Estradiol (E2) exerts not only genotropic but also nongenomic actions through nuclear estrogen receptors (ER). Here, we provide a novel paradigm for nongenomic E2 signaling independent of nuclear ER. E2 induces a rapid rise in the intracellular free Ca2+ concentration ([Ca2+]i) through membrane estrogen receptors in murine RAW 264.7 macrophages. This E2-induced Ca2+ signaling is not prevented by different ER blockers and cannot directly activate stably transfected c-fos promoter or the mitogen-activated protein kinases p38, ERK1/2, and SAPK/JNK, or NO production. However, the E2-induced rise in [Ca2+]i is specifically down-regulated by the serum-stimulated activation of c-fos promoter and ERK1/2, and conversely, it specifically up-regulates lipopolysaccharide-stimulated activation of c-fos promoter, p38, and NO production. The E2-related activation of c-fos promoter can be prevented by an intracellular Ca2+ chelator. Our data indicate that E2-induced nongenomic Ca2+ signaling through membrane ER is able to specifically modulate genotropic signaling pathways with impact on macrophage activation.

Estrogens with its most active 17β-estradiol (E2)3 are required not only for development of the female phenotype but also exert a series of both beneficial and adverse effects on human health. For instance, estrogens have been described to be protective in diverse neurodegenerative diseases (1, 2) in human health. For instance, estrogens have been described to be protective in diverse neurodegenerative diseases (1, 2) in particular on gene expression at all. Indeed, estrogens have been described to be protective in diverse neurodegenerative diseases (1, 2).

At present, however, the key question is whether the E2-induced nongenomic rise in [Ca2+]i, through mER, irrespective of its molecular nature, is able to exert any effects on cell functioning, in particular on gene expression at all. Indeed, there is information available that Ca2+ signaling has a profound influence on expression of especially immediate early genes such as c-fos (32–34). In general, however, the E2-induced rises in [Ca2+]i are characterized by low amplitude and short duration, and they are therefore widely regarded as meaningless for affecting gene expression and cell functions. Here, however, we demonstrate that E2-induced Ca2+ signaling through surface receptors, not inhibitable by ER blockers, exerts specific regulatory effects on genotropic signaling pathways induced by serum and lipopolysaccharide (LPS) in murine macrophages.

**EXPERIMENTAL PROCEDURES**

**Construction of Cell Line RAW 264.7**—The c-fos promoter from –520 to +169 was amplified from mouse DNA, cloned into pSEAP2 Basic Vector (CLONTECH, Heidelberg, Germany), and stably transfected with FuGENE 6 (Roche Molecular Biochemicals) in combination with pEGFPN3 (CLONTECH) into the macrophage cell line RAW 264.7 (ATCC TIB-71). The cells were grown in phenol red-free Iscove's modified Dulbecco's medium (Invitrogen) supplemented with 5% heat-inactivated low endotoxin fetal calf serum (FCS) (PAA Laboratories, Coelle, Germany). Clones were selected and maintained in the presence of 250 μg/ml G418. The clone RAW-fos13, which did not express any detectable enhanced green fluorescent protein, was used throughout all experiments. Cell stocks were preserved in liquid nitrogen, and the cells used were passaged not more than eight times.
Reverse Transcription-PCR—Total RNA was isolated from RAW-fos13 cells as well as from the uterus of C57BL/10 mice using TRIzol reagent (Invitrogen). DNA fragments of ERα and ERβ were amplified as described recently (27). The following primer pairs were used: ERα sense, 5′-CCG-TGG-AGA-TTC-TGA-TGA-TTG-G-3′; ERα antisense, 5′-GGG-TAT-GTA-GTA-GTT-TGA-TAA-GG-3′; ERβ sense, 5′-CAG-TGT-GCT-AGT-GCG-CTG-3′; ERβ antisense, 5′-GAC-GGA-AGA-ACT-GGA-ATC-AAG-GTA-AAT-GTG-TGG-3′. PCR fragments were separated in 2% Tris borate-EDTA agarose gels, purified using a PCR product purification kit (Qiagen, Hilden, Germany), and cloned into TOPO TA cloning vector (Invitrogen, Leek, Netherlands). The fragments were sequenced with Thermosequenase fluorescent-labeling sequencing kit (Amersham Pharmacia Biotech) and purified using a PCR product purification kit (Qiagen, Hilden, Germany). The following primer pairs were used: ERα sense, 5′-CTC-CAG-GAG-CAG-GTC-ATA-GAG-G-3′; ERα antisense, 5′-CAG-GCT-CTG-CAT-TCA-GG-CAT-C-3′; ERβ sense, 5′-GAC-GGA-CTA-CTA-GAC-C-3′; ERβ antisense, 5′-CAT-GTC-CTG-GTG-CTG-GGT-GAT-3′. The PCR products were sequenced using fluorescent-labeled sequencing kit (Amersham Pharmacia Biotech) and purified using a PCR product purification kit (Qiagen, Hilden, Germany) as described recently (27).

Antibody Labeling—Both intact cells and permeabilized cells were labeled with the anti-ER antibodies ERα(MC-20) and ERβ(H-184) (Santa Cruz Biotechnology, Heidelberg, Germany) and with the secondary antibody goat anti-rabbit IgG FITC conjugate (Sigma) and donkey anti-rabbit IgG FITC conjugate (Sigma). After serum starvation for 18 h, cells were washed with 1% paraformaldehyde, whereas these two anti-ER antibodies did not react with any ERα on the surface of intact RAW-fos13 cells. Nevertheless, the RAW-fos13 cells exhibit binding sites for ERα on their surface. When intact RAW-fos13 cells were incubated with the plasma membrane-impermeable E2-BSA-FITC for 1 min, the cells revealed an increased fluorescence intensity, as determined by flow cytometry (Fig. 2A). CLSM localized this bound fluorescence exclusively on the cell surface (Fig. 2B). By contrast, the cells did not bind any BSA-FITC under the same experimental conditions (Fig. 2, A and B). Moreover, the red fluorescence of concanavalin A-rhodamine was localized on the surface of intact cells and was colocalized with E2-BSA-FITC (Fig. 2B).

Expression of Nuclear and Membrane ERs—Macrophages, which play a key role in immunity, have been reported to express both nuclear ER (39) and mER (27). The presence of both classical nuclear ERs and mERs is confirmed in the murine macrophage cell line RAW 264.7, which we have stably transfected with the reporter gene human secreted alkaline phosphatase driven by the c-fos promoter. These RAW-fos13 macrophages express ERα, but not ERβ, as revealed by reverse transcriptase-PCR (Fig. 1A). Expression of ERα can be also detected, but only in permeabilized cells, by flow cytometry using the antibody ERα(MC-20) probing the C-terminal part of ERα (data not shown). The majority of ERα was localized in the cytoplasm of cells, as revealed by CLSM (Fig. 1C). However, these two anti-ERα antibodies did not react with any mER on the surface of intact RAW-fos13 cells. Nevertheless, the RAW-fos13 cells exhibit binding sites for mERα on their surface. When intact RAW-fos13 cells were incubated with the plasma membrane-impermeable E2-BSA-FITC for 1 min, the cells revealed an increased fluorescence intensity, as determined by flow cytometry (Fig. 2A). CLSM localized this bound fluorescence exclusively on the cell surface (Fig. 2B).

Ca2⁺ Fluorescence Spectroscopy—Cells at a concentration of 10⁵/ml were suspended in 20 mM HEPES buffer (pH 7.2) containing 130 mM NaCl, 5 mM KCl, 1 mM CaCl₂, 0.5 mM MgCl₂, 1 mM Na₂HPO₄, and 1 mg/ml glucose loading with 1 μM Fura-2/acetoxymethylester (Sigma). Heidelberg, Germany) using a 488-nm argon laser line for excitation of FITC fluorescence and a 568-nm krypton laser line for rhodamine fluorescence. Evaluation was described previously (37).

Ca²⁺-induced Rise in [Ca²⁺]i—At the physiological concentration of 1 nm, E2, but not 17α-estradiol induced a rise in [Ca²⁺]i, as determined in Fura-2-loaded RAW-fos13 cells by Ca²⁺ fluorescence spectroscopy (Fig. 3A). The amount of E2-rais in Ca²⁺ varied from experiment to experiment between about 50 to 90 nm Ca²⁺. About the same increase in [Ca²⁺]i can be induced with the plasma membrane-impermeable E2-BSA, whereas BSA alone was ineffective in affecting [Ca²⁺]i (Fig. 3B). Moreover, the E2-induced rise in [Ca²⁺]i cannot be prevented upon pre-incubation of the cells with different ER blockers such as ICI 182,780, tamoxifen, and raloxifene (Fig. 3, C and D). The rise in [Ca²⁺]i, could be due to an influx of extracellular Ca²⁺ and/or to the release of Ca²⁺ from intracellular Ca²⁺ stores such as endoplasmic reticulum. When extracellular Ca²⁺ was removed by 2 mM EGTA, E2 was still able to induce a slight increase in [Ca²⁺]i (Fig. 3E). In addition, the phospholipase C inhibitor U-73122 prevented most of the E2-induced rise in [Ca²⁺]i, whereas the ineffective analog compound U-73343 did not abrogate the E2-induced increase in [Ca²⁺]i (Fig. 3F). This indicates that E2 induces both influx of extracellular Ca²⁺ and release of Ca²⁺ from intracellular Ca²⁺ stores in RAW-fos13 cells.
transcriptase-PCR was performed with the primer pairs ER/H9251 and ER/H9252. The rise of Ca$^{2+}$ abolished most of the E2-induced rise in Ca$^{2+}$, which suggests participation of G-proteins in the E2-induced rise in Ca$^{2+}$ (Fig. 3G).

Inability of E2 to Activate MAPK and c-fos Promoter — It has been reported that E2 can directly activate MAPKs (15–19). We therefore examined the effect of E2 on the activation of the three MAPK family extracellular signal-regulated kinases (ERK1/2), p38 MAPK, and stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK). When the cells were incubated with 1 nM E2 for various periods up to 180 min, none of the three MAPKs became activated, as revealed by immunodetection (data not shown). Moreover, E2 is reported to induce expression of the Ca$^{2+}$-sensitive immediate early gene c-fos (17). However, 1 nM E2 was not able to induce any significant activation of the stably transfected c-fos promoter in RAW-fos13 cells (Fig. 4A). In line with these negative results, E2 cannot induce any detectable NO production in cells.

E2-induced Up-regulation of LPS Signaling — LPS is known to activate macrophages including induction of the immediate early gene c-fos (40, 41). In accordance, we can show that LPS also stimulates the c-fos promoter by about 4-fold in RAW-fos13 cells (Fig. 4A). E2 even augmented this LPS effect, whereas 17a-E2 was ineffective (Fig. 4B). The up-regulatory E2 effect cannot be prevented by the ER inhibitors ICI-182,780, tamoxifen, and raloxifene (Fig. 4B). E2 exerts its augmentation of LPS stimulation on the c-fos promoter through the rise of [Ca$^{2+}$]. Indeed, 1,2-bis(O-aminophenoxy)ethane $N,N,N',N'$-tetraacetic acid tetra(acetoxymethyl) ester (BAPTA), when used under conditions blocking intracellular free Ca$^{2+}$ accumulation (Fig. 3H), also prevented the E2-induced augmentation of LPS-stimulated c-fos promoter (Fig. 4C). There was also no increase of LPS stimulation by E2 when Ca$^{2+}$ was inhibited with the phospholipase C inhibitor U-73122, in contrast to the ineffective compound U-73343 (Fig. 4C). Moreover, the inhibitor GF109203X of the Ca$^{2+}$-sensitive protein kinase C prevented the E2-induced up-regulation of LPS-activated c-fos promoter (Fig. 4C). Because FTX blocks this E2 activation, G-proteins are obviously involved in the E2-induced augmentation of c-fos promoter activity (Fig. 4C).

Activation of macrophages by LPS is also associated with activation of the three MAPK families ERK1/2, p38, and SAPK/JNK (42, 43). Indeed, when RAW-fos13 cells were stimulated with LPS for various periods up to 180 min, all of the three MAPK families were mostly activated at 15 min, and thereafter, activation was declined but still detectable after 180 min (Fig. 5). E2 selectively interfered with activation of MAPKs induced by LPS. E2 did not affect the activities of ERK1/2 and SAPK/JNK but only the activation of p38 became up-regulated at 15 min (Fig. 5).

Activation of p38 MAPK is known to be involved in the control of NO production of macrophages (44). We have there-
fore examined the effect of E2 on LPS-stimulated NO production. In RAW-fos13 cells, stimulation with LPS for 24 h caused a dramatic increase in NO production to \( \frac{30}{10} \) nitrite (Fig. 6A). Moreover, co-incubation with E2 resulted even in an increase of NO production by about 50%. This stimulatory E2 effect cannot be inhibited by the ER blockers tamoxifen and raloxifene (Fig. 6A). However, the E2 effect can be abrogated by preincubation of cells with the intracellular Ca\(^{2+}\) chelator BAPTA (Fig. 6A). The view that Ca\(^{2+}\) is important for this E2

Fig. 3. E2-induced rise in [Ca\(^{2+}\)]\(_i\) of RAW-fos13 cells. A, E2 triggers an immediate increase in [Ca\(^{2+}\)]\(_i\), whereas 17\(\alpha\)-E2 is largely ineffective. B, cells stimulated with E2-BSA or BSA. C, cells preincubated with ICI 182,780 for 1 h before E2 application. ICI 182,780 alone did not affect [Ca\(^{2+}\)]\(_i\). D, cells pretreated with raloxifene or tamoxifen for 1 h before the addition of E2. E, cells incubated with EGTA for 100 s before the addition of E2. F, cells pretreated with phospholipase C inhibitor U-73122 or the inactive compound U-73343 for 2 min before E2 stimulation. G, cells preincubated with or without PTX for 16 h before E2 application. H, cells pretreated with BAPTA for 10 min before E2 addition. The arrows show the addition of reagents with the indicated concentrations to RAW-fos13 cell suspensions. Representative experiments are shown, and the results were verified in at least four independent experiments.

Fig. 4. Effects of E2 on activation of c-fos promoter induced by LPS. A, no direct effect of E2 on c-fos promoter activity. Cells were cultured in Iscove’s modified Dulbecco’s medium containing 5% charcoal-stripped FCS for 18 h, then treated with 1 nM E2, 1 nM 17\(\alpha\)-E2, 0.5 \(\mu\)M tamoxifen (tam), 0.5 \(\mu\)M raloxifene (ral), 1 \(\mu\)M ICI 182,780 (ICI), or 1 \(\mu\)g/ml LPS for 3 h. The c-fos promoter activity of each group was determined relative to the activity of vehicle-treated control. Values are the means \(\pm\) S.E. of at least three independent experiments performed in triplicate. B, E2-augmented activation of c-fos promoter by LPS. Cells were stimulated with 1 \(\mu\)g/ml LPS for 3 h (control) and in combination with 1 nM E2 and 17\(\alpha\)-E2, 0.5 \(\mu\)M tamoxifen (tam), 0.5 \(\mu\)M raloxifene (ral), and 1 \(\mu\)M ICI 182,780 (ICI). The c-fos promoter activity was expressed relative to the c-fos promoter activity induced by LPS alone. C, cells were stimulated with 1 \(\mu\)g/ml LPS alone for 3 h in combination with 1 nM E2 (control). In the other groups, cells were pretreated with 10 \(\mu\)M BAPTA for 10 min, 2 \(\mu\)M U-73122 for 2 min, 2 \(\mu\)M U-73343 for 2 min, 100 ng/ml PTX for 16 h, and 1 \(\mu\)M GF109203X for 10 min before stimulation with LPS and E2.
whereas E\textsubscript{2}, but not 17\ multiply the activation of the c\textsubscript{fos} promoter by about 5-fold, fos just as did PTX (Fig. 6). The down-regulation of FCS-stimulated c\textsubscript{fos} promoter to about 2 activity of c\textsubscript{fos} promoter (Fig. 7) down-regulation of FCS-stimulated c\textsubscript{fon} production. Also, PTX prevented the E\textsubscript{2}-induced down-regulation of FCS-stimulated signaling. FCS stimulation of RAW-fos13 cells activated ERK1/2 (Fig. 8) but not p38 and SAPK/JNK (data not shown). The presence of E\textsubscript{2} during FCS stimulation down-regulated ERK1/2 activation to a similar extent as it did in c\textsubscript{fos} promoter activation (Fig. 8).

**DISCUSSION**

Our data provide evidence for a novel paradigm of E\textsubscript{2} action at the cellular level: E\textsubscript{2} triggers nongenomic signaling, independent of the classical nuclear ER, and this nongenomic signaling specifically regulates genotropic signaling induced by FCS or LPS in murine macrophages.

Nongenomic E\textsubscript{2} signaling manifests itself as an E\textsubscript{2}-induced rapid rise in [Ca\textsuperscript{2+}]i, of RAW-fos13 cells. This rise is due to both influx of extracellular Ca\textsuperscript{2+} and release of Ca\textsuperscript{2+} from intracellular Ca\textsuperscript{2+} stores, as we have recently also found in mouse IC-21 macrophages (27). E\textsubscript{2}-induced nongenomic Ca\textsuperscript{2+} signaling has been described to be independent of the classical nuclear ER (25, 27) as well as to be dependent on ER (15).

Although the RAW-fos13 cells express ER\textsubscript{A} and ER\textsubscript{B}, the E\textsubscript{2}-induced Ca\textsuperscript{2+} signaling is not mediated through ER\textsubscript{A} but rather through ER\textsubscript{B}. This view is supported by the following findings. First, the E\textsubscript{2}-induced rise in [Ca\textsuperscript{2+}]i, cannot be prevented by the ER blockers ICI 182,780, tamoxifen, and raloxifene. Second, E\textsubscript{2}-BSA, which is not able to enter the cells and which binds to neither ER\textsubscript{A} nor ER\textsubscript{B} (45), is also capable of rapidly raising [Ca\textsuperscript{2+}]i, just as free E\textsubscript{2}. Third, the RAW-fos13 cells exhibit distinct binding sites for E\textsubscript{2}-BSA-FTIC on their surfaces that are not accessible for anti-ER antibodies on intact cells. Fourth,
our finding that the E2-induced increase in [Ca^{2+}], via phospholipase C is insensitive to ICI 182,780 contrasts to recent
membrane. Fifth, inhibition of the E2-induced Ca^{2+} signaling via transfected ERα and ERβ, which also are expressed in the plasma membranes of Chinese hamster ovary cells (23). This strongly supports the view that the E2-induced nongenomic Ca^{2+} signaling in RAW-fos13 cells does not rely on the classical ER linked somehow to the plasma membrane. Fifth, inhibition of the E2-induced Ca^{2+} signaling by PTX indicates that the mER is not identical with the classical nuclear ER, but rather the mER belongs to the class of G-protein-coupled receptors. As with numerous other G-protein-coupled receptors, the mER is agonist-sequestrable, as recently characterized in detail in mouse IC-21 macrophages (27).

There is accumulating evidence that classical nuclear ERs mediate nongenomic E2 effects such as activation of MAPK (15–19), activation of endothelial nitric oxide synthase (20, 46–48), and activation of c-fos (17) as well as activation of NO production (46, 48). Although RAW-fos13 cells express ERα, E2 is not able to directly induce any activation of the c-fos promoter or the NO production or one of the three MAPK families p38, ERK1/2, SAPK/JNK. Nonetheless, all these parameters except SAPK/JNK are responsive to E2, which becomes apparent only when cells are activated by LPS or FCS. Indeed, E2 down-regulates FCS-stimulated c-fos promoter activation, whereas it up-regulates LPS-induced c-fos promoter activation in RAW-fos13 cells. These E2 effects are not mediated through ERα but rather through nongenomic Ca^{2+} signaling. This view is substantiated by our findings that (i) these E2 effects are not prevented by the ER blockers ICI 182,780, tamoxifen, and raloxifene, (ii) they can be abolished by BAPTA under conditions capturing the intracellular free Ca^{2+} ions generated by E2, and (iii) they are prevented by PTX and inhibitors of phospholipase C, which both inhibit an E2-induced rise in [Ca^{2+}]. The down- and up-regulation of genotropic FCS and LPS signaling, respectively, by an E2-induced rise in [Ca^{2+}], are not simply due to a general dampening or stimulation of all cell activities but, rather, are highly specific. Indeed, although LPS activates all of the three MAPK families, p38, ERK1/2, and SAPK/JNK, only the p38 MAPK is up-regulated by the E2-induced Ca^{2+} signaling. Finally, the specific up-regulatory effect of E2-induced Ca^{2+} signaling on LPS-stimulated p38 and c-fos promoter results in increased activation of macrophage, which becomes evident as increased NO production. Again, this up-regulatory effect of E2 on LPS-stimulated NO production of macrophages is independent of ERα.

Collectively, our data provide the first evidence for a linkage of E2-induced nongenomic Ca^{2+} signaling through mER, independent of the classical nuclear ER, with cell functions. We are aware of the fact that our results are in conflict to numerous other findings showing ER-mediated nongenomic E2 effect (15, 17, 20, 46–48). At present, a plausible explanation for this difference is that nongenomic E2 actions vary among different cell types and that such a nongenomic E2 signaling as we described in RAW-fos13 macrophages is possibly restricted to macrophages. But even if this type of nongenomic E2 signaling were restricted to macrophages, it is presumably of importance.
for human health, for example, with respect to the outcome of infectious diseases. Activation of macrophages, induced by components of infectious agents such as the bacterial LPS, is a prerequisite to effectively recognize and kill microorganisms as well as even malignant tumor cells (49). By contrast, over-activation of macrophages is believed to be responsible for deleterious clinical manifestations of infectious diseases, such as hypercoagulation, hypotension, cachexia, somnolence, multiple organ failure, and even death (50).

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Estradiol-induced Nongenomic Calcium Signaling Regulates Genotropic Signaling in Macrophages
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