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90 CONSEQUENCES OF EXCITOTOXICITY ON IN VIVO-LABELED CHOLINERGIC NEURONS IN RAT NUCLEUS BASALIS: TEMPORAL CHANGES IN AMYLOID PRECURSOR PROTEIN EXPRESSION

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Background: Cholinergic neurons of the nucleus basalis (MBN) are damaged in Alzheimer's disease; and are vulnerable to *N*-methyl-D-aspartate (NMDA) excitotoxicity. *Objective:* As the temporal profile of early pathological changes in the MBN is sparsely known, we investigated several parameters of in vivo-labeled cholinergic neurons 4, 24, and 48 h after NMDA infusion. *Methods:* Cholinergic cells were pre-labeled with carbocyanine 3 (Cy3)-192IgG. Twenty-four hour later 60 mM NMDA was infused in the right MBN, while the contralateral nucleus was sham-lesioned. *Results:* Neuronal damage, as indicated by decreased immunoreactivity for NMDA receptors, choline-acetyltransferase (ChAT) and p75 low-affinity neurotrophin receptor (p75NTR), was detected as early as 4 h post-lesion. Fluoro-Jade, an indicator of cellular damage, only labeled the lesion core at 4 h post-lesion. Longer survival led to enhanced Fluoro-Jade labeling concomitant with loss of ChAT immunoreactivity reaching a maximum at 24 h post-lesion. Significant loss of p75NTR immunoreactivity was only detected 48 h after NMDA infusion. In vivo labeling of cholinergic neurons exhibited a similar temporal profile as ChAT immunoreactivity in the damaged MBN. Analysis of amyloid precursor protein (APP) expression in cholinergic and non-cholinergic neurons revealed that almost all cholinergic cells were immunoreactive for APP, whereas, only a fraction of non-cholinergic neurons expressed APP under control conditions. ChAT-immunopositive cells withstanding NMDA excitotoxicity maintained their APP immunoreactivity throughout the survival period investigated, whereas a decline of APP labeling was found in non-cholinergic neurons. *Conclusions:* Our data demonstrate that excitotoxicity leads to rapid dysfunction of cholinergic MBN neurons. Moreover, cholinergic cells retain their APP expression under excitotoxic conditions that might contribute to increased cortical APP concentrations after MBN lesion. Finally, in vivo labeling with Cy3-192IgG is a sensitive tool to label live cholinergic neurons under experimental circumstances.

91 REDUCED INSULIN DEGRADING ENZYME LEVELS WITH CHRONIC GLUCOCORTICOID ADMINISTRATION IN THE AGED MACAQUE

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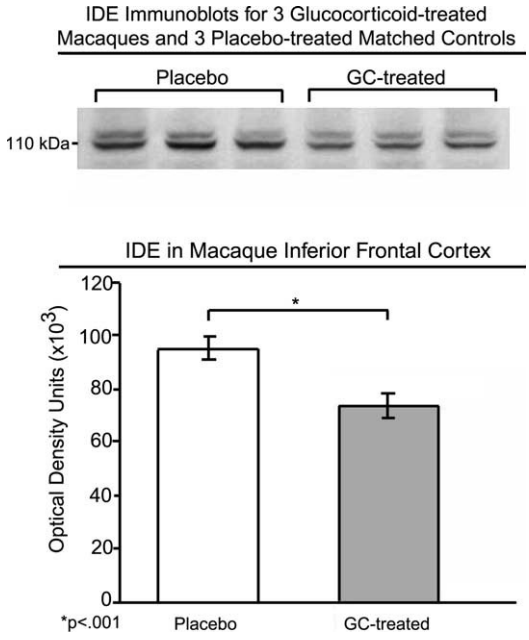
Background: Cortisol levels have been shown to be elevated in AD, and also increased with the presence of the APOE-4 allele for both control and demented subjects (Peskind et al., 2001). Although hypercortisolemia may contribute to the pathology of AD by lowering the threshold for neurodegeneration, it may also inhibit the function of Insulin Degrading Enzyme (IDE) in vitro (Kupfer et al., 1994). IDE has been identified as a major protease involved in Aβ degradation in human brain (Qui et al., 1998). *Objective:* The present study investigated the long term effects of glucocorticoid (GC) administration on IDE levels in the primate brain. *Methods:* Sixteen retired breeder Macaques (Macaca nemestrina) in middle to late life (mean age, 23.1 ± 1.0 years at death) were divided into eight pairs matched for age, gender, and weight. Each pair was randomized to receive either high-dose hydrocortisone (cortisol) acetate or placebo for 12 months. Tissue samples from the inferior frontal cortex were dissected from frozen slides, homogenized and IDE was visualized by Western blot with a rabbit polyclonal antibody IDE-3 (a gift of Dr. D. Selkoe). Samples were run in duplicate, IDE bands were quantified using Kodak 1D software, and comparisons were made by



repeated measures ANCOVA normalized to a linear series of IDE samples from human brain. *Results:* IDE protein levels were more than 22% lower in macaques who received GC treatment compared with placebo treated controls ($P < 0.001$). *Conclusions:* These preliminary findings indicate that chronically elevated cortisol levels such as have been reported in AD may contribute to a reduction in IDE protein levels in the brain.

92 COMPARATION OF THREE NEURODEGENERATIVE ANIMAL MODELS INDUCED BY MITOCHONDRIAL DEFICIT

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Background: Mitochondrial deficiency occurs in Pakinson's disease (PD), Huntington's disease (HD) and Alzheimer's disease (AD). *Objective:* We compared the difference of behavior, pathology and neuro-transmitters among these three neurodegenerative animal models to study the mechanisms of the diseases. *Methods:* C57BL mice were treated with MPTP (mitochondrial complex I inhibitor, ip) to mimic PD; SD rats treated with 3-NPA (complex II inhibitor, ip) to mimic HD; SD rats administrated with NaN3 (complex IV inhibitor) subcutaneously via a Alzet minipump to mimic AD. Learning memory ability was determined by water maze and passive avoidance tests. Rolling hole test, spontaneous motor activity and climing test were investigated to show the movement ability. HE staining to detect the neurons in cortex and hippocampus, and immuno-histochemistry for tyrosine hydroxylase (TH) to detect the dopaminergic neurons in striatum. The content of NE, dopamine, 5-HT and their metabolic products in striatum were measured by HPLC. *Results:* (1) MPTP mice showed damage of neurons in striatum and the content of dopamine and its metabolic product DOPAC also decrease. Model mice indicated movement disorder without learning-memory deficit. (2) NaN3 rats showed damage of neurons in cortex and hippocampus, both neurons and neuro-transmitters in striatum did not show any abnormality. So model rats indicated learning-memory deficit without any movement disorder. (3) 3-NPA rats showed damage of neurons in striatum, cortex and hippocampus, and the content of neuro-transmitters decreased in striatum too. Model rats indicated both movement disorder and learning-memory deficit. *Conclusions:* Different inhibition of mitochondrial complex induces the abnormality of neurons, neuro-transmitters and behaviors in disease-special area of brain and results the disease-like disorders. These three animal mod-