Because of increasing evidence that G protein-coupled receptors activate multiple signaling pathways, it becomes important to determine the coordination of these pathways and their physiological significance. Here we show that the β2-adrenergic receptor (β2AR) stimulates p38 mitogen-activated protein kinase (p38 MAPK) via PKA in adipocytes and that cAMP-dependent transcription of the mitochondrial uncoupling protein 1 (UCP1) promoter by β2AR requires p38 MAPK. The selective β2AR agonist CL316,243 (CL) stimulates phosphorylation of MAP kinase kinase 3/6 and p38 MAPK in a time- and dose-dependent manner in both white and brown adipocytes. Isoproterenol and forskolin mimicked the effect of CL on p38 MAPK. In all cases activation was blocked by the specific p38 MAPK inhibitor SB202190 (SB; 1–10 μM). The involvement of PKA in β2AR-dependent p38 MAPK activation was confirmed by the ability of the PKA inhibitors H89 (20 μM) and (R)-cAMP-P-S (1 mM) to block phosphorylation of p38 MAPK. Treatment of primary brown adipocytes with CL or forskolin induced the expression of UCP1 mRNA levels (6.8 ± 0.8-fold), and this response was eliminated by PKA inhibitors and SB202190. A similar stimulation of a 3.7-kilobase UCP1 promoter by CL and forskolin was also completely inhibited by PKA inhibitors and SB202190, indicating that these effects on UCP1 expression are transcriptional. Moreover, the PKA-dependent transactivation of the UCP1 promoter, as well as its sensitivity to SB202190, was fully reproduced by a 220-nucleotide enhancer element from the UCP1 gene. We similarly observed that increased phosphorylation of ATF-2 by CL was sensitive to both H89 and SB202190, while phosphorylation of cAMP-responsive element-binding protein was inhibited only by H89. Together, these studies illustrate that p38 MAPK is an important downstream target of the β-adrenergic/cAMP/PKA signaling pathway in adipocytes, and one of the functional consequences of this cascade is stimulation of UCP1 gene expression in brown adipocytes.

β-Adrenergic receptors (βARs) play a pivotal role in the regulation of adipose tissue lipolysis and thermogenesis. Brown and white adipocytes contain all three βAR subtypes, each of which is coupled to Gαs to stimulate the cAMP/PKA pathway. This apparent redundancy in signal-generating capacity in response to the same neurotransmitter may be related, in part, to the ability of these receptors to differentially couple to multiple G proteins and other signaling pathways.

During the past several years, transmembrane signaling traffic through G protein-coupled receptors has grown from the classic G protein effectors such as adenylyl cyclase and phospholipases to include novel mechanisms for activation of mitogen-activated protein (MAP) kinase cascades. These signaling systems typically involve receptor and non-receptor tyrosine kinases as scaffolds and intermediaries (6–11). An interesting example of this flexibility in G protein-coupled receptors signaling is illustrated by our recent studies of the β2AR. We have shown that β2AR is coupled to both Gα and Gβγ in adipocytes, leading to the activation of the PKA and ERK1/2 pathways, respectively (3). A unique feature of the β2AR-ERK signaling mechanism is that intracellular proline-rich domains of the receptor serve as docking sites for the direct binding of c-Src in response to agonist, and this interaction is critical for triggering the ERK pathway (5).

In both white and brown fat, the responses to catecholamine stimulation clearly have a prominent cAMP-dependent component (see complete citations in Ref. 12 and updated in Ref. 13). Although adrenergic control of brown fat thermogenesis and the transcriptional induction of the UCP1 gene clearly require increases in cAMP (see Ref. 14 for review), the molecular mechanisms are still unsettled. A potent ‘brown fat-specific’ enhancer has been identified in the rodent UCP1 gene (15, 16), which contains a peroxisome proliferator response element (17), but the mechanism by which increases in cAMP and presumably PKA activity translate into increased UCP1 gene transcription are not fully understood.

To further address the hypothesis that individual βARs can activate multiple signaling pathways within the adipocyte, we have continued our efforts to assess the physiological significance of these parallel signaling mechanisms (3, 5). In the present studies, we show that in both brown and white adipocytes the β2AR activates the p38 MAP kinase pathway as a downstream consequence of the generation of cAMP and PKA activity. We further show that p38 MAP kinase activity is required for the βAR-dependent increase in UCP1 expression in brown adipocytes and transactivation of UCP1 promoter-reporter constructs.

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EXPERIMENTAL PROCEDURES

Chemicals and Plasmide—The β3AR-selective agonist CL316,243 (CL) was a gift from American Cyanamid Co. (Pearl River, NY). BRL49653 (BRL) and GF218135x (LGD-1069) were gifts from Glaxo Wellcome Inc. Wortmannin, LY294002, PP2, H89, SB202190, and PD98059 were from Calbiochem. Isoproterenol (ISO), (R)α-cAMP-S, and forskolin (FSK) were from Sigma. The β3AR expression vector pG2-β3AR was constructed as previously described (5). The 3.7-kilobase mouse UCP1 promoter-CAT construct (BCCAT) was a gift from Dr. Leslie P. Korak. The plasmid UCPIENtk-CAT was constructed by subcloning the –2530/-2310 fragment of the mouse UCP1 promoter from the HindIII to BamHI sites into the pBLCAT6 vector. Expression vectors for human PPARγ and RXRα were gifts from Dr. Steven A. Kliwer. The construction of the β3AR-luciferase plasmid was previously described (18).

Cell Culture and Transfection—The C3H10T1/2 (T1/2) pluripotent cell line was obtained from American Type Culture Collection. T1/2 cells were grown in Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum in six-well cluster plates and differentiated at confluence by addition of 1 μM BRL, 0.1 μM LGD, and 200 nM insulin (19). Cells were treated with 10 μM CL (20 min), 10 μM ISO (5 min), or 20 μM FSK (10 min) without or with the prior treatment of 10 μM SB202190 (30 min), 20 μM H89 (1 h), or 1 μM (R)α-cAMP-S (10 min). The HIB-1B brown preadipocytes (20) were maintained in Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum. Cells were transfected with a total amount of plasmid DNA equal to 2.2 μg/well and 5 μl of LipofectAMINE (Life Technologies, Inc.) in 2 ml/well in six-well plates. As indicated, three DNA mixtures included BCCAT or UCPIENtk-CAT (1.0 μg), β-actin-luc (0.2 μg), and pG2-β3AR or pGEM-3Z (1.0 μg/well). At the initiation of transfection BRL (1 μM) was added to HIB-1B cells to promote differentiation and was present throughout the experiment. Where indicated, HIB-1B cells were treated for 1 h with 10 μM SB202190, 20 μM PKA inhibitor H89, or 1 μM (R)α-cAMP-S prior to treatment with CL or FSK.

Primary brown adipocyte cultures were prepared by isolating and differentiating interscapular brown adipose tissue of C57BL/6J mice (21) with minimal modifications (22). Differentiated brown adipocytes were treated with 10 μM CL (20 min) in the absence or presence of the following pretreatment: 10 μM SB202190 (30 min), 20 μM H89 (1 h), or 1 μM (R)α-cAMP-S (10 min), or 25 μM PD98059 (30 min). Immediately prior to treatment with CL, all cells received 0.1 μM propranolol (5 μM).

CAT and Luciferase Assays—HIB-1B cells were transfected and described as treated above. Cells were harvested to assay UCP1 promoter or enhancer activities 48 h after transfection. Treatment with CL or FSK occurred during the last 8 h of incubation, whereupon cell extracts were prepared in lysis buffer from a CAT enzyme-linked immunometric assay kit (Roche Molecular Biochemicals). CAT and luciferase assays were performed as previously described (23).

Western Blotting—Whole cell lysates were prepared by rinsing cells with cold phosphate-buffered saline, followed by addition of 2 × Laemmli sample buffer. An aliquot (5 μg/well) was resolved by SDS-polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes. The levels of phosphorylated and total p38 MAPKs (catalog no. in parentheses; 9112S/9121, MKK3/6 (9231S/9232), ERK1/2 (9101S/9102), ATF-2 (9235S/9222), or CREB (9191S/9192) were detected with a 1:1000 dilution of each specific antisera (New England Biolabs) followed by a 1:10,000 dilution of goat anti-rabbit IgG conjugated with alkaline phosphatase (RPN5783, Amersham Pharmacia Biotech). UCP1 protein in whole cell lysates of brown adipocytes was determined using antisera to rat UCP1 raised in sheep (1:2000 dilution, Ref. 24) and alkaline phosphatase-conjugated rabbit anti-sheep IgG (1:10,000 dilution; KPL 152306). Immunoreactive bands were visualized by Storm PhosphorImager (Molecular Dynamics).

Isolation of RNA and Northern Blotting—Total cellular RNA was prepared using the Trizol method according to manufacturer’s protocol (Molecular Research Center, Inc.). For Northern blot analysis, RNA was denatured, fractionated through 1.2% agarose gels and transferred to Biorex nylon membranes (ICN Biomedicals, Inc.) (25). Radiolabeled probes were prepared by random primer extension (Prime-It RmT, Stratagene) in the presence of [α-32P]dCTP to a specific activity >2 × 106 dpm/μg DNA. The UCP1 probe was a 300-base pair BglII fragment (26). A rat cDNA probe for cyclophilin was used as an internal hybridization/quantification standard, and all the blots were hybridized and washed as previously described (27, 28).

RESULTS

It is well established that activation of β3AR leads to cAMP accumulation in adipocytes. We have recently shown that activation of β3AR also leads to ERK1/2 activation (3, 5). We have now investigated whether the β3AR agonist can stimulate p38 MAPK in adipocytes. As shown in Fig. 1A, treatment of differentiated T1/2 white adipocytes with the β3AR-selective agonist CL316,243 (CL, 10 μM) led to a time-dependent increase in the phosphorylation of p38 MAPK (5.05 ± 0.66-fold) compared with non-stimulated cells, and this effect was sustained through 40 min. The p38 MAPK inhibitor SB202190 (10 μM) completely abolished this stimulation, as shown in Fig. 1B. As shown in Fig. 2, the ability of CL to activate p38 MAPK was concentration-dependent, and the upstream p38 MAPK kinase, MKK3/6, was stimulated by CL in a parallel fashion. Significant levels of phospho-p38 and phospho-MKK3/6 were consistently evident at 2 μM CL and reached their maximum (3.2 ± 0.4-fold and 2.6 ± 0.3-fold, respectively) at 4 μM CL. Because of an early report that the D1-dopamine receptor appeared to activate p38 in a PKA-dependent manner (29), we investigated the possibility that PKA was also responsible for p38 activation by β3AR in adipocytes. As shown in Fig. 3, we found that both the PKA catalytic inhibitor H89 (20 μM) and the cAMP competitive antagonist (R)α-cAMP-S (1 μM) completely eliminated the activation of p38 MAPK by CL. Furthermore, we assessed whether β3AR activation of p38 MAPK could be similarly stimulated by β3AR or β2AR. Indeed, the non-selective β-agonist ISO produced a similar effect. We also tested the adenyl cyclase activator FSK and dibutyryl cAMP (not shown) on the activity of p38 MAPK. Similar to the results with CL and ISO, both of these agents stimulated phosphorylation of p38 MAPK, and this activation was blocked by H89 and (R)α-cAMP-S. Our analyses indicated that the amplitude of p38 MAPK stimulation by FSK or dibutyryl cAMP was significantly less than that achieved by CL or ISO. In other experiments, we tested the effects of pertussis toxin (100 ng/ml for 16 h (30), the phosphoinositide-3-kinase inhibitors LY294002 (10 μM) or wortmannin (25 μM), or the
ERK1/2 activation by CL in brown adipocytes was blocked by PKA inhibitors as well as by SB202190. Not surprisingly, ERK1/2 activation in these brown adipocytes was also insensitive to PKA.

Fig. 2. Coordinate- and dose-dependent stimulation of p38 MAPK and MKK3/6. Differentiated C3H10T1/2 adipocytes were treated with increasing concentrations of CL for 20 min, and cell lysates were analyzed by Western blotting for levels of phosphorylated (-P) and total (-T) p38 MAPK and MKK3/6. Results are the average (± S.D.) of three independent experiments.

Fig. 3. Activation of p38 MAPKs by βARs requires cAMP and PKA. Differentiated C3H10T1/2 cells were pretreated with H89 (20 μM, 1 h) or (R)-cAMP-SiH89 (1 mM, 10 min), followed by CL (10 μM, 20 min), isoproterenol (ISO, 10 μM, 5 min) or forskolin (FSK, 20 μM, 10 min). Cell lysates were analyzed by Western blotting for phosphorylated and total p38 MAPK. The results show levels of phospho-p38 normalized to total p38 MAPK and are the mean ± S.D. of three independent experiments.

Fig. 4. β3AR utilizes separate signaling pathways to activate p38 MAPK and ERK1/2 in brown adipocytes. A, cultures of mouse brown adipocytes were prepared as described in under “Experimental Procedures.” The cells were treated with 10 μM SB202190 (30 min), 20 μM H89 (1 h), or 25 μM PD98059 (30 min), followed by treatment of CL (10 μM, 20 min). All cells were also pretreated with 0.1 μM propranolol for 5 min prior to the treatment with CL. Cell lysates were prepared and immunoblotted with antibodies against p38 MAPK (p38-P), ERK1/2 (ERK1/2-T), or their phosphorylated forms (p38-P or ERK1/2-P). B, quantification of two independent experiments (mean ± S.D.). * indicates the values that are significantly different from non-stimulated control group by one-way ANOVA (analysis of variance) and Tukey’s multiple comparison post-hoc analysis (p < 0.01).

PD98059. Together, these results demonstrate that the stimulation of β3AR can activate both p38 MAPK and ERK1/2 in primary brown adipocytes, but these pathways are controlled by completely different mechanisms.

To study the p38 MAPK kinases, as well as certain relevant substrates of p38 MAPK, primary brown adipocytes were treated with CL from 3 to 60 min in the absence or presence of H89 or SB202190, and levels of phosphorylated MKK3/6, p38 MAPK, ATF-2, and CREB were measured. As shown in Fig. 5A, CL stimulated the phosphorylation of MKK3/6 and p38 MAPK as well as the transcription factors ATF-2 and CREB, both of which have been reported to be substrates of p38 MAPK (30, 31). Maximal activation of MKK3/6, p38 MAPK, ATF-2, and CREB persisted through 40 min of stimulation but had returned to non-stimulated levels by 1 h. As shown in Fig. 5, B and C, the phosphorylation of MKK3/6 by CL was blocked by H89, indicating that PKA is required to activate MKK3/6. When comparing CREB and ATF-2, different patterns of activation were observed. The phosphorylation of both CREB and ATF-2 was inhibited by H89, but only ATF-2 phosphorylation was blocked by SB202190. These results position MKK3/6 downstream of PKA and also suggest that while CREB is a direct target of PKA, ATF-2 is an indirect target of PKA and instead appears to be a direct target of p38 MAPK in adipocytes.

Src tyrosine kinase inhibitor PP2 (5 μM) prior to treatment with CL or ISO. The results (data not shown; for PD see also Fig. 4) revealed that none of these kinase inhibitors affected the activation of p38 MAP kinase in adipocytes. Together these data demonstrate that the activation of p38 MAPK by β3AR, as well as β1/β2AR, appears to be mediated by PKA in T1/2 white adipocytes, although it is true that the involvement of other kinases, for example AMP-activated protein kinases, cannot be completely ruled out.

To address whether p38 MAPK was similarly activated by β3AR and cAMP in brown adipocytes as in white adipocyte cell lines, we isolated and differentiated primary mouse brown adipocytes. As shown in Fig. 4, CL stimulated the phosphorylation of p38 MAPK by 4-fold, which was completely blocked by SB202190, H89, and (R)-cAMP-S but not by the MEK1/2 inhibitor PD98059. On the contrary, we have previously shown that activation of the ERK pathway by β3AR in white adipocytes is completely independent of cAMP and PKA (3), and as shown in the lower panels of Fig. 4A and quantified in Fig. 4B, ERK1/2 activation in these brown adipocytes was also insensitive to PKA inhibitors as well as to SB202190. Not surprisingly, ERK1/2 activation by CL in brown adipocytes was blocked by
promoter 4.7-±0.9-fold (n=3), and this induction was completely blocked by H89, (R_p)-cAMP-S, and SB202190 (Fig. 7A). FSK produced a similar effect on UCP1 promoter activity (3.4-±0.3-fold, n=3), which again was completely blocked by H89, (R_p)-cAMP-S, or SB202190 (data not shown). In addition, this result was completely reproduced by the 220-nucleotide brown-fat specific enhancer (−2530/−2231) of the UCP1 gene (15–17) when placed upstream of the thymidine kinase minimal promoter (Fig. 7B). Together, these data strongly indicate that β3AR or cAMP stimulates the expression of the UCP1 gene in brown adipocytes not only in a PKA-dependent manner but it is contingent on the subsequent activation of p38 MAPK.

**DISCUSSION**

In the adipocyte, the classic pattern of signal transduction through which βAR agonists exert their effects is increased cAMP production and activation of PKA. However, through the use of selective kinase inhibitors and cAMP mimetics, our results clearly show that cAMP and PKA activity are required for the subsequent activation of p38 MAPK by β3AR in adipocytes. This pathway appears to be functional in both white and brown adipocytes. Because β3AR-selective agonists have thermogenic and anti-obesity effects, we also investigated the consequences of the p38 pathway on induction of the UCP1 gene in brown adipocytes. We show that p38 MAPK activity is absolutely required for the β-agonist-dependent increase in UCP1 mRNA and protein levels as well as transcriptional activation of the UCP1 promoter.

We did not focus extensively on the other members of the βAR family in these studies but our data further suggest that all βAR subtypes are capable of activating p38 MAPK in adipocytes because ISO, as well as provision of the adenyl cyclase...
The class activator FSK or the cAMP mimic dibutyryl cAMP, could elicit the same response. However, it is noteworthy that the amplitude of the stimulation of p38 MAPK by dibutyryl cAMP or FSK was smaller than that by CL or ISO. The reasons for this are not clear but appear to indicate the need for a signal that is specific to βAR stimulation in addition to elevation of cAMP levels. One possibility could also be related to the isozymes of adenylyl cyclase that are expressed in adipocytes. We and others have shown that multiple adenylyl cyclase isoforms are expressed in white and brown adipocytes including the relatively abundant Type IX (32, 33), which is insensitive to FSK (34, 35).

Based upon our results, together with other reports that certain Gs-coupled receptors activate p38 MAPK (29, 36–38), we propose the following model (Fig. 8). The activation of βAR stimulates cAMP production and activation of PKA. However, the nature of the kinase(s) that links PKA to MKKs is unknown. As yet, we cannot unequivocally rule out AMP-activated kinases or certain Ca2+-regulated kinases. However, some insight into this pathway has been gleaned from studies of the thyroid-stimulating hormone receptor where there was evidence for involvement of Rac1 (38), but this may not be universal for all receptors. Because cAMP and PKA can activate cdc42 (39), which has been shown to stimulate mixed-lineage kinases (MLKs) (40) and p21-activated kinase (41, 42), one possible pathway is through Rac1/cdc42 and mixed-lineage kinases (MLKs) to MKK or through Rac1/cdc42 and p21-activated kinase to MKK. Another possibility that cannot yet be ruled out is that PKA may directly activate MLKs to stimulate the p38 MAPK pathway. Consensus sites for PKA phosphorylation are found in both MLK2 (GenBank™ U37709) and MLK3 (GenBank™ AF155142). Clearly this aspect of the signaling cascade needs to be pursued in a future study.

Our results in both primary brown adipocytes and in transfected HIB-1B cells show that the cAMP-dependent increase in UCP1 expression through PKA and p38 MAPK targets the −2530/−2310 enhancer region of the UCP1 promoter. This potent brown fat-specific enhancer was identified in the UCP1 gene as being responsible for tissue-specific and catecholamine-stimulated expression (15, 16, 43). This region also contains a PPRE that appears critical for activity and when attached to a heterologous promoter also appeared to contribute to cAMP-responsiveness (17). Nevertheless, despite intensive investigation of the role of UCP1 in thermogenesis and the undisputed induction of UCP1 gene expression by catecholamine-stimulated cAMP levels, the exact mechanism and transcription factors required for this response are still not clear. Our studies in primary brown adipocytes show that phosphorylation of ATF-2 and CREB occur in the same time-frame as p38 MAPK activation. However, because phosphorylation of CREB is insensitive to the p38 inhibitor (SB202190), a role for CREB in UCP1 gene transactivation would need to be contingent on the parallel activation of other factors by p38 MAPK (Fig. 8). Also to be considered is the possible modulation of the p38 MAPK pathway by a cAMP sensitive pathway. Wahl and colleagues (44) reported increased PPARγ-mediated transcriptional activation of several PPREs, and we find similar results.2A. V. Lazennec et al. (44) proposed that PPARγ is phosphorylated by PKA but that p38 or other kinases need to be explored as well. It will now be important to establish not only which kinase(s) links PKA to MKK3/6 but of equal importance to identify the combination of transcription factors that orchestrate this highly tissue-specific and hormonally controlled response.

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**Fig. 7.** Transactivation of the UCP1 promoter requires p38 MAPK. HIB-1B cells were transfected with UCP1-BBCAT, β-actin-luciferase and mouse pG2-βAR (A) or UCP1ENtk-CAT and β-actin Luciferase (B) as described under “Experimental Procedures.” For the final 8 h of transfection, cells were treated with CL (5 μM) or forskolin (FSK, 20 μM) in the absence or presence of SB202190, H89, or (R)-cAMP-S. CAT and luciferase activities were assayed in lysates 48 h after initiation of transfection. Results shown are mean ± S.E. of three independent assays each in duplicates. * indicates value is significantly different from non-stimulated control (p < 0.001).

**Fig. 8.** Proposed pathway for activation of UCP1 gene by βAR through PKA and p38 MAPK.

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β-Adrenergic Activation of p38 MAP Kinase
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β-Adrenergic Activation of p38 MAP Kinase in Adipocytes: cAMP INDUCTION OF THE UNCOUPLING PROTEIN 1 (UCP1) GENE REQUIRES p38 MAP KINASE

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