β-Arrestin-mediated Recruitment of the Src Family Kinase Yes Mediates Endothelin-1-stimulated Glucose Transport*

Takeshi Imamura‡, Jie Huang‡, Stephane Dalle‡, Satoshi Ugi‡, Isao Usui‡, Louis M. Luttrel¶, William E. Miller¶, Robert J. Lefkowitz‡, and Jerrold M. Olefsky‡**

From the ‡Department of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego, La Jolla, California 92039-0673 and the Veterans Affairs Medical Center, San Diego, California 92161 and the ¶Geriatric Research, Education and Clinical Center, Durham Veterans Affairs Medical Center and the Departments of Medicine and Biochemistry, Howard Hughes Medical Institute, Duke University Medical Center, Durham, North Carolina 27710

The insulin and the endothelin type A (ETA) receptor both can couple into the heterotrimeric G protein Goq11 (Goq11), leading to Goq11 tyrosine phosphorylation, phosphatidylinositol 3-kinase activation, and subsequent stimulation of glucose transport. In this study, we assessed the potential role of Src kinase in ET-1 signaling to glucose transport in 3T3-L1 adipocytes. Src kinase inhibitor PP2 blocked ET-1-induced Src kinase activity, Goq11 tyrosine phosphorylation, and glucose transport stimulation. To determine which Src family kinase member was involved, we microinjected anti-c-Src, -c-Fyn, or -c-Yes antibody into these cells and found that only anti-c-Yes antibody blocked GLUT4 translocation (70% decreased). Overexpression or microinjection of a dominant negative mutant (K298M) of Src kinase inhibited ET-1-induced Goq11 tyrosine phosphorylation and GLUT4 translocation. In co-immunoprecipitation experiments, we found that β-arrestin 1 associated with the ETA receptor in an agonist-dependent manner and that β-arrestin 1 recruited Src kinase to a molecular complex that included the ETA receptor. Microinjection of β-arrestin 1 antibody inhibited ET-1- but not insulin-stimulated GLUT4 translocation. In conclusion, 1) the Src kinase Yes can induce tyrosine phosphorylation of Goq11 in response to ET-1 stimulation, and 2) β-arrestin 1 and Src kinase form a molecular complex with the ETA receptor to mediate ET-1 signaling to Goq11 with subsequent glucose transport stimulation.

The major metabolic effect of insulin involves stimulation of glucose transport into target tissues, and this has generated intense interest in understanding the cellular mechanisms of this action of insulin (1–3). The insulin receptor is a tyrosine kinase, and after ligand binding the receptor phosphorylates a number of substrates including the IRS1 family of proteins. Based on a variety of in vitro biochemical studies (4), as well as results drawn from IRS-1 knockout animals (5, 6), IRS-1 has been proposed as one mechanism coupling the insulin receptor to GLUT4 translocation. Others have shown an alternate pathway that is IRS- and phosphatidylinositol 3-kinase-independent involving CAP, Cbl, and TC10, which are also required for insulin stimulation of glucose transport (7). Recently we have demonstrated that insulin receptors can also couple to the heterotrimeric G protein Goq11 as a necessary step in this stimulatory process in 3T3-L1 adipocytes. Activated insulin receptors tyrosine phosphorylate Goq11 leading to stimulation of phosphatidylinositol 3-kinase and downstream signaling to glucose transport. Recently Kanzaki et al. (8) have also demonstrated the necessity for Goq11 in insulin-stimulated glucose transport, although these workers did not find a phosphatidylinositol 3-kinase dependence of this G protein action. Endothelin-1 (ET-1) can also stimulate glucose transport in insulin target tissues (9), and the signaling pathway utilized by this GPCR also involves tyrosine phosphorylation of Goq11 with subsequent stimulation of glucose transport (10). Thus, both the insulin receptor and ETA receptor can utilize a common signaling pathway for transport stimulation involving Goq11 tyrosine phosphorylation.

The insulin receptor is a tyrosine kinase (11–13), and therefore the mechanism of insulin-stimulated Goq11 tyrosine phosphorylation is straightforward. However, the ETA receptor does not possess intrinsic tyrosine kinase activity (14), and therefore the mechanisms responsible for ET-1-stimulated phosphorylation of this G protein are less obvious. In the current studies, we show that after ET-1 treatment, the ETA receptor forms a molecular complex with Goq11, β-arrestin 1, and the Src family kinase Yes to stimulate GLUT4 translocation.

EXPERIMENTAL PROCEDURES

Materials—Mouse monoclonal anti-GLUT4 antibody (1F8) was from Biogenesis Inc. (Brentwood, NH), and rabbit polyclonal anti-GLUT4 antibody (P349) was kindly provided by Dr. Michael Mueckler (Washington University, St. Louis, MO). Sodium azide-free monoclonal anti-phosphotyrosine (PY-20), β-arrestin 1, -c-Fyn, and -c-Yes antibodies were from Transduction Laboratories (Lexington, KY). Horseradish peroxidase-linked anti-rabbit, -mouse, and -goat antibodies and anti-Goq11, -pan-Src, -c-Src, -c-Fyn, and -c-Yes antibodies were from Santa Cruz Biotechnology (Santa Cruz, CA). Anti-ETA receptor antibodies were from Maine Biotechnology, Inc. (Portland, ME) and Calbiochem. Sheep IgG and fluorescein isothiocyanate-, tetramethyl rhodamine isothiocyanate-, and aminomethylcoumarin acetate-conjugated anti-rabbit, -mouse, -goat, and -sheep IgG antibodies were from Jackson Immunoresearch Laboratories Inc. (West Grove, PA). ETA receptor inhibitor (BQ610) was from Peninsula Laboratories, Inc. (San Carlos, CA). Src kinase inhibitor (PP2) was from Calbiochem. Wild type, constitutively active (Y529F), and dominant negative (K298R/Y528F) mutants of Src kinase expression vectors were from Upstate Biotechnology.
Inc. (Lake Placid, NY). Dulbecco’s modified Eagle’s medium and fetal bovine serum were purchased from Life Technologies, Inc. All radioisotopes were from ICN (Costa Mesa, CA). All other reagents were purchased from Sigma.

Cell Culture, Treatments, and Microinjection—3T3-L1 cells were cultured and differentiated as described previously (15). Microinjection of various reagents was carried out using a semiautomatic Eppendorf micromanipulation system. All reagents for microinjection were dissolved in microinjection buffer containing 5 mM sodium phosphate (pH 7.2), 100 mM KCl, 5 mg/ml antibody or control sheep IgG was injected into the cell cytoplasm, and the microinjected volume represented ~10% of the cytoplasmic volume. For inhibitor treatments, starved 3T3-L1 adipocytes were incubated with 200 nM PP2, 1 μM ETA receptor inhibitor (BQ610), or 0.1% Me2SO vehicle for 1 h or the indicated time period at 37 °C. For GLUT4 translocation, cells were stimulated with ligands for 20 min.

Transient Transfection—Differentiated 3T3-L1 adipocytes were trypsinized and transiently transfected by electroporation (0.15–0.3 kV and 960 microfarads) with 100 μg of endotoxin-free plasmid DNA/cuvette. Following electroporation, the cells were replated on collagen-coated tissue culture dishes and allowed to recover for 24–36 h before use. For adenovirus infection, 3T3-L1 adipocytes were transduced at a multiplicity of infection of 10 plaque-forming units/cell for 16 h with the recombinant adenovirus encoding constitutively active (Q209L) mutant Goq as described previously (16).

Immunostaining and Immunofluorescence Microscopy—Immunostaining of GLUT4 was performed essentially as described previously (17). The cells were fixed in 3.7% formaldehyde in phosphate-buffered saline for 10 min at room temperature. Following washing, the cells were permeabilized and blocked with 0.1% Triton X-100 and 2% fetal calf serum in phosphate-buffered saline for 10 min. The cells were then incubated with anti-GLUT4 antibody in phosphate-buffered saline with 2% fetal calf serum overnight at 4 °C. After washing, GLUT4 and injected IgG were detected by incubation with tetramethyl rhodamine isothiocyanate-conjugated donkey anti-rabbit IgG antibody and fluorescein isothiocyanate-conjugated donkey anti-sheep antibody, respectively, followed by observation under an immunofluorescence microscope. In all counting experiments, the observer was blinded to the experimental condition of each coverslip.

Western Blotting—3T3-L1 adipocytes were starved for 12 h in Dulbecco’s modified Eagle’s medium supplemented with 0.1% bovine serum albumin. The cells were stimulated with 17 nM insulin or 10 nM ET-1 for the indicated time period at 37 °C and lysed in a solubilizing buffer containing 20 mM Tris, 1 mM EDTA, 140 mM NaCl, 1% Nonidet P-40, 50 mM a-glycerophosphate, 1 mM Na3VO4, 1 mM phenylmethylsulfonyl fluoride, and 10 mM NaF, pH 7.5 for 30 min at 4 °C. The cell lysates were centrifuged to remove insoluble materials. For Western blot analysis, whole cell lysates (30–80 μg of protein/lane) were denatured by boiling in Laemmli sample buffer containing 100 mM dithiothreitol and resolved by SDS-polyacrylamide gel electrophoresis. Gels were transferred to a polyvinylidene difluoride membrane (Immobilon-P, Millipore, Bedford, MA) using a Transblot apparatus (Bio-Rad). For immunoblotting, membranes were blocked and probed with specific antibodies. Blots were then incubated with horseradish peroxidase-linked secondary antibody followed by chemiluminescence detection according to the instructions of the manufacturer (Pierce). Images were scanned and quantitated by the NIH Image program.

Src Kinase Assay—After 60 h of adenovirus infection or after 36 h of electroporation, serum-starved 3T3-L1 adipocytes were incubated in the absence or presence of 200 nM PP2 for 1 h prior to ligand stimulation with or without ET-1 (10 nM) or insulin (17 nM) for 10 min. Cells were then lysed and subjected to immunoprecipitation with anti-pan-Src antibody (Src-2, Santa Cruz Biotechnology) for 2 h at 4 °C. Src kinase activity of the immunoprecipitants was analyzed using a kinase detection kit (Upstate Biotechnology Inc.). Briefly, immunoprecipitants were incubated with a synthetic peptide (KVEKIGEQGTEGVVYK), corresponding to amino acids 6–20 of p34 Cdc2, and [γ-32P]ATP (3000 Ci/mmol) for 10 min at 30 °C. Reactions were stopped with 40% trichloroacetic acid precipitation, and reaction products were spotted on Whatman p81 paper. After washing five times with 0.75% phosphoric acid, 32P incorporation into the substrate peptide was measured by a scintillation counter. Using a positive control (active Src kinase, Upstate Biotechnology Inc.), we confirmed that all data were within the linear response range for this determination.

**RESULTS AND DISCUSSION**

Src Kinase Mediates ET-1-induced Glucose Transport—The insulin receptor is a tyrosine kinase (11, 18), and therefore a clear-cut mechanism for insulin-induced Goq/11 tyrosine phosphorylation can be visualized. However, the ETA receptor does not possess intrinsic kinase activity, and the mechanism of ET-1-mediated Goq/11 phosphorylation is not obvious. After ligand binding, the GPCR β2-adrenergic receptor forms a molecular complex that includes β-arrestin 1 and activated Src kinase to facilitate tyrosine kinase-mediated signaling events (19). Since the ET-1 receptor is also a GPCR, these findings raise the possibility that analogous β-arrestin-Src kinase complexes might play a role in ET-1-stimulated glucose transport. To test this hypothesis, we measured ET-1-stimulated 2-DOG uptake in 3T3-L1 adipocytes pretreated with the Src family kinase inhibitor PP2. Insulin-induced 2-DOG uptake or GLUT4 translocation were not affected by PP2 at concentrations below 400 nM (data not shown), therefore we used 200 nM PP2 pretreatment in these studies. As shown in Fig. 1A, pre-treatment with 200 nM PP2 decreased ET-1-induced 2-DOG uptake by 61%. This was comparable to the inhibitory effect achieved by pretreating cells with the ETA receptor antagonist BQ610 (20, 21). In contrast, neither PP2 nor BQ610 affected insulin-induced 2-DOG uptake. We have previously shown that...
Fig. 2. Effects of Src kinase inhibitor PP2 on ET-1-induced Go_{q/11} phosphorylation and ET-1-induced Src activity. A, serum-starved 3T3-L1 adipocytes were incubated with or without ET-1 (10 nM) for 3 min or insulin (17 nM) for 1 min after pretreatment with 200 nM PP2 or 0.1% MeSO vehicle for 1 h. Cell lysates were immunoprecipitated with anti-Go_{q/11} antibody, and immunoprecipitates were analyzed by Western blotting with anti-phosphotyrosine (PY-20) antibody (upper panel). The images from three independent experiments were quantitated by the NIH Image program (lower panel), and the data represent the mean ± S.E. B, serum-starved 3T3-L1 adipocytes, transfected with wild type, dominant negative, or constitutively active mutant of Src kinase expression vectors, were lysed and immunoprecipitated with anti-Go_{q/11} antibody. Immunoprecipitates (upper panel) or whole cell lysates (middle panel) were analyzed by Western blotting using anti-phosphotyrosine (PY-20) or neomycin phosphotransferase II (NPT-II, expression marker) antibody; and immunoprecipitates were analyzed by Western blotting with anti-phosphotyrosine (PY-20) antibody, and immunoprecipitates were quantitated by the ability of Src immunocomplexes to phosphorylate the Src kinase substrate peptide. Phosphorylation of the peptide was quantitated by a scintillation counter, and the data are presented as the mean ± S.E. of four independent experiments. Ab, antibody; IP, immunoprecipitation; Ins, insulin; Stimu., stimulation.

overexpression of constitutively active Go_{q} (Q209L) protein mimics the actions of ET-1 and insulin on glucose transport and can stimulate GLUT4 translocation and glucose transport by itself (16). Fig. 1A shows that the stimulatory effect of Q209L expression is not inhibited by PP2, indicating that the site of action of Src kinase is upstream of Go_{q/11}.

Similar results were observed for ET-1-induced GLUT4 translocation. PP2 treatment decreased ET-1-induced GLUT4 translocation to near basal levels as did the ETA receptor antagonist BQ610. On the other hand, insulin-stimulated GLUT4 translocation was unaffected by these reagents (Fig. 1B).

We have previously shown that ET-1 stimulation leads to Go_{q/11} tyrosine phosphorylation (10), and this is consistent with other reports showing that a tyrosine residue in the C terminus of Go_{q/11} becomes phosphorylated after GPCR activation (22). To determine whether activation of a Src kinase by the ETA receptor might mediate ET-1-stimulated Go_{q/11} tyrosine phosphorylation, we examined the effects of the Src kinase inhibitor PP2 on ET-1-induced phosphorylation of Go_{q/11}. Fig. 2A shows that insulin and ET-1 stimulate Go_{q/11} tyrosine phosphorylation 6.9 ± 0.9-fold and 5.2 ± 0.6-fold, respectively, and that pretreatment with PP2 decreases the effect of ET-1 (73% decrease) but not of insulin. These results are quite consistent with the notion that the ET-1 receptor forms a complex with a Src kinase, leading to Go_{q/11} phosphorylation.

To further explore the importance of Src kinase in ET-1-mediated Go_{q/11} phosphorylation, we used electroporation to overexpress wild type, constitutively active, or dominant negative Src kinase mutant in 3T3-L1 adipocytes. For these experiments, constitutively active Src was a full-length Src construct with Tyr to Phe substitution at position 529 (Y529F) (23). Dominant negative Src contained inactivating point mutations at positions 298 and 528 (K298R/Y528F) (24). The results in Fig. 2B showed that expression of the dominant negative Src kinase decreased ET-1-induced Go_{q/11} phosphorylation by 85%, whereas constitutively active Src kinase expression stimulated the phosphorylation of Go_{q/11} to the same degree as ET-1 stimulation.

We also determined whether ET-1 could stimulate Src kinase activity by measuring the ability of Src immunoprecipitates prepared from whole cell lysates to phosphorylate a Src kinase substrate. As seen in Fig. 2C, insulin did not enhance Src kinase activity, whereas ET-1 stimulation led to a dose-dependent increase of 1.5- and 1.8-fold at 1 and 10 nM ET-1, respectively. This increase in Src kinase activity was blocked by pretreatment of cells with PP2, which decreased Src kinase activity below basal values. Interestingly overexpression of constitutively active Q209L did not lead to an enhancement of Src kinase activity (Fig. 2C). This latter result reinforces the concept that Src kinase is located upstream of Go_{q/11} and that there is no activating input from this G protein to Src kinase.

β-Arrestin 1 Forms a Molecular Complex with Src Kinase and the ETA Receptor and Mediates ET-1 Signaling to GLUT4 Translocation—In the β-adrenergic receptor system, β-arrestin 1 binds to the receptor and serves as a docking protein to recruit Src kinase to the receptor complex (25, 26). Other reports have also observed the formation of a molecular complex between β-arrestin 1 and Src kinase in different cell systems.

2 Amino acid numbering of Src kinase is according to the human c-Src sequence (25).
The Mechanism of ET-1-induced Goq11 Activation

(27, 28). To determine whether β-arrestin 1 could play a similar role with the ETA receptor/Src kinase/glucose transport signaling cascade, we conducted co-immunoprecipitation experiments. As demonstrated in Fig. 3A, incubation with ET-1 (10 nM) stimulated β-arrestin 1 association with the ETA receptor by 4.5 ± 0.5-fold (at 3 min). To assess the functional role of β-arrestin 1 in this signaling system, we microinjected anti-β-arrestin 1 antibody into 3T3-L1 adipocytes followed by ET-1 treatment and measurement of GLUT4 translocation by immunofluorescence microscopy. As seen in Fig. 3B, β-arrestin 1 antibody inhibited the effects of 1 and 10 nM ET-1 by 90 and 73%, respectively, but did not inhibit insulin stimulation. These results suggest that β-arrestin 1 may be necessary to recruit Src kinase into a molecular complex with the ETA receptor to effect tyrosine kinase signaling to Goq11 and glucose transport stimulation.

β-Arrestin 1 binds to Src kinase, at least in part, through interactions of β-arrestin 1 with the Src kinase catalytic domain (25). To further evaluate the role of β-arrestin 1-Src kinase complexes in ET-1 signaling to glucose transport, we utilized a Src construct, SH1KD, containing only the catalytic domain (positions 250–536) with a point mutation in the ATP binding site (K298M), which disables kinase activity but does not impair association with β-arrestin 1 (25). This SH1KD Src construct does not contain the Src SH2 or SH3 domains and is a selective inhibitor of β-arrestin-mediated Src function. Thus, the SH1KD mutant should behave as a dominant negative inhibitor of β-arrestin 1-Src-mediated ET-1 signaling. The SH1KD plasmid was injected into the nuclei of 3T3-L1 adipocytes along with a green fluorescent protein expression vector as a marker. GLUT4 staining and scoring were as described under “Experimental Procedures.” The data are the mean ± S.E. from three independent experiments. Ab, antibody; ETαR, ETA receptor; IP, immunoprecipitation.

FIG. 3. The role of β-arrestin 1 in ET-1 signaling to GLUT4 translocation. A, serum-starved 3T3-L1 adipocytes were incubated with or without ET-1 (10 nM) for 3 or 10 min. Cell lysates were immunoprecipitated with anti-ETA receptor antibody or control IgG (IgG), and immunoprecipitates were analyzed by Western blotting (upper and middle panels). The images were quantitated by the NIH Image program, and the data represent the mean ± S.E. of three independent experiments (lower panel). B, serum-starved 3T3-L1 adipocytes on coverslips were incubated with or without ET-1 (1 or 10 nM) or insulin (0.5 or 1.7 nM) for 20 min after microinjection of anti-β-arrestin 1 antibody (5 mg/ml) or sheep IgG (5 mg/ml) as control. GLUT4 staining and scoring were as described under “Experimental Procedures.” The data are the mean ± S.E. from three independent experiments. Ab, antibody; ETαR, ETA receptor; IP, immunoprecipitation.

FIG. 4. Effects of Src kinase on ET-1 signaling from ETA receptor to GLUT4 translocation. A, serum-starved 3T3-L1 adipocytes on coverslips were incubated with or without ET-1 (10 nM) for 20 min, 24 h after nuclear microinjection of the expression vector (0.2 mg/ml DNA) for wild type Src kinase (Src-WT) or the isolated Src kinase domain (250–536) containing a point mutation (K298M) in the ATP binding site (SH1KD) with a green fluorescent protein expression vector as a marker. GLUT4 staining and scoring were as described under “Experimental Procedures.” The data are the mean ± S.E. from three independent experiments. B, serum-starved 3T3-L1 adipocytes on coverslips were incubated with or without ET-1 (1 or 10 nM) or insulin (0.5 or 1.7 nM) for 20 min after microinjection of anti-c-Src, -c-Fyn, or -c-Yes antibodies (5 mg/ml) or sheep IgG (5 mg/ml) as control. GLUT4 staining and scoring were as described under “Experimental Procedures.” The data are the mean ± S.E. from three independent experiments. C, serum-starved 3T3-L1 adipocytes were incubated with or without ET-1 (10 nM) for 3 or 10 min. Cell lysates were immunoprecipitated with anti-ETA receptor (left panels) or β-arrestin 1 antibody (right panels) or control IgG (IgG), and immunoprecipitates were analyzed by Western blotting as described under “Experimental Procedures.” The images were quantitated by the NIH Image program, and the data represent the mean ± S.E. from three independent experiments. Ab, antibody; ETαR, ETA receptor; IP, immunoprecipitation.
of a β-arrestin 1-Src kinase complex, with stimulation of Src kinase activity, is necessary for this action of ET-1.

**c-Yes Is Necessary for ET-1-induced GLUT4 Translocation**—There are a large number of c-Src-related family members, including c-Src, c-Fyn, and c-Yes, which are widely expressed (29–31). To determine which Src kinase family member is involved in ET-1 signaling to glucose transport, we microinjected several different Src family-specific antibodies with subsequent measurements of ET-1-induced GLUT4 translocation. To characterize these antibodies, we showed that each was able to inhibit (~100%) the kinase activity of the respective Src kinase member in each antibody immunoprecipitate (data not shown). As seen in Fig. 4B, microinjection of c-Src or c-Fyn antibody had no effect on GLUT4 translocation. However, c-Yes antibody injection had a potent effect to inhibit ET-1 signaling, whereas insulin-stimulated GLUT4 translocation was not impaired. To further assess the role of c-Yes in ET-1 signaling, we determined whether this Src kinase family member was associated with β-arrestin 1 and the ETA receptor. As seen in Fig. 4C (left panels), ET-1-stimulated c-Yes association with the ETA receptor by 5.2 ± 0.7-fold, suggesting that c-Yes was recruited into a complex with the ETA receptor following ligand stimulation. We also found association of β-arrestin 1 with c-Yes, and this was unaffected by ET-1 stimulation (Fig. 4C, right panels).

It is interesting to note that both insulin and ET-1 stimulate Go_q/11 tyrosine phosphorylation and that this appears necessary for downstream signaling to glucose transport. For insulin action, tyrosine phosphorylation is known to mediate many important signaling events, but this is not the case for classical GPCR-induced G protein functions. On the other hand, precedence for such a mechanism does exist. For example, Umemori et al. (22) reported that stimulation of a Go_q/11-coupled heptahelical receptor (a metabotropic glutamate receptor) resulted in Go_q/11 tyrosine phosphorylation and that this phosphorylation event was necessary for activation of the Go_q/11 protein. Further, it is known that in addition to classical GPCR actions mediated through heterotrimeric G proteins, certain GPCRs convey mitogenic signals through the Ras/mitogen-activated protein kinase pathway that are initiated by GPCR-mediated Src kinase activation (14, 32). Thus, since tyrosine phosphorylation is increasingly recognized as a GPCR-initiated event, it seems likely that phosphorylation of Go_q/11 is a mechanism that allows this G protein to direct signals from cell surface receptors to the GLUT4 translocation system.

We have previously shown that insulin and ET-1 stimulate glucose transport through a Go_q/11-mediated process (10), and the current studies have further defined the molecular pathway of these ET-1 signaling events. We have shown that after agonist stimulation, the ETA receptor forms a molecular complex with β-arrestin 1 and the Src kinase c-Yes. This results in activation of Src kinase with phosphorylation of Go_q/11 and subsequent stimulation of GLUT4 translocation and glucose transport. In this respect, Go_q/11 represents a convergence point for the insulin and ET-1 signaling pathways, which lead to glucose transport stimulation. The mechanisms whereby these two receptors affect tyrosine phosphorylation of Go_q/11 differ, but the events downstream of this G protein that lead to glucose transport stimulation appear to be the same. The present results delineate a novel role of β-arrestin as a molecular link between GPCRs and Src family kinases to the regulation of glucose transport.

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