The ryanodine receptor of Jurkat T lymphocytes was phosphorylated on tyrosine residues upon stimulation of the cells via the T cell receptor/CD3 complex. The tyrosine phosphorylation was transient, reaching a maximum at 2 min, and rapidly declined thereafter. In co-immunoprecipitates of the ryanodine receptor, the tyrosine kinases p56\(^{fyn}\) and p59\(^{lck}\) were detected. However, only p59\(^{lck}\) associated with the ryanodine receptor in a stimulation-dependent fashion. Both tyrosine kinases, recombiantly expressed as glutathione S-transferase (GST) fusion proteins, phosphorylated the immunoprecipitated ryanodine receptor in vitro. In permeabilized Jurkat T cells, GST-p59\(^{lck}\), but not GST-p56\(^{fyn}\), GST-Grb2, or GST alone, significantly and concentration-dependently enhanced Ca\(^{2+}\) release by cyclic ADP-ribose. The tyrosine kinase inhibitor PP2 specifically blocked the effect of GST-p59\(^{lck}\). This indicates that intracellular Ca\(^{2+}\) release via ryanodine receptors may be modulated by tyrosine phosphorylation during T cell activation.

Ryanodine receptors (RyR)\(^1\) are large tetrameric Ca\(^{2+}\) channel-forming proteins. Three different isoforms of RyR have been identified, termed types 1, 2, and 3 (also known as skeletal muscle type RyR, cardiac muscle type RyR, and brain type RyR (reviewed in Ref. 1)). There is indeed abundant expression of muscle type RyR, cardiac muscle type RyR, and brain type RyR in cardiac muscle cells, Ca\(^{2+}\) release via RyR is controlled by Ca\(^{2+}\) release (reviewed in Ref. 3). In neuronal cells, Ca\(^{2+}\) release via RyR is involved in fundamental brain function, such as long term depression (4).

In skeletal and cardiac muscle, RyR are the major intracellular Ca\(^{2+}\) release channels, which control contractility by Ca\(^{2+}\)-induced Ca\(^{2+}\) release (reviewed in Ref. 3). In neuronal cells, Ca\(^{2+}\) release via RyR is involved in fundamental brain function, such as long term depression (4).

Ca\(^{2+}\) release via RyR is controlled by Ca\(^{2+}\) itself (5). In addition, investigations in different cell systems suggest that the cyclic nucleotide cADPR may also function as an endogenous ligand for RyR-mediated Ca\(^{2+}\) release (reviewed in Refs 6 and 7). Activation of T lymphocytes is a fundamental part of the immune system to ensure protection against foreign antigens. One of the intracellular signaling pathways essentially necessary for T cell activation is a sustained elevation of [Ca\(^{2+}\)]\(_i\) (reviewed in Ref. 8). The sustained elevation of [Ca\(^{2+}\)]\(_i\) results in activation of many proteins (reviewed in Ref. 9). Of particular interest is the protein phosphatase calcineurin, which, upon activation by Ca\(^{2+}\)/calmodulin, dephosphorylates the transcription factor nuclear factor of activated T cells (10). Only this dephosphorylated form of nuclear factor of activated T cells can enter the nucleus to activate multiple gene expression, e.g. expression of interleukin-2 (10).

Among the first biochemical events that are observed during T cell activation is phosphorylation of multiple proteins on tyrosine residues. These phosphorylation events are mediated by a concerted action of several protein-tyrosine kinases (PTK), including Src family PTKs p56\(^{fyn}\) and p59\(^{lck}\) (11–14).

Recently, we have provided evidence that cADPR and RyR play an important role in the sustained phase of Ca\(^{2+}\) signaling in T cells (15). Since TCR/CD3 complex-mediated Tyr phosphorylation of the type 1 Ins(1,4,5)\(^3\)P\(_3\) receptor has been described recently (16), in this study we investigated (i) whether also RyR might be phosphorylated on tyrosine residues in a stimulation-dependent fashion, and (ii) whether such tyrosine phosphorylation might have a functional effect on Ca\(^{2+}\) release via RyR.

**EXPERIMENTAL PROCEDURES**

**Materials—**Antibodies and antisera were obtained as follows: anti-RyR\(^{common}\) mouse monoclonal antibody (mAb) from Calbiochem, Egggenstein, Germany; anti-RyR\(^{common}\) antiserum (no. C-18) from Santa Cruz Biotechnology, Heidelberg, Germany; anti-phosphotyrosine mAb (clone PY 99) from Santa Cruz Biotechnology, anti-phosphotyrosine antisem (rabbit polyclonal IgG) from Upstate Biotechnology, Lake Placid, NY, obtained via Biomol, Hamburg, Germany; anti-p56\(^{fyn}\) mAb (clone 3A5) and anti-p59\(^{lck}\) mAb (clone 15) both from Santa Cruz Biotechnology. The Src-type PTK inhibitor PP2 (4-amino-5-(4-chlorophenyl)-7-(t-butylypyrazolo[3,4-d])pyrimidine; Ref 17) was obtained from Calbiochem, Egggenstein, Germany.

All other chemicals used were of the highest purity grade available. MilliQ water (Millipore Waters, Eschborn, Germany) was used for the preparation of all buffers.

**Cell Culture—**Jurkat T lymphocytes (subclone JMP) were cultured as described previously (18) in RPMI 1640 medium containing Glutamax I (Life Technologies, Eggenstein, Germany) and supplemented with newborn calf serum (7.5%), penicillin (100 units/ml), and streptomycin (50 \(\mu\)g/ml; all from Life Technologies). The cells were cultured at 37 °C in a humidified atmosphere in the presence of 5% CO\(_2\).
methanol for 5 min at room temperature. Afterwards, the cells were again rinsed twice with buffer A. Subsequently, the cells were incubated with anti-RyR<sub>common</sub> mAb (Calbiochem) at 1 μg/100 μl for 60 min at room temperature. Then, excess of mAb was removed by rinsing the cells twice with buffer A. Finally, a secondary fluorescein isothiocyanate-labeled goat anti-mouse antiserum (anti-phosphotyrosine antiserum, Santa Cruz Biotechnology) was coupled to Protein G-Sepharose (50 μg/100 μl) for 1 h at room temperature, and immunostained with the primary antibody (in TBS buffer; the washing procedure was then repeated three times (for co-puriﬁcation and Western blotting) (Fig. 1B), and confocal microscopy (Fig. 1B). The amount of RyR detected by an anti-RyR<sub>common</sub> mAb did not change signiﬁcantly within the ﬁrst minutes upon stimulation of the TCR/CD3 complex (Fig. 1A). When 10,000 g membranes were prepared in the presence of the Tyr phosphatase inhibitor dephostatin (100 μM), a transient phosphorylation of RyR residues of the RyR in response to stimulation of the TCR/CD3 complex was observed (Fig. 1A).

Using anti-RyR<sub>common</sub> mAb and a ﬂuorescein isothiocyanate-labeled goat anti-mouse antiserum as secondary antibody in confocal microscopy, the main localization of the RyR was the inner surface of the plasma membrane. Confocal microscopy revealed very weak phosphorylation on Tyr residues of the RyR in response to stimulation of the TCR/CD3 complex. The results were obtained with two different anti-phospho-Tyr antibodies, the mAb PY99 (Santa Cruz Biotechnology) and a polyclonal anti-phosphotyrosine antiserum (rabbit polyclonal IgG; Upstate Biotechnology).

Membrane distribution of RyR, taken together with an extensive detailed analysis of the time course revealed very weak phosphorylation by 15 and 30 s, whereas substantial phosphorylation was observed at 1 and 2 min (Fig. 1C). At later time points, e.g. 5 min (Fig. 1A) or 10 or 20 min (data not shown), no phosphorylation on Tyr residues could be detected. These results were obtained with two different anti-phospho-Tyr antibodies, the mAb PY99 (Santa Cruz Biotechnology) and a polyclonal anti-phosphotyrosine antiserum (rabbit polyclonal IgG; Upstate Biotechnology).

Phosphorylation of Tyr residues of the RyR was transient, showing marked phosphorylation at 2 min (Fig. 1A). A more detailed analysis of the time course revealed very weak phosphorylation by 15 and 30 s, whereas substantial phosphorylation was observed at 1 and 2 min (Fig. 1C). At later time points, e.g. 5 min (Fig. 1A) or 10 or 20 min (data not shown), no phosphorylation on Tyr residues could be detected. These results were obtained with two different anti-phospho-Tyr antibodies, the mAb PY99 (Santa Cruz Biotechnology) and a polyclonal anti-phosphotyrosine antiserum (rabbit polyclonal IgG; Upstate Biotechnology).

Membrane distribution of RyR, taken together with an ex-
Experimental Procedures.

Corresponds to the mass of RyR immunoprecipitated by 4 µg of anti-RyRcommon polyclonal antisemur and separated by SDS-PAGE (3% stacking gel, 6% separation gel). The mass of protein in individual lanes corresponds to the mass of RyR immunoprecipitated by 4 µg of anti-RyRcommon polyclonal antisemur in case of anti-RyR Western blot (A, three lanes on the left side; C, five lanes on the right side) and to 1 µg of anti-RyRcommon polyclonal antisemur in case of anti-phosphotyrosine Western blot (A, three lanes on the right side; C, five lanes on the left side). Subsequent tank blotting and immunostaining were carried out as described under “Experimental Procedures.” Antibodies used for immunostaining: A, anti-RyRcommon mAb (Calbiochem) and anti-phosphotyrosine rabbit polyclonal antisemur (Upstate Biotechnology); C, anti-RyRcommon mAb (Calbiochem) and anti-phosphotyrosine rabbit polyclonal antisemur (Upstate Biotechnology); C, anti-RyRcommon mAb (Calbiochem) and anti-phosphotyrosine rabbit polyclonal antisemur (Upstate Biotechnology). To identify PTK(s) phosphorylating RyR in Jurkat T cells, co-immunoprecipitation experiments using anti-RyR antisemur were carried out (Fig. 2). In addition to tyrosine phosphorylation of the RyR, phosphorylation of p59fyn and p56lck was observed. These PTKs are localized to the membrane due to their N-terminal myristoylation (22, 23) and palmitoylation (24, 25); are constitutively associated with the intracellular domains of several surface proteins, including TCR/CD3 (p56lck) and CD4 (p56lck) (26, 27); and respond very rapidly to TCR/CD3 stimulation (12, 28). Therefore, p59fyn and p56lck are candidates to be implicated in Tyr phosphorylation of the RyR.

To identify PTK(s) phosphorylating RyR in Jurkat T cells, co-immunoprecipitation experiments using anti-RyR antisemur were carried out (Fig. 2). In addition to tyrosine phosphorylation of the RyR, phosphorylation of p59fyn and p56lck was observed. These PTKs are localized to the membrane due to their N-terminal myristoylation (22, 23) and palmitoylation (24, 25); are constitutively associated with the intracellular domains of several surface proteins, including TCR/CD3 (p56lck) and CD4 (p56lck) (26, 27); and respond very rapidly to TCR/CD3 stimulation (12, 28). Therefore, p59fyn and p56lck are candidates to be implicated in Tyr phosphorylation of the RyR.

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Tyrosine Phosphorylation of Ryanodine Receptor

In the present study we have shown that (i) the RyR of T cells is localized in intracellular membrane systems close to the plasma membrane, (ii) the RyR was transiently phosphorylated on Tyr residues upon stimulation of the TCR/CD3 complex, (iii) p59\textsuperscript{fyn} and p56\textsuperscript{lck} were detected in co-immunoprecipitates of the RyR, (iv) recombinant GST fusion proteins of p59\textsuperscript{fyn} and p56\textsuperscript{lck} both phosphorylated immunoprecipitated RyR on tyrosine residues in vitro, and (v) GST-p59\textsuperscript{fyn}, but not GST-p56\textsuperscript{lck}, GST-Grb2, or GST alone, enhanced Ca\textsuperscript{2+} release by cADPR.

Although phosphorylation on tyrosine residues has not yet been demonstrated for RyR, there are several reports on phosphorylation of serine and threonine residues. The type 1 RyR toward Ca\textsuperscript{2+} and ATP (32). The type 2 RyR was phosphorylated by exogenously added protein kinase A, Ca\textsuperscript{2+}/calmodulin-dependent protein kinase, and cyclic GMP-dependent protein kinase. However, the Ca\textsuperscript{2+}/calmodulin-dependent protein kinase was much more effective than the other kinases; additionally, endogenous Ca\textsuperscript{2+}/calmodulin-dependent protein kinase appears to associate firmly with the Type 2 RyR (33). Type 2 RyR phosphorylation by protein kinase A dissociated FK506-binding protein 12.6 from the channel complex, leading to enhanced channel opening; importantly, it has been shown in failing hearts that the type 2 RyR is hyper-phosphorylated by protein kinase A, leading to markedly increased channel opening (34). Pancreatic β-cells also express the type 2 RyR; in those cells activation of protein kinase A enhanced activation of RyR by caffeine, 4-chloro-3-ethylphenol, or 3,9-dimethylxanthine (30). Importantly, \textsuperscript{3}Hryanodine binding was also found to be stimulated by phosphorylation of the brain type (type 3) RyR (35).

Analysis of the type 3 RyR amino acid sequence reveals that multiple tyrosine residues, such as tyrosines 810, 1022, 2289, 4045, and 4684, could well be targeted by Src family PTKs, based on the substrate specificity of these kinases (36). Among the potential substrate sites, tyrosines 4045 and 4684 are also good candidates for binding to Src homology 2 domains of Src...
Tyrosine kinase inhibitor PP2 was added 1 min after cADPR, but 1 min before addition of GST-p59 and p56\(^{lck}\), and ATP. Left panel shows representative tracings obtained with additions of GST or GST fusion proteins (2 \(\mu\)g each) followed by cADPR (10 \(\mu\)M); the bar chart below is the data summary as mean \pm S.E. (n = 3). Middle panel represents the concentration-response curve for the enhancing effect of GST-p59 when added after cADPR; data in the lower part are mean \pm S.E. (n = 3–5). In the right panel, additional GST fusion proteins or GST alone (each 2 \(\mu\)g) were added as indicated; the bar chart represents mean values \pm S.E. (n = 5–8).

**Table I**

Tyrosine kinase inhibitor PP2 inhibits the effect of GST-p59\(^{en}

\([Ca^{2+}]\) was measured in permeabilized Jurkat T cells by ratiometric fluorimetry in the presence of fura2/free acid (1 \(\mu\)M) as described under "Experimental Procedures." The experiments described here are identical to those in Fig. 4. Middle panel, using 2 \(\mu\)g of GST-p59\(^{en}\) to enhance the cADPR-mediated \(Ca^{2+}\) release, except that the tyrosine kinase inhibitor PP2 was added 1 min after cADPR, but 1 min before GST-p59\(^{en}\).

### Table I

| PP2 | \(\Delta [Ca^{2+}]\) | n |
|-----|------------------|---|
| \(\mu\)g | \% \(\pm\) S.E. |
| 0 | 100 \(\pm\) 19 | 7 |
| 0.5 | 25 \(\pm\) 13 | 4 |
| 5 | 13 \(\pm\) 6 | 6 |

**Table II**

GST-p59\(^{en}\) enhanced \(Ca^{2+}\) release stimulated by Ryr agonists

\([Ca^{2+}]\) was measured in permeabilized Jurkat T cells by ratiometric fluorimetry in the presence of fura2/free acid (1 \(\mu\)M) as described under "Experimental Procedures." The experiments described here are identical to those in Fig. 4. Middle panel, using 2 \(\mu\)g of GST-p59\(^{en}\) to enhance the cADPR-mediated \(Ca^{2+}\) release, except that the tyrosine kinase inhibitor PP2 was added 1 min after cADPR, but 1 min before GST-p59\(^{en}\).

| Agonist | Tyrosine kinase | \(\Delta [Ca^{2+}]\) | n |
|--------|-----------------|------------------|---|
| cADPR  | GST-p59\(^{en}\) | 100 \(\pm\) 27 | 3 |
| 4-CEP  | GST-p59\(^{en}\) | 120 \(\pm\) 37 | 3 |
| CaCl\(_2\) | GST-p59\(^{en}\) | 73 \(\pm\) 43 | 3 |

family PTKs, based on the specificity of phosphotyrosine sequences recognized by various Src homology 2 domains (37).

The observed p56\(^{lck}\)/p59\(^{en}\)-mediated tyrosine phosphorylation of RyR is consistent with the notion of the central role of these PTKs in early events of T cell signaling. p59\(^{en}\) and p56\(^{lck}\) are thought to trigger the signal transduction pathways initiated by TCR/CD3 ligation by phosphorylating cytoplasmic domains of the TCR/CD3 complex and activating other PTKs involved in these events (38, 39). These PTKs, in turn, phosphorylate phospholipase C-\(\gamma\) and linker for activation of T cells, thus triggering one pathway of \(Ca^{2+}\) mobilization in T cells (38, 39). Furthermore, it has been shown that p59\(^{en}\) and p56\(^{lck}\) can phosphorylate phospholipase C-\(\gamma\) directly in vitro (40). Therefore, p59\(^{en}\) and p56\(^{lck}\) play a crucial role in \(Ca^{2+}\) mobilization in T cells. The tyrosine phosphorylation of RyR described in this report may represent another mechanism by which p59\(^{en}\) affects \(Ca^{2+}\) concentrations in T cells in vivo. Interestingly, tyrosine phosphorylation of RyR at the 2-min time point was in the same order of magnitude as compared with the band likely representing p59\(^{en}\) (Fig. 2, left panel). It is difficult to relate these relative staining intensities to the proportion of RyR that are actually tyrosine-phosphorylated. However, even a smaller fraction of tyrosine-phosphorylated RyR may in fact be sufficient to act as a triggering system for \(Ca^{2+}\)-induced \(Ca^{2+}\)-release, thereby also engaging non-phosphorylated RyR. Thus, such a model is well compatible with a functional role of a tyrosine-phosphorylated subfraction of RyR during TCR/CD3-mediated \(Ca^{2+}\) signaling.

Marks and colleagues (16) have shown recently that the type 1 Ins(1,4,5)P\(_3\) receptor is tyrosine-phosphorylated in Jurkat T cells upon stimulation of the TCR/CD3 complex. In addition, they could show that this phosphorylation increased the open probability of the isolated Ins(1,4,5)P\(_3\) receptor as measured in lipid planar bilayer experiments (16). To investigate a possible similar influence of tyrosine phosphorylation of the RyR of T cells, we have used permeabilized Jurkat T cells (29). In such permeabilized cells, recombinant GST-p59\(^{en}\), but not GST-p56\(^{lck}\), GST-Grb2, or GST alone, concentration-dependently and specifically enhanced cADPR-mediated \(Ca^{2+}\) release in the presence of ATP and an ATP-regenerating system. Surprisingly, this effect required initial activation of RyR by cADPR. This activation changed two parameters of the system; first, \([Ca^{2+}]\) was elevated, and second, the RyR \(Ca^{2+}\) channels switched to the open conformation. Thus, one possible explanation would be that an elevated \(Ca^{2+}\) concentration alone is sufficient for the catalytic effect of GST-p59\(^{en}\) on RyR. However, GST-p59\(^{en}\) does not require \(Ca^{2+}\) ions for its catalytic activity. On the other hand, it is well demonstrated that \(Ca^{2+}\) ions act as agonists at the RyR and thereby induce a conformational change of the RyR/\(Ca^{2+}\) channel, as visualized by cryo-electron microscopy and subsequent image processing techniques (41). This view is supported by the finding that activation of RyR by the agonists 4-CEP and \(Ca^{2+}\) was en-
The enhancement of Ins(1,4,5)P₃ stimulation of the type 1 Ins(1,4,5)P₃ receptor was observed only at high [Ca²⁺] at the cytosolic side, indicating a similar Ca²⁺-mediated conformational change of the type 1 InsP₃ receptor (16). Taken together, these data indicate that the tyrosine residue(s) that could theoretically be phosphorylated by GST-p59⁶⁵ are not accessible when the RyR Ca²⁺ channel is in the closed conformation.

In conclusion, we have shown transient tyrosine phosphorylation of the RyR of T cells in response to stimulation of the TCR/CD3 complex. In addition, in permeabilized cells Ca²⁺ release by cADPR and 4-CEP were significantly enhanced by GST-p59⁶⁵. Our demonstration that the effect of GST-p59⁶⁵ was specific, concentration-dependent, and could be inhibited by the tyrosine kinase inhibitor PP2 provides strong evidence that tyrosine phosphorylation of RyR may play a crucial role in the early phase of T cell Ca²⁺ signaling and thereby may constitute an additional element of fine tuning of T lymphocyte Ca²⁺ signaling. In a broader context, our data provide first evidence that, in addition to serine/threonine protein kinases, PTKs are also involved in regulation of RyR.

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Transient Tyrosine Phosphorylation of Human Ryanodine Receptor upon T Cell Stimulation
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J. Biol. Chem. 2001, 276:34722-34727.
doi: 10.1074/jbc.M100715200 originally published online July 20, 2001

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