This article has been withdrawn by the authors. The DP immunoblot in Fig. 1A, the DP immunoblot on the right in Fig. 2B, the DP immunoblot in Fig. 6, the DP immunoblot on the left in Fig. 7, and the DP immunoblot in Fig. 8 were inappropriately manipulated. Because the original data are no longer available, in the interest of maintaining accuracy in the published scientific literature, the authors wish to withdraw this article. However, the authors have full confidence in the findings and conclusions of this paper and have replicated the findings in subsequent work.
On the other hand, dynamin seems to be important for this pathway, because it is essential for the activation of Ras, in a PKC-independent manner. Thus, although the GnrHR to ERK signaling is mainly mediated by Gβγ-PK, another pathway involving dynamin is required for the Src-mediated activation of Ras, which supports the step of Raf-1 activation by PKC.

MATERIALS AND METHODS
Buffers—Homogenization buffer (buffer H) consisted of 50 mM β-glycerophosphate (pH 7.3), 1.5 mM EGTA, 1 mM EDTA, 1 mM DTT, 0.1 mM sodium orthovanadate, 1 mM benzamidine, aprotinin (10 μg/ml), leupeptin (1 μg/ml), and pepstatin (2 μg/ml). Buffer A contained 250 mM β-glycerophosphate (pH 7.3), 1.5 mM EGTA, 1 mM EDTA, 1 mM DTT, 0.1 mM sodium orthovanadate. Radioimmune precipitation buffer consisted of 137 mM NaCl, 20 mM Tris, pH 7.4, 10% (v/v) glycerol, 1% Triton X-100, 0.5% (w/v) deoxycholate, 0.1% (w/v) SDS, 2.0 mM EDTA, 1.0 mM phenylmethylsulfonyl fluoride, and 20 μM leupeptin. Rat buffer consisted of 40 mM Tris-HCl, pH 7.5, 200 mM NaCl, 2 mM MgCl₂, 1% Nonidet P-40, 1 μg/ml aprotinin, 1 μg/ml leupeptin, 250 mM phenylmethylsulfonyl fluoride, 10 mM NaF, and 1 mM sodium orthovanadate.

Stimulants, Inhibitors, Antibodies, and Miscellaneous Reagents—in-Trp³[GnRH], a stable GnrHR analog (GnRH-a), genistein (PTK inhibitor), enolase, protein A-Sepharose, and protein G-Sepharose were obtained from Chemical Co. (St. Louis, MO). GF109203X, PD098059, SB203580, Wortmannin, and 12-tetradecanoylphorbol-13-acetate were purchased from Calbiochem. AG18 and AG1478 were obtained from Calbiochem. Polyclonal anti-hemaggulutinin epitope antibody was from Santa Cruz Biotechnology. Monoclonal anti-GFP was from Roche Molecular Biochemicals. Mouse monoclonal anti-active MAPK antibody (DP-ERK antibody) was from Sigma, Israel (Rehovot, Israel). Antiphosphotyrosine antibody was from Santa Cruz Biotechnology. Antibody to β-epitope of PKC was a gift from Dr. Chaim Brodie (Bar-Ilan University, Israel).

Plasmids—N-terminally truncated FAK (DN-FAK), ERK2, or Raf was cloned in pcDNA1 using BamHI/XhoI sites. HA-ERK2, N-17 Ras, and β-arrestin2 in pCMV5, and dominant negative-α-arrestin2 in pcDNA1 were kindly provided by Dr. Zvi Vogel (Weizmann Institute of Science, Rehovot, Israel). The cell lysates were incubated with 5 μg of protein G-Sepharose as described above, and the activated GFP-Ras was then detected with anti-GFP antibody.

RESULTS
Role of PTKs in ERK Activation by GnrHR—Various MAPK cascades (ERK, JNK, and BMK) are activated in response to GnrHR stimulation of αT3-1 cells. We have previously shown that the stimulation of JNK activity by GnrHR is mediated by a unique pathway, which includes sequential activation of PKC, Src, MEK1, and p38 MAPK, and probably also MEK1 (32). This was implicated also in the activation of ERK by GnrHR (25), but the other components involved in this pathway remained unclear. In this study we used anti-double phosphorylated ERK (DP-ERK) antibody to detect its phosphorylation and activation on GnrHR stimulation of αT3-1 cells. ERK phosphorylation was detected 5 min after GnrHR-a treatment (Fig. 1A), peaked at 15 min, and was slightly reduced 15 min later. No change was detected in the total amount of ERK as judged by the equal amount of unphosphorylated ERK. In brief, cells were lysed in Ral buffer, and lysesates (300 μg of protein) were incubated with 20 μg of GST-Raf (RBD) and were washed three times in a buffer containing 20 mM Hepes, pH 7.5, 150 mM NaCl, 0.1% Triton X-100, and 10% glycerol. The amount of Ras pulled-down was then assessed by Western blotting using anti-Ras antibody. To study Raf activity in transfected cells, a construct of GFP-Ras was used. After GnrHR stimulation, the cells were lysed in Ral buffer and 300 μg of protein was subjected for further treatment. The active, GTP-bound form of Ras was precipitated by the GST-Raf (RBD, 20 μg) and washed as above, and the activated GFP-Ras was then detected with anti-GFP antibody.
staining with anti-general ERK antibody (Fig. 1A). These results appear similar to the trend of ERK activation by GnRH (Ref. 25 and data not shown), indicating that the anti-DP-ERK antibody can serve as a tool to study ERK activation in αT3-1 cells.

To study the mechanism of ERK activation we first used inhibitors of various intracellular signaling cascades. As previously reported (25), the PTK inhibitor genistein partially (40%) inhibited, and the PKC inhibitor GF109203X abolished the GnRH-induced ERK activation. The MEK inhibitor PD98059 inhibited not only GnRH-stimulated ERK-activity but abolished also its basal activity, whereas the PI3K inhibitor wortmannin and the p38 MAPK inhibitor SB203580 had no significant effect on ERK activation. The results suggest that GnRH signaling toward ERK is mainly transmitted via PKC and to a lesser extent also by PTKs. Interestingly, the moderate effect of genistein on ERK activation was achieved under conditions where it completely abolished the GnRH activation of JNK (28). One possibility for this differential effect is that the PTK involved in the GnRH to ERK pathway is distinct from Src, which is the PTK operating in the GnRH-JNK pathway (28), and this distinct PTK is only mildly sensitive to genistein. To test this possibility, we examined the effects of additional PTK inhibitors on ERK activation by GnRH-a. We found (Fig. 1B) that the specific inhibitor of Src, PP1, which abolished endogenous src activation (data not shown), inhibited the GnRH-induced ERK activation to a similar extent as genistein. Similarly, the general PTK inhibitor AG18 had a small effect (~25%) on the GnRH-induced ERK activation. However, the EGF receptor inhibitor AG1478, which abolished the EGF-induced ERK activation in αT3-1 cells (data not shown), had no effect on ERK activation by GnRH-a. The data suggest that Src is partially involved in the activation of ERK by GnRH but probably not via transactivation of EGF or other growth factor receptors as suggested for other GPCRs (31, 32).

Src, but Not FAK or EGF Receptor, Plays a Role in GnRH to ERK Signaling—Signaling by Src is often mediated via the focal adhesion kinase (FAK), which is usually instrumental in
The Mechanism of ERK Activation by GnRH

FIG. 2. Activation of Src and FAK by GnRH-a and the effect of Src and FAK inhibitors on Src and FAK activation.

A. Activation of Src and FAK by GnRH-a. Subconfluent αT3-1 cells were treated with GnRH-a (10^{-7} M) for the indicated times. Stimulation was terminated by washing the cells with an ice-cold PBS followed by Src and FAK immunoprecipitation. A, activation of Src; B, activation of FAK. Activity was determined using acid-denatured enolase. FAK activity was detected by anti-phosphotyrosine antibody. The amount of immunoprecipitated HA-ERK2 was determined with anti-diphospho antibody (28). These results, together with the lack of effect of AG1478 strongly suggest that EGF receptor is not involved in the activation of ERK by GnRH.

Activation of Raf-1 and Ras by GnRH—To understand the nature of the partial involvement of Src in the GnRH to ERK pathway, we studied the effect of GnRH on the upstream components of the ERK cascade, including the protein serine/threonine kinase Raf-1. After treatment of αT3-1 cells with GnRH-a and inhibitors, the cells were lysed, Raf-1 was immunoprecipitated, and its activity toward recombinant MEK was measured as described (37). Raf-1 activity was stimulated within 5 min after GnRH activation (data not shown); its activity peaked 10 min after stimulation and declined thereafter (Fig. 4). Similar to the inhibition of ERK activation by GnRH, we found that GF109203X completely inhibited Raf-1 activation by GnRH-a, whereas PP1 and genistein had a partial inhibitory effect (~30% inhibition) and AG1478 had no significant influence on Raf-1 activation by GnRH-a. The small GTP-binding protein Ras, was also transiently activated by GnRH-a. Using a pull-down and a GTP loading assays, we found that activation of Ras was detected within 2 min from activation, peaked at 5–10 min, and declined thereafter (Fig. 5 and data not shown). However, the mechanism involved in this activation seems to be distinct from that of Raf-1 and ERK as judged from the differential sensitivity to the various inhibitors used. Thus, the Src inhibitors genistein and PP1 abolished the activation of Ras.
Ras by GnRH-a, GF109203X had only a partial effect, and the EGF receptor inhibitor AG1478 had no effect upon Ras activation. These data indicate that, although both Ras and Raf-1 are activated in response to GnRH in αT3-1 cells, the upstream mechanism that leads to this activation is different. Indeed, when a dominant negative form of Ras (N-17 Ras) was transfected into the αT3-1 cells, it only partially (30%) inhibited ERK activation by GnRH-a (Fig. 6), whereas a constitutively active form of Ras (L61-Ras) caused a large elevation of ERK (18- to 22-fold above basal level). Therefore, although Ras is capable of activating the Raf-1/ERK pathway, GnRH activation of Raf-1/ERK is only partially Ras-dependent. The most plausible explanation for these data is that the main pathway operates via direct activation of Raf-1 by PKC (38), and that this activation requires only a minor contribution of activated Ras as previously suggested for the activation of Raf-1 by 12-O-tetradecanoylphorbol-13-acetate (39).

The Involvement of Dynamin, but Not β-Arrestin or Gβγ, in ERK Activation by GnRH—Recently, the βγ subunits of G-proteins as well as β-arrestin and dynamin have been implicated in the Go-independent GPCR-ERK signaling (reviewed in Ref. 12). For example, it was shown that G-coupled receptor stimulation of mitogen-activated protein kinase is mediated by Gβγ-induced activation of Ras (40). To study the possible role of the βγ subunit in GnRH to ERK signaling, we used a chimera of CD8 (which allows anchoring to the membrane) fused to the C terminus of β-adrenergic receptor kinase (ARK-C), which contains a Gβγ binding domain (CD8-ARK-C). It has been previously shown that this chimera acts as a scavenger of the βγ dimer (41, 42). Although this construct was able to inhibit GPCR signaling toward ERK in COS7 cells, its overexpression had no significant effect on either the basal or the GnRH-induced activation of ERK in αT3-1 cells (Fig. 7), indicating that the signaling from GnRHR to ERK utilizes a Gβγ-independent pathway. Another protein that was implicated in the signal transmission of GPCRs is β-arrestin, which acts as a mediator of receptor internalization (43). Recently, it was also shown that β-arrestin can act as a scaffold protein and transmit the signals of Gq-coupled receptors toward ERK by forming a complex that contains internalized receptor, Raf-1, and activated ERK (44). We examined the possible involvement of β-arrestin using either an inactive form of this protein (V54D-β-arrestin2), which inhibits the activity of all endogenous β-arrestins (43), or by overexpressing wild-type β-arrestin2, which should increase ERK activation by GPCRs (16, 45). Thus, we coexpressed these two constructs in αT3-1 cells together with...
HA-ERK2 and followed HA-ERK activation using anti-phospho ERK antibodies. As seen in Fig. 7, neither form of β-arrestin had any effect on ERK activation by GnRH. Both the Gbg subunits and β-arrestin do not seem to participate in the process of ERK activation by GnRH, although they can influence GPCR signaling in other systems.

As well as β-arrestin, dynamin seems to be a key regulator of the internalization processes of GPCR (46). As such, dynamin has also been implicated in GPCR signaling, including the activation of MAPKs by several GPCRs (16). The role of this protein in the αT3-1 cells was examined, as described for β-arrestin, by co-overexpression of either wild-type or a dominant negative form of dynamin (K44A-dynamin (16, 47)) together with HA-ERK2. Although the wild-type form of dynamin had no significant influence on the activation of ERK by GnRH, the dominant negative form of dynamin partially inhibited (45%) both the basal and the GnRH-induced ERK activation (Fig. 8). This inhibition of both basal and GnRH-stimulated activities is similar to the results obtained with dominant negative Ras (Fig. 6) and to some extent also to the results with CSK, suggesting that dynamin, Src, and Ras operate on the same signaling pathway.

Dynamin, but Not β-Arrestin, Is Involved in Ras Activation by GnRH—To confirm that β-arrestin is not involved in GnRH-induced stimulation of ERK and to further study the role of
dynamin in this process, we undertook to explore the influence of dynamin on other components of the GnRH to ERK signaling pathway. First, we examined whether dynamin had an effect on the GnRH activation of Ras. To this end, we cotransfected negative forms of β-arrestin together with GFP-Ras into T3-1 cells. Two days after transfection, the cells were serum-starved for 16 h and then either treated with GnRH-a (10^{-7} M) for the indicated times, with peroxovanadate (Na_{3}VO_{4} (100 μM) and H_{2}O_{2} (200 μM); VOOH), or left untreated. Activated GFP-Ras was then detected with anti-GFP antibody and subsequent Western blot analysis using antibody to the PKC epitope tag. The results in the bottom bar graph are an average of three experiments. Activation (-fold) (GnRH-stimulated/basal for each of the constructs) is indicated in the bar graph.

Unlike β-arrestin, the other internalization mediator, dynamin appears to be involved in GnRH-induced internalization of the GnRHR (48), suggesting that β-arrestin does not play a significant role in GnRH signaling.

Unlike β-arrestin, the other internalization mediator, dynamin appears to be involved in GnRH-induced internalization of the GnRHR (48) and, as demonstrated above (Fig. 8), in the activation of ERK by GnRH. We then undertook to elucidate the possible mechanism by which dynamin transmits the GnRH signals toward the downstream components of the ERK cascade. First, the possible involvement of dynamin in Ras activation by GnRH was examined by cotransfecting either wild-type or dominant negative (K44A) forms of dynamin together with GFP-Ras. Similar to the effect on ERK, wild-type dynamin had no influence on Ras activity under the conditions examined. However, the dominant negative form of dynamin completely abrogated the GnRH activation of Ras under the conditions examined, indicating that dynamin lies upstream of Ras in the pathway that leads from the GnRHR. Similar to ERK, MEK activity was only partially inhibited by the dominant negative and to some extent also by wild-type dynamin (Fig. 9B). The fact that the inhibition of MEK activity by dominant negative dynamin was very similar to the inhibition of ERK activity makes it unlikely that dynamin
influences the MEK-ERK level of the cascade as previously suggested in other systems (49). Moreover, unlike the inhibition of Ras, ERK, and MEK activities by dominant negative dynamin, there was no influence of this construct on the GnRH-induced membranal translocation of PKC. The reason for this could be the different length of serum starvation, which modifies the content of many signaling components (53). We have previously shown that Src is activated by GnRH and has a major role in the transmission of signals to the JNK cascade, the most likely explanation for our results is that the activation of ERK is supported to some extent by Src, although the main pathway leading to ERK activation is PTK-independent.

PTK-induced activation of ERK is known to involve the small GTP-binding protein Ras. Interestingly, although GnRH causes a significant activation of Ras, a dominant negative form of Ras had only a minor inhibitory effect on ERK activation. Because the effect was similar to that exerted by Src, it is likely that Ras acts downstream of Src in a pathway that partially supports the activation of ERK (Fig. 10). Indeed, Ras activation by GnRH was abolished by the Src inhibitor, PP1. Interestingly, it has been previously demonstrated (39) that stimulation of PKC in COS-7 cells led to activation of Ras and formation of Ras-Raf-1 complexes, but the activation of Raf-1 by PKC was not completely blocked by dominant negative Ras. These data indicate that PKC activates Raf-1 by a mechanism distinct from that initiated by PTKs and that only a small amount of activated Ras is needed to allow the activation of Raf-1 by PKC. Therefore, ERK activation is only partially dependent on Src, independent on PKC agrees well with this assumption. Therefore, we believe that, upon GnRH stimulation, Raf-1 is activated by PKC but requires a different mechanism to be fully activated in PC12. These explanations can be used also for the different results obtained in regard to the activation of JNK by GnRH in different laboratories (54).

Another point of interest is the mechanism of Src activation by GnRH. We have previously shown that Src is activated by GnRH via a mechanism that is partially (~70%) dependent on PTK (28). Similarly, we found that the activation of Ras is only partially dependent on PTK, but fully dependent on Src, supporting the notion that Ras is activated by Src. Such pathway of sequential activation of Src-Ras-ERK was reported also for some other GPCRs (12, 55–57). However, the fact that Src and Ras are only partially dependent on PTK raises the question as to what might be the other pathway involved in the activation of Src/Ras. An answer to this question may come from the recent observations that, upon GPCR stimulation, Src can be activated in a Go-independent manner and therefore we un-
dertook to study the role of these additional signaling molecules as outlined below. Many GPCRs were shown to transmit their signal through transactivation of either EGF receptor- or cytoskeleton-associated PTKs (FAK and PYK). Our results indicate that those components are not involved in GnRH signaling to ERK. Thus, EGF receptor does not seem to be activated in response to GnRH (25), and the specific inhibitor of EGF receptor (AG1478) or dominant negative form of the EGF receptor had no effect on GnRH-induced ERK stimulation. Moreover, FAK does not seem to participate in GnRH to ERK signaling, because a dominant negative FAK had no effect on ERK activation by GnRH. Finally, PYK does not seem to be expressed to any detectable level in αT3-1 cells as judged by immuno blotting and immunoprecipitation experiments (data not shown), and therefore is unlikely to participate in the GnRH to ERK pathway.

Although the Go subunits are important transducers of GPCR signaling, dissociated βγ subunits have been implicated in the transmission of GPCRs signaling as well. Thus, βγ dimers can act via PTKs (such as Src), via a direct activation of Ras or via a direct activation of either the protein serine/threonine kinase KSR-1 or activation of phosphatidylinositol 3-kinase (58, 59). In addition, GPCRs can operate via β-arrestin- and dynamin-mediated internalization (16), and β-arrestin may serve as a scaffold for additional signaling molecules and initiate a second wave of G-protein-independent, heptahelical receptor-mediated signals that activate the MAPK cascades (12). Interestingly, in the αT3-1 system, we found that neither a scavenger of βγ dimer nor the dominant negative β-arrestin affect the GnRH-induced ERK activation, indicating that the inhibition, unlike the other pathways examined, may participate in the MAPK cascade of Src/Ras.

Recently it was shown that β-arrestin internalization of GPCRs, dynamically regulating the direct activation of ERK by MEK (49), may serve as a scaffold for additional signaling molecules and initiate a second wave of G-protein-independent, heptahelical receptor-mediated signals that activate the MAPK cascades (12). Interestingly, in the αT3-1 system, we found that neither a scavenger of βγ dimer nor the dominant negative β-arrestin affect the GnRH-induced ERK activation, indicating that the inhibition, unlike the other pathways examined, may participate in the MAPK cascade of Src/Ras.

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Role ofDynamin, Src, and Ras in the Protein Kinase C-mediated Activation of ERK by Gonadotropin-releasing Hormone
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