In neuronal cells, activation of a certain heterotrimeric G protein-coupled receptor causes neurite retraction and cell rounding via the small GTPase Rho. However, the specific heterotrimeric G proteins that mediate Rho-dependent neurite retraction and cell rounding have not yet been identified. Here we investigated the effects of expression of constitutively active Gα subunits on the morphology of differentiated PC12 cells. Expression of GTPase-deficient Gα12, Gα13, and Gαq, but not Gα13, caused neurite retraction and cell rounding in differentiated PC12 cells. These morphological changes induced by Gα12, Gα13, and Gαq were completely inhibited by C3 exoenzyme, which specifically ADP-ribosylates and inactivates Rho. The tyrosine kinase inhibitor tyrphostin A25 blocked the neurite retraction and cell rounding induced by Gα12 and Gαq. However, tyrphostin A25 failed to inhibit the Gα12-induced neuronal morphological changes. On the other hand, inhibition of protein kinase C or elimination of extracellular Ca2+ blocked the neurite retraction and cell rounding induced by Gαq, whereas the morphological effects of Gα12 and Gα13 did not require activation of protein kinase C and extracellular Ca2+. These results demonstrate that activation of Gα12, Gα13, and Gαq induces Rho-dependent morphological changes in PC12 cells through different signaling pathways.

The function of the nervous system depends on the highly specific pattern of connections formed between neurons during development. The specificity of these connections requires neurite extension toward the correct targets guided by the growth cone and remodeling of the initial pattern of connections in response to environmental signals (1). The Rho family of small GTPases (Rac, Cdc42, and Rho) has been demonstrated to play critical roles in the regulation of the cytoskeleton required for neurite extension and retraction. Studies on neuronal cell lines have shown that Rac and Cdc42 are required for the outgrowth of neurites, whereas Rho is required for their retraction (2–5). The downstream effectors involved in these GTPase-mediated neuronal morphological effects have been elucidated. The p21-activated kinase PAK1 was shown to act downstream of Rac and Cdc42 to induce neurite outgrowth (4). On the other hand, we recently revealed that the p160 ROKα induces neurite retraction acting downstream of Rho (5). However, little is known about the signaling pathways upstream of these Rho family small GTPases in neuronal cells.

The activation of a certain heterotrimeric G protein-coupled receptor, such as the lysophosphatidic acid (LPA), sphingosine-1-phosphate, thrombin, and prostaglandin EP3 receptors, was shown to cause Rho-dependent neurite retraction in several neuronal cell lines (6–9). However, the heterotrimeric G proteins, which are coupled to those receptors for induction of neurite retraction, have not yet been identified. Previous studies demonstrated that pertussis toxin did not inhibit receptor-mediated neurite retraction (9, 10), indicating that this action is not mediated by Gi or Gq. Furthermore, the activation of Gq by choler toxin or an elevation of cAMP by forskolin failed to induce neurite retraction, but rather suppressed the receptor-mediated neurite retraction (9, 11), suggesting that Gq activation is not linked to induction of neurite retraction.

The Gα12 family of heterotrimeric G proteins, defined by Gα12 and Gα13, is the most recent family to be identified using a homology-based polymerase chain reaction (PCR) strategy (12). Although immediate downstream effectors have not yet been identified, studies with the constitutively active mutants of Gα12 and Gα13 have resulted in the identification of several novel functions regulated by these Gα subunits, including transformation of fibroblasts (13, 14), activation of the c-Jun N-terminal kinase cascade (15–17), stimulation of stress fiber formation and focal adhesion assembly (18, 19), stimulation of the Na+/H+ exchanger (20–22), activation of phospholipase D (23), and induction of apoptosis (24). These studies also indicated that the Ras or Rho family small GTPases appear to be involved in the downstream responses regulated by Gα12 and Gα13.

Rat pheochromocytoma PC12 cells have served as a useful model system for studies of neuronal differentiation and morphology. When PC12 cells are exposed to nerve growth factor (NGF) for several days, they acquire many features of sympathetic neurons, such as an outgrowth of neurites. To investigate the role of the Gα12 family and other Gα subunits in neuronal cell morphology, we microinjected expression plasmids encoding GTPase-deficient mutants of Gα subunits into the nuclei of NGF-differentiated PC12 cells bearing neurites. We report here that expression of constitutively active mutants of Gα12, Gα13, and Gαq induced Rho-dependent neurite retraction and cell rounding through different pathways.

EXPERIMENTAL PROCEDURES

Materials—NGF (2.5 S) was purchased from Promega, and Clostridium botulinum C3 exoenzyme was obtained from Seikagaku Kogyo.
Fig. 1. Neurite retraction and cell rounding induced by constitutively active \( \text{Ga}_{12} \) and \( \text{Ga}_{13} \). Expression plasmids (30 \( \mu \)g/ml) encoding \( \text{Ga}_{12} \), \( \text{Ga}_{12} \), or the empty vector were microinjected into the nuclei of NGF-differentiated PC12 cells. Cells were photographed before (left panels) and 3 h after (middle panels) microinjection under a phase-contrast microscope or by fluorescence of Texas Red-coupled dextran. The arrows indicate injected cells. The results shown are representative of three independent experiments. The bar represents 50 \( \mu \)m.

Expression of Constitutively Active \( \text{Ga} \) Subunits in NGF-differentiated PC12 Cells—To determine the role of the \( \text{Ga}_{12} \) family of heterotrimeric \( G \) proteins in neuronal cell morphology, we expressed constitutively active mutants of \( \text{Ga}_{12} \) and \( \text{Ga}_{13} \) in NGF-differentiated PC12 cells by nuclear microinjection of expression plasmids. Replacing a conserved glutamine with a leucine in the G3 region of the \( \text{Ga} \) subunit, which corresponds to residue 229 in \( \text{Ga}_{12} \), and residue 226 in \( \text{Ga}_{13} \), has been shown to result in a GTPase-deficient, constitutively active form of the \( \text{Ga} \) subunit (26, 27). As shown in Fig. 1, microinjection of expression plasmids (30 \( \mu \)g/ml) encoding constitutively active \( \text{Ga}_{12} \) and \( \text{Ga}_{13} \) in NGF-differentiated PC12 cells caused retraction of their extended neurites and rounding of the cell body within 3 h. Cells microinjected with the empty vector did not exhibit any morphological changes, indicating that there are non-specific effects due to nuclear microinjection itself. We also examined the effects of GTPase-deficient mutants of \( \text{Ga}_{4} \) (\( \text{Ga}_{4} \)QL) and \( \text{Ga}_{4} \)QL on differentiated PC12 cell morphology. As shown in Fig. 2, when expressed in differentiated PC12 cells, \( \text{Ga}_{4} \)QL mimicked \( \text{Ga}_{12} \) and \( \text{Ga}_{13} \)QL in induction of neurite retraction and rounding of the cell body. In contrast,
expression of GαqQL neither stimulated outgrowth nor caused retraction of neurites.

Effect of C3 Exoenzyme on Constitutively Active Ga Subunit-induced Neuronal Morphological Changes—Previous studies have shown that the small GTPase Rho is required for neurite retraction in response to a certain G protein-coupled receptor agonist such as LPA (6–9). As shown in Fig. 2, microinjection of expression plasmids encoding a constitutively active form of RhoA, RhoAV14, caused the retraction of neurites and rounding of the cell body. These morphological changes induced by RhoAV14 were quite similar to those induced by Gα12QL, Gα13QL, and GαqQL (Figs. 1 and 2). Therefore, to examine whether the neuronal morphological changes induced by constitutively active forms of Ga subunits were Rho-dependent, we co-microinjected the constitutively active Ga-encoding plasmids into the cells with C3 exoenzyme from C. botulinum, which has been shown to catalyze ADP-ribosylation of Rho and specifically suppress the action of Rho (28, 29). As shown in Figs. 3 and 4, co-microinjection of C3 exoenzyme (100 μg/ml) completely blocked both neurite retraction and cell rounding induced by Gα12QL, Gα13QL, and GαqQL. We also co-microinjected expression plasmids encoding the dominant-negative form of RhoA, RhoAN19, into the cells with the constitutively active mutants of Ga subunits. Coexpression of RhoAN19 slightly blocked neurite retraction induced by Ga subunits, but was less effective than co-injection of C3 exoenzyme (data not shown). RhoAN19 would not be an effective inhibitor for complete suppression of Ga subunit-induced morphological changes due to coexpression of RhoAN19 and Ga subunits or the requirement of a large amount of RhoAN19 for suppression.

Effect of the Tyrosine Kinase Inhibitor Tyrophostin A25 on Neuronal Morphological Changes Induced by Constitutively Active Ga Subunits—A previous study showed that the tyrosine kinase inhibitor tyrophostin A25 inhibited stress fiber formation stimulated by LPA, but not by microinjection of constitutively active Rho into quiescent Swiss 3T3 cells, indicating that a tyrosine kinase is involved in the LPA-stimulated stress fiber formation acting upstream of Rho (30). Therefore, we examined the effect of tyrophostin A25 on the neuronal morphological changes induced by constitutively active Ga subunits. As shown in Figs. 5 and 6, treatment of differentiated cells with tyrophostin A25 (150 μm) inhibited the Gα13QL- and GαqQL-induced neurite retraction and cell rounding. In contrast, the neurite retraction and cell rounding induced by Gα12QL were not influenced by this tyrosine kinase inhibitor. Thus, tyrophostin A25 specifically inhibited the signaling of Gα13QL and GαqQL. In addition, we examined the effect of another tyrosine kinase inhibitor, tyrophostin AG1478, on morphological changes induced by constitutively active Ga subunits. Treatment of differentiated cells with tyrophostin AG1478 (10 μm) also specifically inhibited the Gα13QL- and GαqQL-induced neurite retraction and cell rounding, and Gα12QL-induced morphological changes were not inhibited by this inhibitor (data not shown).

Effects of Protein Kinase C Inhibition and Elimination of Extracellular Ca2+ on Neuronal Morphological Changes Induced by Constitutively Active Ga Subunits—A number of the cellular responses caused by activation of Gaq have been shown to be mediated by activation of protein kinase C (PKC) or elevation of the intracellular Ca2+ concentration. Therefore, we examined whether activation of PKC was required for the neuronal morphological changes induced by constitutively active Gaq and Gα12/Gα13. As shown in Figs. 7 and 9, down-regulation of endogenous PKC by a 24-h exposure to 1 μM TPA diminished the amount of neurite-retracted cells caused by GαqQL, whereas the Gα12QL- and Gα13QL-induced morphological changes were not inhibited by this inhibitor (data not shown).
ical changes were not significantly altered by PKC depletion of cells. Similar results were obtained by treatment of cells with the PKC inhibitor Ro31-8220 (300 nM) (Fig. 9). These results indicate that inhibition of PKC activity specifically interferes with the signaling pathway of Gaq for neurite retraction and cell rounding.

Next we examined the role of Ca2+ signaling in the neuronal morphological changes induced by activated Ga subunits. Differentiated PC12 cells were incubated in a Ca2+-free medium in the presence of 2 mM EGTA during expression of Ga subunits. Under these conditions, expression of GaqQL failed to induce neurite retraction and cell rounding. In contrast, the neuronal morphological changes induced by Ga12QL and Ga13QL normally occurred in a Ca2+-free medium with EGTA (Figs. 8 and 9). These results indicate that Ca2+ influx is required for the GaqQL-induced neuronal morphological changes.

DISCUSSION

Activation of a certain G protein-coupled receptor has been reported to induce Rho-dependent neurite retraction and cell rounding in neuronal cell lines (6–9). Here we have demonstrated that constitutively active forms of Ga12, Ga13, and Gaq, but not Gas, can trigger neurite retraction and cell rounding in NGF-differentiated PC12 cells. These morphological changes were similar to those induced by a constitutively active form of RhoA, RhoAV14 (Fig. 2); and C3 exoenzyme, which specifically ADP-ribosylates and inactivates Rho (28, 29), completely inhibited both neurite retraction and cell rounding induced by Ga12QL, Ga13QL, and GaqQL (Figs. 3 and 4), indicating that activation of Ga12, Ga13, and Gaq induces neurite retraction and cell rounding through the Rho-dependent signaling pathway in differentiated PC12 cells.

Ga12 and Ga13, the members of the Ga12 class of heterotrimeric G proteins, show 67% amino acid identity to each other and often cause similar responses in various cell types, including transformation of fibroblasts, activation of the c-Jun N-terminal kinase cascade, and stimulation of stress fiber formation and focal adhesion assembly (31). We have also shown that both Gaq and Gas can trigger Rho-dependent neurite retraction and cell rounding. These findings suggest that Ga12 and Ga13 may interact with a common effector. In this study, however, the tyrosine kinase inhibitor tyrphostin A25 blocked the
Ga13QL-induced neurite retraction and cell rounding, whereas the Ga12QL-induced effects were not influenced by this tyrosine kinase inhibitor (Figs. 5 and 6), indicating that a tyrphostin-sensitive tyrosine kinase is involved in the signaling of Ga13, but not in that of Ga12. This finding strongly suggests that Ga13 and Ga13 interact with different effectors to regulate neuronal cell morphology. The differences in the sensitivity to tyrphostin between Ga12 and Ga13 were also shown in the signaling of Ga12- and Ga13-stimulated stress fiber formation and focal adhesion assembly in Swiss 3T3 fibroblasts (19). Furthermore, it was previously reported that Ga12 and Ga13 stimulate Na+−H+ exchangers through different mechanisms in COS-7 cells (32, 33). Therefore, it is likely that Ga12 and Ga13 activate different pathways to regulate their cellular functions.

Activation of Gaq can stimulate the phospholipase C-β family, which results in stimulation of PKC activity and elevation of the intracellular Ca2+ concentration. In this study, depletion of endogenous PKC by both TPA and the PKC inhibitor Ro31-8220 specifically diminished the amount of neurite-retracted cells induced by Gaq, whereas the Ga12QL- and Ga13QL-induced morphological changes were not influenced (Figs. 7 and 9). In addition, elimination of extracellular Ca2+ also inhibited the effects of Gaq, but not those of Ga12QL and Ga13QL (Figs. 8 and 9). It has been shown that inositol 1,4,5-trisphosphate and inositol 1,3,4,5-tetrakisphosphate, products of phospholipase C activation pathways, activate Ca2+-permeable channels in plasma membranes (34, 35). Recently, Gaq was reported to activate inositol 1,4,5-trisphosphate-operated Ca2+-permeable channels (36). The requirement of extracellular Ca2+ for the Gaq-induced morphological changes could be interpreted by this Gaq-mediated Ca2+-permeable channel activation. Therefore, both PKC activation and Ca2+ influx are essential elements in the signaling of Gaq upstream of Rho. We also examined the involvement of phospholipase C in the Gaq QL signaling using the phospholipase C inhibitor U-73122, but this compound was cytotoxic for differentiated PC12 cells, and treatment with U-73122 alone caused cell detachment.2 Interestingly, both PKC activity and Ca2+ influx as a result of

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2 H. Katoh, J. Aoki, Y. Yamaguchi, Y. Kitano, A. Ichikawa, and M. Negishi, unpublished observation.
phospholipase C activation appeared to be required for LPA-induced neurite retraction in NGF-differentiated PC12 cells (7). Therefore, it is likely that a Gq-coupled LPA receptor stimulates phospholipase C activity, and the resultant activation of PKC and Ca\(^{2+}\) influx induces Rho-dependent neurite retraction in PC12 cells. In contrast, prostaglandin EP3 receptor-induced neurite retraction was mediated through a PKC-independent pathway (9), indicating that G12 or G13 mediates the action of the EP3 receptor.

Interestingly, the G\(\alpha_q\)QL-induced neurite retraction and cell rounding were also blocked by treatment of cells with the tyrosine kinase inhibitor tyrphostin A25 (Figs. 5 and 6), indicating that a tyrphostin-sensitive tyrosine kinase is involved in the signaling from G\(\alpha_q\) to Rho. This study did not show whether this tyrphostin-sensitive tyrosine kinase acts upstream or downstream of Ca\(^{2+}\) and PKC in the signaling from G\(\alpha_q\) to Rho. Since activation of G\(\alpha_q\) can directly stimulate phospholipase C, which results in stimulation of PKC activity and elevation of the intracellular Ca\(^{2+}\) concentration, this tyrphostin-sensitive tyrosine kinase may act downstream of Ca\(^{2+}\) and PKC. Recently, the novel nonreceptor tyrosine kinase PYK2 has been shown to mediate G\(\alpha_q\)-coupled receptor-stimulated activation of the mitogen-activated protein kinase cascade in PC12 cells, and the activity of this tyrosine kinase appears to be regulated by elevation of the intracellular Ca\(^{2+}\) concentration as well as by PKC activation (38). Therefore, PYK2 can be speculated to be a candidate for the tyrosine kinase, which links the signal of G\(\alpha_q\) to Rho for the induction of neurite retraction and cell rounding. A tyrosine kinase-sensitive tyrosine kinase was of course involved in the signaling of G\(\alpha_{12}\) and G\(\alpha_{13}\) to Rho. However, in contrast to G\(\alpha_q\), G\(\alpha_{13}\) did not require either PKC activation or Ca\(^{2+}\) influx. Two potential explanations for the difference between the signaling pathways of G\(\alpha_{13}\) and G\(\alpha_q\) can be presented. One explanation is that an identical tyrosine kinase mediates the signals of G\(\alpha_{12}\) and G\(\alpha_q\) to Rho, but the pathways of both \(\alpha\) subunits to activate the tyrosine kinase are different; G\(\alpha_q\) activates the kinase through PKC and Ca\(^{2+}\) influx, whereas G\(\alpha_{13}\) activates the kinase independent of PKC. The other explanation is that different tyrosine kinases are involved in the pathways of both \(\alpha\) subunits. We have summarized these possible pathways of signal transduction of three \(\alpha\) subunits for Rho-dependent neurite retraction and cell rounding (Fig. 10).

Expression of a GTPase-deficient form of G\(\alpha_q\) in undifferentiated PC12 cells was recently shown to induce neurite outgrowth during 2–3 weeks using the retrovirus-mediated infection procedure (39). In contrast, our results showed that expression of G\(\alpha_q\)QL in NGF-differentiated PC12 cells triggered neurite retraction within 3 h after microinjection. Therefore, these opposite effects of G\(\alpha_q\) on the regulation of neurites may be due to different conditions of cells in differentiation or to a different time scale for examination of morphological effects.

The data presented here demonstrated that constitutively active mutants of G\(\alpha_{12}\), G\(\alpha_{13}\), and G\(\alpha_q\) can induce neurite retraction and cell rounding through different signaling pathways, which, however, finally converge at activation of Rho (Fig. 10). Rho, like other small GTPases, functions as a molecular switch; it is active in its GTP-bound state and inactive in its GDP-bound state. Upstream activation of the cycle is mediated by guanine nucleotide exchange factors, which promote the exchange of GDP for GTP (40). A number of putative guanine nucleotide exchange factors for Rho and other Rho
family GTPases have been identified, and some of these demonstrate Rho-specific guanine nucleotide exchange factor activity in vitro, including Lbc, Lfc, and Lsc (3, 41–43). In addition, they appear to be expressed in the same cell type (42). Therefore, one possibility for the existence of multiple guanine nucleotide exchange factors for Rho in the same cell type may be related to the existence of different signaling pathways from Ga subunits to Rho activation.

Recent studies have shown the involvement of the Rho family of small GTPases in the regulation of neurite outgrowth in primary neurons (37, 44). In embryonic chick dorsal root ganglion, inhibition of Rho with C3 exoenzyme stimulated the outgrowth of neurites (44), suggesting that activation of Rho suppresses neurite outgrowth in primary neurons. Therefore, Ga12, Ga13, and Gaq may play a negative regulator for neurite outgrowth.

**FIG. 8.** Effect of elimination of extracellular Ca$^{2+}$ on neuronal morphological changes induced by constitutively active Ga subunits. After differentiated PC12 cells had been microinjected with expression plasmids (30 μg/ml) encoding Ga$_{12}$QL, Ga$_{13}$QL, or Ga$_q$QL, they were incubated in Ca$^{2+}$-free medium containing EGTA (2 mM) for 3 h. Cells were photographed before (left panels) and 3 h after (middle panels) microinjection under a phase-contrast microscope or by fluorescence of Texas Red-coupled dextran co-microinjected with the expression vectors (right panels). The arrows indicate injected cells. The results shown are representative of three independent experiments. The bar represents 50 μm.

**FIG. 9.** Quantification of effects of inhibition of PKC and elimination of extracellular Ca$^{2+}$ on neurite retraction induced by constitutively active Ga subunits. After differentiated PC12 cells had been microinjected with expression plasmids (30 μg/ml) encoding Ga$_{12}$QL, Ga$_{13}$QL, or Ga$_q$QL, they were incubated in the absence (Control) or presence of 300 nM Ro31-8220 (+ Ro31-8220) or in Ca$^{2+}$-free medium containing 2 mM EGTA (Ca$^{2+}$-free) for 3 h. The expression plasmids were microinjected into differentiated cells that had been treated with 1 μM TPA for 24 h before microinjection to induce down-regulation of endogenous PKC (PKC-depleted). The percentages of neurite-retracted cells were determined 3 h after microinjection as described under “Experimental Procedures.” Data are the means ± S.E. of triplicate experiments.

**FIG. 10.** Model for signal transduction pathways from Ga subunits to Rho activation leading to neurite retraction and cell rounding in differentiated PC12 cells. Expression of constitutively active mutants of Ga$_{12}$, Ga$_{13}$, and Ga$_q$ induces neurite retraction and cell rounding through different signaling pathways, which, however, converge at activation of Rho.
outgrowth through activation of Rho in primary neurons.

In conclusion, we have here shown that activation of $G_{\alpha 12}$, $G_{\alpha 13}$, and $G_{\alpha q}$ can trigger Rho-dependent neurite retraction and cell rounding in differentiated PC12 cells through different signaling pathways. This study will contribute to the understanding of the signal transduction between heterotrimeric G protein-coupled receptors and Rho in neuronal cells.

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