The trp gene encodes subunits of a highly Ca\(^{2+}\)-permeable class of light-activated channels of Drosophila photoreceptors. The recently characterized mutation in this gene, TrpP\(^{365}\), is semidominant and causes massive degeneration of photoreceptors by making the TRP channel constitutively active. We show that a single amino acid change, Phe-550 to Ile, near the beginning of the fifth transmembrane domain of TRP channel subunits is necessary to induce, and sufficient to closely mimic, the original mutant phenotypes of TrpP\(^{365}\). Hypotheses are presented as to why the amino acid residues at position 550 and its immediate vicinity might be important in influencing the regulation of the TRP channel and why the substitution of Phe for Ile at this position, in particular, could result in constitutive activity of the channel.

Drosophila photoreceptors have two classes of light-activated channels, the highly calcium-permeable TRP channels and the non-specifically cation-selective TRPL channels (1). The TRP channels, the subunits of which are encoded by the trp gene (1–5), are thought to carry most of the phototransduction current (5). The TRP protein is widely conserved throughout animal phylogeny (6–8). However, the mechanisms of activation or regulation of TRP or TRP-related channels are still obscure.

Yoon et al. (9) recently described a new mutation in the trp gene, TrpP\(^{365}\), which confers on the mutant a set of phenotypes unlike any seen in previously isolated trp mutants. The TrpP\(^{365}\) mutants do not display photoreceptor responses that terminate prematurely during light stimulus, a phenotype that had been considered to be the defining hallmark of mutants in this gene (10, 11). TrpP\(^{365}\) responses are small but are maintained throughout the duration of light stimulus. The most striking feature of TrpP\(^{365}\) mutants, however, is that their photoreceptors undergo rapid degeneration. Moreover, unlike any other known trp mutants, these TrpP\(^{365}\) phenotypes are semidominant, i.e. TrpP\(^{365}\) heterozygotes also display mutant phenotypes though they are not as severe as those of homozygotes. From whole cell patch-clamp recordings, Yoon et al. (9) concluded that these phenotypes arise as a result of excessive Ca\(^{2+}\) entry caused by constitutive activity of the TRP channel. We now show that the above phenotypes are because of a single amino acid change, Phe-550 to Ile, in the fifth transmembrane segment of the TRP channel. We present, in addition, a possible mechanism by which the phenotypes might arise.

**EXPERIMENTAL PROCEDURES**

**Minigene Construction and Germ Line Transformation—**A trp minigene was constructed and subcloned into the pcAsper-3 vector for germ line transformation. The minigene consisted of three DNA fragments, the trp promoter and 5′-untranslated regions (−681 to −1 of genomic DNA, where +1 is the trp translation start site), the coding region (ATG to the stop codon), and the 390-bp region immediately downstream of the stop codon. The minigene was subcloned into the XbaI and StuI sites of the CaSpeR-3 transformation vector. The vector containing the minigene was injected into early embryos in the presence of helper plasmid (12).

**Site-directed Mutagenesis—**All four mutations detected in the TrpP\(^{365}\) mutant were located within a 2444-bp Smal fragment (from +647 to +3090) in the trp coding region. The 2444-bp Smal fragment was isolated from wild-type trp cDNA, subcloned into the M13mp18 vector, and mutagenized as described in Kunkel (13). The following primers were used in site-directed mutagenesis: F500T (mutation 1), 5′-GAAACATAGCACTTATTGTTGCA; H532N (mutation 2), 5′-TCGATCCCATTGG, where the target bases are underlined. Following mutagenesis, the F500T and H532N fragments were sequenced to ascertain only the intended mutations had been made. Each mutagenized Smal fragment was then swapped with the corresponding Smal fragment in the trp minigene, which had been previously cloned into pcAsper-3.

The following nine mutant trp minigene constructs were generated, and transgenic flies carrying each mutant minigene were generated by P-element-mediated germ line transformation in a wild-type background: P[trp(1)], with mutation 1; P[trp(2)], with mutation 2; P[trp(3)], with mutation 3; P[trp(4)], with mutation 4; P[trp(123)], with mutations 1, 2, and 3; P[trp(124)], with mutations 1, 2, and 4; P[trp(134)], with mutations 1, 3, and 4; P[trp(234)], with mutations 2, 3, and 4; and P[trp(1234)], with all four mutations.

In addition to these transgenic lines in a wild-type background, three of the lines, that carrying mutation 3, that carrying mutations 1, 2, and 4, and that carrying all four mutations, were also placed in a trp-null (trp\(^{-}\)) background by appropriate genetic crosses. The trp\(^{-}\) mutant was generated in this laboratory and was shown by others (14) to be functionally null.

**Confocal Microscopy—**Fly eyes were dissected in a fixative (4% formaldehyde in phosphate-buffered saline with 0.3% Triton X-100), and the dissected retinas (photoreceptor layers) were allowed to remain in the
shown in Fig. 1 are electroretinograms (ERGs), extracellular recordings were taken at 7 days post-eclosion. The background wild-type stock was marked with w+ to allow a mini-white marker in the transformation vector to be detected. In all ERG recordings shown, both in this and subsequent figures, the stimuli consisted of a white stimulus (Wh) followed by an orange stimulus (Or), each of 4 s duration presented 20 s apart. Except where otherwise specified, all recordings were taken at 7 days post-eclosion.

The same fixative for 1 h. After incubation in phosphate-buffered saline that contained 4% normal goat serum, the fixed retinas were stained with phalloidin-tetramethylrhodamine B isothiocyanate (Sigma) to label filamentous actin in the rhabdomeres. Transverse optical sections of ~1 μm thickness were taken from transgenic flies each carrying a single copy of one of the four mutations in a wild-type background. A single copy of one of the four mutations in a wild-type background. The resulting mutant minigene constructs were introduced into a wild-type background causes the ERGs of the transgenic flies now carried two copies of the transgene and two copies of endogenous wild-type trp gene. The stimuli and the age of the flies were the same as in Fig. 1.

Transgenic Flies Carrying Each of the Four Mutations—To examine to what extent the other three mutations might play a role in producing the TrpP365 mutant phenotype, we generated transgenic flies carrying various triplet combinations of the four mutations in a wild-type background. a, mutation 3; b, all four mutations; c, mutations 1, 2, and 3; d, mutations 1, 2, and 4. Transgenic flies carrying mutations 134 and 234 were also tested. They yielded ERGs very similar to those obtained from transgenic flies carrying mutations 123, and their ERGs are not shown. The flies were made homozygous for the transgene, so that each fly carried two copies of the transgene and two copies of endogenous wild-type trp gene. The stimuli and the age of the flies were the same as in Fig. 1.

Results

Yoon et al. (9) showed that the TrpP365 mutant carries four protein sequence-altering mutations within its trp gene, P500T, H531N, F550I, and S867F. To simplify notations, these mutations will be referred to as mutations 1, 2, 3, and 4, respectively. To determine which of these four mutations is responsible for the TrpP365 phenotype, site-directed mutagenesis was carried out on a trp minigene to generate mutants carrying each of the four mutations singly, three of the four in all possible triplet combinations, or all four mutations together. The resulting mutant minigene constructs were introduced into a wild-type background by P-element-mediated germ line transformation (see “Experimental Procedures”). A single copy of the trp minigene, which has no introns, was found to fully complement the trp mutant phenotype when introduced into the null trpP343 background (not shown).

Transgenic Flies Carrying Each of the Four Mutations—Shown in Fig. 1 are electroretinograms (ERGs), extracellularly recorded, light-evoked mass responses of the eye, obtained from transgenic flies each carrying a single copy of the recombinant trp minigene harboring mutation 1, 2, 3, or 4, i.e. P[trp (1)]+/+, P[trp(2)]+/+, P[trp(3)]+/, or P[trp(4)]+/+, all in a wild-type background. Thus, these transgenic flies had two copies of the endogenous wild-type trp gene and one copy of the mutagenized recombinant trp minigene. ERGs of P[trp(1)]+/+, P[trp(2)]+/+, or P[trp(4)]+/+ were indistinguishable from those of wild-type (Fig. 1, a, b, and d). Only those obtained from P[trp(3)]+/+ were distinctly different from wild-type ERGs in that they showed markedly slower kinetics of decay at stimulus off-set (Fig. 1c). There was little variation in the ERG decay times among individuals of P[trp(3)]+/+ so that the P[trp(3)]+/+ ERG could always be distinguished from that of wild-type by inspection. Yoon et al. (9) have shown previously that one copy of TrpP365 introduced into a wild-type background causes the ERGs of the transgenic host to become somewhat smaller in amplitude and slower in the kinetics of decay than those of wild-type. Thus, the slow time courses of decay observed in this study were consistent with the previous findings, although little or no change in amplitudes was detected in the present study.

We next made the P[trp (3)] transgene homozygous so that the transgenic flies now carried two copies of P[trp(3)] and two copies of the endogenous wild-type trp gene. The main effect of making P[trp(3)] homozygous on the ERG was to slow down the kinetics of response decay even further (Fig. 2a). Thus, mutation 3 was the only one of the four that had any effect at all on the ERG, suggesting that mutation 3, i.e. F550I, might be the primary contributor to the TrpP365 mutant ERG phenotype.

Transgenic Flies Carrying Triplet Combinations of Mutations—To examine to what extent the other three mutations might play a role in producing the TrpP365 phenotype, we generated transgenic flies carrying various triplet combina-
trp-null stock was marked with TrpP365 type, and 2) the other mutations contributed very little to the were wild-type. The results were clear-cut in suggesting that 1) tant, and whenever they did not carry mutation 3 their ERGs were mu-

trp(1234) gene. ERGs obtained from three of the triplet combination with the other mutations, their ERGs were mu-

trp(1234)] transgene was also placed in a trp-null background. If mutation 1, all at day 0 (first column) and day 3 (second column) post-eclosion. ERGs were also obtained from flies of all five genotypes at 7 days post-eclosion, but they were very similar to those obtained from 3 days post-eclosion and are not shown. The flies were made homozygous for the transgene so that each class of transgenic flies carried two copies of the mutant transgene but no wild-type trp gene. In all transgenic lines, the background trp-null stock was marked with w-. The control TrpP365 hetero-

ERGs showed very little age-dependent variations, particularly between 3 and 7 days post-eclosion, results from 7 days were not included in Fig. 3. They were very similar to those at 3 days post-eclosion.

At all three ages tested, the ERGs obtained from transgenic flies carrying (P[trp(124)]) were completely wild-type (Fig. 3a).

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Confla microscopy—To determine whether the ERG phe-

To assess properly whether or not mutation 3 corresponds to mutation 3 alone to be somewhat less severe than those of flies carrying all four mutations (compare Fig. 3, c and d), but even the latter did not quite match ERGs of trpP365 in severity (compare Fig. 3, d and c). At least four different transgenic lines were tested for each genotype, and the above generalizations held true across different transgenic lines, making it unlikely that the minor differences in phenotype between the transgenic flies and the original mutant are due to differences in the sites of insertion of transgenes.

Thus, the results of the complementation test were consistent with the idea that mutation 3, and it alone, corresponds to the original trpP365 mutation, although mutation 3 alone never quite matched the severity of trpP365 in ERG phenotypes. The slight disparity between behaviors of the transgenes and trpP365 will be discussed under “Discussion.”

Confocal Microscopy—To determine whether the ERG phe-

Transgenic Flies in a trp-null Background—All transgenic lines tested to this point were generated in a wild-type back-

Thus, whenever the transgenic flies carried mutation 3, whether by itself or in combination with the other mutations, their ERGs were mu-

3, indeed, is the same as TrpP365, one would expect that transgen-

FIG. 3. Comparison of ERGs recorded from transgenic flies carrying mutation 3 or all four mutations in a null trp background with those recorded from flies of three different geno-

tions of the four mutations (123, 124, 134, and 234) or all four mutations together (1234). These transgenic lines, too, were made homozygous for the transgene so that each carried two copies of the transgene and two copies of the endogenous trp + gene. ERGs obtained from three of the triplet combination lines, P[trp(123)], P[trp(134)], and P[trp(234)], were very similar to each other, with slow decay time courses much like that seen in P[trp(3)] flies (compare Fig. 2, c and a). For this reason, an ERG obtained from only one of these three lines, P[trp(123)], is shown in Fig. 2. On the other hand, ERGs of transgenic flies of the P[trp(124)] line, the only line that did not carry mutation 3, were completely wild-type (Fig. 2d). Thus, whenever the transgenic flies carried mutation 3, whether by itself or in combination with the other mutations, their ERGs were mu-

2) the other mutations contributed very little to the mutant phenotype.

Transgenic Flies in a trp-null Background—All transgenic lines tested to this point were generated in a wild-type back-

Therefore, they were not genotypically comparable with TrpP365/+ because of the presence of endogenous trp +, even though the ratio of mutant to wild-type trp gene copy number was one, as in TrpP365/+ (2:2 in the transgenic flies and 1:1 in TrpP365/×+). In fact, ERGs of all transgenic flies carrying two copies of mutation 3 tested were not nearly as severely mutant as that of TrpP365/×+ (compare Fig. 2, a–c and Fig. 3b), suggesting that the presence of the extra wild-type copies of the trp gene might be influencing the ERG phenotype. To assess properly whether or not mutation 3 corresponds to TrpP365/+ , we needed to carry out a complementation test in the absence of the endogenous wild-type trp. Accordingly, we placed the P[trp(3)] and P[trp(1234)] transgenes in a trp-null (trpP365) background. As a positive control, the P[trp(124)] transgene was also placed in a trp-null background. If mutation 3, indeed, is the same as TrpP365, one would expect that transgen-

The control TrpP365 hetero-

homozygous stocks were also marked with w-. ERGs recorded from transgenic flies of the genotype, P[trp(124)]/TrpP365, (a) are indistinguishable from those of wild-type. The stimuli were as described in Fig. 1.
respectively), were intermediate between those of \textit{TrpP}\textsubscript{365} homozygotes and heterozygotes but more closely resembled that of homozygotes than that of heterozygotes. The resemblance to \textit{TrpP}\textsubscript{365} homozygotes was much stronger than was evident from ERG recordings. Thus, the degree of degeneration in transgenic flies carrying all four mutations was almost indistinguishable from that of homozygotes, particularly at days 3 and 7 post-eclosion (compare Fig. 4, B-c and B-d). Degeneration in the transgenic flies carrying only mutation 3 was somewhat milder. At day 0 post-eclosion, most rhabdomeres appeared nearly normal. However, the label was very faint, and some rhabdomeres appeared to be splitting up (Fig. 4B-b, left panel; B-b, middle panel, arrow), and some appear elongated in cross section (B-a, middle panel; B-b, left panel). Phalloidin was used to label filamentous actin in the rhabdomeres. All transgenic flies were generated in a \textit{trp}-null background marked with \textit{w}–, and all the other flies were also marked with \textit{w}–.

**DISCUSSION**

By whole cell recordings from dissociated photoreceptor cells, Yoon \textit{et al.} (9) showed earlier that in \textit{TrpP}\textsubscript{365} the TRP Ca\textsuperscript{2+}/H11001 channels are constitutively open, suggesting that the excessive influx of Ca\textsuperscript{2+} through the TRP channels causes the massive photoreceptor degeneration observed in the mutant. These au-
thors proposed that the mutation(s) in the \textit{trp} gene of \textit{TrpP365} renders the regulation of the TRP channel unstable, leading to an increased likelihood that the channels open and remain open spontaneously in an age-dependent and \textit{TrpP365} dosage-dependent manner. Their results thus suggested that the amino acid residues that are altered in the TRP channel of \textit{TrpP365} might be important for the regulation of the TRP channel activity. We have shown in the present work that, of the four amino acid alterations detected in the TRP channel of \textit{TrpP365} (9), the F550I change in the fifth transmembrane segment is the critical mutation for the \textit{TrpP365} phenotype.

The ERG and degeneration phenotypes of transgenic flies homozygous for mutation 3 alone or all four mutations together nearly approximate the phenotypes of \textit{TrpP365} homozygotes when the transgenes are placed in a \textit{trp}-null background (\textit{P[trp (3);trpP365 and P[trp(1234);trpP365} (Figs. 3 and 4). However, these phenotypes do not quite attain the severity of \textit{TrpP365} homozygotes (Figs. 3 and 4). Moreover, the phenotypes of transgenic flies carrying only mutation 3 tend to be slightly milder than those of transgenic flies carrying all four mutations (compare Fig. 3, c and d, Fig. 4, B-b and c). Because these behaviors of transgenics are observed in several different lines of transgenic flies for each transgene, they are not likely to be due to differences in expression levels arising from different sites of transgene insertion. On the other hand, the transgenes had a \textit{trp} promoter sequence of only \textendash680 bp and were devoid of introns (see “Experimental Procedures”). This use of abbreviated gene constructs in the transgenics could potentially account for the minor differences in behavior between the mutation 3-harboring transgenics and the original \textit{TrpP365} mutation. The abbreviated gene construct could, for example, affect the level of protein expression or the processing of gene products. The effects appear to be weak because the observed differences are only minor. On the other hand, the slight difference in ERG and degeneration phenotypes between transgenic flies carrying mutation 3 alone and those carrying all four mutations cannot be explained either by differences in sites of transgene integration or the abbreviated gene constructs used in transgenics. It may well be that mutations 1, 2, and 4 have minor synergistic effects on mutation 3, even though alone they do not produce any phenotype. The fact remains, however, that mutation 3 must be present for the mutant phenotypes to appear at all (Figs. 1, 2, 3a, and 4a-c). Moreover, mutation 3 alone is sufficient to produce phenotypes closely mimicking those of \textit{TrpP365} (Figs. 1–4). That is, mutation 3 alone is necessary for the ERG and degeneration phenotypes of \textit{TrpP365} and sufficient for phenotypes closely matching those of \textit{TrpP365}. We conclude that, in all likelihood, mutation 3 corresponds to the original mutation \textit{TrpP365}.

The amino acid alteration caused by mutation 3 is surprisingly subtle considering the drastic effect it has on the mutant phenotype. It involves the substitution of one non-polar residue for another. Alignment of the TRP S5 sequence with those of \textit{Caenorhabditis elegans} TRP-related proteins tested (Fig. 5). In the two \textit{Caenorhabditis elegans} TRP-related proteins examined, this position is occupied by Phe in one, as in flies, and Cys in the other. On the other hand, in all mammalian TRP-related proteins tested (a total of 14 mammalian TRP sequences) a \textit{trp} gene of \textit{Drosophila} and \textit{Leu} for mammals, perhaps because of slightly different channel environments. 3) Ile appears to be particularly poorly tolerated at this position. In the following, we explore speculatively why this position might be important for the regulation of TRP channel opening and why Ile, in particular, may be a poor residue to occupy this position.

In a classic study, Doyle \textit{et al.} (16) determined the structure of the \textit{KcsA} K\textsuperscript{+} channel of \textit{Streptomyces lividus} by x-ray crystallography. The \textit{KcsA} channel is formed by four subunits, each of which contributes two transmembrane \(\alpha\)-helices, one (inner helix) facing the pore and the other (outer helix) facing the hydrophobic membrane; these \(\alpha\)-helices form the backbone of the channel. The four inner helices are arranged like the posts of an inverted teepee and cross in a bundle to produce a small hole near the intracellular entrance of the channel. Results of Cys accessibility studies (17) on voltage-gated Shaker K\textsuperscript{+} channels suggest that the hole formed by the bundle crossing serves as the gate for these channels. This picture of the channel structure probably applies to such other ion channels as various voltage-gated channels and TRP-related channels. Most of these channels, however, have six transmembrane segments, rather than two, in each subunit or homology domain. For these channels, the sixth transmembrane segment, S6, corresponds to the inner helix, and the fifth transmembrane segment, S5, corresponds to the outer helix of the \textit{KcsA} channel. Thus, while the S5 segments do not define the channel gate themselves, they are immediately adjacent to S6 segments and are in a position to influence the movements of S6 segments. Hydropathy analysis places Phe-550 near the N-terminal end of S5, corresponding to the intracellular end of the segment. This is also the region of the channel at which S6 segments are thought to make bundle crossing to form the gate. Thus, the residues at positions 550 or in its immediate vicinity may be in a position to critically affect channel gating.

Why would Ile at this position cause constitutive activity of the channel but not the residues normally found at this position? It turns out that Ile has a side chain property that it does not share with Phe, Leu, or Cys. Ile is branched at the \(\beta\)-carbon position, whereas none of the other three has ramifications at the \(\beta\)-position. Branching at \(\beta\) is expected to decrease the flexibility of the main chain through steric hindrance provided by the \(\beta\)-branched side chains (15). The presence of a \(\beta\)-branched residue close to the gate may restrict the movements of the helices forming the gate and could lock the gate in its resting state. Agam \textit{et al.} (18) showed that the default state of the TRP and TRP-like channels is the open state and that a continuous energy input from an ATP-dependent process is required to keep the channels closed in the absence of light stimulus. Thus, constitutive opening of the TRP channel may represent locking the channel in the lower-energy, default state, \textit{i.e.} its resting state.

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Single Amino Acid Change in the Fifth Transmembrane Segment of the TRP Ca\(^{2+}\) Channel Causes Massive Degeneration of Photoreceptors

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