To elucidate the mechanisms of specific coupling of bovine rhodopsin with the G protein transducin (Gt), we have constructed the bovine rhodopsin mutants whose second or third cytoplasmic loop (loop 2 or 3) was replaced with the corresponding loop of the Gt-coupled scallop rhodopsin and investigated the difference in the activation abilities for Gt, Go, and Gi among these mutants and wild type. We have also prepared the Go mutants whose C-terminal 11 or 5 amino acids were replaced with those of Gaq, Gao, and Gag to evaluate the role of the C-terminal tail of the α-subunit on the specific coupling of bovine rhodopsin with Gt. Replacement of loop 2 of bovine rhodopsin with that of the scallop rhodopsin caused about a 40% loss of Gt and Go activation, whereas that of loop 3 enhanced the Gt activation four times with a 60% decrease in the Gt activation. These results indicated that loop 3 of bovine rhodopsin is one of the regions responsible for the specific coupling with Gt. Loop 3 of bovine rhodopsin discriminates the difference of the 6-amino acid sequence (region A) at a position adjacent to the C-terminal 5 amino acids of the G protein, resulting in the different activation efficiency between Gt and Go. In addition, the binding of region A to loop 3 of bovine rhodopsin is essential for activation of Gi but not Gt, even though the sequence of the region A is almost identical between Gaq and Gog. These results suggest that the binding of loop 3 of bovine rhodopsin to region A in Go is one of the mechanisms of specific Gi activation by bovine rhodopsin.

Visual pigment is one of the G protein-coupled receptors that has diverged into a photoreceptive protein in the retinal visual cells (1). It is a 35–55-kDa membrane protein consisting of a single polypeptide opsin and a chromophore 11-cis-retinal. The opsin contains seven transmembrane α-helices, the structural motif typical of the G protein-coupled receptors. Light isomerizes the 11-cis-retinal into the all-cis motif typical of the G protein-coupled receptors. Light isomerization with Gt. Loop 3 of bovine rhodopsin discriminates the difference of the 6-amino acid sequence (region A) at a position adjacent to the C-terminal 5 amino acids of the G protein, resulting in the different activation efficiency between Gt and Go. In addition, the binding of region A to loop 3 of bovine rhodopsin is essential for activation of Gi but not Gt, even though the sequence of the region A is almost identical between Gaq and Gog. These results suggest that the binding of loop 3 of bovine rhodopsin to region A in Go is one of the mechanisms of specific Gi activation by bovine rhodopsin.

Functional Interaction between Bovine Rhodopsin and G Protein Transducin*

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1 The abbreviations used are: Gt, transducin; GTPγS, guanosine 5'-3'-O-(thio)triphosphate.
2 The expression of Gt2 mRNA in rat mesencephalic tissue was recently reported based on reverse transcription PCR (11).
3 We have found that Gt/Gt-coupled m2 muscarinic acetylcholine receptor does not exhibit efficient activation ability for Gt.
(see Fig. 1A) and investigated the difference in the activation efficiencies for Gt, Go, and Gi among these mutants and wild type. Furthermore, to elucidate the mechanism of the specific interaction between the cytoplasmic loops of bovine rhodopsin and the C-terminal region of the G protein α-subunit, we have constructed the Go mutants whose C-terminal 11 or 5 amino acids were replaced with those of Gt, Go, and Gi (see Fig. 1B) and investigated the difference in the activation efficiencies for these mutants between the wild type and the loop-replaced mutants of rhodopsin. These results showed that the third cytoplasmic loop of bovine rhodopsin discriminates between Gt and Gi by recognizing the region including 6 amino acids (see Fig. 1B, region A) adjacent to the region including the C-terminal 5 amino acids (see Fig. 1B, region B), whereas that of the SCOP2 does not discriminate region A. There was little difference in the activation efficiency of Gi between the wild type rhodopsin and the loop 3-replaced mutant, which suggested that the interaction between loop 3 of bovine rhodopsin and region A is not important for catalyzing the GDP-GTP exchange reaction on Gi. From these findings, the molecular mechanism of the coupling specificity of bovine rhodopsin with G proteins and the C-terminal region of the G protein at the C terminus of Gt, Go, and Gi is shown as the bovine rhodopsin system. In B, the numbers above the sequences refer to the bovine rhodopsin system. In B, the numbers above the sequences refer to the bovine rhodopsin system.

Comparison of primary sequence of bovine and scallop Gt-coupled rhodopsins at loops 2 and 3 (A) and G proteins at the C terminus of Go (B). The amino acids in loops 2 and 3 are denoted by the bold characters. In A, the numbering is shown as the bovine rhodopsin system. In B, the numbers above the sequences refer to the bovine rhodopsin system. In B, the numbers above the sequences refer to the bovine rhodopsin system.
should be noted that we selected the experimental conditions under which no intrinsic uptakes of GTP\textsubscript{S} in G\textsubscript{o}, G\textsubscript{t}, and G\textsubscript{i} were observed to precisely compare the activation efficiencies of rhodopsin and its chimeras to one of the G proteins of different characteristics. We also compared the efficiencies of activation of the various G proteins by rhodopsin and chimeras after confirming that the activation efficiencies of G proteins were linearly correlated with the concentrations of pigments and that these pigment concentrations exhibited the linear kinetics up to 90 s in each G protein activation assay (see Fig. 2).

**RESULTS**

Fig. 1A shows the alignment of the amino acid sequences of the second and the third cytoplasmic loops of the rhodopsins. According to the alignment, we prepared mutants of bovine rhodopsin in which the second or the third cytoplasmic loop was replaced with the corresponding loop of SCOP2, the G\textsubscript{o}-coupled scallop rhodopsin. All of the mutants and wild type rhodopsin exhibited almost the same absorption maxima at 499 nm, and upon irradiation at 4 °C, they were converted to meta II intermediates whose maxima were located at 380 nm (data not shown). These results enabled us to use the same irradiation conditions for all of the mutant and wild type rhodopsins for the GTP\textsubscript{S} binding assay.

The ability of the mutant rhodopsins to activate the G protein subtypes was assayed by monitoring the light-dependent GTP\textsubscript{S} binding to the G proteins (Fig. 2). We selected different experimental conditions under which no intrinsic exchanges of GTP\textsubscript{S} in G\textsubscript{o}, G\textsubscript{t}, and G\textsubscript{i} were observed to precisely compare the activation efficiencies of rhodopsin and its chimeras to one of the G proteins of different characteristics. Fig. 2 provides three kinds of information about our G protein activation assays. First, no intrinsic GTP\textsubscript{S} binding to G protein was detected under our experimental conditions. The experimental results of most effective rhodopsin to each G protein are shown in the figure to demonstrate that no intrinsic GTP\textsubscript{S} binding was observed in any rhodopsins. Second, a linear relationship between pigment concentration and G protein activation in each G protein assay is shown, where the G protein activation was measured 45 s after the activation of rhodopsin or the loop-replaced mutant. Finally, these pigment concentrations exhibited the linear kinetics up to 90 s in each G protein activation assay. We also confirmed that other rhodopsins exhibited a linear effect on G protein activation when the same amounts of these rhodopsins were added to the reaction mixture.

It should be noted that the G\textsubscript{o} assay was carried out at a low temperature (0 °C) in the presence of high GDP and low GTP\textsubscript{S} concentrations to diminish a large intrinsic uptake of GTP\textsubscript{S} by G\textsubscript{o}. As a result, we added a relatively large amount of rhodopsin to effectively activate G\textsubscript{o}, although the initial rate of G\textsubscript{o} activation was still smaller than those of others. In the following experiments, we calculated the initial rates of G protein activation from the amounts of GTP\textsubscript{S} binding to G proteins for 45 s and compared the G protein activation efficiencies of wild type and mutant rhodopsin. The rhodopsin concentrations used in Figs. 3–6 (10 nm for G\textsubscript{o}, 100 nm for G\textsubscript{t}, and 10 nm for G\textsubscript{i}) are in the range of the concentration that gave a linear effect on G protein activation.

**Effects of Loop 2 Replacement on the Activation Efficiencies for G\textsubscript{o}, G\textsubscript{t}, and G\textsubscript{i}**—Fig. 3 shows the effects of the loop 2 replacement of bovine rhodopsin with that of SCOP2 on the activation efficiencies for G\textsubscript{o}, G\textsubscript{t}, and G\textsubscript{i}. The replacement caused about a 40% loss of activity to G\textsubscript{i}, suggesting that the loop 2 sequence of SCOP2 affects the activation ability of bovine rhodopsin. A similar loss of activation ability was observed when G\textsubscript{i} was subjected to the experiments, although the loss of the G\textsubscript{i} activation ability was not very prominent. These results showed that the replacement effect was not specifically observed for the G\textsubscript{i} activation, suggesting that the loss of the
activation ability is not due to the deficiency of the specific coupling with Gt but due to the inadequate sequence of the SCOP2 for the formation of the active state of bovine rhodopsin. In a previous study, we have demonstrated that the N-terminal 7 amino acids of loop 2 are important for the formation of active state of bovine rhodopsin (32). Among the 7 amino acids in the introduced loop 2 of SCOP2, the cysteine at position 134 has a characteristic different from that of the glutamic acid in the ERY motif of bovine rhodopsin. In fact, the replacement of Cys134 with glutamic acid in the loop 2-replaced mutant rescued its Gt activation efficiency to 80% of the wild type (data not shown).

Effects of Loop 3 Replacement on the Activation Efficiencies for Gt, Go, and Gi —The replacement of loop 3 with the corresponding loop of SCOP2 resulted in a 60% loss of the activation ability for Gt (Fig. 4A); the extent of the loss is more prominent than that observed in the loop 2-replaced mutant (Fig. 3A). In contrast, the mutant activated Gt four times more efficiently than the wild type (Fig. 4B), suggesting that loop 3 of SCOP2 is more suitable for the Go activation than that of bovine rhodopsin. In fact, the replacement of Cys134 with glutamic acid in the loop 2-replaced mutant rescued its Gi activation efficiency to 80% of the wild type (data not shown).

Because bovine and scallop rhodopsins are colocalized with Gt and Go, respectively (2), in the native photoreceptor cells, it is reasonable that these rhodopsins exhibit some specificity to Gt and Go. The present results showed that loop 3 is one of the regions specifically interacting with the G proteins, which is in contrast to the role of loop 2 that could be related to the conformational change of the rhodopsin molecule to form the state activating the G proteins (32). However, we could not directly compare the activation efficiency of Gi by the wild type or the loop 3-replaced mutant with that of Go, because, in addition to the different character of each G protein, the experimental conditions to assay G protein activations were different among the G proteins. In other words, we could not estimate whether both the loops of the wild type and mutant or either of the loops exhibit different affinities to these G proteins.

One of the ways to overcome these difficulties is the construction of G protein mutants from one of the G protein subtypes, whereas the mutants have the sequences responsible for the specific coupling with the receptor subtypes. Several mutational analyses of the G protein α-subunit suggested that the C terminus is one of the determinants for the characteristics of the G protein subtype in receptor coupling, which is well conserved among each subtype (33–35). Therefore, we have prepared the Gi mutants in which the C-terminal sequences were replaced with the corresponding sequences of Go, Go, and Gq, respectively. Under the same experimental conditions as wild type Gi, no Gi mutant exhibited a significant uncatalyzed rate of exchange of GTPγS (data not shown).

Activation Efficiencies of Gi Mutants by Wild Type and Loop-replaced Mutants of Bovine Rhodopsin —To examine the effect of the C terminus replacements, we first prepared the Gi mutants whose C-terminal 5 amino acids were replaced with those of Go and Gq. Hereafter, the mutants are referred to as Go5 and Gq5, respectively. It should be noted that the C-terminal 5 amino acids of Go are identical to those of Gq (Fig. 1B).

The wild type rhodopsin and the loop 3-replaced mutant exhibited a similar ability to activate Gi/wild and Gi5, whereas they exhibited little ability for Gq5 (Fig. 5). The latter
is consistent with the fact that the C terminus sequence of G \textsubscript{i} is different from those of the G \textsubscript{q} group and is one of the regions for the impairment of the G \textsubscript{i}/G \textsubscript{o}-coupled receptor (33). On the other hand, we observed differences in the activation ability between the wild type and the mutant when the G \textsubscript{o} mutants having the C-terminal 11 amino acids of G \textsubscript{o}/H9251 \textsubscript{t} and G \textsubscript{o}/H9251 \textsubscript{o} (G \textsubscript{o}/t11 and G \textsubscript{o}/o11, respectively) were subjected to the experiments (Fig. 6).

As expected from the sequence similarity of the C-terminal 11 amino acids between G \textsubscript{o}/H9251 \textsubscript{i} and G \textsubscript{o}/H9251 \textsubscript{t}, the wild type rhodopsin activated G \textsubscript{o}/t11 with an efficiency similar to that of G \textsubscript{o}/wild. However, it showed only about a 20% efficiency to activate G \textsubscript{o}/o11 (Fig. 6). The mutant having the loop 3 of SCOP2 activated G \textsubscript{o}/o11 as efficiently as G \textsubscript{o}/wild and G \textsubscript{o}/t11, and the activation efficiencies are similar to those of G \textsubscript{o}/wild and G \textsubscript{o}/t11 observed in the wild type (Fig. 6). These results indicated that loop 3 of bovine rhodopsin could not take the proper conformation to interact with the C-terminal 11 amino acids of Go, resulting in a less efficient activation of G \textsubscript{o}/o11. The interesting observation is that the lower activation efficiency of G \textsubscript{o}/o11 shown by the wild type relative to the mutant is comparable with the difference in the G \textsubscript{o} activation efficiency between these pigments (Fig. 4B). Therefore, the difference in the G \textsubscript{o} activation efficiency between the wild type and the mutant could be mainly due to the reduced activation ability of the wild type but not to the efficient activation ability of the mutant. Hereafter, the region of the 6 amino acids from the N terminus and that of the 5 amino acids from the C terminus of the 11 amino acids are referred to as regions A and B, respectively (Fig. 1B).

The mutant activated G \textsubscript{o}/o11 as efficiently as G \textsubscript{o}/wild, suggesting that the interaction of the loop 3 of SCOP2 with region A is not essential for the activation mechanism of G \textsubscript{o}. These results also suggested the specific role of the interaction be-

![Fig. 4. Initial rates of G protein activations by wild type and loop 3 replaced mutant rhodopsin.](http://www.jbc.org/)

![Fig. 5. Initial rates of activation of G \textsubscript{i} mutants having the C-terminal 5 amino acids of different G \textsubscript{o}s.](http://www.jbc.org/)
CASE, the binding of the loop 3 of bovine rhodopsin with region A induces a proper conformational change(s) in the Gt molecule to efficiently activate Gt, whereas the proper conformational change(s) could not occur upon binding of the loop 3 with region A of Go. In the latter case, there is a specific activation mechanism of Gt different from Gt and Go, and the mechanism could not work upon the interaction of region A of Gt with loop 3 of SCOP2. In either case, the experimental results could be explained by the specific interaction between the loop 3 of bovine rhodopsin and region A of Gt.

Several kinds of evidence demonstrated the involvement of the δ helix adjacent to the C terminus in G protein activation (36–41). In addition to the sequence of region A, the sequence of the δ helix is also highly homologous between Gt and Go (40). These facts suggest that the conformational changes of the δ helix upon binding of the loop 3 of bovine rhodopsin to region A could be similar between Gt and Go. Thus it is likely that the binding of loop 3 of bovine rhodopsin to region A (and region B) could facilitate an additional conformational change(s) in the region other than the δ helix in the Gt molecule to induce the GDP-GTP exchange reaction on Gt, whereas an additional conformational change, if any, may not be essential for the exchange reaction on Gt. The difference in structure in the region other than the δ helix between Gt and Go, which affects the GDP-GTP exchange reactions of these proteins (42), was recently reported. Thus identification of the region that is affected upon binding of loop 3 of bovine rhodopsin to the region A will be our future research.

It remains to be determined which region in loop 3 of bovine rhodopsin is responsible for the binding to region A, although our experiments clearly showed a specific interaction between the loop 3 and region A.5 To specify the binding region in loop 3, we divided loop 3 of bovine rhodopsin into three segments and prepared six chimerical mutants between bovine rhodopsin and SCOP2, as has already been done in the loop 2 mutants of bovine rhodopsin (32). However, we were unable to specify the region, probably because the number of amino acids in the loop 3 of bovine rhodopsin is different from those in the loop 3 of SCOP2 (Fig. 1A). On the other hand, we found that the mutant of bovine rhodopsin, where amino acids at positions 237 to 249 were deleted (Δ237-249; Ref. 15), showed no ability for both Gt and Gi activation as described above. Because the deleted mutant still contains the four hydrophobic residues (Val250, Thr251, Val254, and Ile255) responsible for the selective interaction with the Gt group of the G protein by binding to the C-terminal 5 amino acids (34), it is reasonable that the deleted region 237–249 in the loop 3 is important for the binding to region A. The interesting observation is that the deleted mutant showed a partial ability to activate Gt (30% of that shown by the wild type), whereas it showed a loss of Gt and Go activation as described above. Because the deleted region forms a unique loop structure with the extrusion to the cytoplasmic surface in the crystal structure of bovine rhodopsin (43), its binding to region A might cause the proper conformation of the region adjacent to the δ helix in the Go molecule, but the binding to region A may not be necessary for the conformational change of the corresponding region in the Gt molecule.

In summary, the present study shows the presence of a specific interaction between the loop 3 of bovine rhodopsin with region A in Go, which is one of the candidates to account for

5 During the course of the preparation of this manuscript, Khorana and co-workers (47, 48) published the cross-linking data showing that the cysteine introduced at position 240 in the third cytoplasmic loop of the light-activated rhodopsin could contact with residues 342–345 in the C-terminal region, residues 310–313 in the δ-β6 loop, and residues 19–28 at the N-terminal helix.

**DISCUSSION**

As already described, bovine rhodopsin can be classified as one of the receptors that couple with the Gt family of the G protein, but it has a specific ability to activate Gt. The present studies using the loop-replaced rhodopsin mutants and the C terminus-replaced Gaα mutants strongly suggest the specific role of region A (Fig. 1B) in the activation mechanism of Gt by bovine rhodopsin. That is, bovine rhodopsin can discriminate the difference in the amino acid sequence of region A between Gt and Gaα, suggesting that region A is one of the recognition sites of Gt by bovine rhodopsin. Our spectroscopic experiments by using the C-terminal peptide (regions A + B) supported our conclusion that is based on the analyses of G protein C terminus mutants; the peptide of the C-terminal 11 amino acids of Gaα stabilizes the meta II intermediate of bovine rhodopsin in the rod outer segments more than two times greater than that of Gaα (dissociation constants are about 2 and 5 mM, respectively; data not shown). Because the sequence of Gt is identical with that of Gaα up to the 9 amino acids adjacent to the C-terminal 11 amino acids, it is likely that the 6 amino acids in region A are enough for the difference in the stabilization of meta II between Gt and Gaα. Therefore, there could be present a specific interaction between loop 3 of bovine rhodopsin and region A of Gt for the efficient activation of Gt.

On the other hand, the wild type and loop-replaced mutant showed the activation ability for Gt similar to each other (Figs. 3C, 5, and 6). This is in contrast to the fact that they showed the activation ability for Gt considerably different from each other (Fig. 4). Because the sequence of region A is almost identical between Gt and Gaα, these facts could originate from the different role of the interaction between loop 3 and region A. The difference in the activation efficiency of Gt between the wild type and the loop 3-replaced mutant could be explained either by the efficient activation of Gt by the loop 3 of bovine rhodopsin or less activation of Gt by loop 3 of SCOP2. In the former case, the binding of the loop 3 of bovine rhodopsin with region A induces a proper conformational change(s) in the Gt molecule to efficiently activate Gt, whereas the proper conformational change(s) could not occur upon binding of the loop 3 with region A of Go. In the latter case, there is a specific activation mechanism of Gt different from Gt and Go, and the mechanism could not work upon the interaction of region A of Gt with loop 3 of SCOP2. In either case, the experimental results could be explained by the specific interaction between the loop 3 of bovine rhodopsin and region A of Gt.

**FIG. 6. Initial rates of activation of G protein mutants by rhodopsin mutants.** Three kinds of G protein mutants were prepared by substitution of the C-terminal 11 amino acids of Gaα (Gt/wild) by those of Gaα (Gt/t11), Gaα (Gt/o11), and Gaα (Gt/q11). Activation of these G proteins by wild type and rhodopsin mutants, which possessed loop 3 of SCOP2, was measured. The data are the means ± S.D. of three separate experiments. Wild type and mutant G proteins bound ~9000 f mol GTP-S in the presence of 60 nM light-stimulated mutant rhodopsin having loop 3 of Gt rhodopsin upon incubation for 10 min, and the initial rates of wild type and mutant Gs, which were catalyzed by unirradiated rhodopsins, were less than 14 μmol/min/mol rhodopsin (data not shown). Note that the different absolute amounts of Gt bound between Figs. 4 and 5 were due to different preparations of G proteins.
the coupling specificity of bovine rhodopsin with Gα. As far as we know, this is the first experimental evidence that accounts for the specificity of bovine rhodopsin to Gα. Further experiments via a strategy of deletional and site-directed mutagenesis will shed light on the mechanism of the Gα specificity of vertebrate rhodopsin and its relation to the diversity of the receptor-G protein coupling.

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