 30 μl of LipofectAMINE (2 mg/ml; Life Technologies, Inc.) and 2.5 μg of each DNA. After a 5-h incubation in the 2% serum-DNA mix, cells were washed twice with Dulbecco’s modified Eagle’s medium and fed with growth medium. For experiments involving the pharmacological kinase inhibitors, growth media were supplemented with or without 100 ng/ml NGF and with or without inhibitors, as indicated. All inhibitors were purchased from Calbiochem (San Diego, CA) and were used at the following concentrations: MEK inhibitor PD98059 at 100 μM (31), PI3-K inhibitor LY294002 at 50 μM (12, 32), phospholipase C inhibitor U-73122 at 1 μM (33), and protein kinase C inhibitors calphostin C (33) and bisinodylmalemide (BIM) (34) at 400 nM and 1 μM, respectively. SL2 cells were transfected as previously described (28), except that 100 ng of the effector DNAs (pActSp1 or pPacJun) were used. The pPacJun plasmid was a kind gift of Dr. J. Noti and is described elsewhere (35). Forty-eight h following transfection, cells were harvested and assayed for luciferase activity using a commercially available kit (Promega Corp., Madison, WI) and an Autolumat LB953 luminometer (EG&G Berthold, Gaithersburg, MD). All transfections were done a minimum of two times with two different preparations of plasmid DNAs. To correct for differences in transfection efficiencies between dishes, the luciferase activity in each sample was normalized to the β-galactosidase activity in the same sample, which was measured using a commercially available kit (Galacto-Light; Tropix, Inc., Bedford, MA).

Immunoprecipitations and Western Blotting—Immunoprecipitations and Western blotting were performed as previously described (36) using 250 μg of nuclear extracts prepared from NGF-treated PC12 cells. Anti-c-Jun rabbit polyclonal antibody was from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Nuclear extracts were prepared by the method of Dignam et al. (37) as previously described (38), except that nuclear extracts were dialyzed against RIPA buffer (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1% nonidet P-40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate).

RESULTS

PI3-K and MEK Activation Are Necessary for the Induction of the β4 Promoter in Response to NGF—NGF-dependent up-regulation of neuronal nAChR gene expression in PC12 cells is thought to occur partly at the level of transcription (25). To investigate which of the NGF-activated pathways is involved in the transcriptional regulation of neuronal nAChR gene expression in PC12 cells, we examined the effects of blocking several of these pathways on the transcriptional activity of the β4 gene promoter. We previously identified a 226-bp promoter fragment of the β4 gene that can confer neuron-specific expression to a reporter gene in transient transfection assays (27). We have also demonstrated that treatment of PC12 cells with NGF results in a significant increase in β4 promoter activity and that the 226-bp region is sufficient to mediate this response (25, 27). We therefore investigated whether MEK, PI3-K, protein kinase C, or phospholipase C is involved in the regulation of transcription of the β4 gene through elements in the 5′ regulatory region of the gene. The 226-bp β4 fragment fused upstream of the luciferase gene (pX1B4FH) was transiently transfected into PC12 cells. Following transfection cells were treated with NGF for 36 h. A parallel set of transfected cells was left untreated and served as a control. Consistent with our previous results, 36 h of NGF treatment stimulated β4 promoter activity and resulted in induction of reporter gene activity (Fig. 1). When NGF treatment of the transfected cells was carried out in the presence of PD98059, a selective pharmacological agent that blocks activation of MEK, or LY294002, a specific pharmacological inhibitor of PI3-K, stimulation of the β4 promoter was significantly reduced, as judged by reporter gene activity (Fig. 1). In contrast, inhibitors of phospholipase C, U-73122, and protein kinase C, calphostin C, and bisinodylmalemide, had little effect on the activity of the β4 promoter in transfected cells in response to NGF (Fig. 1). These results suggest that activation of the β4 promoter in response to NGF is mediated in part via the MAPK- and PI3-K-dependent pathways in PC12 cells. This is consistent with a model suggesting that these two pathways share overlapping functions in neuronal cells (12). In addition, these data indicate that the 226-bp fragment of the β4 promoter contains the necessary elements to mediate the response to ERK activation, a common downstream target of MEK and PI3-K (12).

Fig. 1. Pharmacological blockade of MEK and PI3-K prevents NGF activation of the β4 promoter. PC12 cells were transiently transfected with pX1B4FH as described under “Experimental Procedures.” Following transfection, cells were treated with 100 ng/ml NGF in the presence or absence of specific pharmacological kinase inhibitors for 36 h, as indicated. Luciferase values were normalized to β-galactosidase expression as driven by the CMV promoter (see “Experimental Procedures”). Fold induction was calculated relative to the normalized luciferase activity obtained from transfected cells that were not treated with NGF. Error bars represent standard deviations of the means. PD, PD98059; LY, LY294002; U, U-73122; CalC, calphostin C.
that has been implicated in regulation of gene expression in response to multiple extracellular stimuli (39). To address the question whether c-Jun is capable of regulating the activity of the \( \beta 4 \) promoter, PC12 cells were transiently transfected with the 226-bp \( \beta 4 \) promoter-luciferase construct (WT) (pX1B4FH) or the mutant construct (mut) (pX1B4FHmut4) alone or with pCMV5 or pCMV-jun (c-Jun). Luciferase values were normalized to \( \beta \)-galactosidase expression as driven by the CMV promoter. Error bars represent standard deviations of the means.

![Fig. 2. c-Jun transactivates the \( \beta 4 \) promoter through an Sp1-binding site. PC12 cells (A) or SN17 cells (B) were transfected with either the wild type \( \beta 4 \) promoter/luciferase construct (WT) (pX1B4FH) or the mutant construct (mut) (pX1B4FHmut4) alone or with pCMV5 or pCMV-jun (c-Jun). Luciferase values were normalized to \( \beta \)-galactosidase expression as driven by the CMV promoter. Error bars represent standard deviations of the means.](http://www.jbc.org/)

![Fig. 3. Immunoprecipitations of c-Jun-Sp1 complexes from NGF-treated PC12 cell lysates. Anti-c-Jun, anti-Sp1, or preimmune rabbit serum (PIRS) was used to immunoprecipitate (IP) proteins from a PC12 cell extract. Western analysis of the immunoprecipitated material was carried out using anti-Sp1 or anti-c-Jun antiserum as indicated.](http://www.jbc.org/)
c-Jun, pCMV-jun. As mentioned earlier, c-Jun was able to strongly transactivate the wild type β4 promoter, pX1B4FH (Fig. 2A). However, when the β4 promoter-luciferase reporter containing mutations in the CA box, pX1B4FHmut4, was used in this experiment, c-Jun activation of the promoter was marginal (Fig. 2A). Similar results were obtained from transfections performed in SN7 cells (Fig. 2B). Thus, the CA box appears to be critical for c-Jun-mediated transactivation of the β4 promoter.

**c-Jun and Sp1 Synergistically Activate the β4 Promoter in Drosophila SL2 Cells**—To further investigate the importance of c-Jun-Sp1 interactions for the transactivation of the β4 promoter, we performed transfection experiments using the *Drosophila* SL2 cell line. These cells lack endogenous Sp1 activity (43–46), as well as endogenous c-Jun activity (35), making them a useful system to study the functional consequences of the protein-protein interactions mentioned above. We previously reported that Sp1 can strongly transactivate the wild type β4 promoter-luciferase expression construct, pX1B4FH, or with the construct in which the CA box is mutated, pX1B4FHmut4. The observed reporter gene activity was comparable with that of Sp1 alone on the wild type promoter (Fig. 4). Together, these results indicate that Sp1 and c-Jun can cooperate to activate the β4 promoter in *Drosophila* cells and that an intact Sp1-binding site is important for this cooperativity.

**The CA Box Is Important for the NGF Responsiveness of the β4 Promoter in PC12 Cells**—Collectively, the data presented above suggest that the CA box of the β4 promoter might be a target for NGF signaling in PC12 cells. To address this question, we transfected PC12 cells with a wild type β4 promoter-luciferase expression construct, pX1B4FH, or with the construct in which the CA box is mutated, pX1B4FHmut4. Consistent with our previous findings (30), the basal activity of the mutant promoter was significantly lower than that of the wild type in untreated PC12 cells (Fig. 5). Thirty-six h of NGF treatment of the transfected cells resulted in a dramatic increase in the activity of the wild type β4 promoter, as judged by reporter gene activity (Fig. 5). However, activity of the mutated promoter was increased only slightly, resulting in reporter gene activity similar to that produced by the wild type β4 promoter in unstimulated PC12 cells (Fig. 5). These data suggest that the CA box is necessary, but probably not sufficient, to mediate the response of the β4 promoter to NGF in PC12 cells.

**DISCUSSION**

To date, twelve genes (α2-α10, β2-β4) encoding subunits of neuronal nAChRs have been identified. Assembly of the different subunits into pentameric homo- or heteromeric receptors results in formation of ion channels with distinct physiological and pharmacological profiles (24). This diversity is thought to be a consequence of differential expression of the subunit genes and subsequent incorporation of their respective products into mature receptors (47). Whereas the implications of the func-

**FIG. 4.** Sp1 and c-Jun synergistically transactivate the β4 promoter in *Drosophila* cells. *Drosophila* SL2 cells were transfected with pX1B4FH or pX1B4FHmut4 (WT or mut, respectively) alone, with “empty” expression vectors (pAct, pPacO), or with expression constructs for c-Jun and Sp1, individually and together. Fold induction was calculated as above.

**FIG. 5.** Mutation of the Sp1-binding site prevents NGF activation of the β4 promoter. PC12 cells were transfected with pX1B4FH (WT) or pX1B4FHmut4 (mut). Following transfection, cells were treated with 100 ng/ml NGF for 36 h. A parallel set of cells was left untreated. Luciferase values were normalized to β-galactosidase expression as driven by the CMV promoter. Error bars represent standard deviations of the means.
tional diversity of nAChR are beginning to be understood, relatively little is known regarding regulation of their gene expression in general and in response to neurotrophin signaling in particular. NGF-driven differentiation of PC12 cells has been extensively used as a model system to study the physiological, biochemical, and molecular mechanisms of neurotrophin signaling. In regard to neuronal nAChR, it has been demonstrated that in PC12 cells, NGF increases ACh-induced channel activity and ACh-induced macroscopic current density (4, 21, 48), phenomena that are thought to be a consequence of an increase in the number of functional nAChR (21). This hypothesis is consistent with observed increases in the binding of [3H]nicotine (49) and of anti-nAChR antibodies (50) that occur in PC12 cells in response to NGF. Whereas the exact mechanisms of the increase in the number of nAChRs are unknown, NGF-driven induction of nAChR gene expression is clearly important (21). Previously, we showed that the NGF-induced up-regulation of nAChR expression and increases in ACh-induced current density are independent of cAMP-dependent protein kinase activity (21). In this study, using specific chemical inhibitors, we demonstrate that the MAPK and PI3-K signal transduction cascades, but not the phospholipase C or protein kinase C pathways, are important for NGF-mediated induction of the promoter of the β4 subunit gene in PC12 cells. Significantly, positive stimulation of β4 promoter activity in response to NGF was considerably reduced by the addition of a pharmacological inhibitor of MEK, PD98059, and was reduced to a similar extent by addition of a PI3-K inhibitor, LY294002. These data suggest that activation of the MAPK and PI3-K pathways is clearly necessary for the induction of nAChR gene expression. Moreover, they indicate that MAPK and PI3-K pathways might have common downstream targets in PC12 cells. Originally, PI3-K and MAPK were thought to initiate two distinct signal transduction cascades in neuronal cells. However, in a recent report York et al. (12) convincingly demonstrated that inhibitors of PI3-K block well known targets of the MAPK pathway, namely ERK and B-Raf, therefore indicating that the MAPK and PI3-K pathways are indeed interconnected.

The MAPK pathway, through a series of phosphorylation events (that include phosphorylation of ERK), is thought to relay signals received by NGF receptors in the plasma membrane to specific transcription factors in the nucleus (51). These activated transcription factors are required for expression of the delayed early and late genes, some of which, such as neuronal nAChR, contribute to the neuronal phenotype developed by PC12 cells in response to NGF. c-Jun is believed to be one of the key factors activated by the MAPK signaling cascade (39). c-Jun is an inducible transcription factor that is activated in response to multiple extracellular stimuli, including growth factors, cytokines, neurotransmitters, T cell activators, various forms of stress, and UV radiation (39). Regulation of c-Jun activity occurs at the level of transcription, resulting in an increase in c-Jun mRNA, as well as post-transcriptionally, resulting in an enhancement of its transactivation potential through phosphorylation (39). Leppa et al. (20) recently demonstrated that in PC12 cells, activation of the MAPK pathway, more specifically ERK, results in stimulation of both c-Jun synthesis and phosphorylation. Moreover, they showed that an exogenous activated form of c-Jun induced marked neurite outgrowth and that overexpression of wild type c-Jun potentiated differentiation induced by MEK1, whereas dominant-negative mutants of c-Jun inhibited it (20). Thus, proper c-Jun activation appears to be necessary for neuronal differentiation of PC12 cells. We therefore investigated whether c-Jun is capable of regulating the promoter of the β4 subunit gene. Using the same fragment of the β4 promoter that confers neuron-specific expression to a reporter gene (24) and that is sufficient to mediate responses to NGF in PC12 cells (25), we showed that c-Jun can strongly transactivate the β4 promoter in both PC12 and SN17 cells. Surprisingly, this 226-bp region of the β4 promoter does not contain “classic” Jun-binding sites, AP-1 elements, to which c-Jun normally binds as a dimer with Jun-Fos proteins (52). Thus, we hypothesized that c-Jun transactivates the β4 promoter through protein-protein interactions with a nuclear factor bound to β4 regulatory elements.

c-Jun has been shown to directly interact with a number of transcription factors, for example, members of the cAMP responsive element-binding protein family, glucocorticoid receptor (53), Smad proteins (54, 55), and members of the Sp family, Sp1 and Sp3 (35, 40–42). Interestingly, we have previously demonstrated that both Sp1 and Sp3 can strongly transactivate the β4 promoter (28, 30, 36). Sp1 and Sp3 are zinc finger DNA-binding proteins that bind a CA box element in the 226-bp region of the β4 promoter (30, 36). Originally, Sp family members were thought to be ubiquitous factors contributing to core promoter activities (56). However, more recently, they have been shown to participate in regulated and cell type-specific gene expression, including regulation of transcription of a number of neuron-specific genes (30, 36, 57–62). Moreover, in PC12 cells, NGF treatment has been shown to stimulate Sp1-dependent transcription (63). Although the exact mechanism of this stimulation is unknown, it is thought that post-translational modifications and/or association with other factors may play a role (63). Hence, NGF-induced activation of β4 gene expression may occur through functional interactions between c-Jun and Sp1. Consistent with this idea are results of our immunoprecipitation/Western blot analysis demonstrating that c-Jun and Sp1 can physically associate in NGF-treated PC12 cells. Furthermore, the Sp1-binding site in the 226-bp region of the β4 promoter, a CA box, is important for the ability of c-Jun to transactivate this promoter in both PC12 and SN17 cells. In contrast to PC12 and SN17 cells, c-Jun by itself had no effect on reporter gene activity in Drosophila SL2 cells that were devoid of endogenous Sp proteins. c-Jun was able to transactivate the β4 promoter in SL2 cells only when cotransfected with Sp1, providing additional support for the hypothesis that it does so through direct interactions with the latter protein. Interestingly, transactivation by c-Jun and Sp1 occurred in a synergistic manner and did so in a CA box-dependent manner. Together, these data suggest that Sp1 and c-Jun can cooperate to activate the β4 promoter and that an intact Sp1-binding site is important for this cooperativity. Moreover, the CA box of the β4 promoter appears to be critical for NGF signaling, because the responsiveness of the β4 promoter to NGF is dramatically reduced when the CA box is mutated. Previous studies demonstrated that c-Jun and Sp1 functionally interact on both synthetic and natural promoters (40, 41); however, to our knowledge, this study is the first demonstration of cooperativity of these proteins in neuronal cells. Whether, similar to Sp1, Sp3 can functionally interact with c-Jun to regulate nAChR gene expression remains to be elucidated.

It should be noted that the β4 subunit, together with the α3 and α5 subunits, forms the predominant neuronal nAChR subtype expressed in the peripheral nervous system (64, 65). These three genes are tightly clustered in mammalian genomes, raising the possibility that they are coordinately expressed via a common regulatory mechanism. Indeed, it has been demonstrated that Sp1 is important for the regulation of expression of all three genes (30, 36, 61, 62). Therefore, it is possible that
through interactions with Sp1, c-Jun might regulate the promoters of the α3 and α5 subunit genes as well.

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