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Effect of p75^{NTR} on the regulation of photoreceptor apoptosis in the *rd* mouse

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Purpose: Apoptosis is the final common pathway for photoreceptors in several forms of retinitis pigmentosa. Recent study has shown that continuous light exposure upregulates low-affinity neurotrophin receptor p75 (p75^{NTR}), which is involved in light-induced photoreceptor apoptosis in rat retina. However, the function of p75^{NTR} in inherited forms of photoreceptor degeneration has not yet been examined. This study was conducted to elucidate the potential role of p75^{NTR} in the *rd* mouse, one of the best characterized animal models of retinitis pigmentosa.

Methods: Double-mutant (*rd/rd*, p75^{NTR}-/-) mice were crossbred from *rd/rd* and p75^{NTR}-/- mice. Retinas from control (+/+, p75^{NTR}+/+; *rd/rd*, p75^{NTR}+/+; *rd/rd*, p75^{NTR}+/-), and double-mutant (*rd/rd*, p75^{NTR}-/-) mice were examined by light microscopy and TdT-mediated dUTP nick end labeling (TUNEL) from postnatal day (P)9 through P20. p75^{NTR} mRNA expression in +/+, p75^{NTR}+/+, and *rd/rd*, p75^{NTR}+/+ mice were examined by real-time PCR analysis. p75^{NTR} protein expression in +/+, p75^{NTR}+/+; *rd/rd*, p75^{NTR}+/+; and *rd/rd*, p75^{NTR}-/- mice were examined by immunohistochemistry.

Results: p75^{NTR} mRNA expression in *rd/rd*, p75^{NTR}+/+ mice was significantly upregulated compared with +/+, p75^{NTR}+/+ mice at P13 and P20. p75^{NTR} protein expression was observed mainly in Müller glial cells, and its expression was upregulated in the outer nuclear layer during photoreceptor degeneration. However, histochemical analyses showed that the time course of retinal degeneration and the extent of photoreceptor apoptosis in *rd/rd*, p75^{NTR}-/- double-mutant mice was indistinguishable from that in *rd* mice carrying functional p75^{NTR} (*rd/rd*, p75^{NTR}+/+, and *rd/rd*, p75^{NTR}+/-).

Conclusions: These results suggest that in contrast to its role in light-induced photoreceptor degeneration, p75^{NTR} is not essential for apoptosis in the *rd* mouse.

Several pathological conditions result in loss of vision due to photoreceptor degeneration, such as retinitis pigmentosa (RP). RP is the most common inherited form of blindness, affecting approximately 100,000 people in the United States, and one out of every 3,000 to 4,000 people in all ethnic groups worldwide [1]. Although the mechanism is not fully understood, apoptosis has been implicated in photoreceptor degeneration and other neurodegenerative diseases [2-5]. In an effort to develop novel treatment approaches for these diseases, many growth factors and neurotrophins have been shown to promote survival of retinal neurons. For example, intraocular injection of brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and basic fibroblast growth factor (bFGF) rescue photoreceptors in animal models of both inherited and light-induced retinal degeneration [6-10]. Neurotrophins, such as nerve growth factor (NGF), BDNF, NT-3, and neurotrophin-4/5 (NT-4/5), can support the survival and differentiation of neural cells during retinal development and regeneration [11,12]. Control of cell survival by neurotrophins is mediated by two types of transmembrane glycoproteins, the trk tyrosine kinase receptors (TrkA, TrkB and TrkC) and the neurotrophin receptor p75 (p75^{NTR}) [13-15]. Neurotrophins act in neural cell survival by activating trk tyrosine kinases, downstream of which a ras-dependent pathway leads to the activation of mitogen-activated protein (MAP) kinases [16]. Contrary to the action of neurotrophins on trk receptors, NGF binding to p75^{NTR} activates an intracellular pathway similar to that activated by death receptors such as tumor necrosis factor and Fas receptors [17,18]. In fact, p75^{NTR} is expressed in postmitotic mouse retinal ganglion cells (RGCs), and RGC number in the early phase of retinal development (before embryonic day 15) is regulated by p75^{NTR} [19]. p75^{NTR} may also interact with Nogo-66 receptor as a co-receptor for Nogo, myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin glycoprotein (OMgp), activation of which lead to neurite outgrowth inhibition [20].

Recent studies have proposed that neurotrophic rescue of photoreceptors may be indirect, mediated by interaction of the neurotrophic factors with Müller glial cells that in turn release secondary factors that act directly on photoreceptors [21-27]. Using a light-induced retinal degeneration model of Wistar rat, we showed that degeneration is associated with an increase in Müller cell expression of p75^{NTR} and TrkC [5]. Administration of exogenous NT-3, which is photoreceptor cell

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protective, increased Müller cell production of bFGF, while NGF decreased its production. In addition, p75^{NTR}-/- mice on a pigmented C57BL/6J background were resistant to light damage. However, loss of p75^{NTR} did not protect against light-damage in an albino Institute for Cancer Research (ICR) strain [28]. These discrepancies suggest that the function of p75^{NTR} may vary among different systems, which prompted us to revisit the question of whether p75^{NTR} is a pro-apoptotic signal for photoreceptors by investigating the potential role of p75^{NTR} in the inherited retinal degeneration. For this purpose, we chose the *rd* mouse because it is a well-established model of RP that is often used to determine the effect of various genes on photoreceptor apoptosis [29-31]. Homozygous *rd* (*rd/rd*) animals develop photoreceptors with outer segments, but these degenerate rapidly beginning at postnatal day 8 (P8) due to recessive mutation of the gene coding for the rod cGMP phosphodiesterase β-subunit [32]. This same gene is affected in cases of human recessive RP [33]. In the present study, to determine whether the absence of p75^{NTR} may interfere with apoptotic photoreceptor loss in inherited retinal degeneration, we have generated *rd/rd*, p75^{NTR}-/- double-mutant mice.

METHODS

Experimental animals: Experiments were performed using p75^{NTR}-/- (purchased from the Jackson Laboratory, Bar Harbor, ME) and *rd/rd* (C57BL/6 background) mice in accordance with the ARVO statement for the use of animals in vision research. Light intensity inside the cages ranged from 100 to 200 lux under a 12 light:12 dark cycle. Homozygous *rd* mice were crossed with p75^{NTR}+/- mice. Mice with the genotype *rd/+*, p75^{NTR}+/- were used to obtain control (+/+, p75^{NTR}+/+; *rd/rd*, p75^{NTR}+/+; *rd/rd*, p75^{NTR}+/-), and an *rd/rd*, p75^{NTR}-/- double-mutant mouse strains. Additionally, *rd/rd*, p75^{NTR}+/- mice were used to obtain control (*rd/rd*, p75^{NTR}+/+; *rd/rd*, p75^{NTR}+/-), and double-mutant mouse strains. The p75^{NTR} and the *rd* alleles were identified by PCR analyses of mouse tail genomic DNA as described previously [34,35].

Histology and morphometric studies: Mice at P9, P12, P15, and P20 were deeply anesthetized with diethylether and perfused transcardially with saline, followed by 4% paraformaldehyde in 0.1 M phosphate buffer containing 0.5% picric acid at room temperature. The eyes were removed and postfixed overnight in the same fixative and then embedded in paraffin. Histological sections 7 μm thick were made along the vertical meridian, mounted, and stained with hematoxylin and eosin. At least three animals were used at each time point. The thickness of the outer nuclear layer (ONL) was measured as described [5]. Forty-eight measurements of the ONL were made at 16 contiguous fields around the entire retinal section (three measurements per field). These 48 measurements were averaged to provide a single value for each retina to allow statistical comparison (Figure 1).

Immunohistochemistry: Sections were incubated with phosphate-buffered saline (PBS, pH 7.4) containing 10% normal horse serum containing 0.4% Triton X-100 for 60 min at room temperature. They were then incubated overnight with a rabbit polyclonal antibody against p75^{NTR} (Promega, Madison, WI; 5.0 μg/ml) and mouse monoclonal antibody against glutamine synthetase (GS; 1.0 μg/ml; Chemicon, Temecula, CA), and visualized with Cy3-conjugated goat anti-rabbit IgG (Jackson Immunoresearch, West Grove, PA; 1000x) and Cy2-conjugated donkey anti-mouse IgG (Jackson Immunoresearch; 200x).

TUNEL staining: Sections were incubated in 0.26 U/ml TdT in the supplied 1X buffer (Invitrogen, Carlsbad, CA), and 20 mM biotinylated-16-dUTP (Roche, Basel, Switzerland) for 60 min at 37 °C. Sections were washed three times in PBS (pH 7.4) and blocked for 30 min with 2% BSA in PBS (pH 7.4). The sections were then incubated with peroxidase-conjugated streptavidin (Nichirei, Tokyo, Japan) for 30 min and visualized with DAB substrate kit (DAKO Corporation, Carpinteria, CA). To quantify photoreceptor apoptosis, the number of TUNEL-positive nuclei in the ONL was counted separately in central and peripheral retina. A point midway between the optic nerve and ora serrata divided the retina into central and peripheral halves. Six measurements per field were made for each retina examined: three central fields and three peripheral fields. These measurements were averaged to provide a single value for each retina to allow statistical comparison (Figure 2).

Quantitative real-time PCR analysis: Quantitative real-time polymerase chain reaction (PCR) analysis was performed with the ABI 7500 fast real-time PCR system (Applied Biosystems, Foster City, CA) according to manufacturer's protocol. Briefly, retinas were carefully removed from eyes at P8, P13, and P20. Total retinal RNA from six +/+, p75^{NTR}+/+, and *rd/rd*, p75^{NTR} +/+ mice at each point was extracted with Isogen (Nippon Gene, Tokyo, Japan). For cDNA synthesis, 1 μg of total RNA was transcribed with Revertra ace reverse transcription reagents (Toyobo, Osaka, Japan) using oligo-dT primers. The internal probe was labeled with the reporter dye FAM (6-carboxyfluorescein) at the 5' end, and with the quencher dye TAMRA (6-carboxytetramethyl-rhodamine) at the 3' end. For p75^{NTR}, two primers (forward primer, 5'-GCA GCT CCC AGC CTG TAG TG-3'; reverse primer, 5'-TAA GCC ACA AGG CCC ACA AC-3'), and one TaqMan probe (5'-FAM-AGG CAC CGC TGA CAA CCT CAT TCC T-TAMRA-3') were used. For G3PDH, two primers (forward primer, 5'-TGC ACC ACC AAC TGC TTA G-3'; reverse primer, 5'-GGA TGC AGG GAT GAT GTT C-3'), and one TaqMan probe (5'-VIC-CAG AAG ACT GTG GAT GGC CCC TC-TAMRA-3') were used.

cDNA (50 ng) was reacted in a total volume of 20 μl of TaqMan Universal PCR Master Mix (Applied Biosystems). The final concentration of TaqMan probe and other primers was 200 nM and 100 nM, respectively. The conditions for the TaqMan PCR were as follows: 50 °C for 2 min, 95 °C for 10 min, and 40 cycles of 95 °C for 15 s, and 60 °C for 1 min. The difference in the initial amount of total RNA between the samples was normalized in every assay using a G3PDH gene expression as an internal standard. In each cDNA, the ratio of the copy number of p75^{NTR} mRNA was divided by that of the G3PDH mRNA. This normalized value was used to determine the relative expression level of p75^{NTR}.

Statistics: Data are presented as mean±SEM except as noted. Student's t-test was used to estimate the significance of results. Statistical significance was accepted at $p<0.05$.

RESULTS

Expression of p75^{NTR} in rd *mouse retina:* We first examined the distribution of p75^{NTR} in wild type (+/+, p75^{NTR}+/+) mouse retina at P15 (Figure 3A). p75^{NTR}-like immunoreactivities were observed mainly in the inner retina, and judging from the staining pattern, p75^{NTR} seemed to be expressed in Müller glial cells and neurons such as RGC and amacrine cells. To determine this possibility, we carried out double-labeling immunohistochemistry using antibodies for p75^{NTR} and glutamine synthetase (GS), a specific marker for Müller glial cells [36]. As shown in Figure 3B, many p75^{NTR}-positive cells were double-labeled with GS. In the inner nuclear layer (INL), GS-positive Müller cell bodies were surrounded by p75^{NTR} (Figure 3C). In addition, p75^{NTR} immunoreactivities in *rd/rd*, p75^{NTR}+/+ mice (Figure 3D) seemed to be slightly upregulated compared with those in control retina (Figure 3A), especially in the ONL. These results are consistent with our previous study using light-damaged Wistar rat retina [5]. Immunoreactivities for p75^{NTR} were completely absent in *rd/rd*, p75^{NTR}-/- mice (Figure 3E). We next examined p75^{NTR} mRNA expression levels in both

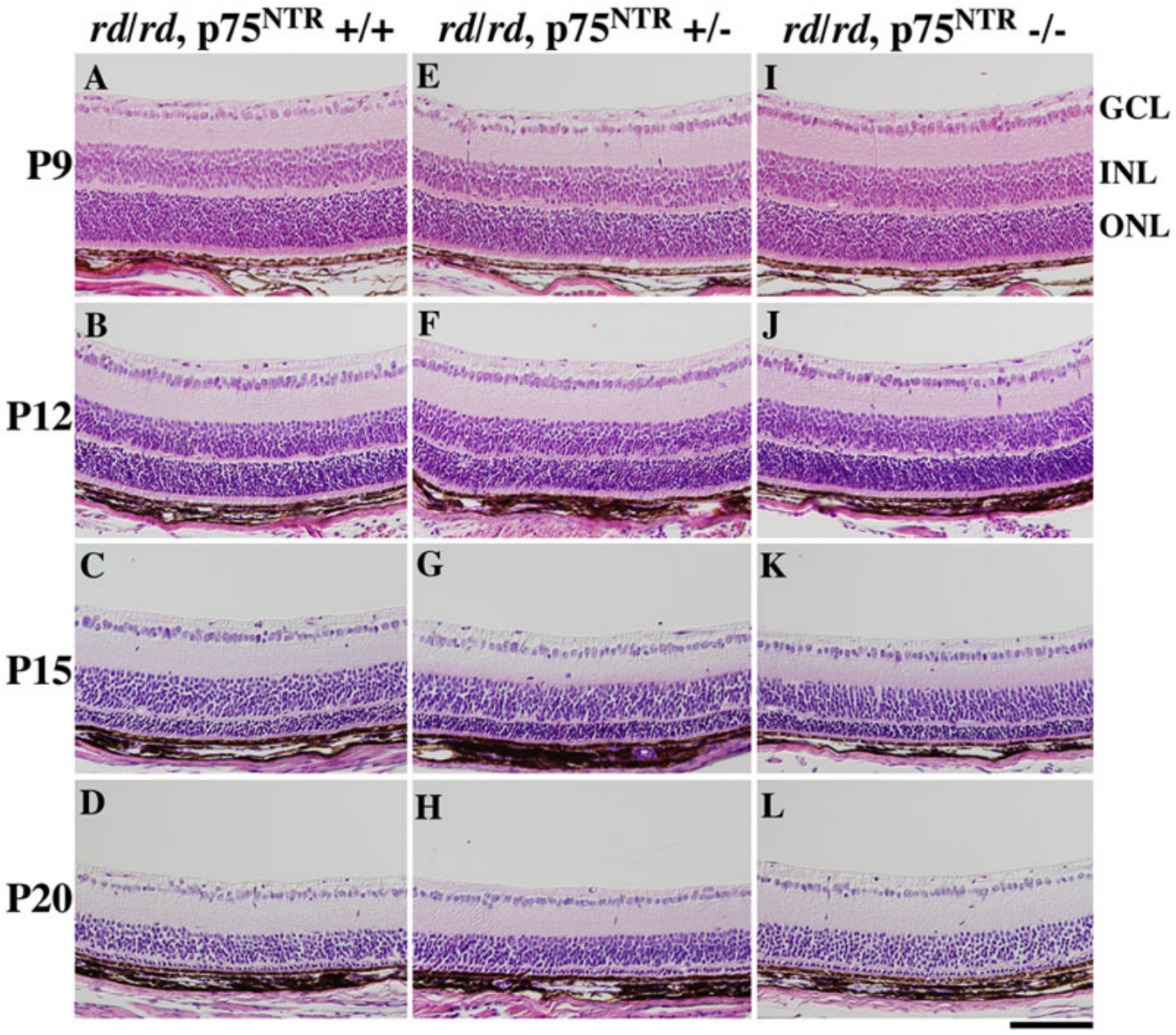

Figure 1. No effect of p75^{NTR} on the time course of photoreceptor degeneration in *rd/rd* mice. Histology of retinas from *rd/rd*, p75^{NTR}+/+ mice, *rd/rd*, p75^{NTR}+/- mice, and *rd/rd*, p75^{NTR}-/- mice. *rd/rd*, p75^{NTR}+/+ mice displayed a progressive reduction of outer nuclear layer (ONL) thickness from P9 to P15 (**A**-**C**), leading to a single row of photoreceptors at P20 (**D**). Retinas from *rd/rd*, p75^{NTR}+/- (**E**-**H**) and *rd/rd*, p75^{NTR}-/- (**I**-**L**) mice showed continuous thinning of the ONL that is indistinguishable from *rd/rd*, p75^{NTR}+/+ mice. The ganglion cell layer (GCL) and inner nuclear layer (INL) are also identified. Scale bar represents 100 μm.

wild type and *rd/rd*, p75^{NTR}+/+ mice retina. As shown in Figure 4, quantitative real-time PCR analysis revealed that p75^{NTR} mRNA expression in *rd/rd*, p75^{NTR}+/+ mice is increased at P13 (368±33%; n=6, p<0.001) and P20 (645±74%; n=6, p<0.001) compared with that in +/+, p75^{NTR}+/+ (104±18% and 82±7%; n=6). These results suggest the possibility that p75^{NTR} has some effect on photoreceptor apoptosis in *rd/rd*, p75^{NTR}+/+ mice.

Morphogenic analysis: In *rd/rd*, p75^{NTR}+/+ retina, the structure of the ganglion cell layer (GCL), INL, and the ONL are clearly discernable at P9 (Figure 1A) and morphologically similar to that of (+/+, p75^{NTR}+/+) control mice by light microscopy (data not shown). Thereafter, *rd/rd*, p75^{NTR}+/+ mice showed continuous thinning of the ONL from P12 to P20 (Figure 1B-D and black bars in Figure 2). However, retinas from *rd/rd*, p75^{NTR}+/- (Figure 1E-H), and *rd/rd*, p75^{NTR}-/- (Figure 1I-L) mice showed a pattern of degeneration indistinguishable from *rd/rd*, p75^{NTR}+/+ retinas with progressive loss of the outer retina resulting in a single row of photoreceptor nuclei at P20 (Figure 1D,H,L). Quantitative analysis of ONL thickness showed no statistically significant differences between these three strains (Figure 2).

TUNEL staining: We next examined the extent of photoreceptor cell apoptosis in *rd/rd*, p75^{NTR}+/+ mice at P9, P12, P15, and P20 using TUNEL staining. For quantitative analy-

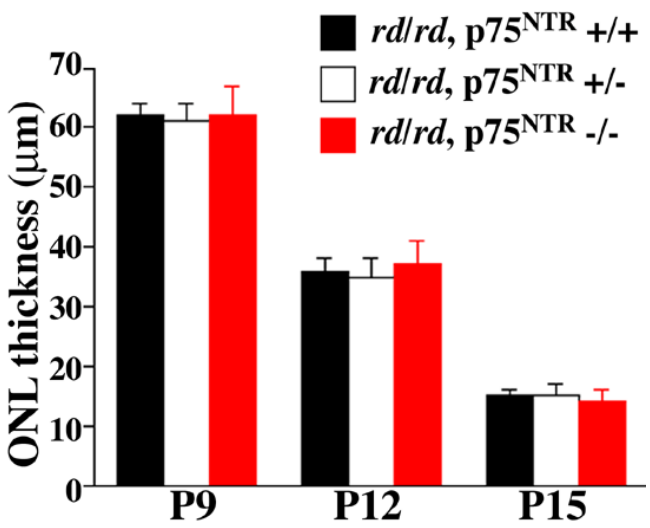

Figure 2. No effect of p75^{NTR} on the outer nuclear layer thickness in *rd/rd* mice. Quantitative analysis of outer nuclear layer (ONL) thickness in *rd/rd*, p75^{NTR}+/+ mice (black bars), *rd/rd*, p75^{NTR}+/- mice (white bars), and *rd/rd*, p75^{NTR}-/- mice (red bars). ONL thickness was examined in each genotype at P9, P12, and P15. No statistically significant differences were observed between these groups. Each data point represents the mean of values obtained from three independent experiments; error bars represent the SEM.

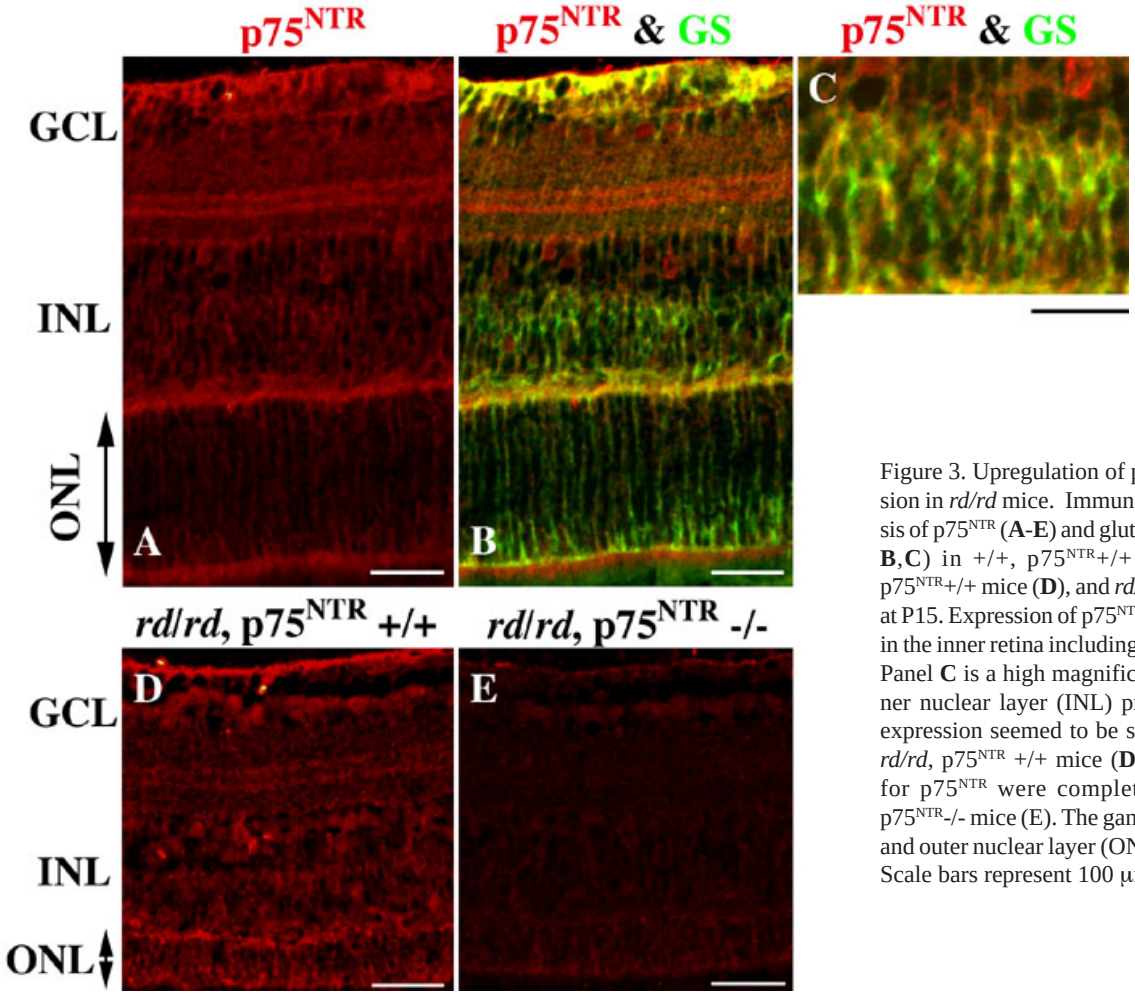

Figure 3. Upregulation of p75^{NTR} protein expression in *rd/rd* mice. Immunohistochemical analysis of p75^{NTR} (**A**-**E**) and glutamine synthetase (GS; **B**,**C**) in +/+, p75^{NTR}+/+ mice (**A**-**C**), *rd/rd*, p75^{NTR}+/+ mice (**D**), and *rd/rd*, p75^{NTR}-/- (**E**) mice at P15. Expression of p75^{NTR} was observed mainly in the inner retina including Müller glial cells (**B**). Panel **C** is a high magnification image of the inner nuclear layer (INL) presented in **B**. p75^{NTR} expression seemed to be slightly upregulated in *rd/rd*, p75^{NTR} +/+ mice (**D**). Immunoreactivities for p75^{NTR} were completely absent in *rd/rd*, p75^{NTR}-/- mice (E). The ganglion cell layer (GCL) and outer nuclear layer (ONL) are also identified. Scale bars represent 100 μm.

sis, we counted the number of TUNEL-positive nuclei separately in the central and peripheral regions. As shown in Figure 5 (black bars), photoreceptor apoptosis was most prominent at P12, especially in central region (Figure 6A). However, retinas from *rd/rd*, p75^{NTR}+/- (Figure 6B), and *rd/rd*, p75^{NTR}-/- (Figure 6C) mice showed a pattern of labeling indistinguishable from *rd/rd*, p75^{NTR}+/+ retinas (Figure 6A). No significant differences in TUNEL staining nor ONL thickness were detected between these three strains at P9, P12, and P15 (Figure 5). Fewer TUNEL-positive photoreceptors were observed at P20 (data not shown).

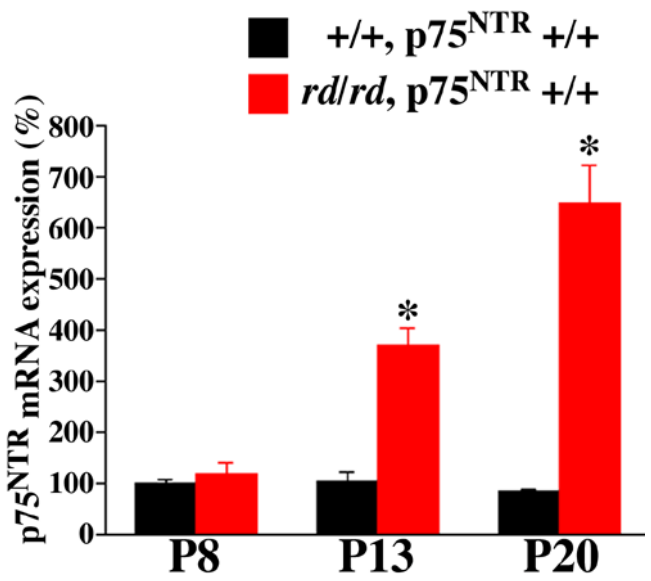

Figure 4. Upregulation of p75^{NTR} mRNA expression in *rd/rd* mice. Quantitative analysis of p75^{NTR} mRNA expression in +/+, p75^{NTR} +/+ mice (black bars) and *rd/rd*, p75^{NTR}+/+ mice (red bars). Real-time PCR analysis was carried out at P8, P13, and P20. p75^{NTR} mRNA expression in +/+, p75^{NTR}+/+ mice at P8 is shown as 100%. Note the significant upregulation of p75^{NTR} in *rd/rd*, p75^{NTR}+/+ mice at P13 and P20. No statistically significant differences were observed from P8 to P20 in +/+, p75^{NTR}+/+ mice. On the other hand, p75^{NTR} mRNA expression in rd/rd, p75^{NTR}+/+ mice was increased at P13 and P20 compared with that in +/+, p75^{NTR}+/+ mice. Each data point represents the mean of values obtained from six independent experiments; error bars represent the SEM. Asterisk (*) indicates p<0.001 for comparison to +/+, p75^{NTR}+/+.

DISCUSSION

Recent findings indicate an involvement of p75^{NTR} in light-induced photoreceptor degeneration in albino rat [5,24,25]. Consistently, a small neuroprotective effect was observed in the pigmented p75^{NTR}-/- mice, resulting in reduced retinal apoptosis following intense light exposure [5]. However, the

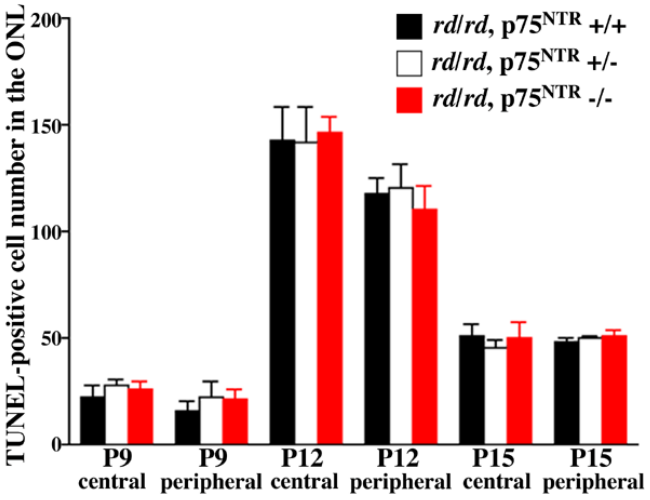

Figure 5. No effect of p75^{NTR} on the number of TUNEL-positive cells in *rd/rd* mice. Quantitative analysis of photoreceptor apoptosis in *rd/rd*, p75^{NTR}+/+ mice (black bars), *rd/rd*, p75^{NTR}+/- mice (white bars), and *rd/rd*, p75^{NTR}-/- mice (red bars). Number of TUNEL-positive cell nuclei in the outer nuclear layer (ONL) was counted in central and peripheral retina at P9, P12, and P15. No statistically significant differences were observed between these groups from P9 to P15. Results of at least three independent experiments are presented; error bars represent the SEM.

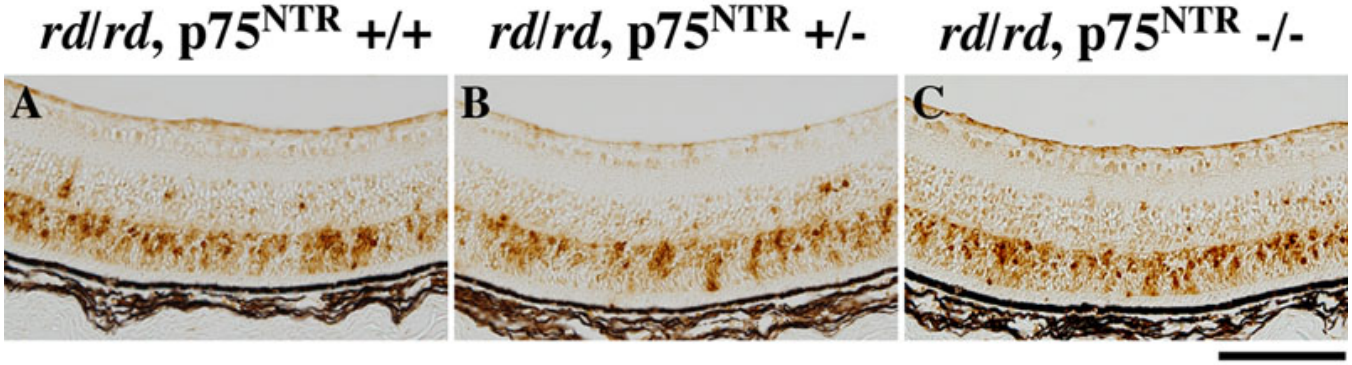

Figure 6. No effect of p75^{NTR} on the photoreceptor apoptosis in *rd/rd* mice. Detection of TUNEL-positive cells in *rd/rd*, p75^{NTR}+/+ mice, *rd/rd*, p75^{NTR}+/- mice, and *rd/rd*, p75^{NTR}-/- mice retina at P12. Many TUNEL-positive cell nuclei were observed in central retina of *rd/rd*, p75^{NTR} +/+ mice (**A**). Retinas of *rd/rd*, p75^{NTR}+/- (**B**) and *rd/rd*, p75^{NTR}-/- (**C**) mice also showed many TUNEL-positive cells in the outer nuclear layer (ONL) that is indistinguishable from *rd/rd*, p75^{NTR} +/+ mice. Scale bar represents 100 μm.

morphologic and histochemical analyses of *rd* mice (*rd/rd*, p75^{NTR}+/+) and *rd* mice without a functional p75^{NTR} gene (*rd/rd*, p75^{NTR}-/-) showed that the levels of apoptosis during retinal degeneration are not measurably affected by the absence of p75^{NTR}. Similar findings are reported in *c-fos*-/- mice [29,37]. Loss of *c-fos* gene prevents light-induced photoreceptor apoptosis [37], but has no effect in *rd* mice [29]. These results suggest a redundancy of other genes for photoreceptor apoptosis or the absence of a role for p75^{NTR} and *c-fos* in this process, in contrast to the induction of apoptosis by acute light. Another possibility is the different sensitivity to trophic factors between rat and mouse. We previously suggested a model in that p75^{NTR} in Müller glial cells decreases bFGF production in response to NGF, which leads to photoreceptor apoptosis in light-damaged rat retina [5,24,25]. However, this may not be the case in *rd* mice, because bFGF failed to protect photoreceptors in both *rd* and light-damaged mouse retina, whereas it showed a strong protective effect in the rat [6-9]. Thus, the species difference may explain the different role of p75^{NTR} for photoreceptor apoptosis.

Rohrer et al. [28] recently reported that p75^{NTR}+/- albino mice show significant neuroprotection against light exposure, whereas no difference was found between p75^{NTR}+/+ and p75^{NTR}-/- mice. We previously demonstrated that light injury to Wistar rat induces TrkC expression in photoreceptor cells, and exogenous NT-3 decreases photoreceptor apoptosis by activating the TrkC receptors [5]. It may be that the concomitant upregulation of TrkC suppresses the apoptotic action of p75^{NTR} in p75^{NTR}+/-, but not in p75^{NTR}+/+ and p75^{NTR}-/- mice, allowing for some photoreceptor survival in p75^{NTR}+/- mice. On the other hand, in the absence of p75^{NTR}, other pathways such as the *c-fos* triggered pathway [38] may dominate, and produce the apoptotic signal activated by the continued absorption of photons.

In the present study, *rd/rd*, p75^{NTR}+/- mice showed a pattern of photoreceptor apoptosis indistinguishable from *rd/rd*, p75^{NTR}+/+ retinas. However, due to differences in animal models examined (we have determined TrkC upregulation in light-damaged Wistar rats [5], but not in other rat and mouse strains), these results are difficult to interpret and to compare with each other. Similar phenotype differences between rat and mice are observed in the p53 gene. p53+/- mice provided significant neuroprotection against ischemia, whereas no difference was found between p53+/+ and p53-/- mice [39]. On the other hand, light-induced apoptosis of photoreceptors is independent of functional p53 [40], and p53 has no effect in *rd* mice [30,31]. Furthermore, absence of p53 delays apoptotic photoreceptor cell death in the *rds* mouse [41]. Thus, the function of these genes for neuroprotection may vary under different stimuli and genetic conditions.

In conclusion, our data shows that retinal degeneration in *rd* mice is independent of a functional p75^{NTR} gene. These results suggest that photoreceptor death in inherited and light-induced retinal degeneration is mediated by a number of different pathways including glia-neuron network [5,24-27]. Further investigation on the precise role of p75^{NTR} and its related molecules during photoreceptor degeneration will be needed.

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