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Fra-1 substitutes for c-Fos in AP-1-mediated signal transduction in retinal apoptosis

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Abstract

Lack of the AP-1 member c-Fos protects photoreceptors against light-induced apoptosis, a model for retinal degeneration. In mice, light damage increases the activity of the transcription factor AP-1, while pharmacological suppression of AP-1 prevents apoptosis, suggesting the involvement of pro-apoptotic AP-1 target genes. Recently, however, it was shown that photoreceptors expressing Fra-1 in place of c-Fos ($Fos^{Fosl1/Fosl1}$) are apoptosis competent despite the lack of transactivation domains in Fra-1. Here, we show that morphological features of light-induced apoptosis were indistinguishable in $Fos^{Fosl1/Fosl1}$ and wild-type mice. Furthermore, light exposure comparably increased AP-1 activity in both genotypes. Opposite to wild-type mice, Fra-1, but not c-Fos, was detectable in AP-1 complexes of $Fos^{Fosl1/Fosl1}$ mice. Importantly, AP-1 responsiveness for glucocorticoid receptor-mediated inhibition was preserved in $Fos^{Fosl1/Fosl1}$ mice. Thus, Fra-1 takes over for c-Fos in pro- and anti-apoptotic signal transduction. As Fra-1 lacks transactivation domains, AP-1 may not induce, but rather suppress genes in retinal light damage.

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c-Fos (encoded by *Fos*) and Fra-1 (fos-related antigen-1, encoded by *Fosl1*) both are components of the dimeric transcription factor AP-1. To form a functional AP-1 complex, c-Fos and Fra-1 have to combine with Jun proteins (Angel and Karin 1991). While AP-1 complexes containing c-Fos or Fra-1 bind to the same regulatory DNA sequences, the most prominent difference between these two proteins is the lack of transactivation domains in Fra-1 (Cohen *et al*. 1989). Despite this fundamental difference, Fra-1 can substitute for the lack of c-Fos in a variety of cellular processes in $Fos^{Fosl1/Fosl1}$ knock-in mice in which *Fosl1* is expressed in place of *Fos* (Fleischmann *et al*. 2000).

AP-1, and in particular c-Fos, has been shown to play an important role in light-induced degeneration of photoreceptors, a model widely used to study apoptosis, the common death pathway in retinal degeneration (Remé *et al*. 1998). Exposure to damaging doses of light induces AP-1 DNA binding activity in retinal cells (Wenzel *et al*. 2000) and ablation of c-Fos protects photoreceptors from light-induced apoptosis (Hafezi *et al*. 1997). Likewise, inhibition of AP-1 by activated glucocorticoid receptor (GR) renders photoreceptors resistant to light damage (Wenzel *et al*. 2001). Based on these findings it was assumed that increased AP-1 DNA binding activity during light-induced apoptosis reflects increased expression of pro-apoptotic target genes. However, this model was challenged by the finding that Fra-1 could substitute for c-Fos in AP-1-mediated retinal apoptosis. We therefore analyzed in detail several molecular aspects of AP-1 during light-induced apoptosis in $Fos^{Fosl1/Fosl1}$ mice to understand how Fra-1 may compensate for c-Fos at the molecular level.

Materials and methods

All procedures concerning animals adhered to the Association for Research in Vision and Opthalmology (ARVO) statement for the use

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Abbreviations used: AP-1, activator protein-1; BSA, bovine serum albumin; DTT, dithiothreitol; Fra-1, fos-related antigen-1; GR, glucocorticoid receptor; Dex, dexamethasone; EMSA, electrophoretic mobility shift assay; TUNEL, TdT-mediated dUTP nick-end labelling; ONL, outer nuclear layer; ROS, rod outer segments; RIS, rod inner segments; PE, pigment epithelium.

of animals in ophthalmic and vision research. Wild-type and $Fos^{Fosl1/Fosl1}$ mice (129/Sv) were kept under a 12 h : 12 h (6 : 00/6 : 00) light–dark cycle (60 lux at bottom of cages). For experiments offspring at the age of 4–8 weeks was used. Reagents were obtained from Sigma Aldrich Corp. (St Lois, MO, USA) and Fluka Holding AG (Buchs, Switzerland) if not indicated otherwise.

Light exposure

Prior to light exposure, animals were dark-adapted for 16 h overnight. The pupils of the animals were dilated under dim red light (Cyclogyl 1%, Alcon, Cham, Switzerland and phenylephrine 5%, Ciba Vision, Niederwangen, Switzerland) and the mice were exposed to diffuse white fluorescent light (TLD-36 W/965 tubes, Philips, Hamburg, Germany; UV-impermeable diffuser) for 2 h (lights on at 10 : 00 am) with an intensity of 15 klux in cages with a reflective interior. After light exposure, animals were analyzed immediately or following a period in darkness.

Microscopy

Eyes were enucleated and fixed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.3 at 4°C overnight. For each eye, the superior central and the inferior central retina adjacent to the optic nerve were trimmed, washed in cacodylate buffer, incubated in osmium tetroxide for 1 h, dehydrated in increasing ethanol concentrations and embedded in Epon 812. For light microscopy, sections (0.5 μm) were prepared from the lower central retina (most affected in our light-damage model), counterstained with methylene blue and analyzed using an Axiophot microscope (Zeiss, Oberkochen, Germany).

TUNEL assay

Eyes were fixed in 2% paraformaldehyde for 2 h at 4°C followed by dehydration and paraffin embedding. TdT-mediated dUTP nick-end labelling (TUNEL) was performed with modifications using the 'in situ cell death detection kit' (Boehringer Mannheim, Mannheim Germany) on 5-μm paraffin sections. DNA strand breaks were labelled with fluorescein and visualized with a FITC filter.

Electrophoretic mobility shift assay (EMSA)

Nuclear extracts were prepared as described previously (Hafezi *et al*. 1999b). Briefly, one retina was homogenized in 400 μL 10 mM HEPES–KOH pH 7.9, 1 mM β-mercaptoethanol, 1 mM dithiothreitol (DTT) in the presence of protease inhibitors. After incubation on ice for 10 min, the homogenate was vortexed for 10 s and centrifuged at 2300 *g*. The pellet was resuspended in 50 μL 20 mM HEPES–KOH pH 7.9, 25% glycerol, 420 mM NaCl, 1.5 mM $MgCl_2$, 0.2 mM EDTA, 1 mM β-mercaptoethanol, 1 mM DTT in the presence of protease inhibitors and incubated on ice for 10 min. Cellular debris was removed by centrifugation at 23 000 *g* for 30 min at 4°C. Protein concentrations were determined using the Bradford protein assay (Bio-Rad, Hercules, CA, USA) with bovine serum albumin (BSA) as standard.

EMSAs were performed as described previously (Hafezi *et al*. 1999b). Briefly, the oligonucleotides coding for an AP-1 specific (5′-AAGCATGAGTCAGACAC-3′) DNA binding sequence (TPA response element, TRE) were labelled using polynucleotide kinase (Boehringer Mannheim) and [γ-^{32}P]ATP (Hartmann Analytic GmbH, Braunschweig, Germany). For EMSA, 2–5 μg (5 μL) protein of nuclear extract were incubated on ice for 20 min with 19 μL 5 mM $MgCl_2$, 0.1 mM EDTA, 0.75 mM DTT, 7.5% glycerol, 0.05% NP-40 containing 24 μg BSA and 2 μg poly d(I-C) (Boehringer Mannheim). Radiolabelled oligonucleotide (1 μL) was added and incubation was continued for another 20 min. Protein/DNA complexes were resolved at 150 V on a 1.5-mm 6% polyacrylamide gel using 0.25 × TBE (22.5 mM Tris, 22.5 mM Borate, 5 mM EDTA, pH 8.3) buffer and visualized on X-ray film.

For antibody interference analyses, rabbit polyclonal antibodies directed against c-Fos (3 μL), Fra-1 (3 μL) or a mixture of antibodies directed against c-Jun, JunB and JunD (each 2 μL) (Santa Cruz, Santa Cruz, USA; Cat. nos: sc-052, sc-183, sc-045, sc-046, sc-074) were added to nuclear extracts 30 min prior to the oligonucleotides and incubated at room temperature.

Results

Untreated retinas from wild-type and $Fos^{Fosl1/Fosl1}$ mice (129/Sv) showed no morphological difference (Figs 1a and e). Exposure to 15 000 lux of diffuse fluorescent white light induced retinal degeneration in both, wild-type and $Fos^{Fosl1/Fosl1}$ mice. Morphologically, light-induced apoptosis of photoreceptors in $Fos^{Fosl1/Fosl1}$ mice proceeded as in wild-type mice: 24 h after light exposure the light-sensitive outer segments of photoreceptors appeared disintegrated, inner segments containing mitochondria were swollen and nuclear chromatin in a major proportion of photoreceptors of the affected area was condensed (Figs 1b and f). The adjacent pigment epithelium was filled with ingested debris from deteriorating photoreceptors. TUNEL staining revealed the presence of internucleosomal DNA cleavage in photoreceptor nuclei (Figs 1c and g) indicating that cell death in both genotypes occurred by apoptosis.

Also, 10 days following light exposure, no difference could be observed between light-exposed wild-type and $Fos^{Fosl1/Fosl1}$ mice: The thickness of the outer nuclear layer was reduced from 10–13 (Figs 1a and e) to 3–5 rows (Figs 1d and h) of photoreceptor nuclei, indicating that in the most affected area approximately 70% of the photoreceptors had died. The continuous presence of nuclei with condensed chromatin 10 days after light exposure was suggestive of still ongoing apoptosis. Thus, replacement of *Fos* with *Fosl1* did not result in any difference regarding the outcome of light exposure as judged by morphological criteria.

To investigate whether Fra-1 directly replaces c-Fos in $Fos^{Fosl1/Fosl1}$ mice during light-induced apoptosis, we monitored the activity of AP-1 in retinal nuclear extracts derived from mice following light exposure. In wild-type mice, light damage to photoreceptors increases the DNA binding activity of AP-1 (Fig. 2a and Wenzel *et al*. 2000). Like in wild-type mice (Wenzel *et al*. 2000), AP-1 activity in $Fos^{Fosl1/Fosl1}$ mice was elevated immediately following light exposure and remained high for at least the following 6 h (Fig. 2c). Thus, there was no apparent difference in timing of the AP-1 response. The composition of light-induced AP-1 was analyzed by antibody interference assays. In EMSA

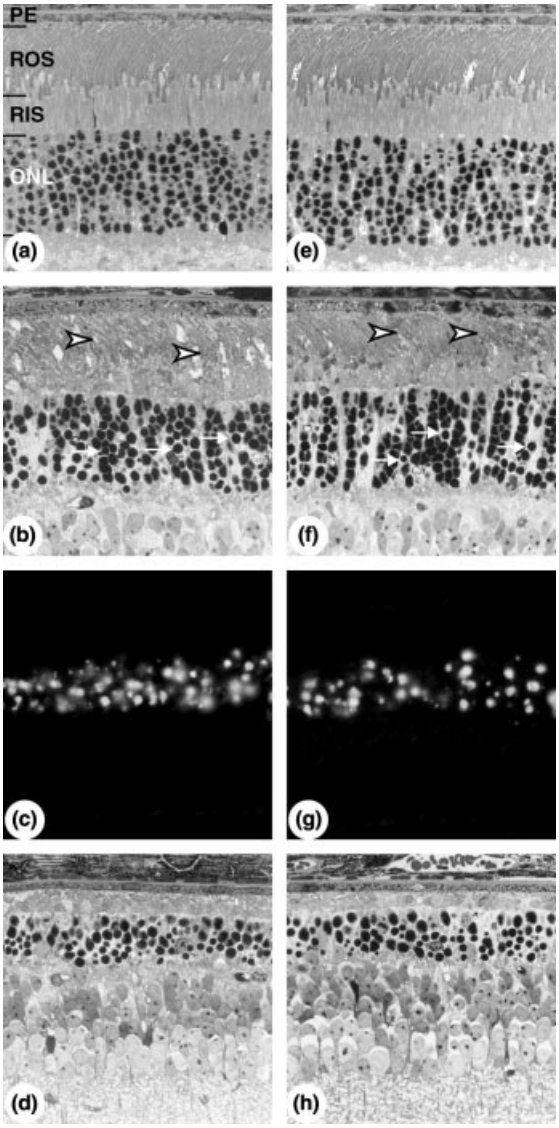

Fig. 1 No morphological difference between light-induced apoptosis of photoreceptors in wild-type and *Fos*$^{Fosl1/Fosl1}$ mice. (a and e) No morphological difference was observed between wild-type (left panel) and *Fos*$^{Fosl1/Fosl1}$ (right panel) mice before light exposure. (b and f) Twenty-four hours after light exposure, most of the photoreceptor nuclei within the outer nuclear layer (ONL) contained condensed chromatin (arrows), the outer (ROS, arrowheads) and inner (RIS) segments of rods appeared disintegrated. The pigment epithelium (PE) was swollen. (c and g) At the same time point, TUNEL staining revealed DNA fragmentation in photoreceptor nuclei. (d and h) Ten days after light exposure, the thickness of the ONL was reduced by approximately 70% in the most affected area and ROS were almost completely absent.

from nuclear extracts derived from wild-type mice 6 h following light exposure, antibodies directed against c-Fos and Jun proteins interfered with AP-1, resulting in a changed mobility of the AP-1/DNA complex and/or an inhibition of AP-1 DNA binding (Fig. 2b). Antibodies directed against

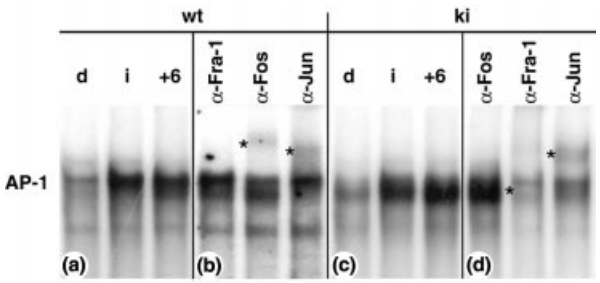

Fig. 2 Composition of AP-1 following light exposure. AP-1 activity in retinal nuclear extracts was analyzed by EMSA. Complex-composition was investigated by antibody interference using antibodies directed against c-Fos (α-Fos), Fra-1 (α-Fra-1) and a mixture of antibodies directed against c-Jun, JunD and JunB (α-Jun). (a) Typical time course of AP-1 induction in wild-type (wt) mice. Before light exposure (d) activity is at low basal levels. Immediately following light exposure (i) activity is strongly elevated and remains high at least until 6 h after light exposure (+ 6). (b) Antibody interference with AP-1 DNA binding 6 h after light exposure shows that c-Fos and Jun but not Fra-1 proteins are part of the active complex. (c) Time course of AP-1 induction in *Fos*$^{Fosl1/Fosl1}$ (ki) mice. Before light exposure (d) activity is at low basal levels. Immediately following light exposure (i) activity is strongly elevated and remains high at least until 6 h after light exposure (+ 6). (d) Antibody interference with AP-1 DNA binding at 6 h after light exposure shows that Fra-1 and Jun but not c-Fos proteins constitute the active complex. *Indicates antibody interference with AP-1 DNA complexes resulting in a supershift and/or decreased DNA binding.

Fra-1 had no such effect (Figs 2a and b, compare '+ 6' with 'α-Fra-1'). These data are consistent with previous observations indicating that in wild-type mice light-induced AP-1 mainly consists of c-Fos and JunD or c-Jun but not Fra-1 (Hafezi *et al*. 1999b). In contrast, addition of a Fra-1 antibody to nuclear extracts derived from *Fos*$^{Fosl1/Fosl1}$ mice had a strong inhibitory effect on AP-1 DNA binding, while addition of a c-Fos antibody was without effect (Figs 2c and d, compare '+ 6' with 'α-Fos'). Thus, in *Fos*$^{Fosl1/Fosl1}$ mice, Fra-1 directly substitutes for c-Fos in AP-1 complex formation induced by exposure to damaging light.

To further analyze the capacity of Fra-1 in *Fos*$^{Fosl1/Fosl1}$ mice to restore the wild-type phenotype in retinal apoptosis, dexamethasone (Dex) was applied to prevent retinal degeneration. In wild-type mice, treatment with Dex protects photoreceptors against light damage and, by activation of GR, post-transcriptionally interferes with AP-1 activity (Wenzel *et al*. 2001). Wild-type and *Fos*$^{Fosl1/Fosl1}$ mice that had been pretreated with Dex showed no signs of morphological damage when analyzed 10 days following exposure to 15 000 lux for 2 h (Figs 3b and f compared with Figs 3c and g). As described for wild-type mice (Wenzel *et al*. 2001), application of Dex also suppressed light-induced AP-1 activity in *Fos*$^{Fosl1/Fosl1}$ mice (Figs 3d and h). These results suggest that Fra-1 not only substitutes for c-Fos in AP-1-mediated pro-apoptotic signal transduction, but also in anti-apoptotic transcription factor cross talk between AP-1 and GR.

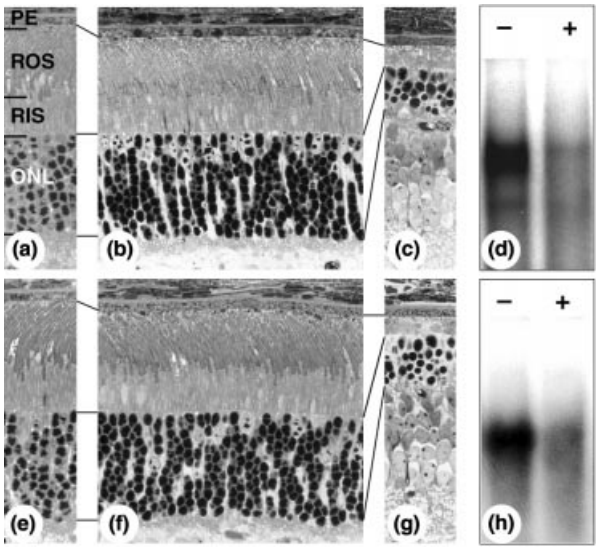

Fig. 3 AP-1 and GR: transcription factor cross-talk. Treatment of wild-type (a–d) and knock-in (e–h) mice with dexamethasone (DEX) prior to light exposure completely blocked light-induced retinal degeneration and impaired AP-1 activity. (a and e) Control retina. (b and f) Retina 10d following exposure to light after DEX treatment (52 mg/kg i.p.). (c and g) Retina 10d following exposure to light without DEX treatment. (d and h) AP-1 DNA binding activity in retinal nuclear extracts 6 h after light exposure without (–) or with (+) DEX treatment (52 mg/kg i.p.) as analyzed by EMSA. Lines indicate changes in layer thickness.

Discussion

Based on previous findings that expression of Fra-1 in place of c-Fos restores apoptosis competence in retinal photoreceptors (Fleischmann *et al*. 2000) while endogenous Fra-1 can not substitute for loss of c-Fos (Hafezi *et al*. 1999a; Hafezi *et al*. 1999b; Wenzel *et al*. 2000), we analyzed the morphological aspects of apoptosis, the molecular composition of AP-1 and AP-1's ability to interact with GR in $Fos^{Fosl1/Fosl1}$ mice.

Pro-apoptotic signalling

Ectopic Fra-1 took over for c-Fos in all aspects of light-induced photoreceptor apoptosis. Morphologically, time course and extent of retinal degeneration induced by light were indistinguishable between wild-type and $Fos^{Fosl1/Fosl1}$ mice. Likewise, changes in AP-1 DNA binding activity upon light exposure were comparable in both types of mice.

These results suggest that Fra-1 placed under the control of the *Fos* regulatory sequences phenotypically behaves like c-Fos in the light damage model. Therefore, it appears that endogenous Fra-1 fails to substitute for c-Fos in $Fos^{-/-}$ mice (Hafezi *et al*. 1999a; Hafezi *et al*. 1999b; Wenzel *et al*. 2000), due not to functional inability of the protein itself, but rather to the differential responsiveness of *Fos* and *Fosl1* regulatory sequences to signals triggered by light exposure. As c-Fos expression is increased by light (Grimm *et al*. 2000), placing Fra-1 under the control of *Fos* regulatory sequences may enable Fra-1 expression and thus AP-1-mediated signalling despite the lack of c-Fos. Indeed, the *Fosl1* knock-in allel recapitulates the temporal and spatial expression pattern of c-Fos *in vivo* and *in vitro* (Fleischmann *et al*. 2000).

In light-induced retinal degeneration, as in several other systems stimuli finally leading to apoptosis, a rapid increase of c-Fos/AP-1 DNA binding activity results, suggesting transactivation/up-regulation of AP-1 target genes, which in turn may contribute to the execution of an affected cell. However, evidence accumulates that this concept may not be valid for light-induced apoptosis of photoreceptors: Fra-1 has no identifiable transactivation domains (Cohen *et al*. 1989), thus the pro-apoptotic function of AP-1 complexes containing Fra-1 may not be based on the transactivation/up- regulation of pro-apoptotic AP-1 target genes. In wild-type mice, light-induced AP-1 complexes apart from c-Fos contain the Jun family proteins c-Jun and JunD (Hafezi *et al*. 1999b). Absence of JunD has no effect on the outcome of light damage, suggesting that among the Jun proteins c-Jun alone may be able to mediate the death signal (Hafezi *et al*. 1999a). Interestingly, interference with N-terminal phosphorylation of c-Jun (Behrens *et al*. 1999), which is crucial for its transactivational activity, does not change the light damage susceptibility of photoreceptors (Grimm *et al*. 2001). Like Fra-1 here, the non-transactivating mutant c-Jun protein was constituent of light-induced AP-1 (Grimm *et al*. 2001). Thus, although AP-1 DNA binding is increased in mice with mutant c-Jun or in $Fos^{Fosl1/Fosl1}$ mice it may not result in transactivation of AP-1 target genes. Nevertheless, induction of AP-1 appears essential for light-induced photoreceptor apoptosis, as suppression of AP-1 activity by activation of GR (see below), like in wild-type mice, prevents photoreceptor apoptosis in $Fos^{Fosl1/Fosl1}$ mice. These results suggest that AP-1 instead of up-regulating pro-apoptotic genes may rather mediate repression of anti-apoptotic or survival genes.

Anti-apoptotic signalling

Not only pro-apoptotic features of AP-1 but also the responsiveness to GR-mediated inhibition of AP-1 was preserved in AP-1 containing Fra-1 in place of c-Fos. These findings may shed new light on the interaction of GR with AP-1, which in several instances has been described to specifically involve c-Fos (Lucibello *et al*. 1990; Kerppola *et al*. 1993). Mechanistically, the inhibitory cross talk of the activated GR with AP-1 is not well resolved and various models have been proposed:

(i) Inhibition of AP-1 by the GR has been attributed to a protein–protein interaction of both factors (Jonat *et al*. 1990; Schule *et al*. 1990; Yang-Yen *et al*. 1990). In particular, the

interaction of GR with AP-1 containing c-Fos was assigned to a functional domain in c-Fos, which is poorly conserved in other Fos family members like Fra-1 (Lucibello *et al*. 1990). Yet, GR-mediated inhibition of AP-1 in our system was independent of the presence of c-Fos.

(ii) Activation of GR may induce the expression of the glucocorticoid-inducible leucine zipper GILZ, which in turn can inhibit AP-1 (Mittelstadt and Ashwell 2001). However, systemic application of Dex in our system results in strong inhibition of AP-1 within 1 h (Wenzel *et al*. 2001), making it unlikely that *de novo* synthesis of GILZ is involved. Furthermore, application of Dex 2 h prior to light exposure has no protective effect (unpublished), suggesting that GILZ is not essential.

(iii) GR-mediated inhibition of AP-1 has also been attributed to interference with N-terminal phosphorylation of c-Jun (Gonzalez *et al*. 2000; De Bosscher *et al*. 2001), one of the major partners of c-Fos. Nevertheless, since lack of N-terminal phosphorylation of c-Jun does not prevent light damage (Grimm *et al*. 2001), this mechanism may not apply for this system.

(iv) Competition for cofactors that interact with and potentiate the activity of both transcription factors. In particular, steroid receptor coactivator-1 and CREB-binding protein have been shown to coactivate transcriptional activity of AP-1 and GR (Kamei *et al*. 1996; Lee *et al*. 1998), and for both co-activators an interaction with c-Fos has been described (Bannister and Kouzarides 1995; Lee *et al*. 1998). Although it is unknown whether c-Fos is essential for interaction with and competition for coactivators, the competition mechanism when applicable to our model may also work when c-Fos is replaced by Fra-1.

Thus, based on our results, we will focus on two of the four models for future research. First, the competition model, which obtains support from the observation that activation of GR, once AP-1 DNA binding is established, lacks a protective effect (Wenzel *et al*. 2001). Second, the direct interaction model although with a special focus on interactions of Jun proteins with GR.

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