Memory Function and Brain Glucose Metabolism

S. Hoyer

Memory formation and memory retrieval are subject to complex cellular and molecular processes. Increasing evidence exists that neuronal glucose metabolism and its control by the insulin signal transduction cascade are the main players in such processes. Acetylcholine synthesis depends on the availability of acetyl CoA, provided from glucose breakdown, and insulin, which controls the activity of acetylcholine transferase. ATP is necessary for both synaptic activity and plasticity. This is also true for APPs, the secreted derivative of APP. Trafficking of the latter protein is controlled by insulin and insulin receptor function also acting on activity-regulated cytoskeleton-associated gene expression, which induces biochemical stimuli involved in synaptic activity and plasticity. Any damage in neuronal glucose metabolism and its control may, therefore, cause disturbances in memory function – as is found for example in sporadic Alzheimer's disease. Mimicking these metabolic and behavioral abnormalities in experimental animals, it was found that EGb 761® (definition see editorial) shows beneficial effects both on brain glucose and energy metabolism and on behavior.

Introduction

Numerous studies have provided clear evidence that memory function is highly dependent on the cholinergic system's functionality [9]. The degeneration of forebrain cholinergic projections has been demonstrated to be one of the most salient neurobiological and/or neuropathological features of both normal aging and sporadic Alzheimer's disease [6,7,14,63], although alterations in other neurotransmitter systems may also contribute to memory function [45,49,57]. Besides its effect on memory function, acetylcholine, together with norepinephrine, acts on the regulation of cerebral microvessel diameter in a concerted action in maintaining the supply of substrates, such as oxygen and glucose, to the brain [1,59,60]. In the brain, acetylcholine is formed from the energy-rich compound acetyl-CoA, which is generated by oxidation of pyruvate, the glycolytic end product [13]. The activity of the acetylcholine formation catalyzing enzyme, acetylcholine transferase, is controlled by insulin [34]. In this article, it is especially focused on the role of cerebral glucose metabolism and the function of insulin in the brain regarding memory capacity under normal and pathological conditions.

Insulin, Insulin Receptor and Glucose and Energy Metabolism in Normal Brain

The central significance of glucose as the major nutrient of the brain, its metabolism and control, have been well documented [24,26,27]. The derivative acetyl-CoA is used for acetylcholine formation (see above) for intracellular formation of cholesterol, which is the main sterol in membranes, and mainly for further oxidation to ATP that maintains most cellular and molecular functionalities. Therefore, the work of the endoplasmic reticulum and Golgi apparatus is highly dependent on a pH maintained at 6, which is ensured by an ATP-driven H^+-pump [53,61].

There is increasing evidence that neuronal glucose metabolism is antagonistically controlled by insulin and cortisol. Insulin in the brain originates from the pancreatic β-cells, but is also partially formed in pyramidal neurons such as those in the hippocampus, prefrontal cortex, entorhinal cortex and the olfactory bulb, but not in glial cells. Insulin receptors are widely distributed in the brain, with the highest densities in the olfactory bulb, hypothalamus, cerebral cortex and hippocampus (for details, see [21]). Insulin stimulates neuronal insulin receptor function [20,29]. In con-

Affiliation
Dept. of Pathochemistry and General Neurochemistry, Institute of Pathology of the University, Heidelberg, Germany

Correspondence
Dr. med. Siegfried Hoyer · Dept. of Pathochemistry and General Neurochemistry · Institute of Pathology of the University · Im Neuenheimer Feld 220/221 · 69120 Heidelberg · Germany

Bibliography
Pharmacopsychiatry 2003; 36 Suppl 1: S62–S67 · © Georg Thieme Verlag Stuttgart · New York · ISSN 0936-9589

trast, both glucocorticoids and catecholamines have been reported to cause insulin receptor desensitization [15,18]; the former have been shown to have drastic effects on glucose metabolism [47].

Effects of Insulin and Insulin Receptor on Amyloid Precursor Protein (APP) Metabolism and Tau Phosphorylation

Full-length APP normally undergoes processing by as yet undetected enzymatic activity known as 'α-secretase,' which cleaves the holoprotein precluding the formation of βA40 and βA42, the amyloidogenic derivatives. More detailed recent studies have given rise to the assumption that APP trafficking in the endoplasmic reticulum and Golgi apparatus is controlled by insulin and insulin receptor tyrosine kinase [12,56]. Insulin increased extracellular levels of the secreted form of APP (APPs) and the contrations of both βA40 and βA42 dose-dependently, and reduced the intracellular concentrations of these three derivatives. The insulin-mediated reduction of intracellular βA40 and βA42 was found to be the result of an increasing egress from the Golgi apparatus and the trans-Golgi network. Interestingly, the insulin receptor tyrosine kinase activity appeared to be essential for the effect of insulin on βA trafficking – that is, reduction of both intracellular βA40 and βA42. Inhibition of the insulin receptor function resulted in adverse effects – retention of APPs, βA40 and βA42 within the cell, and reduction in the extracellular milieu. Interestingly, recent evidence was provided that accumulation of intracellular βA42 may play a direct pathogenetic role in sporadic Alzheimer's disease [16,62].

Insulin has been shown to regulate the phosphorylation state of tau protein by regulating the activity of phosphorylating enzymes. Insulin concentration deficit increased the activity of glycogen synthase-3 kinase [22], which was found to cause tau-hyperphosphorylation [38]. ATP acts in a similar way; reduction of ATP activates both protein kinases erk36 and erk40 [51], which in turn causes tau-hyperphosphorylation [5].

Interrelationship between Memory and Brain Glucose Metabolism (Table 1)

A. Normal condition

As mentioned above, synthesis of the memory enhancing and memory stabilizing neurotransmitter, acetylcholine, from the glucose metabolism compounds acetyl-CoA and choline is controlled by insulin [34]. The binding of acetylcholine to its muscarinergic m1 and m3 receptors stimulates the formation of APPs, the amyloid precursor protein in its secreted form [43], which exerts multifold effects. APPs modulates synaptic plasticity in the hippocampus [31] and promotes dendritic outgrowth [39]. Together with the increase in synaptic density, the morphologic basis is formed to enhance memory capacity [41,50]. Besides acetylcholine, insulin enhances the extracellular levels of APPs as a consequence of its increasing egress from the Golgi apparatus and the trans Golgi-network in a dose-dependent fashion [12,56]. It is not yet clear whether or not the secretion of APPs from the cell mediated by acetylcholine and insulin occurs independently or in a concerted action. The energy-rich phosphate, ATP, strengthens synaptic transmission [30], and is itself a very rapid-acting extracellular neurotransmitter [4].

Functionally, synaptic plasticity forms the most important site of neuronal plasticity. Recent evidence exists that both synaptic activity and plasticity depend on biochemical stimuli that were found to be induced by the expression of the activity-regulated cytoskeleton-associated gene regulated by the insulin and insulin receptor signal transduction cascade [17,33,44,58,64].

B. Pathological condition

The most frequent pathologic condition associated with memory disturbances, dementia, is sporadic Alzheimer's disease. Early and severe abnormalities were found in the cerebral glucose metabolism, which worsened in parallel with dementia symptoms (for review, see [24]). As a consequence, the synthesis of acetylcholine in the presynaptic neuron is markedly diminished [55], and a fall of ATP production from glucose by around 50% in the beginning of sporadic Alzheimer's disease occurs, declining thereafter throughout the course of the disease [23]. The abnormality in neuronal glucose metabolism is assumed to be caused by a disturbance in the control of this metabolic pathways at the level of the insulin signal transduction [11,25]. Both the deficit in ATP availability and the abnormality in the insulin signal transduction cascade may have a severe impact on APP trafficking [12,61] causing a reduction in extracellular APPs concentration [12,56], thereby reducing synaptic activity and morphologically reducing neuronal activity (for review [52]). In all probability, the disturbance in the insulin signal transduction cascade reduces the expression of the activity-regulated cytoskeleton-asso-

Table **1** Effects of glucose on memory

Acetylcholine synthesis	ATP formation	APP trafficking	Activity-regulated cytoskeleton- associated gene expression
Acetylcholine function	Synaptic acitivity	APPs βA4 function	Synaptic activity and plasticity

Acetyl-CoA is generated from glycolytic glucose breakdown [13]. Acetyl-CoA and choline form acetylcholine under insulin control [34]. Acetylcholine stimulates the formation of the secreted form of the amyloid precursor protein [APPs] after binding to acetylcholinergic muscarinergic m1- and m3-receptors [43]. APPs has been found to promote dendritic outgrowth [39] and to increase synaptic density, thus enhancing memory capacity [50].

In the normal brain, ATP is formed from glucose only [23]. In the present context, ATP has two important functions – first, it acts as a rapid extracellular neurotransmitter [4] and second, it maintains synaptic transmission [30].

Full-length APP normally undergoes processing by an enzymatic activity known as α-secretase (for review, see [54]). However, recent findings give rise to the assumption that APP trafficking is controlled by insulin and the tyrosine kinase insulin receptor. Insulin increases the extracellular levels of APPs, βA40 and βA42, dose-dependently, and reduces the intracellular concentrations of all three APP derivatives [12,56]. Besides the beneficial effects of APPs (see text), the APP derivative βA40 has been found to promote cell proliferation and tyrosine phosphorylation in nanomolar concentration [37].

The insulin and insulin receptor signal transduction cascade has been found to induce the expression of the activity-regulated cytoskeleton-associated gene, which in turn mediates biochemical stimuli necessary for both synaptic activity and plasticity for memory formation and for memory function [17,33,44,58,64].

ciated gene, which mediates biochemical stimuli necessary for both synaptic activity and plasticity for memory formation and for memory function [17,33,44,58,64].

Thus, the brain glucose/energy metabolism and its control by the regulatory insulin signal transduction cascade participate greatly in diverse memory processes. Disturbances in this central metabolism may be most important mechanisms in the development of dementia.

In vivo experimental approach

To test the relationship between neuronal glucose metabolism and its control on the one hand, and behavior on the other, an *in vivo* animal model was established in which the neuronal insulin signal transduction cascade was damaged by intracerebroventricular application of the diabetogenic substance streptozotocin (STZ). STZ is known to inhibit the phosphorylation of tyrosine kinase of the insulin receptor [32]. At the neuronal receptor level, upregulation was observed in the hippocampus [36]. Regional glucose consumption was found to be reduced in 17 out of 35 brain structures, with the parietotemporal cortex, the entorhinal cortex and hippocampal subfields being most markedly affected [10]. The activities of glycolytic key enzymes were clearly diminished in cerebral parietotemporal cortex and in hippocampus [46]. The reduction in both glucose consumption and glycolytic flux caused a drop in the cellular energy pool after short-term and long-term effects of STZ slightly but permanently deteriorating over time [35,42] (Fig. **1**). In addition to the glucose and energy metabolism, a cholinergic deafferentiation along with a reduced activity of acetylcholine transferase have been observed [19,48]. These abnormalities in the cerebral glucose and energy metabolism and related metabolism were found to be accompanied by disturbances in learning, memory and cognitive ability [2,3,40,48]. In long-term studies, the abnormalities in learning, memory and cognitive ability deteriorated progressively [35] (Fig. **2**).

Ginkgo biloba extract (EGb 761®) exerts beneficial effects on neurons after hypoxic damage [8]. Studies performed on streptozotocin-damaged rats clearly showed a return to almost completely normal values of cerebral energy metabolism (Table **2**),

Fig. **1** Significant percent changes of energy rich phosphates after a triplicate intracerebroventricular injection of streptozotocin (STZ) 90 days after the first treatment. ATP, adenosine triphosphate; CrP, creatine phosphate; ADP, adenosine diphosphate; ~P, sum of available phosphate; $p < 0.05$.

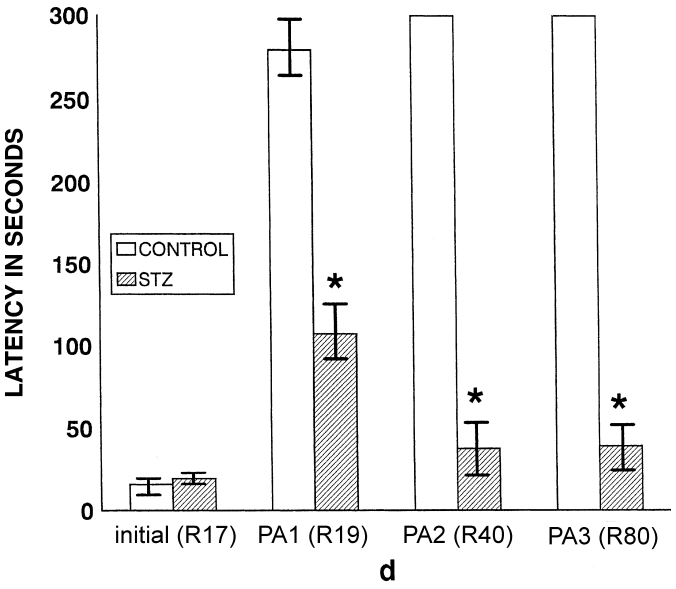

Fig. **2** Effects of intracerebroventricular streptozotocin (STZ) on retention passive avoidance behavior in rats. STZ was administered first 18 days before training. STZ did not affect the step through latency (R 17). Foot shock was applied at day R 18. Retention tests were conducted at days R 19, R 40 and R 80. White columns represent controls. *$p < 0.05$.

whereas deficits in learning, memory and cognitive ability were partly compensated [28] (Fig. **3**). Additionally, EGb 761® shifted STZ-induced abnormalities in glucose transporters and insulin binding to its receptor to normal ranges [36] (Fig. **4**, **5**, **6**).

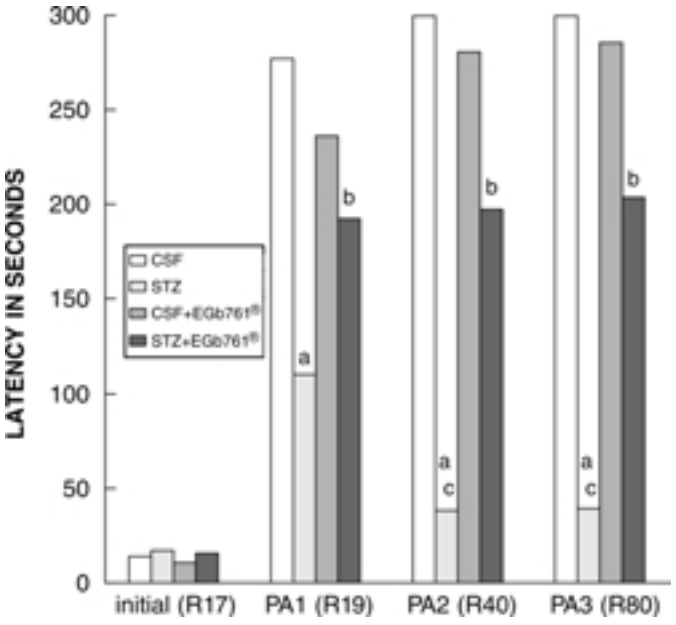

Fig. **3** Passive avoidance behavior after a triplicate intracerebroventricular STZ application and under treatment with EGb 761®. Initially, no differences were found between the experimental groups (R 17). EGb 761® improved latency significantly after icv STZ damage as compared to icv STZ (see also Fig. **2**). PA 1, passive avoidance test at day R 19; PA 2, at day 40; PA 3, at day 80; a, $p < 0.05$ between CSF and STZ; b, $p < 0.05$ between STZ and STZ + EGb 761®; c, $p < 0.06$ between R 19 and R 40/80.

Table **2** Energy-rich compounds in cerebral cortex

	ATP	*ADP*	*ATP/ADP*	*CrP*	*GTP*	*~P*
CSF	2.48 ± 0.33	0.42 ± 0.07	6.05 ± 1.17	5.76 ± 0.99	0.62 ± 0.08	1.31 ± 0.20
STZ	1.90 ± 0.29[a]	0.77 ± 0.21[a]	2.69 ± 0.89[a]	4.85 ± 0.62[a]	0.47 ± 0.06[a]	1.07 ± 0.14[a]
CSF + EGb 761®	2.20 ± 0.26[a]	0.49 ± 0.16	4.88 ± 1.47[a]	5.17 ± 0.85	0.56 ± 0.04[a]	1.17 ± 0.16
STZ + EGb 761®	2.13 ± 0.39[a,b]	0.68 ± 0.24[a]	3.52 ± 1.48[a]	5.36 ± 0.94[b]	0.51 ± 0.09[a]	1.19 ± 0.20[b]

Mean values and standard deviations of energy rich phosphates in parietotemporal cerebral cortex of rats after icv STZ and treatment with EGb 761®; [a] $p < 0.05$ vs CSF; [b] $p < 0.05$ between STZ and STZ + EGb 761.

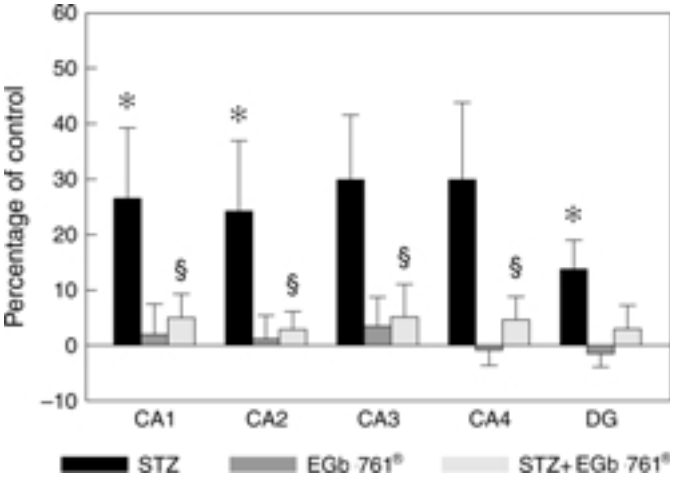

Fig. **4** Quantitation of autoradiography of [^{3}H]cytochalasin-B binding to total glucose transporter in hippocampal brain sections from good performing (GP) rats. Data are expressed as percentage change over control values and represent the mean ± SEM obtained from five animals. STZ, streptotozotocin-treated rats; EGb671, rats treated with EGb 761®; STZ-EGb761®, STZ-damaged rats treated with EGb 761® (see also Table **1**). *p < 0.05 *vs.* control; §p < 0.05 *vs.* STZ-treated group, two-tailed Student's *t*-test (from [36]; with permission of Springer Publ. Vienna).

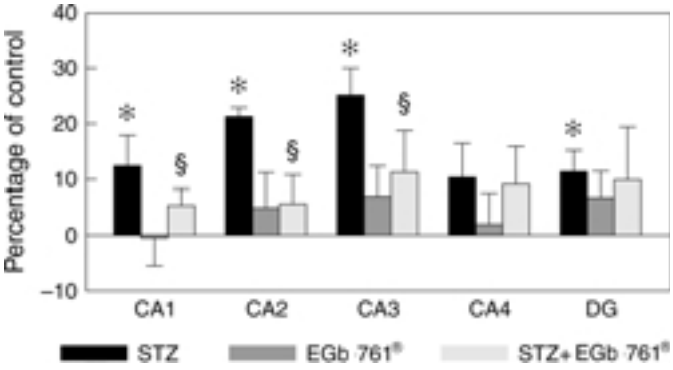

Fig. **5** Quantitation of autoradiography of [^{3}H]cytochalasin-B binding to total glucose transporter in hippocampal brain sections from poor performing (PP) rats. Data given are expressed as percentage change over control values and represent the means ± SEM obtained from five animals. STZ, streptotozotocin-treated rats; EGb 761®, EGb 761® Ginkgo biloba extract; STZ-EGb 761®, STZ-damaged rats treated with EGb 761® (see also Table **1**). *p < 0.05 vs. control; §p < 0.05 *vs.* STZ-treated group, two-failed Student's *t*-test (from [36]; with permission of Springer Publ. Vienna).

These results from this pathophysiological model of both behavior and oxidative brain metabolism underscore the beneficial effect of EGb 761® on these abnormalities, which represent the defective sites in dementia. Our tentative conclusion is that EGb 761® may act in a regulatory manner on the function of the neuronal insulin receptor.

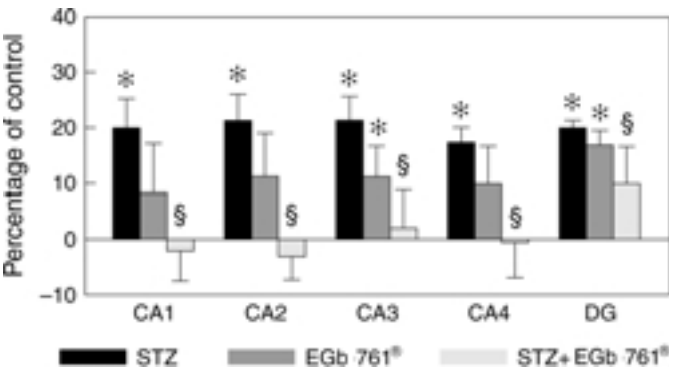

Fig. **6** Quantitation of autoradiography of [^{125}]Insulin receptor binding in hippocampal brain sections from good performing (GP) rats. Data are expressed as percentage change over control values and represent the mean ± SEM obtained from five animals. STZ, streptotozotocin-treated rats; EGb 761®, rats treated EGb 761® Ginkgo biloba extract; STZ-EGb 761®, STZ-damaged rats treated with EGb 761® (see also Table **1**). *p < 0.05 vs. control; §p < 0.05 *vs.* STZ-treated group, two-tailed Student's *t*-test (from [36]; by permission of Springer Publ. Vienna).

References

[1] Biesold D, Inanami O, Sato A, Sato Y. Stimulation of the nucleus basalis of Meynert increases cerebral cortical blood flow in rats. Neurosci Lett 1989; 98: 39 – 44

[2] Blokland A, Jolles J. Spatial learning deficit and reduced hippocampal Ch AT activity in rats after an icv injection of streptozotocin. Pharmacol Biochem Behav 1993; 44: 491 – 494

[3] Blokland A, Jolles J. Behavioral and biochemical effects of an icv injection of streptozotocin in old Lewis rats. Pharmacol Biochem Behav 1994; 47: 833 – 837

[4] Burnstock G. Overview. Purinergic mechanisms. Ann NY Acad Sci 1990; 603: 1 – 17

[5] Bush ML, Niyashiro JS, Ingram VM. Activation of a neurofilament kinase, a tau kinase and tau phosphatase by decreased ATP levels in nerve growth factor-differentiated PC 12 cells. Proc Natl Acad Sci USA 1995; 92: 1962 – 1965

[6] Coyle JT, Donald LP, Delong MR. Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 1983; 219: 1184 – 1186

[7] Davies P, Maloney AJR. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet 1976; 2: 1403 – 1405

[8] DeFeudis FV editor. Ginkgo biloba extract (Egb-761). From chemistry to clinic. Wiesbaden: Ullstein Medical, 1998

[9] Drachman DA, Noffsinger D, Sahakian BJ, Kurdziel S, Fleming P. Aging, memory and the cholinergic system: a study of dichotic listening. Neurobiol Aging 1980; 1: 39 – 43

[10] Duelli R, Schröck H, Kuschinsky W, Hoyer S. Intracerebroventricular injection of streptozotocin induces discrete local changes in cerebral glucose utilization in rats. Int J Dev Neurosci 1994; 12: 737 – 743

[11] Frölich L, Blum-Degen D, Bernstein HG, Engelsberger S, Humrich J, Laufer S, Muschner D, Thalheiner A, Türk A, Hoyer S et al. Insulin and insulin receptors in the brain in aging and sporadic Alzheimer's disease. J Neural Transm 1998; 105: 423 – 438

[12] Gasparini L, Gouras GK, Wang R, Gross RS, Beal MF, Greengard P, Xu H. Stimulation of β-amyloid precursor protein trafficking by insulin reduces intraneuronal β-amyloid and requires mitogen-activated protein kinase signaling. J Neurosci 2001; 21: 2561 – 2570

[13] Gibson GE, Jope R, Blass JP. Decreased synthesis of acetylcholine accompanying impaired oxidation of pyruvic acid in rat brain minces. Biochem J 1975; 148: 17 – 23

[14] Gibson GE, Peterson C, Jenden DJ. Brain acetylcholine synthesis declines with senescence. Science 1981; 213: 673 – 676

[15] Giorgino F, Almahfouz A, Goodyear LJ, Smith RJ. Glucocorticoid regulation of insulin receptor and substrate IRS-1 tyrosine phosphorylation in rat skeletal mucle in vivo. J Clin Invest 1993; 91: 2020 – 2030

[16] Gouras GK, Tsai J, Naslund J, Vincent B, Edgar M, Greenfield JP, Haroutunian V, Buxbaum JD, Xu H, Greengard P, Relkin NR. Intraneural Aβ42 accumulation in human brain. Am J Pathol 2000; 156: 15 – 20

[17] Guzowski F, Lyford GL, Stevenson GD, Houston F, McGaugh JL, Worley PF, Barnes CA. Inhibition of activity dependent ARC protein expression in the rat hippocampus impairs the maintenance of long-term potentiation and the consolidation of long-term memory. J Neurosci 2000; 20: 3993 – 4001

[18] Häring H. The insulin receptor: signaling mechanism and contribution to the pathogenesis of insulin restistance. Diabetologia 1991; 34: 848 – 861

[19] Hellweg R, Nitsch R, Hock C, Jaksch M, Hoyer S. Nerve growth factor and choline acetyltransferase activity levels in the rat brain following experimental impairment of cerebral glucose and energy metabolism. J Neurosci Res 1992; 31: 479 – 486

[20] Henneberg N, Hoyer S. Short-term or long-term intracerebroventricular (i. c. v.) infusion oí insulin exhibits a discrete anabolic effect on cerebral energy metabolism in the rat. Neurosci Lett 1994; 175: 153 – 156

[21] Henneberg N, Hoyer S. Desensitization of the neuronal insulin receptor: a new approach in the etiopathogenesis of late-onset sporadic dementia of the Alzheimer type (SDAT)? Arch Gerontol Geriat 1995; 21: 63 – 74

[22] Hong MF, Lee VMY. Insulin and insulin-like growth factor- 1 regulate tau phosphorylation in cultured human neurons. J Biol Chem 1997; 272: 19547 – 19553

[23] Hoyer S. Oxidative energy metabolism in Alzheimer brain. Studies in early-onset and late-onset cases. Mol Chem Neuropathol 1992; 16: 207 – 224

[24] Hoyer S. Oxidative metabolism deficiencies in brain of patients with Alzheimer's disease. ActaNeurol Scand Suppl 1996; 165: 18 – 24

[25] Hoyer S. Is sporadic Alzheimer's disease the brain type of non-insulin dependent diabetes mellitus? A challenging hypothesis. J Neural Transm 1998; 105: 415 – 422

[26] Hoyer S. Brain glucose and energy metabolism abnormalities in sporadic Alzheimer's disease. Causes and consequences: An update. Exp. Gerontol 2000; 35: 1363 – 1372

[27] Hoyer S. The brain insulin signal transduction system and sporadic (type II) Alzheimer's disease: An update. J Neural Transm 2002; 109: 341 – 360

[28] Hoyer S, Lannert H, Nöldner M, Chatterjee SS. Damaged neuronal energy metabolism and behavior are improved by Ginkgo biloba extract (EGb 761). J Neural Transm 1999; 106: 1171 – 1188

[29] Hoyer S, Prem L, Sorbi S, Amaducci L. Stimulation of glycolytic key enzymes in cerebral cortex by insulin. NeuroReport 1993; 4: 991 – 993

[30] Huganir RL, Greengard P. Regulation of neurotransmitter receptor desensitization by protein phosphorylation. Neuron 1990; 5: 555 – 567

[31] Ishida A, Furukawa K, Keller JN, Mattson MP. Secreted form of beta-amyloid precursor protein shifts the frequency dependency for induction of LTD, and enhances LTP in hippocampal slices. NeuroReport 1997; 8: 2133 – 2137

[32] Kadowaki T, Kasuga M, Akanuma Y, Ezaki O, Takaku F. Decreased autophosphorylation of the insulin receptor-kinase in streptozotocin diabetic rats. J Biol Chem 1984; 259: 14208 – 14216

[33] Kremerskothen H, Wendholt D, Teber I, Barnekow A. Insulin-induced expression of the activity-regulated cytoskeleton-associated gene (ARC) in human neuroblastoma cells requires p^{21ras}, mitogen-activated protein kinase/extracellular regulated kinase and src tyrosine kinases but is protein kinase C-independent. Neurosci Lett 2002; 321: 153 – 156

[34] Kyriakis JM, Hausman RE, Peterson SW. Insulin stimulates choline acetyltransferase activity in cultured embryonic chicken retina neurons. Proc Natl Acad Sci USA 1987; 84: 7463 – 7467

[35] Lannert H, Hoyer S. Intracerebroventricular administration of streptozotocin causes long-term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. Behav Neurosci 1998; 112: 1199 – 1208

[36] Löffler T, Lee SK, Nöldner M, Chatterjee SS, Hoyer S. Schliebs R. Effect of Ginkgo biloba extract (EGb 761®) on glucose metabolism-related markers in streptozotocin- damaged rat brain. J Neural Transm 2001; 108: 1457 – 1474

[37] Luo Y, Sunderland T, Wolozin B. Physiological levels of β-amyloid activate phosphatidyl inositol 3-kinase with the involvement of tyrosine phosphorylation. J Neurochem 1996; 67: 978 – 987

[38] Mandelkow EM, Drews G, Biernat J, Gustke N, van Lint J, Vandenheede JR, Mandelkow E. Glycogen synthase kinase-3 and the Alzheimer-like state of microtubule-associated protein tau. FEBS Lett 1992; 314: 315 – 321

[39] Mattson MP. Secreted forms of β-amyloid precursor protein modulate dendritic outgrowth and calcium responses to glutamate in cultured embryonic hippocampal neurons. J Neurobiol 1994; 25: 439 – 450

[40] Mayer G, Nitsch R, Hoyer S. Effects of changes in peripheral and cerebral glucose metabolism on locomotor activity, learning and memory in adult male rats. Brain Res 1990; 532: 95 – 100

[41] Meziane H, Dodart JC, Mathis C, Little S, Clemens J, Paul SM, Ungerer A. Memory- enhancing effects of secreted forms of the beta-aymloid precursor protein in normal and amnestic mice. Proc Natl Acad Sci USA 1998; 95: 12683 – 12688

[42] Nitsch R, Hoyer S. Local action of the diabetogenic drug, streptozotocin, on glucose and energy metabolism in rat brain cortex. Neurosci Lett 1991; 128: 199 – 202

[43] Nitsch RM, Slack BE Wurtman RJ, Growdon JH. Release of Alzheimer amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors. Science 1992; 258: 304 – 307

[44] Park CR. Cognitive effects of insulin in the central nervous system. Neurosci Biobehav Rev 2001; 25: 3 11 – 323

[45] Perry EK. The cholinergic hypothesis: ten years on. Br Med Bull 1986; 42: 63 – 69

[46] Plaschke K, Hoyer S. Action of the diabetogenic drug streptozotocin on glycolytic and glycogenolytic metabolism in adult rat brain cortex and hippocampus. Int J Dev Neurosci 1993; 11: 477 – 483

[47] Plaschke K, Müller D, Hoyer S. Effects of adrenalectomy and corticosterone substitution on glucose and glycogen metabolism in rat brain. J Neural Transm 1996; 103: 89 – 100

[48] Prickaerts J, Blokland A, Honig W, Meng F, Jolles J. Spatial discrimination learning and choline acetyltransferase activity in streptozotocin-treated rats: effects of chronic treatment with acetyl-1-carnitine. Brain Res 1995; 674: 142 – 146

[49] Quirion R, Aubert I, Robitaille Y, Gauthier S, Araujo DM, Chabot J-G. Neurochemical deficits in pathological brain aging: specificity and possible relevance for treatment strategies. Clin Neuropharmacol 1990; 13: S73 – 80

[50] Roch JM, Masliah E, Roch-Levecq AC, Sundsmo MP, Otero DAC, Veinbergs I, Saitoh T. Increase of synaptic density and memory retention by a peptide representing the trophic domain of the amyloid β-A4 protein precursor. Proc Natl Acad Sci USA 1994; 91: 7450 – 7454

[51] Röder HM, Ingram VM. Two novel kinases phosphorylate tau and the KSP site of heavy neurofilament subunits in high stoichiometric ratios. JNeurosci 1991; 11: 3325 – 3342

[52] Salehi A, Swaab DF. Diminished neuronal metabolic activity in Alzheimer's disease. J Neural Transm 1999; 106: 955 – 986

[53] Seksek O, Biwersi J, Verkman AS. Direct measurement of trans-Golgi pH in living cells and regulation of second messengers. J Biol Chem 1995; 270: 4967 – 4970

[54] Selkoe DJ. The cell biology of β-amyloid precursor protein and presenilin in Alzheimer's disease. Trends Cell Biol 1998; 8: 447 – 453

[55] Sims NR, Bowen DM, Allen SJ, Smith CCT, Neary D, Thomas DJ, Davison AN. Presynaptic cholinergic dysfunction in patients with dementia. J Neurochem 1983; 40: 503 – 509

[56] Solano DC, Sironi M, Bonfini C, Solerte SB, Govoni S, Racchi M. Insulin regulates soluble amyloid precursor protein release via phosphatidyl inositol 3 kinase-dependent pathway. FASEB J 2000; 14: 1015 – 1022
[57] Stecher J, Müller WE, Hoyer S. Learninig abilities depend on NMDA-receptor densitiy in hippocampus in adult rats. J Neural Transm 1997; 104: 281 – 289
[58] Steward O, Wallace CS, Lyford GL, Worley P. Synaptic activation causes the mRNA for the IEG ARC to localize selectively near activated postsynaptic sites on dendrites. Neuron 1998; 21: 741 – 751
[59] Suzuki N, Hardebo JE. The cerebrovascular parasympathetic innervation. Cerebrovasc Brain Metab Rev 1993; 5: 33 – 46
[60] Uddman R, Edvinsson L. Neuropeptides in the cerebral circulation. Cerebrovasc Brain Metab Rev 1989; 1: 230 – 252
[61] Verde C, Pascale MC, Martive G, Lotti LV, Torrisi HR, Helenius A, Bonatti S. Effect of ATP depletion and DTT on the transport of membrane proteins from the endoplasmic reticulum and the intermediate compartment to the Golgi complex. Eur J Cell Biol 1995; 67: 267 – 274
[62] Wilson CA, Doms RW, Lee VMY. Intracellular APP processing and Aβ production in Alzheimer's disease. J Neuropathol Exp Neurol 1999; 58: 787 – 794
[63] Wurtman RJ. Choline metabolism as a basis for the selective vulnerability of cholinergic neurons. Trends Neurosci 1992; 15: 117 – 122
[64] Zhao W, Chen H, Xu H, Moore E, Meiri N, Quon MJ, Alkon DL. Brain insulin receptors and spatial memory. J Biol Chem 1999; 274: 34 839 – 34 842