ANTIOXIDANTS & REDOX SIGNALING
Volume 2, Number 3, 2000
Mary Ann Liebert, Inc.

Forum Review Article

Model for Aging in the Basal Forebrain Cholinergic System

ZEZONG GU, GITTA WORTWEIN, JUAN YU, and J. REGINO PEREZ-POLO

ABSTRACT

A key component of the cognitive deficits associated with aging is the loss of function of cholinergic neurons in the basal forebrain due to neuronal losses and decreased cholinergic function of spared neurons. A model to mimic one aspect of this phenomenon is to kill cholinergic neurons selectively in the basal forebrain via administration of the immunotoxin IgG-192-saporin. Here we discuss apoptotic regulators, such as nerve growth factor, in age-associated changes present in the cholinergic system and the role of the NF-κB signaling system in cellular commitment to apoptosis. We also examine the age-associated decline in intrinsic response mechanisms, which may account for the age-associated reduction in recovery from both acute and chronic insults to the central nervous system. Antiox. Redox Signal. 2, 437–447.

INTRODUCTION

THE DEVELOPMENT OF AGE-ASSOCIATED COGNITIVE DEFICITS may be the result of adaptive behaviors by brain structures to increased exposure to reactive oxygen species (ROS) or nitric oxides (NO). The neurotransmitter systems essential to cognitive function (for example, glutamate and acetylcholine, ACh) can also exert toxic effects via NO generation and increased intracellular Ca^{2+} fluxes (glutamate) or postsynaptic stimulation of oxidative processes (ACh), a plausible explanation for the acknowledged "fragility" of some hippocampal and striatal structures in the face of ischemic or traumatic insults. What is not known is the sequence of events that results in the age-associated deficits. Thus, while it is clear that there is some neuronal cell loss and reduced neurotransmitter function in the hippocampii of aged rodents, apes, and humans, we do not know the cause of these losses or their relationship to the more prominent pathological markers present in the aged and Alzheimer's disease (AD) brain.

The need for linkage between the molecular and cellular indices, such as extracellular deposition of amyloid deposits that form senile plaques and the prominent appearance of intracellular neurofibrillary tangles (for reviews, see Coyle *et al.*, 1983; Whitehouse *et al.*, 1985; Yankner, 1996), and behavioral (memory loss) outcomes may perhaps explain the present fascination with "impaired signaling processes" as a possible cause for the described losses of cells and functions. Therefore, it would seem reasonable to ask if pertinent signaling responses to stress are impaired in the aged rodent brain? An extension of the question would ask if any impairment of signaling processes is specific or part of a more general intrinsic metabolic property of aged organisms? Lastly, the

Department of Human Biological Chemistry and Genetics, The University of Texas Medical Branch at Galveston, TX 77555-0652.

proper analyses of these age-induced perturbations of stress response signal transduction pathways might elicit clues as to the nature of the aging process in terms of the respective roles of intrinsically versus extrinsically triggered signaling pathways.

AGE-ASSOCIATED CHOLINERGIC DEFICITS

That there is a relationship between cholinergic function and memory and learning was initially ascertained from observations of aged and demented patients in their responses to various pharmacological manipulations. Application of the muscarinic receptor antagonist scopolamine to young normal subjects produces deficits in cognition and memory that are similar to those seen in aged subjects. Additionally, administration of the cholinergic agonist physostigmine to aged human subjects results in an improvement in memory function (Bartus *et al.*, 1982; Coyle *et al.*, 1983; Drachman, 1977).

Neuropsychological, biochemical, and pharmacological evidence further supports the notion of a significant role for cholinergic function in age-related memory disturbance leading to a proposal of a cholinergic hypothesis of dementia in aging and age-related disorders. The presence of cholinergic deficits and the loss of cholinergic basal forebrain neurons (CBFNs) in the aged and AD brains have been well documented (Davies and Maloney, 1976; Perry *et al.*, 1977; Whitehouse *et al.*, 1982). Postmortem studies have shown that there is a profound reduction in cortical presynaptic cholinergic markers in patients with AD and senile dementia of the Alzheimer's type. For example, choline acetyltransferase (ChAT) activity decreases 60–90% in the cerebral cortices and hippocampi of AD patients. The cholinergic neurons of the nucleus basalis of Meynert (NBM), the major source of cortical cholinergic innervation, undergo a profound (greater than 75%) and selective degeneration in these patients and the degree of loss correlates with the severity of the observed cognitive impairments (Perry *et al.*, 1978; Whitehouse *et al.*, 1982). In addition, an *in situ* hybridization study (Strada *et al.*, 1992) has shown decreased ChAT mRNA expression in the NBM in AD patients, suggesting that expression of ChAT mRNA might be down-regulated in surviving cholinergic neurons. Reductions are also observed in high-affinity choline uptake (HACU) (Rylett *et al.*, 1983), ACh, and acetylcholinesterase (AChE) levels in cortex (Richter *et al.*, 1980) and cerebrospinal fluid (CSF) (Elble *et al.*, 1989). Nerve growth factor (NGF) receptor and ChAT remain colocalized in the NBM in AD patients (Kordower *et al.*, 1989). Apart from the presence of cholinergic dysfunction, there are (Scott *et al.*, 1995) moderate increases in NGF-like activity throughout the brain of AD coupled with significant declines in NBM cell numbers compared to aged healthy individuals. Although the mechanisms that lead to the degeneration of cholinergic neurons in the NBM are unknown, it has been speculated that neuronal death may result in part due to a failure of neurotrophic support for the maintenance of oxidant–antioxidant and glutathione peroxidase homeostasis (Perez-Polo *et al.*, 1990; Jackson *et al.*, 1994; Pan *et al.*, 1997).

There is a substantial decrease in ChAT activity in the striatum, and there are decreases in HACU in the frontal cortex and hippocampus, of 24-month-old rats when compared to 4-month-old rats (Williams and Rylett, 1990). However, Ogawa *et al.*, (1994) found that reduced ChAT activity and muscarinic M1 receptor levels in aged Fisher 344 rat brains did not parallel their mRNA levels, suggesting that some age-related impairments of the cholinergic system may be due to post-transcriptional events. Immunocytochemistry and retrograde transport labeling results have shown that there is a decline in the number of neurons retrogradely transporting tracers and also that there is a significant shrinkage in cell-surface area in the basal forebrain cholinergic system of aged rats, consistent with there being atrophy of cholinergic basal forebrain neurons and impairment of uptake or retrograde transport mechanisms in the aged brain (De Lacalle *et al.*, 1996).

Although the loss of CBFNs in the aged and AD brains has been well documented, the relative contributions of cell death versus other signaling deficits are not known (Davies and

Maloney, 1976; Perry *et al.*, 1977; Whitehouse *et al.*, 1982). In addition to significant cholinergic dysfunction, there are (Scott *et al.*, 1995) increases in NGF-like activity and losses in cholinergic neurons throughout the brain of AD compared to aged healthy individuals. Although the mechanisms that lead to the degeneration of cholinergic neurons are not known, it could be that the decreases in cell number are the result of persistent oxidative stress and perturbed oxidant–antioxidant and glutathione peroxidase homeostasis (Perez-Polo *et al.*, 1990; Jackson *et al.*, 1994; Pan *et al.*, 1997). Thus, it could be hypothesized that as a result of persistent exposure to oxidative stress those signaling pathways that normally mediate stress responses to restore homeostasis gradually and selectively become impaired over time. One can differentiate between an age-associated endogenous or intrinsic change in intracellular signaling pathways versus impairment due to deafferentation by comparing stress responses associated with recovery processes that maintain cholinergic function. For example, the number of neurons actively involved in retrograde transport into the basal forebrain decreases in parallel with increasing atrophy of CBFNs in the aged brain (De Lacalle *et al.*, 1996). Administration of submaximal doses of 192 IgG-saporin can mimic age-associated partial degenerations of basal forebrain cholinergic projections with demonstrable graded behavioral and biochemical changes and reorganization in the cholinoceptive target areas (Waite *et al.*, 1995; Leanza *et al.*, 1996b; Rossner *et al.*, 1996).

IMMUNOLESION MODEL SYSTEM

There are several animal model systems that have attempted to determine the mechanisms of impairment of cholinergic function, cell death and recovery processes that might be useful in the design of relevant therapeutic strategies. These have typically relied on fimbria-fornix transections, mechanical lesions with radiofrequency and electrolysis, systemic or intracerebral injections of excitotoxins, which are analogues of the excitatory amino acid neurotransmitter glutamate (*e.g.*, kainic acid, ibotenic acid, quisqualic acid, N-methyl-D-aspartase (NMDA), and DL-α-amino-hydroxy-methyl-isoxaze propionic acid (AMPA), high-affinity choline transport inhibitors (ethylcholine mustard aziridinium ion, AF64A), or murine anti-AChE monoclonal antibodies. The limitations of these lesion paradigms are that they not only cause cholinergic deafferentation, but that they also deplete noncholinergic projections, such as GABAergic, serotonergic, noradrenergic, and dopaminergic innervations. Thus, the differential affinities of the different excitotoxins to distinct glutamate receptor subtypes may partly explain the differential cytotoxic effects of each glutamate analogue on different regions of the brain.

A more selective approach would be to destroy cholinergic neurons selectively, while sparing other cell types. For example the CBFNs display $p75^{NTR}$ receptors (Gage *et al.*, 1989; Yan and Johnson, 1989; Steininger *et al.*, 1993) that will bind and internalize the well-characterized monoclonal antibody to $p75^{NTR}$, 192 IgG. When 192 IgG is cross-linked via a disulfide bond to the ribosomal inactivating protein, saporin, an immunotoxin (IT), the 192 IgG-saporin complex, results that is also internalized into CBFNs (Wiley *et al.*, 1991). Thus, after an intra cerebroventrical (i.c.v.) injection of 192 IgG-saporin, the IT is specifically internalized by the terminals of $p75^{NTR}$-bearing CBFNs, retrogradely transported and accumulated in the cell bodies of CBFNs. Treatment with intraventricular administration of IT produces selective and dose-dependent cell death among $p75^{NTR}$-bearing CBFNs best measured by substantial reductions in AChE and ChAT activity in the rat basal forebrain and its neocortical and hippocampal afferents (Wiley *et al.*, 1991; Book *et al.*, 1992; Berger-Sweeney *et al.*, 1994; Heckers *et al.*, 1994; Torres *et al.*, 1994; Leanza *et al.*, 1995; Rossner *et al.*, 1995a,c; Waite *et al.*, 1995; Yu *et al.*, 1995, 1996). Prelabeling cortical projecting neurons in the NBM with fluoro-gold shows that only those neurons that are also labeled for ChAT are destroyed in the IT-treated animals, suggesting that IT is lethal to cholinergic cells, rather than suppressing cholinergic expression in existing cells (Book *et al.*, 1994). Thus, all evidence points to cell loss and not decreased AChE and ChAT decreases

in surviving cells. There is also evidence that 192 IgG-saporin treatments impair performance in learning and memory tasks in a manner consistent with the extensive loss of CBFNs (Nilsson *et al.*, 1992; Berger-Sweeney *et al.*, 1994; Baxter *et al.*, 1995; Leanza *et al.*, 1995, 1996a; Wiley, 1997).

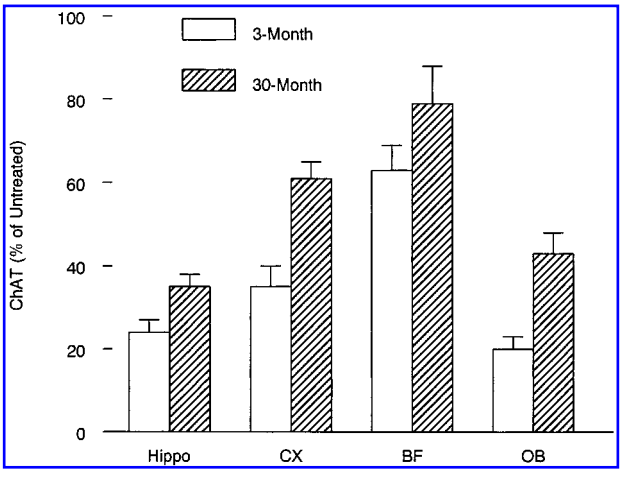
THE NEUROTROPHIC HYPOTHESIS AND THE AGED CNS

The neurotrophic hypothesis, that the survival of neurons depends on their competition for neurotrophic factors synthesized in limiting amounts by their innervation targets, could explain how age-associated changes in retrograde transport of neurotrophins bring about cell losses and recovery processes (Thoenen, 1995; Davies, 1996). NGF is the best-characterized member of the neurotrophin (NT) family, which also includes brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), and neutrophin-6 (NT-6) (for reviews, see Thoenen, 1991; Lindsay, 1994b; Bothwell, 1995; Thal, 1996; Hefti, 1997; Ibanez, 1998). NTs are highly basic proteins (pI 9–10.5) of approximately 120 amino acids with three intrachain disulfide bonds; they share 50–60% amino acid homology and display distinct, yet overlapping, regional distribution and regulate the survival, differentiation, and phenotypic maintenance of specific neuronal populations. In the CNS, NGF is expressed in different brain areas, with the highest levels present in the hippocampus, cerebral cortex, and olfactory bulb, the principal target areas of CBFNs (Thoenen, 1995; Thoenen *et al.*, 1987; Whittemore and Seiger, 1987), and affects a variety of cholinergic populations of the forebrain, including those of the medial septum, NBM, substantia innominata, and striatum.

NT action is via two transmembrane receptor proteins, a $p140^{trkA}$ and a $p75^{NTR}$ (Chao and Hempstead, 1995; Kaplan and Miller, 1997; Chao *et al.*, 1998; Frade and Barde, 1998). NGF receptors in the CNS are synthesized in the CBFNs and anterogradely transported to hippocampal and cortical axon terminals that innervate NGF-producing neurons. There NGF binds to and is internalized at nerve terminals and retrogradely transported to the CBFN soma. The $p75^{NTR}$ receptor is involved in the internalization and retrograde transport of all neurotrophins (Johnson *et al.*, 1987). The $p75^{NTR}$ receptor has been implicated in a NF-κB-mediated signal transduction cascade that decreases apoptotic cell commitment (Rabizadeh *et al.*, 1993; Carter *et al.*, 1996; Casaccia-Bonnefil *et al.*, 1996; Taglialatela *et al.*, 1996, 1997).

NGF treatment at pharmacological doses effectively prevents the degeneration of axotomized CBFNs in both young and aged animals (Hefti, 1986; Williams *et al.*, 1986; Gage *et al.*, 1988; Tuszynski *et al.*, 1990; Koliatsos *et al.*, 1991a; Tuszynski *et al.*, 1991; Kordower *et al.*, 1994). Furthermore, the atrophy of CBFNs and the cognitive deficits displayed by aged rats can be reversed by NGF (Fischer *et al.*, 1987, 1991). Chronic i.c.v. injections of NGF elevate hippocampal ChAT activity in adult rats after partial septohippocampal lesions (Hefti *et al.*, 1984), induce synaptogenesis and hypertrophy after decortication of adult rats (Garofalo *et al.*, 1992), and ameliorate cholinergic neuronal atrophy and behavioral impairment after brain injury or extreme aging (Fischer *et al.*, 1987; Chen and Gage, 1995; Martinez-Serrano and Bjorklund, 1998). Interestingly, injury models (*e.g.*, fimbria fornix transections or immunolesions) increase neurotrophin protein levels in young, but not aged, rats (Fischer *et al.*, 1987; Williams *et al.*, 1993; Scott *et al.*, 1994; Gu *et al.*, 1998; Fig. 1). One explanation for this differential age-associated impairment of a stress response signaling pathway that may regulate the recovery of ACh function and inhibit neuronal commitment to apoptosis would be at the level of transcription factor activation by oxidative stress. That is, the persistent increase in oxidative stress associated with the aging process could serve to desensitize stress response activation of transcription at the level of the activation levels of a transcription factor or at the level of subsequent binding to gene promoter sites and activation of mRNA synthesis.

It has been suggested that oxidative stress due to ischemia, trauma, excitotoxicity, and neurodegenerative diseases may stimulate



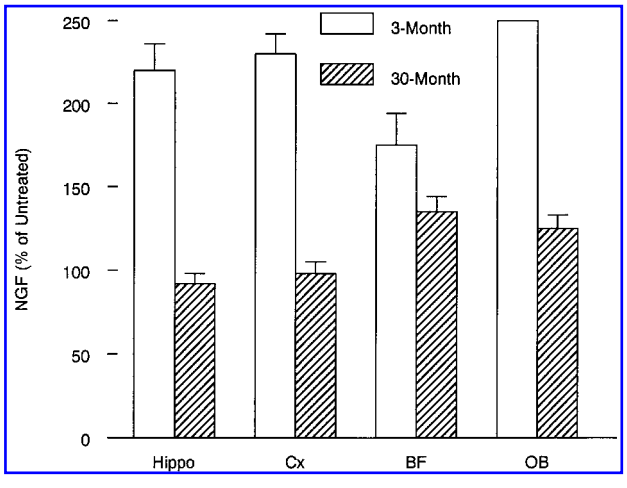


FIG. 1. Effect of total immunolesions on brain ChAT activity and NGF protein levels in the CBFN target areas of young and aged Fischer 344 × Brown Norway hybrid rats at 4 weeks postlesion. Hippo, Hippocampus; Cx, cortex; BF, basal forebrain; OB, olfactory bulb. Values are expressed as percentage of immunolesioned values to treated animals where mean ± SEM of 4 young control, 4 young lesioned, 8 aged control, and 7 aged lesioned animals. $p < 0.05$, significantly different from young control rats; $p < 0.05$, significantly different from young lesioned rats, two-way analysis of variance (ANOVA) with post-hoc Fisher's LSD analysis. Adapted from Gu *et al.* (1998). (**Upper panel**) CHAT. (**Lower panel**) NGF for Fig. 1.

neuronal apoptosis (Siesjo *et al.*, 1989; Coyle and Puttfarcken, 1993; Olanow, 1993). Although many transcription factors are involved in stress response gene regulation, two factors known to play a dominant role are NF-κB and activator protein (AP-1) (Tong *et al.*, 1998). Both transcription factors, AP-1 and NF-κB, play roles in the signal transduction pathways potentially associated with regulation of apoptosis (Tong and Perez-Polo, 1995; Taglialatela *et al.*, 1997; Cui *et al.*, 1999).

NF-κB

While AP-1 activation involves induction of *de novo* synthesis of the AP-1 protein dimers, NF-κB activation is via sudden response to changes in cellular redox state (Bauerle, 1991; Siebenlist *et al.*, 1994). Because NK-κB is a preformed transcriptional factor with regulatory activity, it can be rapidly activated by mechanisms that do not require *de novo* protein synthesis in contrast to the immediate-early transcription factor AP-1 family, whose activity is regulated via prompt, robust, and transient gene induction.

Activation of NF-κB by various stimuli leads to subsequent transcriptional activation of many target genes (Baeuerle and Henkel, 1994; O'Neill and Kaltschmidt, 1997), including proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, and interferon-γ; inducible nitric oxidase synthase (iNOS), manganese superoxide dismutase (Mn-SOD), and cyclooxygenase-2 (COX-2); major histocomatibility complex class-I (MHC-I); vascular cell adhesion molecule-1 (VCAM-1); the neuropeptide dynorphin; and viral human immunodeficiency virus type 1 (HIV-1) gene.

NF-κB belongs to a family of homo- and heterodimeric proteins related by a conserved ~300 amino acid residue amino-terminal Rel/homology domain that includes p65 (also referred to as RelA), p50, and p49 (also referred to as p52) as well as RelB and c-Rel. NF-κB binds to a 10-bp generic DNA consensus sequence 5′-GGGRNNYYCC-3′ (G, guanine; R, purine; N, any nucleotide; Y, pyrimidine; C, cytosine). NF-κB is regulated by redox modification (Mosialos *et al.*, 1991; Matthews *et al.*, 1992; Hayashi *et al.*, 1993; Meyer *et al.*, 1994). A role for ROS as second messengers in NF-κB regulation is suggested by the activation of NF-κB by H_2O_2 and its inhibition by antioxidants, such as *N*-acetylcysteine (NAC) and thioredoxin (Kaltschmidt *et al.*, 1993, 1994, 1995; Meyer *et al.*, 1993; Schenk *et al.*, 1994). Upon stimulation, I-κB is phosphorylated and de-

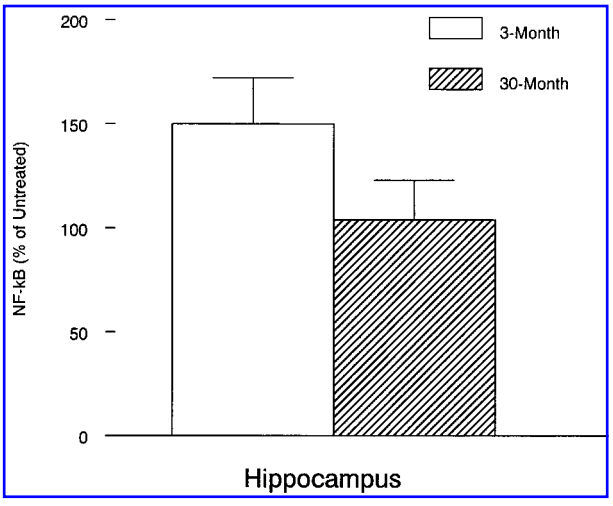


FIG. 2. Effect of partial immunolesions (0.65 μg of 192IgG-Saporin bilateral injections) on hippocampal NF-κB binding activity in young (3-month) and aged (30-month) Fischer 344 × Brown Norway hybrid rats expressed as percentage of activity in immunolesioned as compared to controls at 16 days after the immunolesion. In all cases, DNA-binding activity is larger in the 30-month-olds as compared to the 3-month-olds, $p < 0.001$. Adapted from Gu, Z., Yu, J., and Perez-Polo, J.R. (1998). Responses in the aged rat brain after total immunolesion. J. Neurosci. Res. 54:7–16, Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

graded (Ghosh and Baltimore, 1990; Lin *et al.*, 1995), and nuclear translocation (NLS) domains on NF-κB proteins are exposed, which facilitate translocation to the nucleus for DNA binding.

NF-κB is an inducible transcription factor that is responsive to a broad range of stimuli (Baeuerle, 1991; Baeuerle and Baltimore, 1988), such as IL-1 and other cytokines, TNF, bacterial lipopolysaccharide (LPS), HIV-1, T-cell mitogens (*e.g.*, lectins, phorbol esters), UVA radiation (Vile *et al.*, 1995), hydrogen peroxide (Schmidt *et al.*, 1995), and hypoxia (Koong *et al.*, 1994). The converging event for different stimuli appears to be the removal of IκB proteins from a cytoplasmic complex with NF-κB via phosphorylation of IκB and subsequent ubiquitination and degradation by proteasomes (Baeuerle and Baltimore, 1996; Woronicz *et al.*, 1997; Zandi *et al.*, 1997).

NF-κB has constitutive activity in the hippocampus, cortex, and basal forebrain (Kaltschmidt *et al.*, 1993, 1994; Helenius *et al.*, 1996; Suzuki *et al.*, 1997; Toliver-Kinsky *et al.*, 1997). Increased NF-κB has been identified in neurons and astrocytes of brain sections from AD patients in association with early plaque formation (Boissiere *et al.*, 1997; Kaltschmidt *et al.*, 1997). Interestingly, aged rats display increased basal levels of NF-κB activity and, whereas immunolesions stimulate NF-κB levels in young rats, they have no such effect on their aged counterparts (Fig. 2).

There is ample evidence for increased NF-κB activity after acute injury to the brain and spinal cord, although the role of transient versus persistent NF-κB activation is not understood (Salminen *et al.*, 1995; Yang *et al.*, 1995; Perez-Otano *et al.*, 1996; Tong and Perez-Polo, 1996; Bethea *et al.*, 1998; Clemens *et al.*, 1998). Both the induction of Mn-SOD by TNF-α and C2-ceramide treatment, and the suppression of peroxynitrite formation and membrane lipid peroxidation by the peroxynitrite scavenger uric acid, is via increased NF-κB activation (Mattson *et al.*, 1997). NF-κB mediates increased calcium currents and decreased NMDA- and AMPA/KA-induced currents in hippocampal neurons treated with TNF-α (Furukawa and Mattson, 1998). Also, the sphingomyelin-ceramide signaling pathway stimulates the expression of iNOS via LPS- or cytokine-mediated activation of NF-κB in astrocytes (Pahan *et al.*, 1998). There is evidence that high constitutive NF-κB activity mediates resistance to oxidative stress in neuronal cell populations (Lezoualc'h *et al.*, 1998). Thus, NF-κB is likely to play an antiapoptotic role under neurodegenerative conditions resulting from metabolic and oxidative insults.

ACKNOWLEDGMENTS

This work was supported in part by NINDS NS33288, a grant from the Sealy Center on Aging, and grants from the Spinal Cord Research Foundation and TIRR.

ABBREVIATIONS

ACh, Acetylcholine; AChe, acetylcholin esterase; AD, Alzheimer's Disease; AF64A, ethylcholine mustard aziridinium ion—inhibitor of high-affinity choline transport; BDNF, brain-derived neurotrophic factor; CSF, cerebro-

spinal fluid; CBFN, cholinergic basal forebrain neurons; HACU, high-affinity choline uptake; HIV-1, human immunodeficiency virus type 1; IL-1, interleukin-1; IT, immunotoxin; LPS, lipopolysaccharide; NAC, *N*-acetylcysteine; NBM, nucleus basalis of Meynert; NGF, nerve growth factor; NO, nitric oxide; NT, neurotrophin; p75NTR, low-affinity neurotrophin receptor; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule.

REFERENCES

BAEUERLE, P.A. (1991). The inducible transcription activator NF-kappa B: regulation by distinct protein subunits. Biochim. Biophys. Acta **1072,** 63–80.

BAEUERLE, P.A., and BALTIMORE, D. (1988). Activation of DNA-binding activity in an apparently cytoplasmic precursor of the NF-kappa B transcription factor. Cell **53,** 211-217.

BAEUERLE, P.A., and BALTIMORE, D. (1996). NF-kappa B: ten years after. Cell **87,** 13–20.

BAEUERLE, P.A., and HENKEL, T. (1994). Function and activation of NF-kappa B in the immune system. Annu. Rev. Immunol. **12,** 141–179.

BARTUS, R.T., DEAN, R.L.D., BEER, B., and LIPPA, A.S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. Science **217,** 408–414.

BAXTER, M.G., BUCCI, D.J., GORMAN, L.K., WILEY, R.G., and GALLAGHER, M. (1995). Selective immunotoxic lesions of basal forebrain cholinergic cells: effects on learning and memory in rats. Behav. Neurosci. **109,** 714–722.

BERGER-SWEENEY, J., HECKERS, S., MESULAM, M.M., WILEY, R.G., LAPPI, D.A., and SHARMA, M. (1994). Differential effects on spatial navigation of immunotoxin-induced cholinergic lesions of the medial septal area and nucleus basalis magnocellularis. J. Neurosci. **14,** 4507–4519.

BETHEA, J.R., CASTRO, M., KEANE, R.W., LEE, T.T., DIETRICH, W.D., and YEZIERSKI, R.P. (1998). Traumatic spinal cord injury induces nuclear factor-kappaB activation. J. Neurosci. **18,** 3251–3260.

BOISSIERE, F., HUNOT, S., FAUCHEUX, B., DUYCKAERTS, C., HAUW, J.J., AGID, Y., and HIRSCH, E.C. (1997). Nuclear translocation of NF-kappaB in cholinergic neurons of patients with Alzheimer's disease. Neuroreport **8,** 2849–2852.

BOOK, A.A., WILEY, R.G., and SCHWEITZER, J.B. (1992). Specificity of 192 IgG-saporin for NGF receptor-positive cholinergic basal forebrain neurons in the rat. Brain Res. **590,** 350–355.

BOOK, A.A., WILEY, R.G., and SCHWEITZER, J.B. (1994). 192 IgG-saporin: I. Specific lethality for cholinergic neurons in the basal forebrain of the rat. J. Neuropathol. Exp. Neurol. **53,** 95–102.

BOTHWELL, M. (1995). Functional interactions of neurotrophins and neurotrophin receptors. Ann. Rev. Neurosci. **18,** 223–253.

CARTER, B.D., KALTSCHMIDT, C., KALTSCHMIDT, B., OFFENHAUSER, N., BOHM-MATTHAEI, R., BAEUERLE, P.A., and BARDE, Y.A. (1996). Selective activation of NF-kappa B by nerve growth factor through the neurotrophin receptor p75. Science **272,** 542–545.

CASACCIA-BONNEFIL, P., CARTER, B.D., DOBROWSKY, R.T., and CHAO, M.V. (1996). Death of oligodendrocytes mediated by the interaction of nerve growth factor with its receptor p75. Nature **383,** 716–719.

CHAO, M., CASACCIA-BONNEFIL, P., CARTER, B., CHITTKA, A., KONG, H., and YOON, S.O. (1998). Neurotrophin receptors: Mediators of life and death. Brain Research—Brain Res. Rev. **26,** 295–301.

CHAO, M.V., and HEMPSTEAD, B.L. (1995). p75 and Trk: a two-receptor system. Trends Neurosci. **18,** 321–326.

CHEN, K.S., and GAGE, F.H. (1995). Somatic gene transfer of NGF to the aged brain: behavioral and morphological amelioration. J. Neurosci. **15,** 2819–2825.

CLEMENS, J.A., STEPHENSON, D.T., YIN, T., SMALSTIG, E.B., PANETTA, J.A., and LITTLE, S.P. (1998). Drug-induced neuroprotection from global ischemia is associated with prevention of persistent but not transient activation of nuclear factor-kappaB in rats. Stroke **29,** 677–682.

COYLE, J.T., PRICE, D.L., and DELONG, M.R. (1983). Alzheimer's disease: a disorder of cortical cholinergic innervation. Science **219,** 1184–1190.

COYLE, J.T., and PUTTFARCKEN, P. (1993). Oxidative stress, glutamate, and neurodegenerative disorders. Science **262,** 689–695.

CUI, J.K., HSU, C.Y., and LIU, P.K. (1999). Suppression of postischemic hippocampal nerve growth factor expression by a co-fos antisense oligodeoxynucleotide. J. Neurosci. **19,** 1335–1344.

DAVIES, A.M. (1996). The neurotrophic hypothesis: where does it stand? Phil. Trans. R. Soc. Lond. Series B: Biol. Sci. **351,** 389–394.

DAVIES, P., and MALONEY, A.J. (1976). Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet **2,** 1403.

DE LACALLE, S., COOPER, J.D., SVENDSEN, C.N., DUNNETT, S.B., and SOFRONIEW, M.V. (1996). Reduced retrograde labelling with fluorescent tracer accompanies neuronal atrophy of basal forebrain cholinergic neurons in aged rats. Neuroscience **75,** 19–27.

DRACHMAN, D.A. (1977). Memory and cognitive function in man: does the cholinergic system have a specific role? Neurology **27,** 783–790.

ELBLE, R., GIACOBINI, E., and HIGGINS, C. (1989). Choline levels are increased in cerebrospinal fluid of Alzheimer patients. Neurobiol. Aging **10,** 45–50.

FISCHER, W., BJORKLUND, A., CHEN, K., and GAGE, F.H. (1991). NGF improves spatial memory in aged rodents as a function of age. J. Neurosci. **11,** 1889–1906.

FISCHER, W., WICTORIN, K., BJORKLUND, A., WILLIAMS, L.R., VARON, S., and GAGE, F.H. (1987). Amelioration of cholinergic neuron atrophy and spatial memory impairment in aged rats by nerve growth factor. Nature **329,** 65–68.

FRADE, J.M., and BARDE, Y.A. (1998). Nerve growth factor: two receptors, multiple functions. Bioessays **20,** 137–145.

FURUKAWA, K., and MATTSON, M.P. (1998). The transcription factor NF-kappaB mediates increases in calcium currents and decreases in NMDA- and AMPA/kainate-induced currents induced by tumor necrosis factor-alpha in hippocampal neurons. J. Neurochem. **70,** 1876–1886.

GAGE, F.H., ARMSTRONG, D.M., WILLIAMS, L.R., and VARON, S. (1988). Morphological response of axotomized septal neurons to nerve growth factor. J. Comp. Neurol. **269,** 147–155.

GAGE, F.H., BATCHELOR, P., CHEN, K.S., CHIN, D., HIGGINS, G.A., KOH, S., DEPUTY, S., ROSENBERG, M.B., FISCHER, W., and BJORKLUND, A. (1989). NGF receptor reexpression and NGF-mediated cholinergic neuronal hypertrophy in the damaged adult neostriatum. Neuron **2,** 1177–1184.

GAROFALO, L., RIBEIRO-DA-SILVA, A., and CUELLO, A.C. (1992). Nerve growth factor-induced synaptogenesis and hypertrophy of cortical cholinergic terminals. Proc. Natl. Acad. Sci. USA **89,** 2639–2643.

GHOSH, S., and BALTIMORE, D. (1990). Activation in vitro of NF-kappa B by phosphorylation of its inhibition I kappa B. Nature **344,** 678–682.

GU, Z.Z., YU, J.A., and PEREZ-POLO, J.R. (1998). Responses in the aged rat brain after total immunolesion. J. Neurosci. Res. **54,** 7–16.

HAYASHI, T., UENO, Y., and OKAMOTO, T. (1993). Oxidoreductive regulation of nuclear factor kappa B. Involvement of a cellular reducing catalyst thioredoxin. J. Biol. Chem. **268,** 11380–11388.

HECKERS, S., OHTAKE, T., WILEY, R.G., LAPPI, D.A., GEULA, C., and MESULAM, M.M. (1994). Complete and selective cholinergic denervation of rat neocortex and hippocampus but not amygdala by an immunotoxin against the p75 NGF receptor. J. Neurosci. **14,** 1271–1289.

HEFTI, F. (1986). Nerve growth factor promotes survival of septal cholinergic neurons after fimbrial transections. J. Neurosci. **6,** 2155–2162.

HEFTI, F. (1977). Pharmacology of neurotrophic factors. Ann. Rev. Pharmacol. Toxicol. **37,** 239–267.

HEFTI, F., DRAVID, A., and HARTIKKA, J. (1984). Chronic intraventricular injections of nerve growth factor elevate hippocampal choline acetyltransferase activity in adult rats with partial septo-hippocampal lesions. Brain Res. **293,** 305–311.

HELENIUS, M., HANNINEN, M., LEHTINEN, S.K., and SALMINEN, A. (1996). Changes associated with aging and replicative senescence the regulation of transcription factor nuclear factor-kappa B. Biochem. J. **318,** 603–608.

IBANEZ, C.F. (1998). Emerging themes in structural biology of neurotrophic factors. Trends Neurosci. **21,** 438–444.

JACKSON, G.R., WERRBACH-PEREZ, K., PAN, Z., SAMPATH, D., and PEREZ-POLO, J.R. (1994). Neurotrophin regulation of energy homeostasis in the central nervous system. Dev. Neurosci. **16,** 285–290.

JOHNSON, E.M., JR., TANIUCHI, M., CLARK, H.B., SPRINGER, J.E., KOH, S., TAYRIEN, M.W., and LOY, R. (1987). Demonstration of the retrograde transport of nerve growth factor receptor in the peripheral and central nervous system. J. Neurosci. **7**, 923–929.

KALTSCHMIDT, B., BAEUERLE, P.A., and KALTSCHMIDT, C. (1993). Potential involvement of the transcription factor NF-kappa B in neurological disorders. Mol. Aspects Med. **14,** 171–190.

KALTSCHMIDT, B., UHEREK, M., VOLK, B., BAEUERLE, P.A., and KALTSCHMIDT, C. (1997). Transcription factor NF-kappaB is activated in primary neurons by amyloid beta peptides and in neurons surrounding early plaques from patients with Alzheimer disease. Proc. Natl. Acad. Sci. USA **94,** 2642–2647.

KALTSCHMIDT, C., KALTSCHMIDT, B., and BAEUERLE, P.A. (1995). Stimulation of ionotropic glutamate receptors activates transcription factor NF-kappa B in primary neurons. Proc. Natl. Acad. Sci. USA **92,** 9618–9622.

KALTSCHMIDT, C., KALTSCHMIDT, B., NEUMANN, H., WEKERLE, H., and BAEUERLE, P.A. (1994). Constitutive NF-kappa B activity in neurons. Mol. Cell. Biol. **14,** 3981–3992.

KOLIATSOS, V.E., CLATTERBUCK, R.E., GOURAS, G.K., and PRICE, D.L. (1991a). Biologic effects of nerve growth factor on lesioned basal forebrain neurons. Ann. N.Y. Acad. Sci. **640,** 102–109.

KOONG, A.C., CHEN, E.Y., and GIACCIA, A.J. (1994). Hypoxia causes the activation of nuclear factor kappa B through the phosphorylation of I kappa B alpha on tyrosine residues. Cancer Res. **54,** 1425–1430.

KORDOWER, J.H., GASH, D.M., BOTHWELL, M., HERSH, L., and MUFSON E.J. (1989). Nerve growth factor receptor and choline acetyltransferase remain colocalized in the nucleus basalis (Ch4) of Alzheimer's patients. Neurobiol. Aging **10,** 67–74.

KORDOWER, J.H., WINN, S.R., LIU, Y.T., MUFSON, E.J., SLADEK, J.R., JR., HAMMANG, J.P., BAETGE, E.E., and EMERICH, D.F. (1994). The aged monkey basal forebrain: rescue and sprouting of axotomized basal forebrain neurons after grafts of encapsulated cells secreting human nerve growth factor. Proc. Natl. Acad. Sci. USA **91,** 10898–10902.

LEANZA, G., MUIR, J., NILSSON, O.G., WILEY, R.G., DUNNETT, S.B., and BJORKLUND, A. (1996a). Selective immunolesioning of the basal forebrain cholinergic system disrupts short-term memory in rats. Eur. J. Neurosci. **8,** 1535–1544.

LEANZA, G., NIKKHAH, G., NILSSON, O.G., WILEY, R.G. and BJORKLUND, A. (1996b). Extensive reinnervation of the hippocampus by embryonic basal fore-

brain cholinergic neurons grafted into the septum of neonatal rats with selective cholinergic lesions. J. Comp. Neurol. **373,** 355–357.

LEANZA, G., NILSSON, O.G., WILEY, R.G., and BJORKLUND, A. (1995). Selective lesioning of the basal forebrain cholinergic system by intraventricular 192 IgG-saporin: behavioural, biochemical and stereological studies in the rat. Eur. J. Neurosci. **7,** 329–343.

LEZOUALC'H, F., SAGARA, Y., HOLSBOER, F., and BEHL, C. (1998). High constitutive NF-kappaB activity mediates resistance to oxidative stress in neuronal cells. J. Neurosci. **18,** 3224–3232.

LIN, Y.C., BROWN, K., and SIEBENLIST, U. (1995). Activation of NF-kappa B requires proteolysis of the inhibitor I kappa B-alpha: signal-induced phosphorylation of I kappa B-alpha alone does not release active NF-kappa B. Proc. Natl. Acad. Sci. USA **92,** 552–556.

LINDSAY, R.M. (1994b). Neurotrophins and receptors. Progr. Brain Res. **103,** 3–14.

MARTINEZ-SERRANO, A., and BJORKLUND, A. (1998). Ex vivo nerve growth factor gene transfer to the basal forebrain in presymptomatic middle-aged rats prevents the development of cholinergic neuron atrophy and cognitive impairment during aging. Proc. Natl. Acad. Sci. USA **95,** 1858–1863.

MATTHEWS, J.R., WAKASUGI, N., VIRELIZIER, J.L., YODOI, J., and HAY, R.T. (1992). Thioredoxin regulates the DNA binding activity of NF-kappa B by reduction of a disulphide bone involving cysteine 62. Nucleic Acids Res. **20,** 3821–3830.

MATTSON, M.P., GOODMAN, Y., LUO, H., FU, W., and FURUKAWA, K. (1997). Activation of NF-kappaB protects hippocampal neurons against oxidative stress-induced apoptosis: evidence for induction of manganese superoxide dismutase and suppression of peroxynitrite production and protein tyrosine nitration. J. Neurosci. Res. **49,** 681–697.

MEYER, M., PAHL, H.L., and BAEUERLE, P.A. (1994). Regulation of the transcription factors NK-kappa B and AP-1 by redox changes. Chemico-Biol. Interact. **91,** 91–100.

MEYER, M., SCHRECK, R., and BAEUERLE, P.A. (1993). H2O2 and antioxidants have opposite effects on activation of NF-kappa B and AP-1 in intact cells: AP-1 as secondary antioxidant-responsive factor. EMBO J. **12,** 2005–2015.

MOSIALOS, G., HAMER, P., CAPOBIANCO, A.J., LAURSEN, R.A., and GILMORE, T.D. (1991). A protein kinase-A recognition sequence is structurally linked to transformation by p59v-rel and cytoplasmic retention of p68c-rel. Mol. Cell. Biol. **11,** 5867–5877.

NILSSON, O.G., LEANZA, G., ROSENBLAD, C., LAPPI, D.A., WILEY, R.G., and BJORKLUND, A. (1992). Spatial learning impairments in rats with selective immunolesion of the forebrain cholinergic system. Neuroreport **3,** 1005–1008.

OGAWA, N., ASANUMA, M., KONDO, Y., NISHIBAYASHI, S., and MORI, A. (1994). Reduced choline acetyltransferase activity and muscarinic M1 receptor levels in aged Fisher 344 rat brains did not parallel their respective mRNA levels. Brain Res. **658,** 87–92.

OLANOW, C.W. (1993). A radical hypothesis for neurodegeneration [see comments]. Trends Neurosci. **16,** 439–444.

O'NEILL, L.A., and KALTSCHMIDT, C. (1997). NF-kappa B: a crucial transcription factor for glial and neuronal cell function. Trends Neurosci. **20,** 252–258.

PAHAN, K., SHEIKH, F.G., KHAN, M., NAMBOODIRI, A.M., and SINGH, I. (1998). Sphingomyelinase and ceramide stimulate the expression of inducible nitric-oxide synthase in rat primary astrocytes. J. Biol. Chem. **273,** 2591–2600.

PAN, Z., SAMPATH, D., JACKSON, G., WERRBACH-PEREZ, K., and PEREZ-POLO, R. (1997). Nerve growth factor and oxidative stress in the nervous system. Adv. Exp. Med. Biol. **429,** 173–193.

PEREZ-OTANO, I., McMILLIAN, M.K., CHEN, J., BING, G., HONG, J.S., and PENNYPACKER, K.R. (1996). Induction of NF-kB-like transcription factors in brain areas susceptible to kainate toxicity. Glia **16,** 306–315.

PEREZ-POLO, R. (1991). Mechanisms of cell death. Adv. Exp. Med. Biol. **296,** 345–352.

PERRY, E.K., GIBSON, P.H., BLESSED, G., PERRY, R.H., and TOMLINSON, B.E. (1977). Neurotransmitter enzyme abnormalities in senile dementia. Choline acetyltransferase and glutamic acid decarboxylase activities in necropsy brain tissue. J. Neurol. Sci. **34,** 247–265.

PERRY, E.K., TOMLINSON, B.E., BLESSED, G., BERGMANN, K., GIBSON, P.H., and PERRY, R.H. (1978). Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. Br. Med. J. **2,** 1457–1459.

RABIZADEH, S., OH, J., ZHONG, L.T., YANG, J., BITLER, C.M., BUTCHER, L.L., and BREDESEN, D.E. (1993). Induction of apoptosis by the low-affinity NGF receptor. Science **261,** 345–348.

RICHTER, J.A., PERRY, E.K., and TOMLINSON, B.E. (1980). Acetylcholine and choline levels in post-mortem human brain tissue: preliminary observations in Alzheimer's disease. Life Sci. **26,** 1683–1689.

ROSSNER, S., HARTIG, W., SCHLIEBS, R., BRUCKNER, G., BRAUER, K., PEREZ-POLO, J.R., WILEY, R.G., and BIGL, V. (1995a). 192IgG-saporin immunotoxin-induced loss of cholinergic cells differentially activates microglia in rat basal forebrain nuclei. J. Neurosci. Res. **41,** 335–346.

ROSSNER, S., SCHLIEBS, R., HARTIG, W., and BIGL, V. (1995c). 192IGG-saporin-induced selective lesion of cholinergic basal forebrain system: neurochemical effects on cholinergic neurotransmission in rat cerebral cortex and hippocampus. Brain Res. Bull. **38,** 371–381.

ROSSNER, S., YU, J., PIZZO, D., WERRBACH-PEREZ, K., SCHLIEBS, R., BIGL, V., and PEREZ-POLO, J.R. (1996). Effects of intraventricular transplantation of NGF-secreting cells on cholinergic basal forebrain neurons after partial immunolesion. J. Neurosci. Res. **45,** 40–56.

RYLETT, R.J., BALL, M.J., and COLHOUN, E.H. (1983).

Evidence for high affinity choline transport in synaptosomes prepared from hippocampus and neocortex of patients with Alzheimer's disease. Brain Res. **289,** 169–175.

SALMINEN, A., LIU, P.K., and HSU, C.Y. (1995). Alteration of transcription factor binding activities in the ischemic rat brain. Biochem. Biophys. Res. Commun. **212,** 939–944.

SCHENK, H., KLEIN, M., ERDBRUGGER, W., DROGE, W., and SCHULZE-OSTHOFF, K. (1994). Distinct effects of thioredoxin and antioxidants on the activation of transcription factors NF-kappa B and AP-1. Proc. Natl. Acad. Sci. USA **91,** 1672–1676.

SCHMIDT, K.N., AMSTAD, P., CERUTTI, P., and BAEUERLE, P.A. (1995). The roles of hydrogen peroxide and superoxide as messengers in the activation of transcription factor NF-kappa B. Chem. Biol. **2,** 13–22.

SCOTT, S.A., LIANG, S., WEINGARTNER, J.A., and CRUTCHER, K.A. (1994). Increased NGF-like activity in young but not aged rat hippocampus after septal lesions. Neurobiol. Aging **15,** 337–346.

SCOTT, S.A., MUFSON, E.J., WEINGARTNER, J.A., SKAU, K.A., and CRUTCHER, K.A. (1995). Nerve growth factor in Alzheimer's disease: increased levels throughout the brain coupled with declines in nucleus basalis. J. Neurosci. **15,** 6213–6221.

SIEBENLIST, U., FRANZOSO, G., and BROWN, K. (1994). Structure, regulation and function of NF-kappa B. Annu. Rev. Cell Biol. **10,** 405–455.

SIESJO, B.K., AGARDH, C.D., and BENGTSSON, F. (1989). Free radicals and brain damage. Cerebrovasc. Brain Metab. Rev. **1,** 165–211.

STEININGER, T.L., WAINER, B.H., KLEIN, R., BARBACID, M., and PALFREY, H.C. (1993). High-affinity nerve growth factor receptor (Trk) immunoreactivity is localized in cholinergic neurons of the basal forebrain and striatum in the adult rat brain. Brain Res. **612,** 330–335.

STRADA, O., VYAS, S., HIRSCH, E.C., RUBERG, M., BRICE, A., AGID, Y., and JAVOY-AGID, F. (1992). Decreased choline acetyltransferase mRNA expression in the nucleus basalis of Meynert in Alzheimer disease: an in situ hybridization study. Proc. Natl. Acad. Sci. USA **89,** 9549–9553.

SUZUKI, T., MITAKE, S., OKUMURA-NOJI, K., YANG, J.P., FUJII, T., and OKAMOTO, T. (1997). Presence of NF-kappaB-like and IkappaB-like immunoreactivities in postsynaptic densities. Neuroreport **8,** 2931–2935.

TAGLIALATELA, G., HIBBERT, C.J., HUTTON, L.A., WERRBACH-PEREZ, K., and PEREZ-POLO, J.R. (1996). Suppression of p140trkA does not abolish nerve growth factor-mediated rescue of serum-free PC12 cells. J. Neurochem. **66,** 1826–1835.

TAGLIALATELA, G., ROBINSON, R., and PEREZ-POLO, J.R. (1997). Inhibition of nuclear factor kappa B (NFkappaB) activity induces nerve growth factor-resistant apoptosis in PC12 cells. J. Neurosci. Res. **47,** 155–162.

THAL, L.J. (1996). Neurotrophic factors. Prog. Brain Res. **109,** 327–330.

THOENEN, H. (1991). The changing scene of neurotrophic factors. Trends Neurosci. **14,** 165–170.

THOENEN, H. (1995). Neurotrophins and neuronal plasticity. Science **270,** 593–598.

THOENEN, H., BANDTLOW, C., and HEUMANN, R. (1987). The physiological function of nerve growth factor in the central nervous system: comparison with the periphery. Rev. Physiol. Biochem. Pharmacol. **109,** 145–178.

TOLIVER-KINSKY, T., PAPACONSTANTINOU, J., and PEREZ-POLO, J.R. (1997). Age-associated alterations in hippocampal and basal forebrain nuclear factor kappa B activity. J. Neurosci. Res. **48,** 580–587.

TONG, L., and PEREZ-POLO, J.R. (1995). Transcription factor DNA binding activity in PC12 cells undergoing apoptosis after glucose deprivation. Neurosci. Lett. **191,** 137–140.

TONG, L., and PEREZ-POLO, J.R. (1996). Effect of nerve growth factor on AP-1, NF-kappa B, and Oct DNA binding activity in apoptotic PC12 cells: extrinsic and intrinsic elements. J. Neurosci. Res. **45,** 1–12.

TONG, L., TOLIVER-KINSKY, T., TAGLIALATELA, G., WERRBACH-PEREZ, K., WOOD, T., and PEREZ-POLO, J.R. (1998). Signal transduction in neuronal death. J. Neurochem. **71,** 447–459.

TORRES, E.M., PERRY, T.A., BLOCKLAND, A., WILKINSON, L.S., WILEY, R.G., LAPPI, D.A., and DUNNET, S.B. (1994). Behavioural, histochemical and biochemical consequences of selective immunolesions in discrete regions of the basal forebrain cholinergic system. Neuroscience **63,** 95–122.

TUSZYNSKI, M.H., BUZSAKI, G., and GAGE, F.H. (1990). Nerve growth factor infusions combined with fetal hippocampal grafts enhance reconstruction of the lesioned septohippocampal projection. Neuroscience **36,** 33–44.

TUSZYNSKI, M.H., SANG, H., YOSHIDA, K., and GAGE, F.H. (1991). Recombinant human nerve growth factor infusions prevent cholinergic neuronal degeneration in the adult primate brain. Ann. Neurol. **30,** 625–636.

VILE, G.F., TANEW-ILISCHEW, A., and TYRELL, R.M. (1995). Activation of NF-kappa B in human skin fibroblasts by the oxidative stress generated by UVA radiation. Photochem. Photobiol. **62,** 463–468.

WAITE, J.J., CHEN, A.D., WARDLOW, M.L., WILEY, R.G., LAPPI, D.A., and THAL, L.J. (1995). 192 immunoglobulin G-saporin produces graded behavioral and biochemical changes accompanying the loss of cholinergic neurons of the basal forebrain and cerebellar Purkinje cells. Neuroscience **65,** 463–476.

WHITEHOUSE, P.J., PRICE, D.L., STRUBLE, R.G., CLARK, A.W., COYLE, J.T., and DELON, M.R. (1982). Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science **215,** 1237–1239.

WHITEHOUSE, P.J., STRUBLE, R.G., HEDREEN, J.C., CLARK, A.W., and PRICE, D.L. (1985). Alzheimer's disease and related dementias: selective involvement of

specific neuronal systems. CRC Crit. Rev. Clin. Neurobiol. **1,** 319–339.

WHITTEMORE, S.R., and SEIGER, A. (1987). The expression, localization and functional significance of beta-nerve growth factor in the central nervous system. Brain Res. **434,** 439–464.

WILEY, R.G. (1997). Findings about the cholinergic basal forebrain using immunotoxin to the nerve growth factor receptor. Ann. N.Y. Acad. Sci. **835,** 20–29.

WILEY, R.G., OELTMANN, T.N., and LAPPI, D.A. (1991). Immunolesioning: selective destruction of neurons using immunotoxin to rat NGF receptor. Brain Res. **562,** 149–153.

WILLIAMS, L.R., and RYLETT, R.J. (1990). Exogenous nerve growth factor increases the activity of high-affinity choline uptake and choline acetyltransferase in brain of Fisher 344 male rats. J. Neurochem. **55,** 1042–1049.

WILLIAMS, L.R., RYLETT, R.J., INGRAM, D.K., JOSEPH, J.A., MOISES, H.C., TANG, A.H., and MERVIS, R.F. (1993). Nerve growth factor affects the cholinergic neurochemistry and behavior of aged rats. Progr. Brain Res. **98,** 251–256.

WILLIAMS, L.R., VARON, S., PETERSON, G.M., WICTORIN, K., FISCHER, W., BJORKLUND, A., and GAGE, F.H. (1986). Continuous infusion of nerve growth factor prevents basal forebrain neuronal death after fimbria fornix transection. Proc. Natl. Acad. Sci. USA **83,** 9231–9235.

WORTWEIN, G., YU, J., TOLIVER-KINSKY, T., and PEREZ-POLO, J.R. (1998). Responses of young and aged rat CNS to partial cholinergic immunolesions and NGF treatment. J. Neurosci. Res. **52,** 322–333.

WORONICZ, J.D., GAO, X., CAO, Z., ROTHE, M., and GOEDDEL, D.V. (1997). IkappaB kinase-beta:NF-kappaB activation and complex formation with IkappaB kinase-alpha and NIK. Science **278,** 866–869.

YAN, Q., and JOHNSON, E.M., JR. (1989). Immunohistochemical localization and biochemical characterization of nerve growth factor receptor in adult rat brain. J. Comp. Neurol. **290,** 585–598.

YANG, K., MU, X.S., and HAYES, R.L. (1995). Increased cortical nuclear factor-kappa B (NF-kappa B) DNA binding activity after traumatic brain injury in rats. Neurosci. Lett. **197,** 101–104.

YANKNER, B.A. (1996). Mechanisms of neuronal degeneration in Alzheimer's disease. Neuron **16,** 921–932.

YU, J., PIZZO, D.P., HUTTON, L.A., and PEREZ-POLO, J.R. (1995). Role of the cholinergic system in the regulation of neurotrophin synthesis. Brain Res. **705,** 247–252.

YU, J., WILEY, R.G., and PEREZ-POLO, R.J. (1996). Altered NGF protein levels in different brain areas after immunolesion. J. Neurosci. Res. **43,** 213–232.

ZANDI, E., ROTHWARF, D.M., DELHASE, M., HAYAKAWA, M., and KARIN, M. (1997). The IkappaB kinase complex (IKK) contains two kinase subunits, IKKalpha and IKKbeta, necessary for IkappaB phosphorylation and NF-kappaB activation. Cell **91,** 243–252.

Address reprint requests to:
Dr. J. Regino Perez-Polo
Department of Human Biological Chemistry and Genetics
The University of Texas Medical Branch at Galveston
301 University Blvd.
Galveston, TX 77555-0652

E-mail: regino.perez-polo@utmb.edu

Received for publication January 15, 2000; accepted May 8, 2000.

This article has been cited by:

1. Cholinergic Systems in Aging and Alzheimer's Disease: Neurotrophic Molecular Analysis 249-256. [CrossRef]
2. Li Yang, Lu-Yang Tao, Xi-Ping Chen. 2007. Roles of NF-#B in central nervous system damage and repair. *Neuroscience Bulletin* **23**:5, 307-313. [CrossRef]
3. Steffen Rossner, Christine Lange-Dohna, Ulrike Zeitschel, J. Regino Perez-Polo. 2005. Alzheimer's disease beta-secretase BACE1 is not a neuron-specific enzyme. *Journal of Neurochemistry* **92**:2, 226-234. [CrossRef]
4. Véronique Paban, Caroline Chambon, Magali Jaffard, Béatrice Alescio-Lautier. 2005. Behavioral Effects of Basal Forebrain Cholinergic Lesions in Young Adult and Aging Rats. *Behavioral Neuroscience* **119**:4, 933-945. [CrossRef]
5. P. Clément, N. Sarda, R. Cespuglio, A. Gharib. 2005. Potential role of inducible nitric oxide synthase in the sleep–wake states occurrence in old rats. *Neuroscience* **135**:2, 347-355. [CrossRef]
6. P. R. Wade, T. Cowen. 2004. Neurodegeneration: a key factor in the ageing gut. *Neurogastroenterology and Motility* **16**:s1, 19-23. [CrossRef]
7. L VENG, A GRANHOLM, G ROSE. 2003. Age-related sex differences in spatial learning and basal forebrain cholinergic neurons in F344 rats. *Physiology & Behavior* **80**:1, 27-36. [CrossRef]