Localized distribution of malignant hyperthermia (MH) and central core disease (CCD) mutations in N-terminal and central domains of the ryanodine receptor suggests that the interaction between these domains may be involved in Ca\(^{2+}\) channel regulation. To test this hypothesis, we investigated the effects of a new synthetic domain peptide DP4 corresponding to the Leu\(^{2442}\)–Pro\(^{2477}\) region of the central domain. DP4 enhanced ryanodine binding and induced a rapid Ca\(^{2+}\) release. The concentration for half-maximal activation by agonists was considerably reduced in the presence of DP4. These effects of DP4 are analogous to the functional modifications of the ryanodine receptor caused by MH/CCD mutations (viz. hyperactivation of the channel and hypersensitization of the channel to agonists). Replacement of Arg of DP4 with Cys, mimicking the in vivo Arg\(^{2458}\)–to-Cys\(^{2458}\) mutation, abolished the activating effects of DP4. An N-terminal domain peptide DP1 (El-Hayek, R., Saiki, Y., Yamamoto, T., and Ikemoto, N. (1999) J. Biol. Chem. 274, 33341–33347) shows similar activation/sensitization effects. The addition of both DP4 and DP1 produced mutual interference of their activating functions. We tentatively propose that contact between the two (N-terminal and central) domains closes the channel, whereas removal of the contact by these domain peptides or by MH/CCD mutations de-blocks the channel, resulting in hyperactivation/hyper-sensitization effects.

Skeletal muscle-type excitation-contraction coupling is triggered presumably by the voltage-dependent binding of the dihydropyridine receptor \(\alpha_1\) subunit II-III loop to the Ca\(^{2+}\) release channel protein of the SR, also referred as ryanodine receptor (RyR)\(^1\) (1–7). This signal is transmitted to the transmembrane channel domain to activate the channel by a yet-unidentified mechanism. The RyR Ca\(^{2+}\) channel is also activated by a variety of types of chemical reagents and polypeptides (8–10), most of which are presumably acting on the bulky cytoplasmic domain of the RyR. Thus, there must be intricate mechanisms, which mediate the transmission of various types of signals received at various sites of the RyR to its channel domain. However, very little information is available regarding the putative intra-molecular signal transduction mechanism.

The concept that interactions among several regions of the RyR might be involved in the intra-molecular signal transduction mechanism is suggested from several pieces of evidence as follows. First, several regulatory domains have been deduced from the locations of the putative binding sites for calmodulin (11–13), FK506-binding protein (14, 15), activating Ca\(^{2+}\) (16), the sites for phosphorylation (17), and the mutation sites occurring in MH susceptible animal and in MH and CCD-susceptible human patients (18–26). An antibody raised against the N-terminal region altered the Ca\(^{2+}\) dependence of channel gating, and the construct containing the epitope to this antibody reacted with other regions of the RyR (27). Chemical modification, under conditions that would produce oxidation-induced channel activation in fact altered the intra-molecular cross-linking pattern (28, 29).

We have paid a particular attention to an interesting relation existing between the distribution of the mutation sites of the RyR and the altered function of the RyR in MH and CCD. Namely, most of the reported mutations are localized in either of the two restricted regions of the RyR: one, the domain including several mutation sites in the Cys\(^{325}\)–Arg\(^{614}\) region (designated as N-terminal domain to facilitate discussion), and the other, the domain including the Arg\(^{2458}\) – Arg\(^{2458}\) region (designated as central domain). Furthermore, mutations at different positions of these domains produce the same type of functional modification characterized by two common features: (a) hyperactivation of the Ca\(^{2+}\) channel and (b) an increase in the sensitivity of the RyR to agonists (26, 30–34). The most feasible hypothesis to account for such unique situations would be as follows. The interdomain interactions between the N-terminal domain and the central domain (defined above) may play an important role in the channel regulation mechanism. Thus, mutations in either domain produce the same type of functional abnormality, since the interdomain interaction rather than the domain property itself is the critical factor.

To investigate the above hypothesis, we recently embarked on a series of studies using synthetic peptides corresponding to various regions of the N-terminal domain or the central domain described above. The strategy of such peptide probe studies is as follows. Suppose that \(x\)-region is interacting with \(y\)-region serving as a regulatory mechanism. Then, a synthetic peptide corresponding to the \(x\)-region, i.e. peptide \(x\), would bind to the \(y\)-region, producing interference with the in vivo \(x\)-\(y\) domain-domain interaction. If the \(x\)-\(y\) interdomain interaction is playing a key role in channel regulation, then peptide \(x\) would produce appreciable effects on the mode of regulation of the
RyR channel. Such peptide probes will not only permit us to identify the putative regulatory domains, but also permit us to characterize the mode of channel regulation. Our recent study revealed several interesting RyR-domain peptides (35). For instance, synthetic peptide corresponding to a portion of the N-terminal domain, DP1 (see Table I), activated the RyR2 significantly and the RyR1 to a lesser extent. Another N-terminal domain peptide DP3 was without effect on both RyR1 and RyR2.

In the present study, we selected two new regions from the central domain defined above. One is the Leu^{2442}–Pro^{2477} region of the RyR1, which contains the C-terminal region of the central domain and the putative FK506-binding protein binding segment (36), and a peptide, DP4, corresponding to this region, was synthesized. The other is the Val^{2149}–Ile^{2185} region, which contains an N-terminal region of the central domain, and a peptide, DP5, corresponding to this region, was synthesized. DP4 was found to exert the most conspicuous effect on the RyR1 among the domain peptides we have investigated so far. As shown here, DP4 produced a significant enhancement of ryanodine binding and induced a rapid Ca^{2+} release from the SR. Furthermore, this peptide increased the sensitivity of the RyR to agonists such as peptide A (the activating II-III loop peptide) and polylysine (Ca^{2+} release-inducing RyR-specific ligand). Both of these effects are essentially identical to the types of functional alterations seen in MH/CCD conditions (37).

DP1, which is the N-terminal half of DP1–2, retains the function of peptide (DP) represents the chronological order of the synthesis. DP4, DP4-mut, DP5, and DP6 were used for the first time in this study. Other peptides (DP1, DP1–2, and DP3) were already investigated (35), but DP1 and DP3 were used again with a new perspective in this study. DP1, which is the N-terminal half of DP1–2, retains the function of peptide DP1–2 (35); hence DP1–2 was not used in this study.

Peptides were synthesized on an Applied Biosystems model 431A synthesizer employing Fmoc-(9-fluorenyl)methoxycarbonyl as the a-amino-protecting group. The peptides were cleaved and deprotected with 95% trifluoroacetic acid and purified by reverse-phase high pressure liquid chromatography.

**Table I**

| Domain peptide | Corresponding domain of the RyR1 |
|----------------|----------------------------------|
| DP1            | 530LDKHGRNHKVLVD/LCSLCVC^{509}   |
| DP3            | 321ITAPKRDVEGMGPPFEIKYGESLCFVQHY^{531} |
| DP4            | 2442LQAGKGEALRILSRVLVPLDDLVHISLPLQIP^{5477} |
| DP4-mut        | 2442LQAGKGEALRILSRVLVPLDDLVHISLPLQIP^{5477} |
| DP5            | 210VEDTMLSLECLQIQSLLIVQMGPQENELMIQSIGNI^{185} |
| DP6            | 2035LHALCGIQLGESEEFPFEETSLSSRLL^{2067} |

**EXPERIMENTAL PROCEDURES**

**Preparation**

**Skeletal Microsomes**—Triad-enriched microsomal fractions were prepared from the rabbit back paraspinalis and hind leg skeletal muscle by a method of differential centrifugation as described previously (38). Microsomes from the final centrifugation were homogenized in 0.3 M sucrose, 0.15 M potassium gluconate, proteolytic enzyme inhibitors (0.1 mM phenylmethanesulfonyl fluoride, 10 μg/ml aprotinin, 0.8 μg/ml antipain, 2.0 μg/ml soybean trypsin inhibitor), 20 mM MES, pH 6.8 to a final concentration of 20–30 mM, frozen immediately in liquid N, and stored at −78 °C.

**Cardiac Microsomes**—Cardiac microsomes were prepared from dog ventricular cardiac muscle as described previously (35).

**Domain Peptides Used and Peptide Synthesis**

Six domain peptides were used in this study. The amino acid sequence and the residue numbers of the corresponding sequence of the in *vivo* domain are shown in Table I. The number assigned to the domain peptide (DP) represents the chronological order of the synthesis. DP4, DP4-mut, DP5, and DP6 were used for the first time in this study. Other peptides (DP1, DP1–2, and DP3) were already investigated (35), but DP1 and DP3 were used again with a new perspective in this study. DP1, which is the N-terminal half of DP1–2, retains the function of peptide DP1–2 (35); hence DP1–2 was not used in this study.

**Amino acid sequence of the synthetic peptides corresponding to the selected subdomains of rabbit RyR1**

Sequence is from Ref. 45.

**Domestic Peptide DP4 Activates Both RyR1 and RyR2 in a Concentration-dependent Manner**—Fig. 1 depicts the data of ryanodine binding to the SR vesicles isolated from skeletal and cardiac muscle in the presence of different concentrations of DP4. As seen, DP4 produced significant enhancement of ryan-
odine binding to both RyR1 and RyR2 in a concentration-dependent manner. However, the extent of enhancement in skeletal SR (maximal enhancement: 380% control) was much larger than that in cardiac SR (240% control). The concentration for the half-maximal activation (AC50) was 28 \( \mu M \) for the RyR1 and 100 \( \mu M \) for the RyR2.

DP4 induced a rapid Ca\(^{2+}\) release from the SR. Fig. 2 depicts the time courses of Ca\(^{2+}\) release from skeletal muscle SR induced by various concentrations of DP4. With no added DP4, stopped-flow mixing produced negligible Ca\(^{2+}\) release. At low concentrations (e.g., at 2 \( \mu M \)), DP4 produced a slow Ca\(^{2+}\) release. Upon increasing the concentration of DP4 up to 100 \( \mu M \), both the rate and the size of Ca\(^{2+}\) release increased. The AC50 of the initial rate of Ca\(^{2+}\) release was 34.0 \( \pm \) 5.7 \( \mu M \), which is comparable to the AC50 of RyR1 activation in ryanodine binding experiments. These results indicate that DP4 is a potent activator of both RyR1 and RyR2 and is capable of inducing a rapid Ca\(^{2+}\) release from the skeletal muscle SR. Judging from the rapid induction of Ca\(^{2+}\) release by high concentrations of DP4, it appears that this domain peptide is readily accessible to its target domain within the RyR.

Effects of DP4 on the [Ca\(^{2+}\)]-dependent Activation/Inhibition Profile—The general pattern of the biphasic [Ca\(^{2+}\)] dependence of activation in the lower [Ca\(^{2+}\)] range (0.01–10 \( \mu M \)) and inhibition at higher range (10 \( \mu M \)–3 mM) is nearly identical in the absence and the presence of 100 \( \mu M \) DP4 (see Fig. 3), although the magnitude of ryanodine binding activity is considerably different as described above. However, there are few important differences. First, in the presence of DP4 there is a significant enhancement of ryanodine binding at 0.01 \( \mu M \) Ca\(^{2+}\) (Fig. 3). This suggests that there are [Ca\(^{2+}\)]-independent and [Ca\(^{2+}\)]-dependent components in the mechanism of activation by DP4. Second, the AC50 for the [Ca\(^{2+}\)]-dependent activation by DP4 was 0.15 \( \mu M \) Ca\(^{2+}\), which is significantly smaller than that of control (0.4 \( \mu M \)). Conversely, the concentration for half-maximal inhibition (IC50) in the presence of DP4 (0.8 mM Ca\(^{2+}\)) was significantly larger than that in its absence (0.4 mM). Thus, [Ca\(^{2+}\)]-independent activation/inhibition of the RyR by DP4 is characterized by three aspects: the presence of a [Ca\(^{2+}\)]-independent component of activation, the enhanced affinity for activating Ca\(^{2+}\), and the reduced affinity for inhibitory Ca\(^{2+}\).

Fig. 4 shows the [Mg\(^{2+}\)]-dependent inhibition pattern of the ryanodine binding activity of the RyR1 in the absence and the presence of 100 \( \mu M \) DP4. Interestingly, there was a small but consistent difference in the IC50 for Mg\(^{2+}\) in each experiment as well. Namely, the IC50 was shifted to the higher [Mg\(^{2+}\)] in the presence of DP4; the IC50 calculated from the averaged
data being 0.33 mM and 0.48 mM at 0 and 100 μM DP4, respectively (Fig. 4).

**Fig. 4.** Effects of DP4 on [Mg²⁺]-dependent inhibition of [³H]ryanodine binding to the RyR1. [³H]Ryanodine binding assays were performed in the absence or presence of 100 μM DP4 at various Mg²⁺ concentrations, as described under “Experimental Procedures.” Each datum point represents the mean ± S.D. of at least three experiments carried out in duplicate.

**DP4 Also Affects Activation Patterns of Peptide A and Polylysine**—As shown in our recent studies, peptide A (a synthetic peptide corresponding to the Thr⁶⁷¹–Leu⁶⁹⁰ region of the dihydropyridine receptor α₁ subunit II-III loop) activates the RyR1 in an isoform-specific manner and induces Ca²⁺ release from skeletal muscle SR (41–42). On this basis, we proposed that this peptide mimics the voltage-dependent induction of skeletal muscle-type excitation-contraction coupling (41–43). In the experiments shown in Fig. 5, we investigated the possibility that DP4 might affect the modes of activation by this peptide. As seen, peptide A alone produced a concentration-dependent enhancement of ryanodine binding, with an AC₅₀ of ~20 μM. In the presence of DP4 (100 μM), peptide A produced further activation in an additive fashion. Interestingly, the peptide A dependence of activation showed a considerable shift to the left in the presence of DP4, resulting in an apparent AC₅₀ of ~5 μM. As described previously (41–43), excessively higher concentrations of peptide A becomes inhibitory, resulting in a biphasic activation/inhibition profile. The inhibitory phase was also shifted to the left in the presence of DP4.

**Fig. 5.** DP4 increases the sensitivity of the RyR to peptide A activation. [³H]Ryanodine binding assays were performed in the absence or presence of 100 μM DP4 at various concentrations of peptide A. Each datum point represents the mean ± S.D. of at least three assays carried out in duplicate.

**An Arg-to-Cys Mutation of DP4 Abolishes Its Activating Function**—As deduced from the above finding, DP4 mimics several abnormalities of the Ca²⁺ channel seen in MH and CCD, namely the abnormalities caused by site-specific mutations. The RyR domain corresponding to DP4 contains one Arg⁵⁴⁶⁵-to-Cys⁵⁴⁶⁵ (MH) mutation site (37). We made the same mutation in DP4 and synthesized a peptide DP4-mut as shown...
Interestingly, this mutation completely abolished the activating effect that DP4 must have produced. Thus, as shown in Fig. 7, DP4-mut produced no appreciable effects on ryanodine binding even at high concentrations equivalent to the maximally activating concentrations of DP4. Furthermore, 100 μM DP4-mut produced no appreciable effect on AC50 for peptide A activation either, the AC50 value for peptide A being 12 ± 8 μM and 12 ± 10 μM at 0 μM and 100 μM DP4-mut. This indicates that the highly specific amino acid sequence is required for the regulatory function of the in situ domain and that the corresponding synthetic peptide DP4 represents this situation.

Another Domain Peptide, DP1, Also Produces Activation/Sensitization Effects—As described in the Introduction, another domain peptide DP1 (the peptide corresponding to the N-terminal MH/CCD domain) activated the RyR and induced Ca2+ release in an RyR2-specific manner, as described in our recent report (35). In view of the new finding that DP4 has two effects (activation and sensitization to agonists), we investigated whether this is also the case with DP1. As shown in Figs. 8 and 9, 100 μM DP1 produced a small but appreciable enhancement of ryanodine binding to the RyR1 (see binding in the absence of peptide A or polylysine). In the presence of DP1, the activation/inhibition curves of peptide A (Fig. 8) and polylysine (Fig. 9) were both shifted to the left in the essentially identical manner as seen with DP4.

Counteractions among Various Domain Peptides—According to our working hypothesis (see the Introduction), the interaction between the two MH/CCD domains (the N-terminal domain and the central domain) may be involved in the channel regulation mechanism. Both DP4 (central domain peptide) and DP1 (N-terminal domain peptide) produced similar effects as described above. We investigated whether the addition of both peptides produces additive effects or some other effects.

Fig. 10 depicts the ryanodine binding data obtained with various concentrations of DP1 in combination with 100 μM DP4. As seen, DP1 alone produced appreciable enhancement of ryanodine binding in a concentration-dependent manner (up to 2.5-fold). DP4 alone produced about 4.5-fold enhancement (see the activation level of DP4 at 0 μM DP1). Interestingly, however, upon the addition of increasing concentrations of DP1, the level of enhancement of ryanodine binding that had been produced by DP4 decreased, and reached a plateau at the level nearly identical to the level of maximal activation by DP1 alone. This indicates that the combined effects of the two activating domain peptides are not additive, but competitive. Another unique feature seen in Fig. 10 is that the IC50 for the DP1 inhibition of DP4 (~6 μM) is more than one order of magnitude lower than the AC50 for the activation by DP4 alone (~100 μM), suggesting that there is a unique counteraction between these domain peptides (see “Discussion”).
As described in the Introduction, we synthesized another new peptide DP5 corresponding to the N-terminal region of the central domain. As shown in Fig. 11, DP5 alone produced virtually no effect on ryanodine binding in a broad concentration range investigated. However, if added together with 100 μM DP4, which produced a nearly maximal activation of the RyR, increasing concentrations of the added DP5 produced progressive suppression of the activating function of DP4.

Similarly, another N-terminal MH/CCD domain peptide, DP3, had no appreciable effect on the ryanodine binding in a wide concentration range examined, as shown in Fig. 12 (cf. Ref. 35). However, when DP3 was combined with DP4, it inhibited the DP4 activation in a concentration-dependent manner. Thus, the domain peptides so far examined fall in either of the two categories: those mimicking MH/CCD-like effects (DP4 and DP1) and those removing MH/CCD-like effects (DP5 and DP3).

In the present study, we tested a control peptide DP6, which does not belong to either the N-terminal domain or the central domain (see Table I). This peptide neither mimicked MH/CCD-like effects nor removed MH/CCD-like effects (data not shown).

DISCUSSION

The RyR opens its Ca\(^{2+}\) channel in response to various types of stimuli acting on its cytoplasmic region. Especially, the binding to their common binding site(s) (i.e. the domain 4 counter domain). This will interfere with the interaction between domain 4 and its counter domain; in turn, the contact between these domains will be loosened. Since the outcome of such interference was activation of the channel as seen here, the tight interaction between these domains must have contributed to the channel closing. In the case of MH and CCD, the Arg\(^{2458}\)-to-Cys\(^{2458}\) mutation that has taken place in domain 4 will also interfere with the interdomain interaction, resulting in the hyperactivation of the channel.

The most important evidence supporting the above mechanism is the present finding that the same Arg-to-Cys mutation made in DP4 completely abolished both hyperactivation and hypersensitization effects that must have been produced by DP4. This would indicate that this specific mutation resulted in the loss of the ability of the peptide to bind to the counter domain, in turn resulting in the loss of the ability to interfere with the interdomain interaction. This is in accord with the above concept that the Arg\(^{2458}\)-to-Cys\(^{2458}\) mutation in domain 4 reduces the ability to bind to its counter domain. The result also indicates that the observed activation of the RyR by DP4 requires a very specific amino acid sequence.

In the context of this discussion, it should be noted that
another domain peptide DP1, which corresponds to a part of the N-terminal domain, also produces hyperactivation and hypersensitization effects similar to those of DP4. Again, this would indicate that domain 1 is also involved in the interdomain interaction and the added DP1 competes with domain 1 for the binding to their common counter domain. In light of the interdomain interaction concept, it would be interesting to speculate that the domain 4 of the central domain interacts with the N-terminal domain; conversely, the domain 1 interacts with the central domain. Additional evidence for this hypothesis has been revealed in the present study. First, the addition of both activating domain peptides DP4 and DP1 together produced a much lower level of activation than the level achieved by DP4 alone. As a matter of fact, higher concentrations of DP1 almost completely reversed the activation by DP4. This is consistent with the view that the two peptides are competing to the common “de-blocking” mechanism mediated by the interdomain interaction (see above) but is inconsistent with the view that both peptides bind to activating sites. Second, the IC\textsubscript{50} for the DP1 block of DP4 was much lower than the AC\textsubscript{50} for DP1 activation, suggesting that the competition between the two domain peptides is highly cooperative.

Putting the above pieces of evidence altogether, we tentatively propose the following mechanism. In the normally operating RyR, contact between the N-terminal domain and the central domain would correspond to an Off position of a regulator switch of the channel. In MH/CCD conditions, this putative blocking mechanism is altered (i.e. loosening of the interdomain contact) by the mutations in either of these domains, resulting in the apparent activation and hypersensitization that actually represents a de-blocking phenomenon. The exogenously added domain peptides will bind to their designated interaction sites and interfere with the interdomain contact, resulting in functional alterations similar to those in MH/CCD. This mechanism accounts for the fact that the competition between the two domain peptides is highly cooperative, since the removal of the interdomain contact by one peptide would facilitate further loosening by the other peptide.

The sensitization of the RyR to Ca\textsuperscript{2+} release-inducing peptides by DP4 shown here suggests an interesting new concept as follows. The interdomain interaction postulated here might be used as a device for the intramolecular signal transmission mechanism above. For example, binding of the activating II-III loop peptide (peptide A) or the in vivo II-III loop to the RyR would remove the interdomain contact, changing the regulatory switch from the Off position (see above) to the On position. Thus, the presence of DP4 or DP1, which removes the interdomain contact and, therefore, catalyzes the Off-to-On action, would facilitate the peptide A-induced signal transduction process and would increase the apparent affinity for peptide A as seen in this study.

Another important piece of information obtained in the present study is that one of the new central domain peptides investigated here, namely DP5, by itself produced no appreciable effect, but if added together with DP4, it produced almost complete suppression of the DP4 activation. Similarly, an N-terminal domain peptide DP3 (35) also produced almost complete suppression of the DP4 activation. Thus, it appears that at least four subdomains represented by these peptides (DP4, DP1, DP5, and DP3) are involved in the postulated interdomain interaction.

In conclusion, the data shown here are consistent with the following model. The mode of interaction between the two MH/CCD domains (defined as N-terminal domain and central domain) controls the functional state of the RyR Ca\textsuperscript{2+} channel, and the removal of such contact produces the activated state. Synthetic peptides DP4 and DP1 corresponding to two of such domains produced both activation of the channel and hypersensitization to agonists, mimicking the functional alterations produced by MH/CCD mutations occurring in these domains. According to the above model, these are produced by de-blocking caused by the interference of the interdomain interaction by domain peptides or mutations.

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Postulated Role of Interdomain Interaction within the Ryanodine Receptor in Ca^{2+} Channel Regulation

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