GERIATRICS

A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease.

Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, Conner J.

Nat Med. 2005 Jun;11:551-5.

A decreased rate of decline in Mini-Mental Status Examination scores over a mean 22 months of follow-up, when compared to decline during the year prior to treatment, was seen in 6 Alzheimer's disease patients who received implants of autologous fibroblasts genetically modified to secrete nerve growth factor in an area adjacent to the cholinergic neurons of the nucleus basalis of Meynert; and PET scans showed a general increase in cortical activity. See Figures 1 and 3.

Aged monkeys receiving implants in the basal forebrain of fibroblasts genetically modified to secrete nerve growth factor showed improved recovery of axotomized cholinergic neurons (Proc Natl Acad Sci U S A. 1994 Nov 8; 91:10898-902). Evidence shows some benefit of the cholinesterase inhibitors donepezil (Cochrane Database Syst Rev. 2003; (3):CD001190), galantamine (Cochrane Database Syst Rev. 2004 Oct 18;(4):CD001747), and rivastigmine (Cochrane Database Syst Rev. 2000;(4):CD001191) in the treatment of Alzheimer's.

Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Abeta42 production.

Kukar T, Murphy MP, Eriksen JL, Sagi SA, Weggen S, Smith TE, Ladd T, Khan MA, Kache R, Beard J, Dodson M, Merit S, Ozols VV, Anastasiadis PZ, Das P, Fauq A, Koo EH, Golde TE.

Nat Med. 2005 Jun;11:545-50.

Celecoxib increased, and indomethacin decreased, the in vitro production of amyloid beta-42 peptide, a precursor of Alzheimer's disease; and celecoxib increased amyloid beta-42 peptide in the brain of a transgenic mouse model of Alzheimer's disease, apparently by increasing gamma-secretase activity. See Figures 1 and 4.

Case control and population-based studies have shown reduced rates of Alzheimer's disease in individuals with a history of arthritis or use of nonselective NSAIDs (Neurology. 1996 Aug; 47:425-32); however, there is no evidence to support the use of indomethacin (Cochrane Database Syst Rev. 2002;(2):CD003673) or ibuprofen (Cochrane Database Syst Rev. 2003;(2):CD004031) in the treatment of Alzheimer's.

SUBSTANCE ABUSE

Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000-2001.

O'Brien MS, Anthony JC.

Neuropsychopharmacology. 2005 May;30:1006-18.

Cocaine dependence was seen in 5.4% of 1081 individuals who first used the drug less than 24 months before interview, with increased adjusted relative risk in females and blacks and decreased risk in those aged 21 to 25, in this study of 114,241 respondents to the 2000-2001 National Household Survey on Drug Abuse. See Table 4.

The 1991 National Comorbidity Survey found 7.5% lifetime prevalence of any drug dependence and 1.8% prevalence in the past 12 months (Arch Gen Psychiatry. 1995 Mar;52:219-29). There is no evidence to support antidepressants (Cochrane Database Syst Rev. 2003; (2):CD002950), dopamine agonists (Cochrane Database Syst Rev. 2003;(2):CD003352), or carbamazepine (Cochrane Database Syst Rev. 2002;(2):CD002023) in the treatment of cocaine dependence, partially due to high dropout rates.

EATING DISORDERS

Molecular and anatomical determinants of central leptin resistance.

Munzberg H, Myers MG.

Nat Neurosci. 2005 May;8:566-570.

Leptin, a hormone secreted by adipose tissue, is less effective at suppressing appetite in obese individuals, likely because chronically elevated levels of leptin lead to increased expression of the intracellular protein SOCS3, which then inhibits the signaling cascade of the leptin receptor, particularly in the arcuate nucleus of the hypothalamus, according to this review. See Figure 1.

Leptin is considered a key regulator of mammalian weight control (Nature. 1998 Oct 22;395:763-70). Fluoxetine, orlistat, and

sibutramine can produce modest weight loss in patients with type 2 diabetes (Cochrane Database Syst Rev. 2005 Jan 25;(1):CD004096).

STEM CELLS

Migration and differentiation of neural precursors derived from human embryonic stem cells in the rat brain.

Tabar V, Panagiotakos G, Greenberg ED, Chan BK, Sadelain M, Gutin PH, Studer L.

Nat Biotechnol. 2005 May;23:601-6.

Human embryonic stem cells that were differentiated in vitro into neural precursor cells and then injected into the adult rat subventricular zone – an area with endogenous neural stem cells – migrated via the usual path to the olfactory bulb and further differentiated into neurons and glial cells. See Figure 3.

Similar results were obtained when neural precursors from human embryonic forebrain were transplanted to adult rat subventricular zone, hippocampus, and striatum (J Neurosci. 1999 Jul 15;19:5990-6005); numerous experiments have shown how endogenous neural stem cells can replace dead neurons in adult mammalian brain (Molecular Biology of the Cell, 4 ed.).

MED-PSYCH

Autoantibodies to folate receptors in the cerebral folate deficiency syndrome.

Ramaekers VT, Rothenberg SP, Sequeira JM, Opladen T, Blau N, Quadros EV, Selhub J.

N Engl J Med. 2005 May 12;352:1985-91.

Autoantibodies against folate receptors were detected in the serum of 25 of 28 children with cerebral folate deficiency versus 0 of 28 age-matched control subjects, and oral folinic acid led to normal CSF folate levels and resolution of several neuropsychiatric symptoms. See Table 2.

This is similar to the use of oral folate during pregnancy to protect against neural tube defects (Lancet. 1991 Jul 20;338:131-7), a treatment that should begin before pregnancy and continue for the first 2 months (Cochrane Database Syst Rev. 2001;(3):CD001056).

PSYCHOLOGY

Decoding the visual and subjective contents of the human brain.

Kamitani Y, Tong F.

Nat Neurosci. 2005 May;8:679-85.

Attention to lines oriented at 45 degrees was discriminated from attention to overlapping lines oriented at 135 degrees by analyzing functional MRI images of neuronal ensemble activity in primary and secondary visual cortex, ie, V1 and V2, in 4 healthy adults. See Figure 7.

The perception of faces appears to occur outside of early visual areas in the fusiform gyrus (J Neurosci. 1997 Jun 1;17:4302-11); lesions of the parietal lobe have shown the importance of this area in attention (Neuroscience, 2 ed.).

BIOLOGY

From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome.

Bagni C, Greenough WT.

Nat Rev Neurosci. 2005 May;6:376-87.

Fragile X mental retardation protein (FMRP), mutations of which cause the most common form of inherited mental retardation, is responsible for transporting messenger RNAs to synapses and regulates their translation there, and may also regulate the cytoskeleton of dendritic spines and the internalization of postsynaptic NMDA and AMPA glutamate receptors, as discussed in this review. See Figure 4.

Transgenic mice lacking the fragile X mental retardation gene, Fmr1, and therefore lacking FMRP, exhibited abnormal dendritic spine morphology that resembled that found in patients with the disorder (Proc Natl Acad Sci U S A. 1997 May 13;94:5401-4). Fragile X syndrome is one of the neurodegenerative disorders caused by trinucleotide repeats (Basic Neurochemistry, 6 ed.).

UKE RESEARCH

SUBSTANCE ABUSE

Contrasting predictors of readiness for substance abuse treatment in adults and adolescents: A latent variable analysis of DATOS and DATOS-A participants.

Handelsman L, Stein JA, Grella CE.

Drug Alcohol Depend. 2005 May 12

GERIATRICS

Neuropathologic, biochemical, and molecular characterization of the frontotemporal dementias.

Mott RT, Dickson DW, Trojanowski JQ, Zhukareva V, Lee VM, Forman M, Van Deerlin V, Ervin JF, Wang DS, Schmechel DE, Hulette CM.

J Neuropathol Exp Neurol. 2005 May;64:420-8.

PALLIATIVE CARE

Desire for Hastened Death, Cancer Pain and Depression: Report of a Longitudinal Observational Study.

O'mahony S, Goulet J, Kornblith A, Abbatiello G, Clarke B, Kless-Siegel S, Breitbart W, Payne R.

J Pain Symptom Manage. 2005 May;29:446-457.

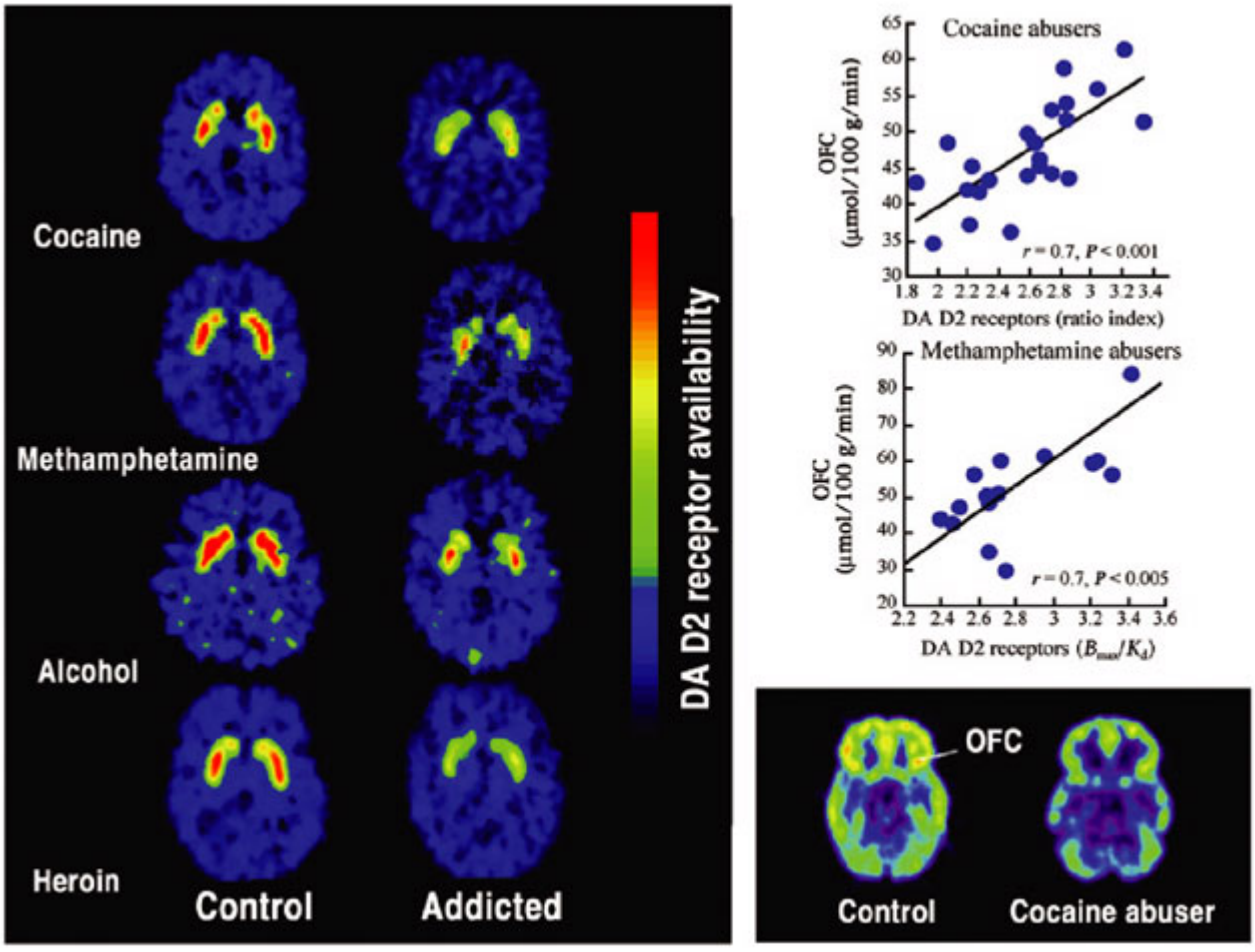
AUTISM

Moderate sedation for MRI in young children with autism.

Ross AK, Hazlett HC, Garrett NT, Wilkerson C, Piven J.

Pediatr Radiol. 2005 May 19

FIGURE OF THE WEEK



Nat Neurosci. 2005 May;8:555-60. Figure 2.