A G Protein-coupled Receptor for UDP-glucose*

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Uridine 5‘-diphosphogluconate (UDP-glucose) has a well established biochemical role as a glycosyl donor in the enzymatic biosynthesis of carbohydrates. It is less well known that UDP-glucose may possess pharmacological activity, suggesting that a receptor for this molecule may exist. Here, we show that UDP-glucose, and some closely related molecules, potently activate the orphan G protein-coupled receptor KIAA0001 heterologously expressed in yeast or mammalian cells. Nucleotides known to activate P2Y receptors were inactive, indicating the distinctly novel pharmacology of this receptor. The receptor is expressed in a wide variety of human tissues, including many regions of the brain. These data suggest that some sugar-nucleotides may serve important physiological roles as extracellular signaling molecules in addition to their familiar role in intermediary metabolism.

G protein-coupled receptors (GPCRs)† are a large family of receptors uniquely characterized by their ability to detect a diverse variety of extracellular signals such as single photons, odorants, inorganic ions, nucleotides, biogenic amines, chemo- kines, lipids, proteases, amino acids, and peptides. In recent years, a large number of DNA sequences have been identified that encode novel proteins with many of the sequence motifs characteristic of GPCRs but for which no natural ligand has been identified. These putative GPCRs have been termed “orphan” receptors. Recently, naturally occurring ligands have been identified for a number of orphans, using the recombinant orphan receptor as the specific sensor component of a bioassay. Tissue extracts have often provided the source of these ligands, but some orphans have been identified by mass screening of large libraries of known or putative GPCR ligands (1–3). Here, we describe how we have employed this latter strategy to identify a naturally occurring ligand for the orphan receptor KIAA0001 (4).

KIAA0001 (GenBank™ accession number D13626) was originally cloned from an immature human myeloid cell line (4) and contains a number of features typical of members of the GPCR superfamily, including a DRY motif at the boundary of transmembrane domain 3 and the second intracellular loop, consen sus sites for asparagine-linked glycosylation on extracellular sequences, and consensus sites for protein kinases A and C phosphorylation on the third intracellular loop. Recently, a putative rat ortholog, termed VTR 15–20, with 81% amino acid identity to KIAA0001 and conserved substitutions was cloned from ventral tegmental tissue (5). This orphan is expressed widely throughout the mammalian nervous system and in rat primary microglial and astrocyte cultures. Furthermore, expression of VTR 15–20 in the brain and spleen is regulated by immunologic challenge. These data have implicated this orphan in neuroimmune function (5). We demonstrate that KIAA0001 and VTR 15–20 are likely to be orthologs and that KIAA0001, like VTR 15–20, is expressed widely throughout the brain and in many other regions of the body.

EXPERIMENTAL PROCEDURES

Bioinformatics—The phylogenetic tree (length = 2167, rescaled consistency index = 0.27, retention index = 0.41) was generated from polypeptide sequences obtained from GenBank™ and Swissprot, using PAUP* (6) with 10,000 replicates of an heuristic search. Identities and similarities were calculated from hand-adjusted alignments.

Expression in Yeast—Expression of KIAA0001 in yeast strains was carried out essentially as described previously (7, 8). Briefly, strain CY10560 (FUS1-HIS3 GPA1) containing the native Gαi2 (7), Gαi2 (8), Gαi2 (9), and Gαi2 (10) was transformed with Cp1584 (containing the native Gαi2 and human Gαi2, 11), Cp1585 (Gαi2, 11), and Cp1586 (human Gαi2, 11). The resulting strains were screened by growth on SD-Leu-Trp medium, and strains expressing wild-type KIAA0001 were identified as non-growing on SD-Leu-Trp medium. These strains were further screened for the expression of VTR 15–20 by Northern blotting.

Screening Yeast Strains—Yeast strains were transformed with pBDG (12) and were screened for yeast growth on SD-Leu-Trp medium, and strains expressing wild-type KIAA0001 were identified as non-growing on SD-Leu-Trp medium. These strains were further screened for the expression of VTR 15–20 by Northern blotting.

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sodium dodecyl sulfate, and 0.05% 5-bromo-4-cho- rolo-3-indolyl β-p-galactopyranoside). The presence of an agonist among the test compounds was evidenced by the development of a blue color at the point of deposition of that compound. A library of over 700 known and putative natural GPCR agonists was assembled, mostly from commercial sources, and screened in this assay. The library included numerous bioactive lipids (leukotrienes, prostaglandins, platelet-activating factor, etc.), steroids (aldosterone, testosterone, etc.), amines (catecholamines, etc.), cannabinoids (anandamide, delta-9-tetrahydrocannabinol), all commonly occurring l-amino acids, and nucleotides (ATP, ADP, UDP, UTP, etc.) and chemically related substances. UDP-glucose, UDP-glucuronic acid, UDP-galactose and UDP were obtained from Sigma and were LC-MS verified to be 98% pure by HPLC. UDP-galactose and UDP-N-acetylglucosamine, from the same source, were approximately 98% pure by HPLC.

A quantitative assay was performed essentially as described (7) except that the assay was developed by the addition of 20 μl of substrate/lysis solution (0.92 mM fluorescein di-β-p-galactopyranoside, 2.3% Triton X-100, and 0.127 M Pipes, pH 7.2). Plates were incubated for 1 h at 37 °C and the reactions stopped by the addition of 20 μl of 1 M Na2CO3. Plates were read in a Spectrafluor fluorimeter (Tecan U.S., Research Triangle Park, NC) at 4585 (excitation) and 5353 (emission) at optimal gain.

Expression in Mammalian Cells—Receptor expression in HEK-293 cells was carried out as follows. Receptors and Gαtq were subcloned into the mammalian expression vector pCDN (9) and transiently transfected into HEK-293 cells using lipofectAMINE Plus (Life Technologies, Inc.), according to the manufacturer’s instructions with minor modifications. Thus, a mixture of 15 μg of receptor DNA and 15 μg of Gαtq DNA was used to transfect a single 175-cm2 culture flask of cells at 80% confluency. For transient transfection of receptor DNA alone, 30 μg of plasmid DNA was used. Stable, clonal cell lines were produced by serial dilution into selective media containing 400 μg/ml G418, and message-positive clones from Northern blot analysis were assayed further. A single clone was designated as the most sensitive to UDP-glucose in a GTP-γ-S assay and was used in all other experiments. Stable clonal HEK-293 cells co-expressing Gαtq and KIAA0001 were generated by transfecting cells with a derivative of pCDN-Gαtq in which the neomycin coding sequence had been replaced with a histidinol selectable marker (10). A single histidine-resistant clone (mRNA-positive for Gαtq) was expanded by 10-fold in antibiotic-containing medium and used for all subsequent experiments. The mRNA expression level of Gαtq was evidenced by the development of a blue color at the point of deposition of that compound. A phylogenetic tree was generated for KIAA0001 and VTR 15–20 by neighbor joining and the tree was rooted by a common ancestor with KIAA0001 and VTR 15–20. The tree is shown in Fig. 1.

Functional Assays with Mammalian Cells—Intracellular Ca2+ assays were carried out as follows. HEK-293 cells were seeded (50,000 cells/well) into poly-L-lysine-coated 96-well black-wall, clear-bottom microtiter plates (Becton Dickinson) 24 h prior to assay. Cells were loaded with 1 μM Fluo-4-AM fluorochrome indicator dye (Molecular Probes) in assay buffer (Hanks’ balanced salt solution, 10 mM HEPES, 200 μM Ca2+, 0.1% bovine serum albumin, 2.5 mM probenecid), washed three times with assay buffer, and then returned to the incubator for 10 min before assay on a fluorimetric imaging plate reader (FLIPR, Molecular Devices). The maximum change in fluorescence over baseline was calculated to yield a relative change in fluorescence. The resulting data sets were analyzed using the computer-assisted nonlinear least square fitting using GRAPHPAD PRIZM (Graphpad Software, Inc., San Diego).

Localization Studies—Quantitative RT-PCR analysis was carried out essentially as described previously (12) but using the following forward, probe, and reverse (respectively) KIAA0001-specific primers: 5′-GCCACACATATTGCACATCGTGTT-3′; 5′-CTTTCATATTGCCAGAAATCCCCCTACAC-3′; and 5′-GCTGTAACTGCCTTGCTCAGC-3′.

RESULTS AND DISCUSSION

Sequence Comparisons—Phylogenetic analysis (Fig. 1) showed that KIAA0001 is most closely related to the orphan receptors H963, GPR34, and EB2 (34.2, 32.1, and 28.4% uncorrected sequence identity and 47.1, 42.9, and 39.6% uncorrected sequence similarity, respectively) but is also a close relative of proteinase-activated receptors (PAR-1, PAR-2, and PAR-3) and the platelet-activating factor receptor (PAF-R). KIAA0001 is a more distant relative of a number of orphan receptors, which have been termed P2Y-like orphans (P2Y2, P2Y4, and P2Y6) on the basis of similarity to the functionally characterized P2Y receptors. Functionally identified receptors with nucleotide ligands (P2Y1,2,4,6,11) also share a common ancestor with KIAA0001 but are clearly more distantly related. GaR1, mt, and NkY receptor sequences were used as outgroups. Note that the International Union of Pharmacology Nomenclature Committee has recommended that the notation P2Y be used to denote cloned GPCRs functionally characterized as extracellular nucleotide receptors and that lower case (p2y) be used to denote cloned orphan GPCRs with similarity to P2Y receptors but that have not yet been unambiguously functionally characterized as such (28).

Activation of KIAA0001 Expressed in Yeast Cells—As part of a large program to identify the natural ligands for orphan GPCRs, we have dissected a number of known and orphan GPCRs, including KIAA0001, in yeast strains engineered to respond to agonist activation with increased expression of a pheromone signaling pathway-inducible Fus1-lacZ reporter gene (7, 8). expression of this gene is easily monitored by a simple colorimetric assay of enzyme activity. As one cannot predict the specific G protein that will transduce signals from a given orphan receptor, we expressed several receptors in several yeast
strains, each carrying a different G protein α-subunit. We then screened multiple receptors, each expressed in several such strains, in parallel, against a large library of over 700 known and putative natural GPCR agonists. UDP-glucose, which was included in this library because it has been reported to possess pharmacological activity (16–20), was the only substance that specifically activated KIAA0001. Two yeast strains responded to UDP-glucose. The first expressed KIAA0001 in conjunction with the endogenous yeast Gα protein, Gpalp (21). The second expressed KIAA0001 and a hybrid of Gpalp and the promiscuous mammalian Gα protein, Gα16 (22). A control yeast strain transformed with empty vector did not respond to UDP-glucose nor did yeast strains transfected with the same G proteins and a number of other receptors.

In a follow-up screen of substances related to UDP-glucose, it was discovered that UDP-galactose, UDP-glucuronic acid, and UDP-N-acetylglucosamine, exhibited agonist activity (Table I). However, a large number of related substances were inactive as agonists (listed in Table I), including various other sugar-nucleotides and the naturally occurring nucleotides known to activate GPCRs of the P2Y class: ATP, ADP, UTP, and UDP.

We investigated the concentration dependence of UDP-glucose on KIAA0001-mediated activity using the Gpalp yeast strains with a modification to the original screen that permitted quantitative pharmacology. In this assay, UDP-glucose activated KIAA0001 with a potency of 67.9 ± 6.8 nm (± S.E., n = 3) (Fig. 2), but no significant response was detected when ATP, ADP, UTP, and UDP were tested at concentrations up to 1 μM, demonstrating that this receptor exhibits a distinctly different pharmacology from that of the P2Y nucleotide receptor family. In addition, UDP-glucose was inactive at concentrations up to 1 μM when tested against control cells carrying an empty vector (Fig. 2).

Activation of KIAA0001 in Mammalian Cells—In parallel studies, we transiently co-transfected mammalian HEK-293 cells with both KIAA0001 and Gα16 to promote coupling to intracellular Ca2+. We screened these cells against the same ligand bank in an intracellular Ca2+ assay, and UDP-glucose was the only substance observed to clearly elicit KIAA0001-mediated Ca2+ responses. Furthermore, we observed that only cells transiently transfected with both KIAA0001 and Gα16 were responsive to UDP-glucose (Fig. 3A); cells transfected with either receptor or G protein alone were unresponsive to UDP-glucose in this assay (Fig. 3A). Co-transfected cells responded to UDP-glucose and UDP-galactose with EC50 values (± S.E., n = 3) of 104 ± 22 and 421 ± 43 nm, respectively (Fig. 3B), but the related sugar-nucleotide, CDP-glucose, was inactive when tested at concentrations up to 10 μM (Fig. 3B). We carried out similar studies with the related human orphan receptors (Fig. 1) H963 (13), GPR34 (14), and P2Y16 (23) but did not observe orphan-mediated responses to either UDP-glucose or UDP-galactose. The specificity of the interaction of UDP-
FIG. 4. HEK-293 cells stably transfected with both KIAA0001 and the promiscuous G protein Go-subunit Gαo respond with robust transient elevations in intracellular Ca2+ to UDP-glucose (open circles), UDP-galactose (filled triangles), UDP-glucuronic acid (open squares), and UDP-N-acetylglucosamine (filled squares) in a concentration-dependent manner. Data shown are from a single representative experiment with each point determined in triplicate and given as a mean. F.I.U., fluorescence intensity units.

FIG. 5. KIAA0001 is coupled to G proteins of the G1/o class and exhibits a pharmacology distinctly different to P2Y receptors. A, UDP-glucose increased binding of GTP-γ-S in membranes prepared from HEK-293 cells stably expressing KIAA0001 (open circles) but not in membranes prepared from nontransfected control cells (crossed bars). B, UDP-glucose, but not four naturally occurring P2Y receptor nucleotide ligands (UTP (open triangles), ATP (open hexagons), UDP (open diamonds), ADP (inverted open triangles), CDP-glucose (open squares)) stimulated GTP-γ-S binding in membranes prepared from HEK-293 cells stably expressing KIAA0001. Pre-incubation of cells with pertussis toxin (25 ng/ml for 18 h) (filled symbols) abolished the response to UDP-glucose (filled circles). Note that at high concentrations (>1 μM) nucleotide triphosphates caused an inhibition of binding. However, this effect was unaffected by pertussis toxin treatment as shown for UTP (filled triangles). Data are shown from two representative experiments, and values are given as the means of three determinations. Errors, where shown, are ± S.E.

or UDP-galactose at a concentration of 10 μM (data not shown).

A stable HEK-293 cell line expressing both recombinant Gα16 and KIAA0001 responded to UDP-glucose, UDP-galactose, UDP-glucuronic acid, and UDP-N-acetylglucosamine with large, concentration-dependent, transient, intracellular Ca2+ responses (Fig. 4) with EC50 values (± S.E., n = 3) of 80 ± 31, 124 ± 17, 370 ± 33, and 710 ± 27 nM, respectively. Control HEK-293 cell lines expressing Gα16 alone were unresponsive to these ligands when tested at concentrations up to 10 μM, and none of the additional compounds listed in Table I exhibited detectable KIAA0001-mediated activity in this assay (data not shown). The presence of endogenous P2Y receptors coupled to Ca2+ mobilization in HEK-293 cells (24) prevented us from assessing in this assay whether nucleotides such as ATP and UTP interact with KIAA0001.

To investigate the natural G protein coupling specificity of KIAA0001 in mammalian cells, we generated a clonal HEK-293 cell line expressing KIAA0001 without additional recombinant G proteins. Membranes prepared from these cells responded to UDP-glucose in a concentration-dependent way with increased binding of radiolabeled GTP-γ-S, a nonhydrolyzable analog of GTP, with an EC50 value of 234 ± 17 nM (± S.E., n = 3), but nontransfected control cells were unresponsive to UDP-glucose at concentrations up to 10 μM (Fig. 5A). Overnight incubation of KIAA0001-expressing cells with pertussis toxin (25 ng/ml) abolished the response to UDP-glucose, suggesting that KIAA0001 is coupled to G proteins of the G1/o class (Fig. 5B). In addition, freshly prepared ATP, ADP, UTP, UDP, and CDP-glucose exhibited no detectable KIAA0001-mediated increase in GTP-γ-S binding activity when tested at concentrations up to 10 μM (Fig. 5B).

Inhibition of basal levels of GTP-γ-S binding
at higher concentrations of nucleotide triphosphates was identical in membranes prepared from pertussis toxin-treated and nontreated KIAA0001-transfected cells (Fig. 5B), and an identical effect was also observed in nontransfected cells (data not shown). These data demonstrate that KIAA0001 exhibits a pharmacology distinct from that of the P2Y family, confirming our conclusions drawn from studies with yeast cells.

Radioligand Binding Studies—We attempted to determine whether uridine diphospho-β-3H[glucose] bound KIAA0001 with high affinity. Membranes prepared from clonal HEK-293 cells expressing KIAA0001 bound uridine diphospho-β-3H[glucose] with an affinity of 8.1 nM and B_max values of 7.8 pmol/mg protein. The specific binding was dependent on the protein concentration and was lost upon boiling membranes prior to assay. In competition assays, UDP-glucose and UDP-galactose competed for specific binding with K_i values of 41.2 and 348 nM, respectively, whereas CDP-glucose, UTP, ATP, and ADP had little effect (K_i > 10 μM). Essentially identical specific binding was also observed in nontransfected HEK-293, 1321N1, and Chinese hamster ovary cells, suggesting the presence of endogenous binding sites on these cells. These data suggest that this radiolabel may not be a suitable radioligand for KIAA0001. Indeed, one might expect that the receptor expression levels required to observe a specific binding signal in transfected cells above nontransfected cells would need to be at least the same order of magnitude as the B_max of the background specific binding (i.e.: 7.8 pmol/mg protein), a level of cloned receptor expression unlikely to be achieved in mammalian cells. Likewise, other workers investigating the use of radioactive forms of the structurally similar molecule ATP to radiolabel P2Y-like receptors report similar technical problems (25).

Expression Pattern of KIAA0001—To investigate the physiological role of KIAA0001, we carried out studies to localize the expression of this receptor in the body. We performed quantitative RT-PCR analysis using KIAA0001-specific primers to determine the relative levels of KIAA0001 mRNA in a variety of human tissues from multiple individuals. We observed a widespread human tissue distribution (Fig. 6), with only some differences to that reported by Northern blot analysis for VTR (1334–1337).

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