Bi-directional Regulation of UV-induced Activation of p38 Kinase and c-Jun N-terminal Kinase by G Protein βγ-Subunits

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Ultraviolet (UV) irradiation induces various cellular responses by activating many UV-responsive enzymes including mitogen-activated protein kinases (MAPKs). Various G protein-coupled receptor agonists also activate MAPKs, but it is not known whether or not G proteins also mediate the UV-induced activation of MAPKs. Therefore, this study was undertaken to determine whether the G protein βγ-subunit (Gβγ) mediates the UV-induced activation of p38 and JNK. Gβγ overexpression in COS-1 cells amplified the UV-induced activation of p38 but reduced JNK activation. The overexpression of the C-terminal region of β-adrenergic receptor kinase (βARKct) decreased the UV-induced activation of p38 but increased JNK activation. Gβγγγ expression increased MKK3/6 phosphorylation with a concomitant decrease in MKK4 phosphorylation, which contrasts with βARKct expression. Gβγγγ or βARKct expression resulted in corresponding changes in the transcriptional activity of CHOP and c-Jun. Treatment with a p38 inhibitor, SB203580, or the expression of a kinase-inactive p38 increased the UV-induced JNK activation. Expression of the constitutively active MKK6 decreased the UV-induced JNK activation. In summary, although the endogenous Gβγ was found to mediate about half of the UV-induced activation of p38, it was found that exogenous Gβγ mediates the bidirectional regulation of UV-induced p38 and JNK activation, and that this bidirectional regulation results from the inhibition of JNK activation by the p38 activated via Gβγ in the COS-1 cells.

Signal-transducing heterotrimeric GTP-binding proteins (G proteins) transduce a signal that is triggered by the binding of a hormone or neurotransmitter with its membrane receptor into intracellular effector activity. The G proteins are composed of α-, β-, and γ-subunits, and both Gβ and Gγ combine tightly and function as a complex. The ligand binding to the G protein-coupled receptors (GPCRs) activates the G protein by stimulating the exchange of GDP with GTP in an α-subunit. In turn, the activated G protein leads to the dissociation of the Go-GTP- and Gβγ-subunits, and both of these subunits regulate a variety of downstream effectors (1). The effectors of the activated G proteins include ion channels and enzymes such as adenylate cyclase, phosphodiesterase, and phospholipase Cβ and A2, which generate second messenger molecules such as cAMP, diacylglycerol, inositol 1,4,5-trisphosphate, and arachidonic acid (2). In addition, mitogen-activated protein kinases (MAPKs) are activated by a variety of GPCR ligands with diverse structures including polypeptides, lipid mediators, and bioactive amines (3).

MAPKs are serine/threonine protein kinases that play important roles in mediating the cellular responses to a variety of stimuli such as growth factors, cytokines, hormones, environmental stresses, and GPCR agonists (4). MAPKs in mammalian cells are classified into at least four subfamilies: extracellular signal-regulated kinases (ERKs), stress-activated protein kinases/c-Jun N-terminal kinase (SAPKs/JNK), p38 kinases, and BMK1/ERK5 (5). ERKs are activated by many growth factors and cytokines and are implicated in both cell growth and differentiation. Two other types of MAPKs, p38 and JNK, are activated by environmental stresses such as gamma and UV radiation, DNA damaging reagents, osmotic shock, and oxidant stresses (4). Therefore, p38 and JNK are collectively referred to as SAPKs. The central cascade of each MAPK activation pathway is well conserved in all eukaryotic cells, from yeast to plants and mammals, and consists of three protein kinases commonly referred to as MAPK, kinase (MAPKKK), and MAPKK kinase (6). Activated MAPKK kinase phosphorylates and activates a specific MAPKK, which in turn activates its cognate MAPK by phosphorylating the conserved threonine and tyrosine residues. Both the activated Gα- and Gβγ-subunits are reported to activate the MAPK families including the ERK (7, 8), JNK/SAPK (9, 10), and p38 kinase (11). Thus, the coupling pathways from activated GPCR to MAPKs are under intense investigation.

UV radiation induces DNA damage by forming pyrimidine dimers, leading to a somatic mutation and possibly cancer. However, it also induces other cellular responses including temporal growth arrest or apoptosis. The response of mammalian cells to UV involves changes in the DNA repair system and the cell cycle checkpoint machinery. It also involves the activation of a number of transcription factors including AP-1, the serum responsive factor, and NF-κB (12). These transcription factors are activated by phosphorylation, which is regulated by
the UV-responsive signal transduction pathways including MAPKs (13).

Recently, a variety of signaling molecules were reported to be involved in UV-triggered MAPK activation in mammalian cells. Ligand-independent activation of the growth factor receptors and Src, Ras, and Rho activation contribute to MAPK activation induced by UV irradiation (14). Although the same molecular events also contribute to the MAPK activation that is induced by GPCR activation (15), it is not known whether the signal-transducing G proteins are involved in UV-induced MAPK activation. Therefore, this study was carried out to determine whether or not the signal-transducing G proteins mediate UV-induced p38 and JNK activation. By analyzing the effects of the overexpression and sequestration of Gβγ on the UV-induced p38 and JNK activation in COS-1 cells, the authors present evidence showing that Gβγ regulates bi-directionally the p38 and JNK activation that is induced by UV irradiation and that the bi-directional regulation results from the inhibition of JNK activation by p38 activated via Gβγ in COS-1 cells.

**EXPERIMENTAL PROCEDURES**

**Cell Cultures and Transfections**—African green monkey kidney cells, COS-1 (ATCC), were grown in Dulbecco’s modified minimal essential medium containing 10% fetal bovine serum. The cells were incubated in a CO₂ incubator at 37 °C. The COS-1 cells were divided in 10-cm dishes 1 day prior to transfection, and the subconfluent cells were co-transfected with 5–10 μg of G and G<sub>βγ</sub>-cDNA together with additional DNA when necessary, using the DEAE-dextran method (16). The control cells were transfected with reagents containing no DNA or the vector DNA without the insert. 24 h after transfection the cells were replated in new dishes, and 48 h later the transfected COS-1 cells were rinsed twice with phosphate-buffered saline and irradiated with UVC (254 nm, 100 J/m²). The UV-irradiated cells were harvested after incubation for a further 40 min.

**Expression Plasmids**—The expression plasmids for the five β isoforms and γ<sub>i</sub> of the G protein were kindly provided by Dr. William F. Simonds (NIDDK, National Institutes of Health). These were subcloned into the pCDNA3 expression vectors (Invitrogen). Dr. Byung-Soo Youn of Korea University kindly provided the plasmid coding the C terminus of the β3-adrenergic receptor kinase (βARKct). A constitutively active MKK6 mutant, MKK6(Glu), containing glutamate instead of Ser-207 and Thr-211 (17), and a dominant negative p38 mutant p38AF (18) were kindly provided by Drs. Sung-Soo Kim (Kyung Hee University) and Dongeun Park (Seoul National University), respectively.

**Immunoblot Analysis**—The UV-irradiated COS-1 cells were harvested in a buffer containing 25 mM HEPES, pH 7.4, 150 mM NaCl, 0.1 mM EDTA, 1 mM Na<sub>2</sub>VO<sub>4</sub>, 1 mM NaF, 20 mM β-glycerophosphate, 1 mM phenylmethylsulfonyl fluoride, a protease inhibitor mix (Roche Molecular Biochemicals), and 1% Triton X-100. The cells were lysed by incubating the suspension on ice for 30 min. The protein concentration of the lysate was measured using the bichinonic acid method.

50–100 μg of the lysate protein was boiled in a Laemmli buffer, separated on a 12% SDS-polyacrylamide gel, and transferred to nitrocellulose. The blot was blocked with 5% non-fat milk in TTBS (20 mM TrisCl, pH 7.5, 500 mM NaCl, and 0.1% Tween 20) for 1 h and then incubated in a cold room overnight with antibodies specific to the C-terminal peptides of Gβ (SW) (19), p38, phosphorylated p38, JNK, phosphorylated JNK, MKK4, phosphorylated MKK4, MKK3, MKK6, and phosphorylated MKK3/6. All antibodies used against MAPK were purchased from New England Biolabs, Inc. The nitrocellulose paper was subsequently washed with TTBS and incubated with a peroxidase-labeled goat anti-rabbit IgG antibody preparation (1:2000 dilution, Pierce) for 2 h at room temperature. The blot was washed with TTBS and incubated with an enhanced chemiluminescence substrate mixture (Pierce). The blot was then exposed on an x-ray film (AGFA Cordix Rxi) to obtain the image. The density of the visualized bands was quantified with an image analyzer (Bio-Rad, Model GS-700), and the relative band density is expressed as a percentage or a multiple of the density in the UV-irradiated vector-transfected cells. A Student’s unpaired t test was used to evaluate the treatment effects, and a p value <0.05 was considered to be statistically significant.

**PathDetect Systems and Luciferase Assay**—A PathDetect CHOP trans-reporting system and a PathDetect c-Jun trans-Reporting system (Stratagene) was used to assess the transcriptional activity of the respective transcription factors. The protocols described by the company were followed with the exception that DEAE-dextran method was used for the cell transfections. The luciferase activity in the cell extracts was assayed using a luminometer with an automated injection device (TR717 Microplate Luminometer, Tropix), and the reaction substrate and buffer were parts of the lucerase assay system (Tropix). Aliquot of the mixture were used for the β-galactosidase assay to determine the transfection efficiency. At least five independent experiments in duplicate were performed, and the data are expressed as the mean light units of luminescence/unit of β-galactosidase activity.

**RESULTS AND DISCUSSION**

**G Protein βγ-Subunits Mediate Bi-directional Regulation of UV-induced Activation of p38 and JNK**—UV irradiation activates the MAPKs including ERK, JNK, and p38 in many cells and elicits various cellular responses. The βγ-subunits of the G proteins also activate the MAPKs following GPCR stimulation by specific ligands. However, it is not known whether or not the G protein βγ-subunits are involved in activating the MAPKs following UV irradiation. Therefore, the effects of Gβγ overexpression on p38 and JNK activation in COS-1 cells were analyzed to determine whether or not Gβγ mediates the UV-induced MAPK activation by co-transfecting the expression plasmids containing G<sub>γi</sub> and each of the five Gβ isoforms. Gβγ overexpression amplified the UV-activated induction of p38, and all of the five Gβ isoforms tested displayed significant augmentative effects on the UV-induced activation of p38, ranging from 1.5- to 2.5-fold increase compared with the UV-irradiated vector-transfected cells (Fig. 1A). In addition, Gβγ overexpression alone increased p38 activity by 11× the unstimulated basal activity, which corresponded to approximately half the p38 activity achieved by UV irradiation in the untransfected COS-1 cells alone (Fig. 1B).

However, Gβγ overexpression (in contrast to p38) reduced the UV-induced activation of JNK, and all of the five Gβ isoforms displayed comparable reductive effects resulting in activities ranging from 56 to 82% of the UV-irradiated vector-transfected cells (p < 0.05) (Fig. 1C). There was no significant change in either p38 or JNK protein expression by UV irradiation. This demonstrates that Gβγ overexpression regulates bi-directionally the UV-induced activation of p38 and JNK. Specifically, it augments p38 activation and reduces JNK activation that is induced by UV irradiation.

To date, six mammalian Gβ isoforms have been cloned. These have different tissue distributions and regulatory functions (20). In COS-1 cells, Gβ<sub>1</sub> and Gβ<sub>2</sub> were found to be expressed in approximately equivalent concentrations, and they were the major isoforms accounting for more than 95% of the total Gβ mRNA analyzed by quantitative reverse transcriptase-PCR (data not shown). However, all of the Gβ isoforms were capable of augmenting the UV-induced activation of p38 and reducing the UV-induced activation of JNK when overexpressed in the COS-1 cells. The effect of Gβγ on these enzyme activities was different among the Gβ isoforms, and the effect of Gβ<sub>1</sub>, Gβ<sub>2</sub>, and Gβ<sub>3</sub> was stronger, but that of Gβ<sub>4</sub> and Gβ<sub>5</sub> was relatively weak. In addition, the effect was not proportional to the expression level of the Gβγ proteins, suggesting that the Gβ isoforms might have different efficiencies in augmenting and reducing the UV-induced activation of p38 and JNK, respectively. However, the different efficacy among the Gβ isoforms was not pursued in this study. On the other hand, transfection with the vector plasmid alone resulted in a slight increase (39%) in the UV-induced activation of p38 and a corresponding reduction (17%) in the UV-induced activation of JNK, although the changes were much smaller than those observed in the Gβγ-transfected cells. Such activity changes were also observed in the mock-transfected cells (data not...
shown), which suggests that the transfection procedure itself might have caused the activity changes in p38 and JNK observed in the COS-1 cells. The SW antibody used to detect \( \text{G}_4/\text{H9252} \) proteins was generated against the carboxyl decapeptide shared by \( \text{G}_1, \text{G}_2, \) and \( \text{G}_3 \) (19). However, \( \text{G}_4 \) has one, and \( \text{G}_5 \) has five mismatched amino acid residues in the corresponding region, which may account for the weak \( \text{G}_4 \) bands in the \( \text{G}_5 \)-transfected COS-1 cells.

To confirm that \( \text{G}_4 \) regulates the UV-induced activation of p38 and JNK bi-directionally, the effect of \( \text{G}_4 \) sequestration on the UV-induced activation of the enzymes was examined. \( \text{G}_4 \) was sequestered from \( \text{GPCR} \) by overexpressing the C-terminal region of ARKct that binds to the \( \text{G}_4 \)-subunits to bring about their sequestration (21). ARKct overexpression decreased the UV-induced activation of p38 to 44% of the vector-transfected cells and also decreased the UV-induced activation of p38 from 170 to 59% in the COS-1 cells overexpressing \( \text{G}_4 \) (Fig. 2A). This result shows that ARKct partially abrogates the actions of endogenous \( \text{G}_4 \) while completely abolishing the effects of the exogenous \( \text{G}_4 \) in UV-induced activation on p38 in the COS-1 cells. This means that endogenous \( \text{G}_4 \) can mediate about half of the UV-induced p38 activity in the COS-1 cells. However, the remaining activity was not inhibited by ARKct overexpression, suggesting that \( \text{G}_4 \)-independent pathways mediate the remaining part of UV-induced p38 activity. On the other hand, ARKct overexpression completely recovered the UV-induced JNK activity from the inhibition caused by the transfection of \( \text{G}_4 \) to the activity of UV-stimulated untransfected COS-1 cells (Fig. 2B). This suggests that ARKct can relieve the inhibition of the UV-induced JNK activity caused by the overexpressed \( \text{G}_4 \). There was no significant change in either p38 or JNK protein expression in the COS-1 cells transfected with the ARKct plasmid.

This result shows that \( \text{G}_4 \) sequestration blocks the augmentative effect of \( \text{G}_4 \) on p38 activation by UV irradiation and relieves the inhibitory effects of exogenous \( \text{G}_4 \) on the UV-induced JNK activation. This confirms that the \( \text{G}_4 \)-subunits mediate the bi-directional regulation of UV-induced acti-
MAPK activation by UV irradiation involves various molecular events including the ligand-independent activation of the growth factor receptors and Src, Ras, and Rho activation (14). The G proteins also activate the MAPKs and their upstream signaling molecules. However, G protein involvement in the UV-induced activation of MAPKs has not been reported. To the our knowledge, this study is the first to demonstrate that Gβγ mediates the regulation of p38 and JNK activation induced by UV irradiation. Although both the p38 and JNK are activated by UV irradiation, the differential regulation of their activation by Gβγ can modify the cellular responses to UV stress. This suggests that GPCRs might be involved in the UV-induced activation of the MAPKs and that the G protein signaling systems can modify the UV response in mammalian cells. Moreover, it is quite possible that the α-subunit of the various G proteins may also mediate UV-induced activation, because the α- and βγ-subunits of the G proteins are usually activated simultaneously, and both are known to activate the MAPKs. However, the question regarding how UV irradiation activates the GPCR to release Gβγ remains to be clarified. One plausible hypothesis is that UV radiation may induce the release of GPCR agonists outside of the cell, and these activate the GPCR in an autocrine or paracrine mode to release the free Gβγ.

Bi-directional Regulation of UV-induced Activation of p38 and JNK by Gβγ Occurs at the Level of MAPKK—To examine whether or not the bi-directional regulation of UV-induced p38 and JNK activity by Gβγ occurs at the MAPKK level, the immediate upstream of the MAPKs, the effects of Gβγ, and βARKct overexpression on the UV-induced activation of MKK3/6 and MKK4, which phosphorylate and activate p38 and JNK, respectively, were examined. Gβ1γ2 expression resulted in an increase in the UV-induced phosphorylation of MKK3/6 by −1.4× that of the vector-transfected control. On the other hand, βARKct overexpression alone resulted in a 65% reduction in MKK3/6 phosphorylation in the UV-stimulated vector-transfected COS-1 cells, which was comparable to that of UV-stimulated untransfected COS-1 cells (Fig. 2A). βARKct overexpression also decreased the UV-induced MKK3/6 phosphorylation to 72% from the 144% in the COS-1 cells overexpressing Gβγ. This demonstrates that Gβγ increases UV-induced MKK3/6 phosphorylation in COS-1 cells under physiological conditions and Gβγ-overexpressed conditions. In contrast to MKK3/6, Gβ1γ2 overexpression resulted in a 38% decrease in UV-induced MKK4 phosphorylation compared with the vector control, and βARKct expression slightly increased MKK4 phosphorylation (Fig. 2B). βARKct expression recovered the MKK4 phosphorylation inhibited by Gβ1γ2 overexpression to the level of the UV-irradiated untransfected COS-1 cells. The observed effects of Gβγ and βARKct overexpression on MKK4 were similar to their respective effects on JNK. Therefore, this result shows that exogenous Gβγ can decrease the UV-induced phosphorylation of MKK4 in COS-1 cells.

MKK4 has been reported to phosphorylate and activate both p38 and JNK. However, MKK3 and MKK6 specifically phosphorylate p38 (22). Thus, any changes in MKK3/6 and MKK4 phosphorylation should result in changes in p38 and JNK activity, respectively. In addition, the observed effects of Gβγ and βARKct expression on MKK3/6 and MKK4 coincide with their respective effects on p38 and JNK. Therefore, the changes in UV-induced MKK3/6 and MKK4 activation caused by either Gβγ or βARKct overexpression can explain the findings that Gβγ overexpression enhances the UV-induced activation of p38 while reducing the UV-induced JNK activation in COS-1 cells and that βARKct overexpression reduces this increase in the UV-induced p38 activation by Gβγ and recovers UV-induced JNK activation from the inhibition caused by Gβγ overexpression in COS-1 cells. Therefore, it is concluded that exogenous Gβγ can regulate the UV-induced p38 and JNK activity through the bi-directional regulation of the UV-induced activation of MKK3/6 and MKK4.
c-Jun activity to 191% of the respective control (Fig. 4). This result demonstrates that Gβγ also regulates the transcriptional activity of CHOP and c-Jun in a similar way to the bi-directional regulation of the p38 and JNK, which are responsible for activating the respective transcriptional factors. Therefore, it is suggested that Gβγ is involved in regulating the UV-induced activation of p38 and JNK followed by the transcriptional activities of the downstream transcription factors including CHOP and c-Jun. These transcription factors, CHOP and c-Jun, can regulate the expression of a great variety of genes involved in various cellular responses. Therefore, the regulation of UV-induced activation of the MAPKs and transcription factors by Gβγ is suggested that play some physiological role in modifying the cellular responses to UV irradiation. Although UV irradiation alone induces a large amount of p38 and JNK activity.

**Inhibition of JNK Activation by p38 Results in Bi-directional Regulation of UV-induced Activation of p38 and JNK by Gβγ**

The next step was to investigate whether or not the reduction in the UV-induced activation of JNK by Gβγ is the result of cross-talk between the MAPKs. This was done to probe the mechanism responsible for Gβγ-controlled bi-directional regulation of the UV-induced activation of p38 and JNK. The effect of ERK and p38 activity on the UV-induced JNK activation was analyzed by blocking the pathways in COS-1 cells with PD98059 and SB203580, respectively. Treating COS-1 cells with SB203580, a p38 inhibitor, increased the UV-induced activation of JNK from 114 to 170% of the vector control, and treating the COS-1 cells transfected with Gβγ with SB203580 increased the UV-induced activation of JNK from 68 to 142% of the vector control (Fig. 5A). The greater UV-induced JNK activation following SB203580 treatment than that of the UV-irradiated control COS-1 cells (p < 0.01) suggests that p38 can inhibit UV-induced activation of JNK in COS-1 cells even in absence of Gβγ overexpression. SB203580 treatment also relieved the inhibitory effects of Gβγ on UV-induced JNK activation. Therefore, it is suggested that the inhibitory effect of Gβγ on UV-induced JNK activation might be mediated by p38 activation. To confirm the result of SB203580 treatment, the effect of a kinase-inactive p38 mutant, p38AF, on UV-induced JNK activation was analyzed. The expression of the kinase-inactive p38 mutant also resulted in an increase in UV-induced activation of JNK in a similar way to SB203580 treatment (Fig. 5B). On the other hand, when a constitutively active mutant MKK6, MKK6(Glu), was overexpressed, the UV-induced JNK activation in COS-1 cells decreased to 60% of the vector control. Gβγ and MKK6(Glu) co-expression did not display any additive effect on inhibiting UV-induced JNK activation, suggesting that Gβγ and p38 might act in the same signaling pathway mediating the inhibition of UV-induced JNK activation (Fig. 5B).
However, treatment with PD98059, a MEK1 inhibitor, had no significant effect on UV-induced JNK activation (data not shown). This shows again that p38 (and not ERK) inhibits UV-induced JNK activation even in the absence of Gβγ overexpression and that Gβγ inhibits UV-induced JNK activation by activating p38.

The results obtained in this study suggest that Gβγ mediates UV-induced p38 activation, and activated p38 inhibits the UV-induced JNK activation. In the absence of Gβγ overexpression, UV-activated p38 represses only a small part of the JNK stimulatory signals resulting in gross activation of both JNK and p38 by UV irradiation. On the other hand, in the presence of Gβγ overexpression Gβγ augments UV-induced p38 activity, which in turn inhibits the stimulatory signals for JNK more strongly, resulting in a large reduction in UV-induced JNK activation. This is in contrast with the augmentation of UV-induced p38 activation by Gβγ overexpression. Hence, it is the inhibition of JNK activation by p38 that causes the bi-directional regulation of the UV-induced activation of p38 and JNK by Gβγ overexpression.

The physiological significance of JNK inhibition by p38 is unclear. However, it might be associated with a regulatory mechanism of the various cellular UV responses including apoptosis, because in some cells JNK can play an essential role in apoptosis (25). Similar cross-talk between the JNK and p38 pathway has also been reported in other systems. The devel-

![Fig. 5. Inhibition of JNK activation by p38 resulted in bi-directional regulation of UV-induced activation of p38 and JNK by Gβγ.](http://www.jbc.org/)

A. increase in UV-induced JNK activation by SB203580 treatment. B. increase in UV-induced JNK activation by overexpression of the kinase-inactive p38 (p38AF). C. decrease in the UV-induced JNK activation by the overexpression of a constitutively active MKK6 mutant, MKK6(Glu). The COS-1 cells were treated with 20 μM SB203580, a p38 inhibitor, for 1 h prior to UV irradiation, or the cells were transfected with p38AF or MKK6(Glu). JNK activity was analyzed by immunoblots using antibodies specific to phosphorylated JNK as described in the legend to Fig. 1. The asterisk (*) represents a statistically significant difference from the vector-transfected control (p < 0.05, Student’s t test).
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opment of myocyte hypertrophy was mediated by p38 but was suppressed by JNK, which was evidenced by the contrasting effects on the expression of the atrial natriuretic factor (26). However, overexpression of the constitutively active p38-activating kinase MEKK1, a JNK kinase, in myocardial cells (27). Cross-talk between p38 and ERK has also been reported in other systems (28, 29). Such cross-talk including the JNK inhibition by p38 observed in this experiment may contribute to integrating the signals from the MAPK pathways before reaching the transcriptional factors and eliciting a final cellular response such as differentiation and apoptosis.

In this study, the Gβγ-subunits were shown to mediate the bi-directional regulation of the UV-induced activation of p38 and JNK. Such enzyme regulation can result in changes in the activity of transcription factors including CHOP and c-Jun, and JNK. Such enzyme regulation can result in changes in the bi-directional regulation of the UV-induced activation of p38 and JNK and eliciting a final cellular response such as UV responses by regulating the activity of the MAPK and its regulatory role in the UV-induced activation of p38 and JNK. 

Another question relates to the mechanism by which activated Gβγ-subunits might modify a variety of cellular signaling from sources other than conventional GPCR agonists.

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