

# Neuroprotektive Therapien für neurodegenerative Erkrankungen

Ludwin Ley und Thomas Herdegen, Kiel

## Literatur

1. Van Rhijn SJ, Glosser G, de Vries JJ, Clark CM, et al. Visual processing impairments and decrements in regional brain activity in Alzheimer's disease. *J Clin Exp Neuropsychol* 2004;26:11–23.
2. Becaria A, Bondy SC, Campbell A. Aluminum and copper interact in the promotion of oxidative but not inflammatory events: implications for Alzheimer's disease. *J Alzheimers Dis* 2003;5:31–8.
3. Rego AC, Oliveira CR. Mitochondrial dysfunction and reactive oxygen species in excitotoxicity and apoptosis: implications for the pathogenesis of neurodegenerative diseases. *Neurochem Res* 2003;28:1563–74.
4. Doraiswamy PM. Alzheimer's disease and the glutamate NMDA receptor. *Psychopharmacol Bull* 2003;37:41–9.
5. Danysz W, Parsons CG. The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence. *Int J Geriatr Psychiatry* 2003;18(Suppl 1):S23–32.
6. Lee HG, Casadesus G, Zhu X, Joseph JA, et al. Perspectives on the amyloid-beta cascade hypothesis. *J Alzheimers Dis* 2004;6:137–45.
7. Takuma H, Tomiyama T, Kuida K, Mori H. Amyloid beta peptide-induced cerebral neuronal loss is mediated by caspase-3 in vivo. *J Neuropathol Exp Neurol* 2004;63:255–61.
8. Braak H, Braak E, Bohl J. Staging of Alzheimer-related cortical destruction. *Eur Neurol* 1993;33:403–8.
9. Birks JS, Harvey R. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev* 2003;CD001190.
10. Olin J, Schneider L. Galantamine for Alzheimer's disease. *Cochrane Database Syst Rev* 2002;CD001747.
11. Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA* 2003;289:210–6.
12. Areosa SA, Sherriff F. Memantine for dementia. *Cochrane Database Syst Rev* 2003;CD003154.
13. Tabet N, Birks J, Grimley Evans J. Vitamin E for Alzheimer's disease. *Cochrane Database Syst Rev* 2000;CD002854.
14. Tabet N, Mantle D, Orrell M. Free radicals as mediators of toxicity in Alzheimer's disease: a review and hypothesis. *Adverse Drug React Toxicol Rev* 2000;19:127–52.
15. Tabet N, Feldmand H. Ibuprofen for Alzheimer's disease (Cochrane Review). *Cochrane Database Syst Rev* 2003;CD004031.
16. Etminan M, Gill S, Samii A. Effect of non-steroidal antiinflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. *BMJ* 2003;327:128.
17. Flicker L, Grimley Evans G. Piracetam for dementia or cognitive impairment. *Cochrane Database Syst Rev* 2001;CD001011.
18. Gertz HJ, Kiefer M. Review about Ginkgo biloba special extract EGB 761 (Ginkgo). *Curr Pharm Des* 2004;10:261–4.
19. Lopez-Arrieta JM, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. *Cochrane Database Syst Rev* 2002;CD000147.
20. Scott HD, Laake K. Statins for the prevention of Alzheimer's disease. *Cochrane Database Syst Rev* 2001;CD003160.
21. Hoglund K, Wiklund O, Vanderstichele H, Eikenberg O, et al. Plasma levels of beta-amyloid(1-40), beta-amyloid(1-42), and total beta-amyloid remain unaffected in adult patients with hypercholesterolemia after treatment with statins. *Arch Neurol* 2004;61:333–7.
22. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003;23:871–80.
23. Miller LJ, Chacko R. The role of cholesterol and statins in Alzheimer's disease. *Ann Pharmacother* 2004;38:91–8.
24. Schubert P, Ogata T, Marchini C, Ferroni S, et al. Protective mechanisms of adenosine in neurons and glial cells. *Ann N Y Acad Sci* 1997;825:1–10.
25. Miki S, Miki Y. Differential effects of propentofylline on the production of cytokines by peripheral blood mononuclear cells in vitro. *Clin Ther* 1991;13:747–53.
26. Frampton M, Harvey RJ, Kirchner V. Propentofylline for dementia (Cochrane Review). *Cochrane Database Syst Rev* 2003;CD002853.
27. Hudson S, Tabet N. Acetyl-L-carnitine for dementia (Cochrane Review). *Cochrane Database Syst Rev* 2003;CD003158.
28. Birks J, Flicker L. Selegiline for Alzheimer's disease. *Cochrane Database Syst Rev* 2003;CD000442.
29. Janus C. Vaccines for Alzheimer's disease: how close are we? *CNS Drugs* 2003;17:457–74.
30. Grundman M, Capparelli E, Kim HT, Morris JC, et al. A multicenter, randomized, placebo controlled, multiple-dose, safety and pharmacokinetic study of AIT-082 (Neotrofin) in mild Alzheimer's disease patients. *Life Sci* 2003;73:539–53.
31. Imbimbo BP. Toxicity of beta-amyloid vaccination in patients with Alzheimer's disease. *Ann Neurol* 2002;51:794.
32. Ferrer I, Boada Rovira M, Sanchez Guerra ML, Rey MJ, et al. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. *Brain Pathol* 2004;14:11–20.
33. Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, et al. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *J Neurol* 2002;249(Suppl 3):III/1–5.
34. Del Tredici K, Rub U, De Vos RA, Bohl JR, et al. Where does Parkinson disease pathology begin in the brain? *J Neuropathol Exp Neurol* 2002;61:413–26.
35. Jellinger KA, Mitter-Ferstl E. The impact of cerebrovascular lesions in Alzheimer disease – a comparative autopsy study. *J Neurol* 2003;250:1050–5.
36. Dawson TM, Dawson VL. Molecular pathways of neurodegeneration in Parkinson's disease. *Science* 2003;302:819–22.
37. Jenner P. Oxidative stress in Parkinson's disease. *Ann Neurol* 2003;53(Suppl 3):S26–36; discussion S36–8.
38. Buhmann C, Arlt S, Kontush A, Moller-Bertram T, et al. Plasma and CSF markers of oxidative stress are increased in Parkinson's disease and influenced by antiparkinsonian medication. *Neurobiol Dis* 2004;15:160–70.
39. Kim KS, Choi SY, Kwon HY, Won MH, et al. Aggregation of alpha-synuclein induced by the Cu,Zn-superoxide dismutase and hydrogen peroxide system. *Free Radic Biol Med* 2002;32:544–50.
40. Stocchi F, Olanow CW. Neuroprotection in Parkinson's disease: clinical trials. *Ann Neurol* 2003;53(Suppl 3):S87–97; discussion S97–9.

*Dr. med. Ludwin Ley, Prof. Dr. med. Thomas Herdegen, Institut für Pharmakologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Hospitalstraße 4, 24105 Kiel, E-Mail: t.herdegen@pharmakologie.uni-kiel.de*

41. Whone AL, Watts RL, Stoessl AJ, Davis M, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. *Ann Neurol* 2003;54:93–101.
42. Stocchi F, Vacca L, Onofri M. Are there clinically significant differences between dopamine agonists. *Adv Neurol* 2003;91:259–66.
43. Clarke CE, Deane KH. Ropinirole for levodopa-induced complications in Parkinson's disease. *Cochrane Database Syst Rev* 2001: CD001516.
44. Clarke CE, Deane KH. Cabergoline for levodopa-induced complications in Parkinson's disease. *Cochrane Database Syst Rev* 2001: CD001518.
45. Crosby NJ, Deane KH, Clarke CE. Amantadine for dyskinesia in Parkinson's disease (Cochrane Review). *Cochrane Database Syst Rev* 2003:CD003467.
46. Schachter SC, Tarsy D. Remacemide: current status and clinical applications. *Expert Opin Investig Drugs* 2000;9:871–83.
47. Jankovic J, Hunter C. A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease. *Parkinsonism Relat Disord* 2002;8:271–6.
48. Parkinson. Effect of lazabemide on the progression of disability in early Parkinson's disease. The Parkinson study group. *Ann Neurol* 1996;40:99–107.
49. Fariass MW, Zhang JG. Vitamin E therapy in Parkinson's disease. *Toxicology* 2003;189: 129–46.
50. Parkinson. DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. Parkinson study group. *Arch Neurol* 1989;46:1052–60.
51. Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. *Ann Neurol* 2003;53(Suppl 3):S39–47; discussion S47–8.
52. Shults CW, Oakes D, Kieburtz K, Beal MF, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol* 2002;59: 1541–50.
53. Muller T, Buttner T, Gholipour AF, Kuhn W. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. *Neurosci Lett* 2003;341: 201–4.
54. Herdegen T, Waetzig V. The JNK and p38 signal transduction following axotomy. *Restor Neurol Neurosci* 2001;19:29–39.
55. Saporito MS, Brown EM, Miller MS, Carswell S. CEP-1347/KT-7515, an inhibitor of c-jun N-terminal kinase activation, attenuates the 1-methyl-4-phenyl-tetrahydropyridine-mediated loss of nigrostriatal dopaminergic neurons in vivo. *J Pharmacol Exp Ther* 1999;288:421–7.
56. Saporito MS, Hudkins RL, Maroney AC. Discovery of CEP-1347/KT-7515, an inhibitor of the JNK/SAPK pathway for the treatment of neurodegenerative diseases. *Prog Med Chem* 2002;40:23–62.
57. Parkinson. The safety and tolerability of a mixed lineage kinase inhibitor (CEP-1347) in PD. *Neurology* 2004;62:330–2.
58. Hood E. RNAi: What's all the noise about gene silencing? *Environ Health Perspect* 2004;112:A224–9.
59. Majoor-Krakauer D, Willems PJ, Hofman A. Genetic epidemiology of amyotrophic lateral sclerosis. *Clin Genet* 2003;63:83–101.
60. Ellis CM, Suckling J, Amaro E Jr., Bullmore ET, et al. Volumetric analysis reveals corticospinal tract degeneration and extramotor involvement in ALS. *Neurology* 2001;57: 1571–8.
61. Conforti FL, Magariello A, Mazzei R, Sprovieri T, et al. Abnormally high levels of SOD1 mRNA in a patient with amyotrophic lateral sclerosis. *Muscle Nerve* 2004;29: 610–1.
62. Jackson CE, Rosenfeld J. Motor neuron disease. *Phys Med Rehabil Clin N Am* 2001;12: 335–52, ix–x.
63. Consilvio C, Vincent AM, Feldman EL. Neuroinflammation, COX-2, and ALS – a dual role? *Exp Neurol* 2004;187:1–10.
64. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4(3):191–206.
65. Miller RG, Moore DH 2nd, Gelinas DF, Dronsky V, et al. Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 2001;56:843–8.
66. Kalra S, Cashman NR, Caramanos Z, Genge A, et al. Gabapentin therapy for amyotrophic lateral sclerosis: lack of improvement in neuronal integrity shown by MR spectroscopy. *AJNR Am J Neuroradiol* 2003;24:476–80.
67. Desnuelle C, Dib M, Garrel C, Favier A. A double-blind, placebo-controlled randomized clinical trial of alpha-tocopherol (vitamin E) in the treatment of amyotrophic lateral sclerosis. *ALS riluzole-tocopherol study group. Amyotroph Lateral Scler Other Motor Neuron Disord* 2001;2:9–18.
68. Lange DJ, Murphy PL, Diamond B, Appel V, et al. Selegiline is ineffective in a collaborative double-blind, placebo-controlled trial for treatment of amyotrophic lateral sclerosis. *Arch Neurol* 1998;55:93–6.
69. Klivenyi P, Ferrante RJ, Matthews RT, Bogdanov MB, et al. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. *Nat Med* 1999;5: 347–50.
70. Groeneveld GJ, Veldink JH, van der Tweel I, Kalmijn S, et al. A randomized sequential trial of creatine in amyotrophic lateral sclerosis. *Ann Neurol* 2003;53:437–45.
71. Yang L, Sugama S, Chirichigno JW, Gregorio J, et al. Minocycline enhances MPTP toxicity to dopaminergic neurons. *J Neurosci Res* 2003;74:278–85.
72. Carter GT, Krivickas LS, Weydt P, Weiss MD, et al. Drug therapy for amyotrophic lateral sclerosis: Where are we now? *Drugs* 2003;6: 147–53.
73. Miller RG, Petajan JH, Bryan WW, Armon C, et al. A placebo-controlled trial of recombinant human ciliary neurotrophic factor (rhCNTF) in amyotrophic lateral sclerosis. *rhCNTF ALS study group. Ann Neurol* 1996;39:256–60.
74. Miller RG, Bryan WW, Dietz MA, Munsat TL, et al. Toxicity and tolerability of recombinant human ciliary neurotrophic factor in patients with amyotrophic lateral sclerosis. *Neurology* 1996;47:1329–31.
75. Dawbarn D, Allen SJ. Neurotrophins and neurodegeneration. *Neuropathol Appl Neurobiol* 2003;29:211–30.
76. Mitchell JD, Wokke JH, Borasio GD. Recombinant human insulin-like growth factor I (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2002:CD002064.
77. Kriz J, Gowing G, Julien JP. Efficient three-drug cocktail for disease induced by mutant superoxide dismutase. *Ann Neurol* 2003;53: 429–36.
78. Klivenyi P, Kiaei M, Gardian G, Calingasan NY, et al. Additive neuroprotective effects of creatine and cyclooxygenase 2 inhibitors in a transgenic mouse model of amyotrophic lateral sclerosis. *J Neurochem* 2004;88:576–82.
79. Mazzini L, Fagioli F, Boccaletti R, Mareschi K, et al. Stem cell therapy in amyotrophic lateral sclerosis: a methodological approach in humans. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4:158–61.
80. Reddy PH, Williams M, Tagle DA. Recent advances in understanding the pathogenesis of Huntington's disease. *Trends Neurosci* 1999;22:248–55.
81. Huntington study group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology* 2001;57:397–404.
82. Lucetti C, Gambaccini G, Bernardini S, Dell'Agnello G, et al. Amantadine in Huntington's disease: open-label video-blinded study. *Neurol Sci* 2002;23(Suppl 2): S83–4.
83. Smith DL, Woodman B, Mahal A, Sathasivam K, et al. Minocycline and doxycycline are not beneficial in a model of Huntington's disease. *Ann Neurol* 2003;54:186–96.
84. Goldstein LB. Neuroprotective therapy for acute ischaemic stroke: down, but not out. *Lancet* 2004;363:414–5.
85. Endres M, Dirnagl U. Ischemia and stroke. *Adv Exp Med Biol* 2002;513:455–73.
86. Horn J, Limburg M. Calcium antagonists for ischemic stroke: a systematic review. *Stroke* 2001;32:570–6.
87. Lees KR. Cerestat and other NMDA antagonists in ischemic stroke. *Neurology* 1997;49(Suppl 4):S66–9.
88. Davis SM, Lees KR, Albers GW, Diener HC, et al. Selfotel in acute ischemic stroke: possible neurotoxic effects of an NMDA antagonist. *Stroke* 2000;31:347–54.
89. Akins PT, Atkinson RP. Glutamate AMPA receptor antagonist treatment for ischaemic stroke. *Curr Med Res Opin* 2002;18(Suppl 2): S9–13.
90. Mohandas S, Mani J, Borgohain R, Sita-jayalakshmi S. Neuroprotection for acute ischemic stroke: an overview. *Neurol India* 2002;50(Suppl):S57–63.
91. Sareen D. Neuroprotective agents in acute ischemic stroke. *J Assoc Physicians India* 2002;50:250–8.
92. Gandolfo C, Sandercock P, Conti M. Lube-luzole for acute ischaemic stroke. *Cochrane Database Syst Rev* 2002:CD001924.

93. Saver JL, Kidwell C, Eckstein M, Starkman S. Prehospital neuroprotective therapy for acute stroke: results of the field administration of stroke therapy-magnesium (FAST-MAG) pilot trial. *Stroke* 2004;11:11.
94. Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (intravenous magnesium efficacy in stroke trial): randomised controlled trial. *Lancet* 2004;363:439–45.
95. Yamaguchi T, Sano K, Takakura K, Saito I, et al. Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. Ebselen study group. *Stroke* 1998;29:12–7.
96. Bath PM, Iddenden R, Bath FJ, Orgogozo JM. Tirilazad for acute ischaemic stroke. *Cochrane Database Syst Rev* 2001:CD002087.
97. Davalos A, Castillo J, Alvarez-Sabin J, Secades JJ, et al. Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials. *Stroke* 2002;33:2850–7.
98. Ricci S, Celani MG, Cantisani AT, Righetti E. Piracetam for acute ischaemic stroke. *Cochrane Database Syst Rev* 2002:CD000419.
99. Vemuganti R, Dempsey RJ, Bowen KK. Inhibition of intercellular adhesion molecule-1 protein expression by antisense oligonucleotides is neuroprotective after transient middle cerebral artery occlusion in rat. *Stroke* 2004;35:179–84. Epub 2003 Dec 4.
100. Enlimomab Acute Stroke Trial Investigators. Use of anti-ICAM-1 therapy in ischemic stroke: results of the Enlimomab acute stroke trial. *Neurology* 2001;57:1428–34.
101. Kidwell CS, Liebeskind DS, Starkman S, Saver JL. Trends in acute ischemic stroke trials through the 20th century. *Stroke* 2001;32:1349–59.
102. Sedarous M, Keramaris E, O'Hare M, Melloni E, et al. Calpains mediate p53 activation and neuronal death evoked by DNA damage. *J Biol Chem* 2003;278:26031–8. Epub 2003 Apr 29.
103. Piao CS, Kim JB, Han PL, Lee JK. Administration of the p38 MAPK inhibitor SB203580 affords brain protection with a wide therapeutic window against focal ischemic insult. *J Neurosci Res* 2003;73:537–44.
104. Passini MA, Watson DJ, Wolfe JH. Gene delivery to the mouse brain with adeno-associated virus. *Methods Mol Biol* 2004;246:225–36.
105. Janson C, McPhee S, Bilaniuk L, Haselgrove J, et al. Clinical protocol. Gene therapy of Canavan disease: AAV-2 vector for neurosurgical delivery of aspartoacylase gene (ASPA) to the human brain. *Hum Gene Ther* 2002;13:1391–412.