ELSEVIER

European Journal of Pharmacology 441 (2002) 1–14

www.elsevier.com/locate/ejphar

Review

Ageing and diabetes: implications for brain function

Geert Jan Biessels [a,b,*], Lars P. van der Heide [a], Amer Kamal [a], Ronald L.A.W. Bleys [c], Willem Hendrik Gispen [a]

[a] Department of Medical Pharmacology of the Rudolf Magnus Institute for Neurosciences, University Medical Centre, Utrecht, Netherlands
[b] Department of Neurology of the Rudolf Magnus Institute for Neurosciences, University Medical Centre, Utrecht, Netherlands
[c] Department of Functional Anatomy of the Rudolf Magnus Institute for Neurosciences, University Medical Centre, Utrecht, Netherlands

Received 3 January 2002; received in revised form 19 February 2002; accepted 26 February 2002

Abstract

Diabetes mellitus is associated with moderate cognitive deficits and neurophysiological and structural changes in the brain, a condition that may be referred to as diabetic encephalopathy. Diabetes increases the risk of dementia, particularly in the elderly. The emerging view is that the diabetic brain features many symptoms that are best described as "accelerated brain ageing." The clinical characteristics of diabetic encephalopathy are discussed, as well as behavioural (e.g. spatial learning) and neurophysiological (e.g. hippocampal synaptic plasticity) findings in animal models. Animal models can make a substantial contribution to our understanding of the pathogenesis, which shares many features with the mechanisms underlying brain ageing. By unravelling the pathogenesis, targets for pharmacotherapy can be identified. This may allow treatment or prevention of this diabetic complication in the future. We discuss changes in glutamate receptor subtypes, in second-messenger systems and in protein kinases that may account for the alterations in synaptic plasticity. In addition, the possible role of cerebrovascular changes, oxidative stress, nonenzymatic protein glycation, insulin and alterations in neuronal calcium homeostasis are addressed.

Keywords: Diabetes mellitus; Ageing; Brain; Dementia; Pathogenesis

1. Introduction

Diabetes mellitus is a heterogeneous metabolic disorder characterised by hyperglycaemia resulting from defective insulin secretion, resistance to insulin action or both (Gavin et al., 1997). Type 1 diabetes is the consequence of an autoimmune-mediated destruction of pancreatic β-cells, leading to insulin deficiency. Patients require insulin treatment for survival. Type 2 diabetes is characterised by insulin resistance and relative, rather than absolute, insulin deficiency. Type 2 diabetes usually occurs in obese individuals and is associated with hypertension and dyslipidaemia. Treatment aims to reduce insulin resistance (diet, exercise and drug therapy) and to stimulate insulin secretion.

Diabetes mellitus is often associated with (severe) complications, such as cardiovascular disease, the "diabetic foot," kidney failure, retinopathy and peripheral and autonomic neuropathy. Although proper metabolic control reduces the development of these complications, it is not sufficient to prevent them completely (The Diabetes Control and Complications Study Group, 1993). In this review, we discuss the neurological complications of diabetes, focussing on the brain. In particular, we explore underlying pathogenetic mechanisms, highlighting the possible interaction of diabetes and ageing.

2. Diabetic neuropathy in the peripheral and central nervous system

2.1. Peripheral neuropathy

Peripheral neuropathy is a frequent complication of diabetes mellitus. Several patterns of neuropathy can be distinguished, of which distal symmetric polyneuropathy is the most common (Dyck et al., 1993; Vinik et al., 1992). Patients can complain of numbness, paraesthesia and a tingling or prickling feeling, mainly affecting the lower limbs. On neurological examination, distal sensory loss and depression or loss of ankle jerks can be detected both in symptomatic and asymptomatic patients (Dyck et al., 1993; Vinik et al.,

* Corresponding author. Department of Neurology, G03.228, University Medical Center, PO Box 85500, 3508 GA Utrecht, Netherlands. Tel.: +31-30-250-8860; fax: +31-30-254-2100.
E-mail address: G.J.Biessels@med.uu.nl (G.J. Biessels).

0014-2999/02/$ - see front matter
PII: S0014-2999(02)01486-3

1992). Electrophysiological examination typically shows impairment of motor and sensory nerve conduction velocity (Arezzo, 1997). Morphological studies of nerve biopsies show myelinated fibre loss in association with an increased number of regenerating myelinated fibres and segmental demyelination (Yagihashi, 1995) .

2.2. Encephalopathy?

In recent years, evidence is emerging that diabetes also affects the central nervous system (Biessels et al., 1994; Stewart and Liolitsa, 1999). Both acute and chronic metabolic and vascular disturbances can impair the functional and structural integrity of the brain in diabetic patients. For example, diabetes increases the risk for stroke and stroke outcome is worse in diabetic patients (Bell, 1994; Mankovsky et al., 1997). In addition, hyper- and hypoglycaemic episodes may result in acute cerebral dysfunction (Biessels et al., 1994; Cryer et al., 1994). The consequences of these acute insults to the brain are well recognised. We do, in contrast, know relatively little of the functional and structural cerebral alterations that develop more insidiously and tend to be subtler. Long-term effects of diabetes on the brain are manifested at the structural, neurophysiological and neuropsychological level. The emerging view is that the diabetic brain features many symptoms that are best described as accelerated brain ageing.

2.2.1. Structural changes

There is only a limited amount of data from brain autopsy studies. In an early study of young (<40 years of age) Type 1 diabetic patients with severe and widespread diabetic angiopathy Reske-Nielsen et al. (1965) observed diffuse degenerative abnormalities of brain tissue. They considered these degenerative changes to be so pronounced that they implied a dual pathogenesis: ''ischaemia caused by an angiopathy and a primary diabetic abnormality of the brain tissue.'' An increased frequency in the occurrence of ischaemic brain lesions among diabetic patients compared to age-matched controls was confirmed by an autopsy study by Peress et al. (1973).

More recently, neuroimaging techniques, such as magnetic resonance imaging and computed tomography, have provided data on structural changes in the brain that may be more relevant to the general population of diabetic patients. Cerebral atrophy, as manifested by widened sulci and/or enlarged lateral ventricles, appears to be more pronounced in diabetic patients than in age-matched controls (Araki et al., 1994; Lunetta et al., 1994; Soininen et al., 1992). As atrophy is one of the hallmarks of brain ageing (Manolio et al., 1994), the radiological appearance of the brain in diabetic patients has been considered to reflect a process of accelerated ageing. In addition to the global subcortical and cortical atrophy, there is a tendency for an increased occurrence of white matter hyperintensities on magnetic resonance imaging studies (Araki et al., 1994; Ylikoski et al., 1995), possibly related to the ischaemic lesions that were observed in the autopsy.

2.2.2. Electrophysiological changes

Measurements of the latencies of evoked potentials have been widely used to examine the functional integrity of the central nervous system in diabetic patients (Di Mario et al., 1995). Increases in the latencies of these evoked potentials provide a central equivalent of reduced conduction velocity in peripheral nerves. The latencies of both central and peripheral components of the brainstem auditory evoked potential are affected in Type 1, as well as in Type 2 diabetic patients (Di Mario et al., 1995; Donald et al., 1984; Khardori et al., 1986). Likewise, the latency of the P100 wave of the visual evoked potential, which is thought to be generated in the visual cortex (Parisi and Uccioli, 2001), is increased (Parisi and Uccioli, 2001; Ziegler et al., 1994). P100 latencies correlate positively with the duration of diabetes and HbA1 levels (Moreo et al., 1995) and can be improved by intensive insulin treatment (Ziegler et al., 1994).

Event-related potentials are a valuable tool for the quantification of changes in cognitive resources in normal ageing and conditions associated with cognitive decline (Anderer et al., 1998; Picton, 1992). The P300 wave is a positive deflection in the human event-related potential that is thought to result from neural activity associated with attentional and memory processes (Picton, 1992). It is most commonly elicited in an ''oddball'' paradigm in which a subject is instructed to detect an occasional ''target'' stimulus in a regular train of standard stimuli (Picton, 1992). The P300 latency increases markedly with age (Anderer et al., 1998), but more so in diabetic patients (Mooradian et al., 1988; Pozzessere et al., 1991), which may be a neurophysiological manifestation of impairment of higher brain functions.

2.2.3. Cognition

As early as in the 1920s, it was recognised that diabetes mellitus may affect cognition (Miles and Root, 1922). Numerous studies have since reported cognitive deficits in both Type 1 and Type 2 diabetic patients. In adult Type 1 diabetic patients, modest reductions in mental efficiency have been reported repeatedly, particularly involving learning and memory, problem solving and mental and motor speed (Ryan, 1988). Severe deficits occur only in few patients (Gold et al., 1994). The pattern of impairments across different cognitive domains is rather inconsistent among studies, probably due to the subtle nature of the deficits, but also to the heterogeneity of the populations studied. In addition, the exposure to the two extremes of blood glucose levels, severe hypoglycaemia on the one hand and chronic hyperglycaemia on the other, varies between patients. Chronic hyperglycaemia and repeated episodes of severe hypoglycaemia may both adversely affect the brain (Langan et al., 1991; Ryan and Williams, 1993; Wredling et

al., 1990), albeit through different mechanisms, thus, leading to different cerebral deficits.

Compared to Type 1 diabetes, neuropsychological studies in Type 2 diabetic patients have provided more consistent results. Moderate degrees of cognitive impairment have been reported, particularly in tasks involving verbal memory or complex information processing (Stewart and Liolitsa, 1999; Strachan et al., 1997). Basic attentional processes, motor reaction time and immediate memory appear to be relatively unaffected (Strachan et al., 1997). Risk factors for cognitive dysfunction in Type 2 diabetes are chronic hyperglycaemia, dyslipidaemia and the presence of peripheral neuropathy (Strachan et al., 1997). Hypoglycaemic episodes do not appear to be a prime determinant, as cognitive deficits also occur in subjects with impaired glucose tolerance and in newly diagnosed Type 2 diabetic patients who had not yet been treated with glucose lowering drugs (Kalmijn et al., 1995; Vanhanen et al., 1997).

2.2.4. Dementia

There is an increasing body of evidence to support a relation between especially Type 2 diabetes and dementia in old age (Leibson et al., 1997; Ott et al., 1999). The Rotterdam Study is a community-based prospective cohort study in which chronic disorders of the elderly are under investigation (Ott et al., 1999). The relative risk for developing dementia was doubled in diabetic patients (Ott et al., 1999), suggesting that diabetes may contribute to the to the clinical syndrome of dementia in a substantial proportion of all dementia patients. In an extensive review of the literature, Stewart and Liolitsa (1999) conclude that there is a cross-sectional and prospective association between Type 2 and cognitive impairment, probably both for memory and executive functions. Their review confirms the elevated risk of both vascular dementia and Alzheimer disease in Type 2 diabetes patients, albeit with strong interactions with other risk factors.

3. Cognition and synaptic plasticity in experimental ageing and diabetes

Animal models have been widely used to explore the connection between age-related memory deficits and changes in the anatomy and physiology of the brain (Foster, 1999). Although aged rodents can learn and retain new information, they exhibit slower learning and rapid forgetting. Spatial learning in a Morris water maze, for example, is much slower than in young adult control rats (Kamal et al., 2000; Pitsikas and Algeri, 1992). In view of the crucial role of the hippocampus in certain types of learning and memory, several groups have studied the functional and structural integrity of the hippocampus in aged rodents. One aspect of hippocampal function, synaptic plasticity, has attracted particular attention, as plastic changes in synaptic strength are assumed to be involved in learning and memory (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999). Long-term potentiation (LTP) and depression (LTD) are two forms of activity-dependent synaptic plasticity that have been studied extensively. In LTP, brief high-frequency afferent activity leads to a long-lasting increase in the strength of synaptic transmission, whereas in LTD prolonged low-frequency activity results in a persistent reduction in synaptic strength. Both processes are triggered by an increase in the level of postsynaptic intracellular calcium concentration $[Ca^{2+}]_i$ (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999; Yang et al., 1999). LTP is triggered by a brief increase of $[Ca^{2+}]_i$ with relatively high magnitude, whereas a prolonged modest rise of $[Ca^{2+}]_i$ induces LTD (Yang et al., 1999). A complex pattern of changes in synaptic plasticity has been observed in hippocampal slices of aged rodents, including an increase in the threshold for LTP induction and a decrease in the threshold for LTD induction (Barnes, 1994; Foster, 1999). These changes have been related to alterations in $[Ca^{2+}]_i$ homeostasis in neurones of aged animals (Foster, 1999; Landfield, 1994).

Animal models have also been used to examine the relation between memory deficits and changes in synaptic plasticity in diabetes. In general, animal models of diabetes can be divided into those in which diabetes is induced by experimental procedures that disturb insulin production, and those in which animals develop diabetes spontaneously, due to a genetic predisposition (Shafrir, 1997). The most commonly used method for induction of diabetes is an intravenous or intraperitoneal injection of the β-cytotoxic agent streptozotocin (STZ). This glucosamine–nitrosourea compound is taken up into the cell via the GLUT-2 glucose transporter, which is highly expressed by the insulin-producing β-cells of the islets of Langerhans (Schnedl et al., 1994). The GLUT-2 glucose transporter is absent at the blood–brain barrier (Kumagai, 1999), thus, excluding direct effects of STZ on the brain following systemic administration. STZ-diabetic rodents are hypoinsulinaemic, but do not require insulin treatment to survive. Blood glucose levels typically are 20–25 mmol/l (normal 5 mmol/l). Like diabetic patients, STZ-diabetic rats develop end-organ damage affecting the eyes, kidneys, heart, blood vessels and peripheral and central nervous system. Although a large variety of spontaneously diabetic rodents have been described (Shafrir, 1997), these models have rarely been used to study the effects of diabetes on the brain.

3.1. Behavioural studies

Studies into cognitive functioning in STZ-diabetic rodents have used several learning tasks. STZ diabetes does not disturb operant behaviour for food reward (Kaleeswari et al., 1986). Retention of passive avoidance in rats and mice is reported to be facilitated (Bellush and Rowland, 1989; Flood et al., 1990), but not invariably (Mayer et al., 1990). In more complex learning tasks, such as an active avoidance T-maze, or a Morris water maze, diabetic rodents

consistently displayed performance deficits (Biessels et al., 1996, 1998; Flood et al., 1990; Popovic et al., 2001). The development of the deficits was dependent on the duration of STZ diabetes (Biessels et al., 1996, 1998). Subcutaneous implantation of insulin pellets at the onset of diabetes, so that blood glucose levels decreased from about 25 mmol/l to about normal (7 mmol/l), completely prevented the learning deficit. If, however, this insulin treatment was started 10 weeks after diabetes onset, when learning is already impaired, there was only partial improvement (Biessels et al., 1998). Control experiments showed that these performance deficits were not due to sensorimotor impairments (Biessels et al., 1996, 1998).

The variation in the results of these behavioural studies may be partially explained by differences in task complexity, animal models used and duration of diabetes. A key factor, however, appears to be the nature of the stimulus used in the behavioural paradigms. There are clear indications that the physiological responses to a novel environment, or to stressful stimuli which are often part of learning paradigms, are larger in STZ-diabetic than in nondiabetic rodents (Bellush et al., 1991; Bellush and Rowland, 1989; Flood et al., 1990). Enhanced retention of simple passive avoidance in diabetic rodents (Bellush and Rowland, 1989), for example, has, therefore, been ascribed to an increased sensitivity to foot shock (Flood et al., 1990).

3.2. Hippocampal synaptic plasticity

Learning deficits in STZ-diabetic rats develop in association with distinct changes in synaptic plasticity in hippocampal slices, which appear to be dependent on diabetes duration and severity (Gispen and Biessels, 2000). A deficit in the expression of *N*-methyl-D-aspartate (NMDA)-dependent long-term potentiation (LTP) in the CA1 field was shown to develop gradually and reach a maximum at 12 weeks after diabetes induction (Biessels et al., 1996; Chabot et al., 1997; Kamal et al., 1999). At this time point, NMDA-dependent LTP in the dentate gyrus and NMDA-independent LTP in the CA3 field are also impaired (Kamal et al., 1999). Insulin treatment prevents the development of the changes in LTP but is less effective against existing LTP deficits (Biessels et al., 1998). In contrast to LTP, expression of long-term depression (LTD) is enhanced in the CA1 field following low-frequency stimulation of slices from diabetic rats (Kamal et al., 1999). This enhancement of LTD appears to be dependent on the stimulus frequency (Gispen and Biessels, 2000).

A number of studies have tried to pinpoint the mechanisms underlying the alterations in hippocampal synaptic plasticity in STZ-diabetic rats. In presynaptic fibres, subtle changes have been detected, including reduced impulse conduction velocity (Candy and Szatkowski, 2000a). However, as paired-pulse facilitation in the CA1 field is unaffected (Biessels et al., 1996), presynaptic function appears to be largely preserved (Zucker, 1989). It is, therefore, likely that the plasticity deficit is mainly postsynaptic in nature, involving membrane excitability and/or the intracellular signalling cascade involved in LTP and LTD induction. Under nondiabetic conditions, the level of postsynaptic depolarisation required to induce plasticity is known to vary with the functional state of the synapse prior to the application of the conditioning stimulus (Ngezahayo et al., 2000). Hence, induction of LTD is facilitated and induction of LTP is inhibited by prior induction of LTP (Artola et al., 1990). With regard to the mechanisms of impaired plasticity in STZ diabetes, changes in postsynaptic excitability are, therefore, of particular interest. The postsynaptic resting membrane potential remains unchanged, at least up to 3 weeks after diabetes induction (Candy and Szatkowski, 2000a). The slope of the field excitatory postsynaptic potential (fEPSP) and the excitability of pyramidal cells in the CA1 and CA3 field, however, was found to be increased in naive slices (Candy and Szatkowski, 2000b; Kamal et al., 1999; Margineanu et al., 1998; Tekkok and Krnjevic, 1999). In contrast, others detected a decrease in the slope of the a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-mediated fEPSP (Chabot et al., 1997).

Studies with the gamma-aminobutyric acid (GABA)-A receptor channel-blocker picrotoxin indicate that the level of GABA-ergic inhibition in the hippocampus appears to be unchanged (Kamal et al., 1999). In contrast, the sensitivity to the inhibitory actions of the neuromodulator adenosine is increased shortly (days to weeks) after induction of diabetes, (Cassar et al., 1998; Morrison et al., 1992). If this increased sensitivity, which has been attributed to the loss of nucleoside uptake processes (Morrison et al., 1992), were to persist for months instead of weeks after induction of diabetes, it may play a role in the LTP deficits seen in diabetic rats, as adenosine directly modulates the induction of LTP (de Mendonca and Ribeiro, 1994).

Age-related changes in cognition and synaptic plasticity have been linked to alterations in glutamatergic neurotransmission (Barnes, 1994; Segovia et al., 2001). The density of NMDA binding sites in the hippocampus, for example, is markedly reduced in aged rodents (Segovia et al., 2001). Relatively little is known about the effects of diabetes on postsynaptic glutamate receptors in the hippocampus. In Sprague–Dawley rats, after 6–8 weeks STZ diabetes, the affinity of glutamate for AMPA, but not for NMDA receptors, was reported to be decreased (Gagne et al., 1997). The reduced affinity for AMPA was associated with reduced levels of the GluR1 subunit of the AMPA receptor (Gagne et al., 1997), whereas the level of GluR2 and GluR3 in the hippocampus and cortex was unaffected (Gagne et al., 1997). After 12 weeks of STZ diabetes, the levels of the NMDA receptor subunits NR1 and NR2A were not changed, but there was a marked decrease (-40%) in NR2B (Di Luca et al., 1999). Furthermore, the phosphorylation of the NR2A/B subunits by Ca^{2+}/calmodulin-dependent protein kinase II was reduced in diabetes (Di Luca et al., 1999). It was suggested that these NMDA

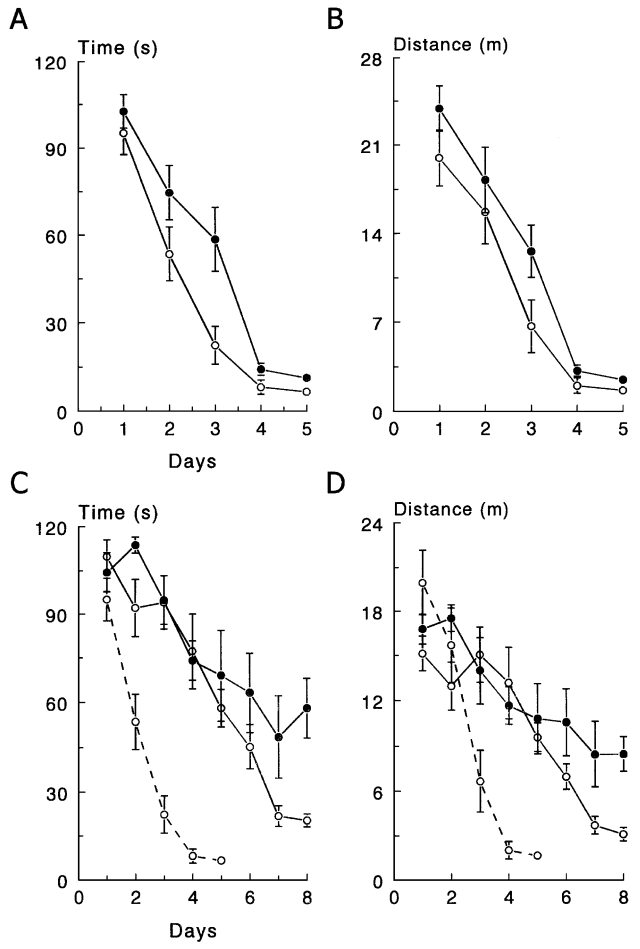

Fig. 1. Effects of STZ diabetes and ageing on spatial learning in a Morris water maze. (A, B) Young adult (5 months) rats were tested after 8 weeks of streptozotocin diabetes. The maze consisted of a large circular black pool (210-cm diameter, 50-cm height), which was placed in a darkened room. A curtain that obscured visual cues surrounded the maze. Rats were trained on 5 consecutive days, three trials per day. Latencies (A) and swimming distances (B) to reach the platform were measured. Young adult diabetic rats (●) ($n=9$) performed significantly worse than age-matched nondiabetic controls (○) ($n=9$): latencies ANOVAR (Days 1–5): $F(1,16)=5.77$, $P<0.05$; swimming distances ANOVAR (Days 3–5): $F(1,16)=4.77$, $P<0.05$. The possible involvement of sensorimotor dysfunction in the performance deficit of diabetic rats was carefully excluded using adapted versions of the maze (Biessels et al., 1996, 1998). (C, D) Aged (2 years) rats were also tested after 8 weeks of streptozotocin diabetes. Rats were trained on 8 consecutive days, three trials per day. Latencies (C) and swimming distances (D) to reach the platform were measured. Aged diabetic rats (●) ($n=7$) performed significantly worse than age-matched nondiabetic controls (○) ($n=6$): latencies ANOVAR (Days 1–8): $F(1,11)=3.66$, $P=0.08$, ANOVAR (Days 6–8): $F(1,11)=5.33$, $P<0.05$; swimming distances ANOVAR (Days 1–8): $F(1,11)=5.29$, $P<0.05$. Note the difference in comparison to the latencies and distances swum by the young adult nondiabetic animals (interrupted line). Data are means ± S.E.M. Adapted from Kamal et al.(2000), with permission.

receptor-related changes underlie the LTP deficits (Di Luca et al., 1999). The recent finding that overexpression of NR2B in the forebrains of nondiabetic transgenic mice facilitates induction of LTP and enhances learning abilities (Tang et al., 1999) supports this suggestion.

3.3. Interaction of diabetes and ageing?

As both ageing and diabetes affect cognition, synaptic plasticity and glutamatergic neurotransmission in rats, it is conceivable that the effects of diabetes and ageing interact. This was examined in a recent study (Figs. 1 and 2), which used an experimental protocol in which each of the two conditions in isolation produces only moderate deficits. Rats were examined after 2 months of STZ diabetes, which produces half-maximal deficits in synaptic plasticity in young adult rats (Kamal et al., 1999). Aged rats were examined at 2 years of age, when they have developed moderate changes in synaptic plasticity due to ageing alone. In aged rats (24 months) the diabetic deficit in water maze performance was larger than expected from the effect in young adult rats (Fig. 1). Likewise, the impairment of hippocampal LTP and enhancement of LTD was accentuated by the combination of the two conditions (Fig. 2),

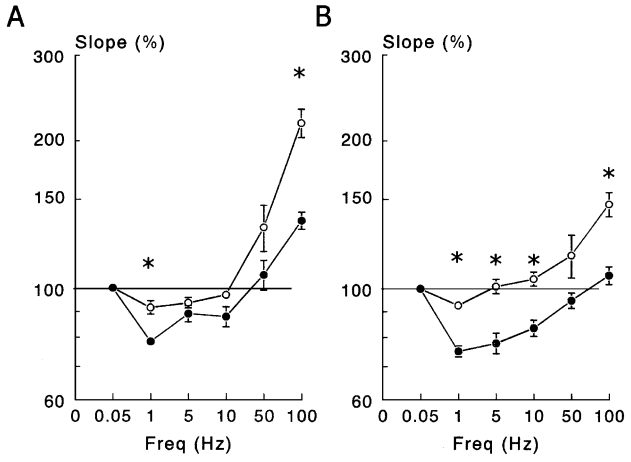

Fig. 2. Effects of STZ diabetes and ageing on hippocampal synaptic plasticity. The same animals from which the behavioural data are depicted in Fig. 1 were used. One to two weeks after the water maze, LTP was measured in the CA1 field of the hippocampus in vitro. The baseline slope of the field excitatory postsynaptic potential (fEPSP) was recorded for 15 min. Next, a conditioning stimulus was applied to the afferent fibres of CA1 field, consisting of 900 pulses, given at different frequencies (from 0.05 to 100 Hz). High-frequency stimulation (HFS; 100 Hz for 1 s and 50 Hz for 2 s) was applied at intervals of 10 s. Low-frequency stimulation (LFS) was given as a single train of 900 stimuli at 10 Hz (for 1.5 min), 5 Hz (for 3 min) or 1 Hz (for 15 min). The change in slope (expressed as percent of baseline) was measured at 30 min after the conditioning stimuli. (A) Hippocampal slices from young adult animals: LFS induced depression of the fEPSP, whereas HFS induced potentiation. In comparison to controls (○) ($n=8$ at each frequency), expression of long-term depression at 1-Hz stimulation was significantly enhanced in diabetic slices (●) ($n=8$), whereas expression of long-term potentiation at 100-Hz stimulation was significantly impaired ($*P<0.05$; t-test). (B) Hippocampal slices from aged animals. In comparison to controls (○) ($n=8$), expression of LTD was significantly enhanced in diabetic slices (●) ($n=7$) after 1-, 5- and 10-Hz stimuli ($*P<0.05$; t-test), whereas expression of LTP after 100 Hz stimulation was significantly impaired ($*P<0.05$). Note the difference in comparison to the frequency curve in hippocampal slices from the young adult nondiabetic animals. Data are means ± S.E.M. Adapted from Kamal et al.(2000), with permission.

suggesting that there is an interaction between ageing and diabetic cerebral dysfunction (Kamal et al., 2000).

4. Ageing and diabetes: shared pathogenetic mechanisms?

The aforementioned clinical and experimental data clearly show that diabetes can affect the brain and that the effects of diabetes and ageing on the brain may interact. The underlying mechanisms, however, are still unclear and subject of current research and speculation. As will be discussed below, some authors emphasise the common feature of advanced glycated end products and reduced antioxidant defence in the brains of Type 2 diabetes and Alzheimer patients. In addition, an extremely interesting lead emerges, suggesting that sporadic Alzheimer disease may reflect the "brain type" of Type 2 diabetes mellitus (Hoyer, 1998). In this concept, hyperinsulinaemia, brain glucose utilisation and insulin signal transduction in the brain play an interconnected role in the pathophysiology. Clinical and experimental studies indeed show that altered glucose regulation impairs learning and memory (Messier and Gagnon, 1996) and defects in insulin action, both in the periphery and the brain, have recently been implicated in the pathogenesis of sporadic Alzheimer's disease (Frolich et al., 1998; Vanhanen and Soininen, 1998). Ryan and Geckle (2000) come to the conclusion that the increased risk of cognitive dysfunction in elderly Type 2 patients is the consequence of a synergistic interaction between diabetes-related metabolic derangements and structural and functional cerebral changes due to the normal ageing process.

4.1. Cerebrovascular changes

Regional cerebral blood flow changes occur in response to alterations in the metabolic demand of brain regions. Apart from this moment-to-moment adaptation, many reports document a decline of regional cerebral blood flow in ageing, which seems to be restricted to regions with cell loss (Kalaria, 1996). Recently, it was demonstrated that after correction for cerebral volume differences, no decline in resting cerebral blood flow was present in most but not all regions in aged patients (Meltzer et al., 2000). There are indications, however, that ageing affects the autoregulatory response of cerebral blood vessels thereby impairing the ability to compensate for changes in perfusion pressure (Lartaud et al., 1993; Toyoda et al., 1997).

Morphological vascular changes in ageing persons have been described frequently. They include changes in the large cerebral vessels and their innervation and changes in the microvessels. The large vessel wall becomes stiffer and contains more collagen (Kalaria, 1996). A decline of the perivascular nerve density has been demonstrated in rats (Cowen and Thrasivoulou, 1990; Thrasivoulou and Cowen, 1995) and humans (Bleys et al., 1996). In vessels smaller than 1 mm, hyaline arteriosclerotic changes are found, characterised by intima thickening by fibrous tissue and fibrous replacement of vascular smooth muscle (Mrak et al., 1997). These vessels have become more rigid, elongated and tortuous. On the microvascular level, thinning of the endothelium and thickening of the basement membrane occur in capillaries and arterioles, in the latter vessels accompanied by fibrous replacement of smooth muscle (Kalaria, 1996).

Studies on the effect of diabetes mellitus on cerebral blood flow have been conflicting: decreased, unchanged and increased cerebral blood flow have been reported (Mankovsky et al., 1997). A recent study using single-photon emission tomography and correction for cerebral atrophy suggested that in humans with diabetic microangiopathy reduced regional cerebral blood flow was due to atrophy and disappeared after correction (Sabri et al., 2000). In experimental studies, differences in the techniques used for assessing blood flow appear to be the major source of the inconsistent findings. For example, studies that assessed blood flow indirectly, by measuring red blood cell velocity in cortical arterioles (Rubin and Bohlen, 1985) or venous outflow (Simpson et al., 1990) reported increases in cerebral blood flow. In contrast, studies that assessed blood flow at tissue level, by measuring the cerebral uptake of tracers like [^{14}C]iodoantipyrine in awake or anaesthetized rats, consistently report flow reductions of 10–15% during the first month of diabetes (Duckrow et al., 1987; Harik and LaManna, 1988) and 10–30% after 4 months of diabetes (Jakobsen et al., 1990; Knudsen et al., 1991), with some degree of regional variation. Nevertheless, literature data also indicate an impairment of cerebrovascular reactivity in diabetes mellitus. This could partially be explained by the development of autonomic neuropathy, as suggested by a study into cerebrovascular control in diabetic patients (Cencetti et al., 1999). Investigation of the effect of streptozotocin-induced diabetes in rats on cerebrovascular nerves demonstrated a decrease in the density of vasoactive intestinal polypeptide and serotonin containing nerves (Lagnado et al., 1987). Endothelium-mediated vascular responses are another factor that may contribute to decreased vasoreactivity. In this respect, several authors reported impairment of nitric oxide-mediated dilation of cerebral arterioles in diabetic rats (Mayhan et al., 1991; Pelligrino et al., 1992). Diabetes mellitus also leads to morphological macrovascular and microvascular abnormalities. Atherosclerotic changes in large vessels are beyond the scope of this review. Microvascular abnormalities include thickening of the capillary basement membrane. This was also found in aging but the basement membrane was considerably thicker in age-matched diabetic humans and rats (Johnson et al., 1982; Junker et al., 1985). Another finding was endothelial cell degeneration of microvessels (Moore et al., 1985).

The morphological and functional vascular changes described above may, together with atherosclerosis of the large extra- and intracranial vessels, underlie increased

incidence of ischaemic stroke and a worse functional outcome that is found in patients with diabetes (Mankovsky et al., 1997). Not all vascular abnormalities will lead to acute disturbances of cerebral blood flow that are severe enough to cause stroke. Chronic hypoperfusion may, however, also result in neuronal and glial changes. A decrease of microtubule-associated protein 2 in dendrites (a marker for early ischaemic damage) accompanied by an increase of astrocyte components was found in chronic hypoperfusion models in rats (de la Torre, 2000; Nanri et al., 1998). Especially the vulnerable CA1 neurones of the hippocampus, which are highly sensitive to ischemia (Schmidt-Kastner and Freund, 1991) seem to suffer from chronic hypoperfusion.

Although many uncertainties about the pathophysiologic mechanisms still exist, it can be concluded that both in ageing and diabetes vascular changes occur that may have consequences for the cerebral circulation.

4.2. Oxidative stress

A common theory for ageing and for the pathogenesis of Alzheimer's disease relates cell death to oxidative stress mediated by free radicals (Beckman and Ames, 1998; Smith et al., 1995). Accumulation of damaged, oxidised, dysfunctional proteins seems to result from a combination of an age-related increase in the rate of oxygen free radical-mediated damage and a loss of the ability to degrade oxidised proteins (Facchini et al., 2000). Indeed, increased levels of oxidised proteins and reduced activity of antioxidant enzymes have been demonstrated in the brains of aged individuals with and without Alzheimer's disease (Gsell et al., 1995; Troni et al., 1984).

Diabetes is associated with increased oxidative stress, as reflected in an increased presence of lipid peroxidation products (Jennings et al., 1987; Rosen et al., 2001). Like in ageing increased oxidative stress appears to be the result of increased formation of reactive oxygen species (ROS), reductions in ROS scavengers or both. Increased ROS production in diabetes is a consequence of the process of glucose autooxidation. This process, in which glucose is oxidised in the presence of free metal ions, leads to superoxide and hydroxyl radical release, and finally causes protein oxidation (Wolff et al., 1991; Wolff and Dean, 1987). The activity of ROS scavenging compounds, like glutathione, catalase and superoxide dismutase may be affected by diabetes (Mukherjee et al., 1994; Wohaieb and Godin, 1987), but experimental data are not always consistent and highly depend on the duration of diabetes and the organ studied (Van Dam et al., 1995). Decreases in ROS scavenging compounds may be due to direct effects of diabetes on scavenger production or activity. For example, enhanced protein glycation may be responsible for the reduced enzymatic antioxidant activity of superoxide dismutase (Adachi et al., 1991). Attenuation of glutathione levels may be related to an increased polyol pathway activity, as this leads to a depletion of NADPH, which is necessary for the enzymatic reduction of oxidised glutathione (Costagliola, 1990). On the other hand, local decreases in endogenous ROS scavenging compounds may be due to increased consumption by ROS. For example, a local endoneurial deficit in the reduced form of glutathione has been attributed to the generation of increased amounts of hydrogen peroxide (Ikebuchi et al., 1993).

Increased concentration of lipid peroxidation by-products has been demonstrated in the brain of diabetic rats (Kumar and Menon, 1993; Mooradian and Smith, 1992). The activity of superoxide dismutase and catalase, enzymes involved in the antioxidant defence of the brain, appears to be decreased in STZ-diabetic rats (Kumar and Menon, 1993; Makar et al., 1995), whereas in Type 2 diabetic mice, increased brain superoxide dismutase activity has been reported (Huang et al., 1999).

4.3. Nonenzymatic protein glycation: accelerated AGEing

Glucose irreversibly modifies long-lived macromolecules by forming advanced glycation end products (AGEs), as a function of glucose concentration and time (Brownlee, 2000; Singh et al., 2001). The glycation reaction is a posttranslational modification process occurring between free reducing sugars and free amino groups of proteins. Amadori products, the first stable products of the reaction, can consequently be transformed in AGEs, irreversible adducts of the Maillard reaction (Brownlee, 2000; Singh et al., 2001). AGEs tend to accumulate in the brain during ageing (Kimura et al., 1996; Mrak et al., 1997), and the accumulation of AGEs has been implicated in the pathogenesis of Alzheimer's disease (Smith et al., 1995; Yan et al., 1996). The formation of AGEs may affect neuronal function through various mechanisms (Brownlee, 2000; Singh et al., 2001), including modification of functionally important proteins like tubulin and Na^+, K^+-ATPase (Garner et al., 1990). The formation of AGEs is also associated with the increased production of ROS (Smith et al., 1995; Wolff et al., 1991), thus, linking the pathophysiological model of nonenzymatic glycation to oxidative stress. In addition, increased circulating levels of AGEs and glycation of basement membranes of vessel walls may affect vascular function, as endothelial oxidative damage and endothelial dysfunction have been observed in the presence of AGEs (Wautier et al., 1994). Furthermore, AGEs may be responsible for the quenching of the vasodilating compound nitric oxide (Bucala et al., 1991).

In tissues affected by diabetic complications the amounts of AGEs are generally increased, leading to structural changes in the extracellular matrix, as well as to modifications to cell membranes and intracellular components (Review Brownlee, 2000; Singh et al., 2001). Increased levels of AGEs have been reported in central and peripheral nervous tissue from diabetic animals, but the number of studies is still limited (Pekiner et al., 1993; Ryle et al., 1997; Vlassara et al., 1983).

4.4. Adverse effects of insulin?

Recent data implicate insulin itself in the pathogenesis of age-related memory decline and diabetic encephalopathy (Gispen and Biessels, 2000; Schulingkamp et al., 2000). Insulin was long considered to be incapable of crossing the blood–brain barrier but insulin and its receptor are now known to be present in the brain (Havrankova et al., 1978). Although widely distributed, the insulin receptor is concentrated in specific brain regions including the olfactory bulbs, limbic system, hypothalamus and hippocampus, whereas insulin itself is particularly abundant in the hypothalamus and olfactory bulb (Schulingkamp et al., 2000). The physiological function of insulin in these regions remains largely unknown. Although glucose uptake by the brain is considered to be mainly insulin-insensitive (Kumagai, 1999), insulin does affect cerebral glucose utilisation to some extent (Duelli et al., 1994; Schulingkamp et al., 2000), analogous to its role in the periphery. In addition, brain insulin does seem to play a role in the regulation of food intake and body weight (Schwartz et al., 1999), and it may act as a "neuromodulator," influencing the release and reuptake of neurotransmitters (Sauter et al., 1983) and probably also learning and memory (Schulingkamp et al., 2000; Zhao et al., 1999).

Impairments in the insulin signalling pathway in the periphery and in the brain have been implicated in Alzheimer's disease, diabetes and ageing (Frolich et al., 1998; Gispen and Biessels, 2000; Hoyer, 1998). Ageing is associated with reductions in the level of both insulin and its receptor in the brain (Frolich et al., 1998). In Alzheimer's disease, this age-related reduction in cerebral insulin levels appears to be accompanied by functional disturbances of the insulin receptor (Frolich et al., 1998), leading to the qualification of Alzheimer's disease as "an insulin-resistant brain state" (Hoyer, 1998). In elderly nondemented, nondiabetic individuals chronic hyperinsulinemia is associated with cognitive decline, even after adjustment for possible confounding factors like cardiovascular disease and glucose levels (Kalmijn et al., 1995; Stolk et al., 1997). In contrast to the apparent negative association between chronic hyperinsulinemia and cognitive functioning, acute insulin administration, while keeping glucose at fasting levels, actually improves memory in individuals with Alzheimer's disease, as well as in healthy controls (Craft et al., 1999).

Which mechanisms underlie the potential adverse effects of defective cerebral insulin signalling? Some suggest that disturbances in cerebral glucose metabolism are involved (Hoyer, 1998). Links may also exist with the formation of AGEs and oxidative stress (Facchini et al., 2000). Degradation of oxidised molecules is mainly mediated by the proteasome, a large intracellular multienzymatic proteolytic complex (Pacifici et al., 1989). Binding of insulin-degrading enzyme to the proteasome increases its activity (Hamel et al., 1998). Insulin-degrading enzyme is a metallo-endopeptidase that is also involved in the extracellular degradation of amyloid beta-protein (Qiu et al., 1998). Beta-amyloid, the main substance of senile plaques, has been implicated in the pathology of Alzheimer's disease and has been shown to induce apoptosis in vitro (Forloni, 1993; Watt et al., 1994). In vitro, insulin inhibits insulin-degrading enzyme activity and proteasomal function competitively (Bennett et al., 2000; Hamel et al., 1997; Qiu et al., 1998) impairing protein turnover, thereby facilitating the gradual accumulation of oxidised proteins. The significance of these in vitro findings for the in vivo situation remains to be determined. An alternative route through which hyperinsulinaemia may favour the accumulation of oxidised proteins was recently demonstrated in *Caenorhabditis elegans*. In this species, a family of transcription factors has been described that is a target of insulin mediated signalling (Ogg et al., 1997). These transcription factors increase the defence against oxidative stress (Johnson et al., 2000), decrease oxidative stress (Honda and Honda, 1999) and increase life-span (Lin et al., 1997). Insulin inactivates these transcription factors, eliminating these effects (Kops and Burgering, 1999).

Diabetes and its treatment with insulin are likely to affect cerebral insulin levels and insulin signalling. It is difficult however, to separate these "direct" effects of alterations in insulin homeostasis on the brain from the consequences of the accompanying alterations in peripheral and central glucose homeostasis, which in themselves can affect the brain. For example, in the Type 2 diabetic population, those individuals who are treated with insulin appear to be at the highest risk of developing dementia(Ott et al., 1999). Does this observation just reflect the severity of diabetes in this subgroup of patients, or could it be related to insulin treatment itself? This ambiguous role of insulin should form a focus of future research.

4.5. The calcium hypothesis

It is generally assumed that ageing is one of the most important and consistent risk factors for Alzheimer disease. The calcium hypothesis of brain ageing and dementia has been put forward to account for a number of the phenomena in the pathogenesis of dementia (Khachaturian, 1994). Whether true or not the hypothesis is certainly of importance of understanding the ageing brain. The hypothesis proposes that cellular mechanisms that regulate the homeostasis of $[Ca^{2+}]_i$ play a critical role in brain ageing, as Ca^{2+}-mediated signal transduction cascades and $[Ca^{2+}]_i$ homeostasis are part of the final common pathway for cellular changes leading to neuronal dysfunction and cell death. Furthermore, the hypothesis proposes that the extent of the perturbation in the $[Ca^{2+}]_i$ and the duration of the deregulation of the Ca^{2+} homeostasis is a constant (Khachaturian, 1994). In other words, a small change in free $[Ca^{2+}]_i$ sustained over a long period of time will result in similar cellular damage as will a large change over a short period. Indeed there is ample evidence for a close relation between Ca^{2+} homeostasis, the production of ROS, ischae-

mia and (brain) cell death (Finkel and Holbrook, 2000; Kristian and Siesjo, 1996).

Disturbed $[Ca^{2+}]_i$ regulation and Ca^{2+} channel activity have been described in various diabetic tissues (arteries, myocardium, muscle, etc.), and have been implicated as important factors in the pathogenesis of secondary complications of diabetes in these tissues (Levy et al., 1994). Considering the peripheral nerve as target of diabetic damage, there are several direct and indirect mechanisms through which diabetes-related disturbances in Ca^{2+} homeostasis may lead to impaired nerve function (Biessels and Gispen, 1996). Using electron probe X-ray probe microanalysis, Lowery et al. (1990) were among the first to provide evidence for a disturbed Ca^{2+} homeostasis in the diabetic peripheral nerve. They observed increased mitochondrial and axoplasmic Ca^{2+} levels. This technique however, does not discriminate between free and bound calcium. Recently, ter Laak et al. (1997) developed a novel method to measure $[Ca^{2+}]_i$ in intact dorsal root ganglia exploiting dextran-conjugated fura-2 and axonal transport. Using this technique, they demonstrated a prolonged, small increase in basal $[Ca^{2+}]_i$ in the dorsal root ganglion and a reduced responsiveness to afferent stimulation (ter Laak et al., 1997).

In individual dorsal root ganglion sensory neurones, obtained from BB/Wor Rats or diabetic mice, voltage-dependent Ca^{2+} current through L- and N-channels were enhanced but not through T-channels as compared to controls (Hall et al., 1995; Kostyuk et al., 1995; Voitenko et al., 1999, 2000). Interestingly, L-channel blockers, such as nimodipine and nifedipine, are able to protect against the development of a diabetic peripheral neuropathy in rats (Kappelle et al., 1994; Robertson et al., 1992). In addition to the enhanced-voltage Ca^{2+} channel activity, Ca^{2+} storage mechanisms in neurons may also be disturbed as a result of experimentally induced diabetes mellitus (e.g. reduced uptake in endoplasmic reticulum and/or mitochondria) (Kostyuk et al., 1999; Voitenko et al., 1999). Within the context of the calcium hypothesis the obvious question is whether the diabetes related changes in the machinery for maintaining $[Ca^{2+}]_i$ homeostasis result in an elevation of the $[Ca^{2+}]_i$ over sufficient time to generate neuronal damage. It appears that neurones in the dorsal horn show variable responses to these perturbations of the homeostatic machinery. Large neurones are able to maintain a proper resting level of $[Ca^{2+}]_i$, whereas small neurones show a significant elevation (Kostyuk et al., 1995, 1999).

The aforementioned studies clearly document changes in $[Ca^{2+}]_i$ homeostasis in peripheral neurones of diabetic rodents. Much less is known about the effects of diabetes on neuronal $[Ca^{2+}]_i$ homeostasis in the central nervous system, although the shift in the balance between the induction of LTP and LTD, that was discussed earlier in this review, is likely to be at least partially determined by disturbed $[Ca^{2+}]_i$ homeostasis. Within the focus of this review it is worth noting that we were recently able to discern a Ca^{2+}-dependent feature of diabetic hippocampal slices that is the phenotype to that seen in aged hippocampi: i.e. an increase in the amplitude of the slow after-hyperpolarisation elicited by a train of action potentials. In fact, an increase in the amplitude and duration of this Ca^{2+}-dependent slow after-hyperpolarisation is considered to be a hallmark of ageing neurones that is linked to disturbed neuronal Ca^{2+} homeostasis (Disterhoft et al., 1996; Landfield, 1994). Recently Kamal and Ramakers (in preparation) demonstrated that hippocampal CA1 neurones in young adult STZ treated rats display a similar frequency-dependent increase in the amplitude of the after-hyperpolarisation as seen in such neurones in aged rats. Thus, it seems tat the disturbed

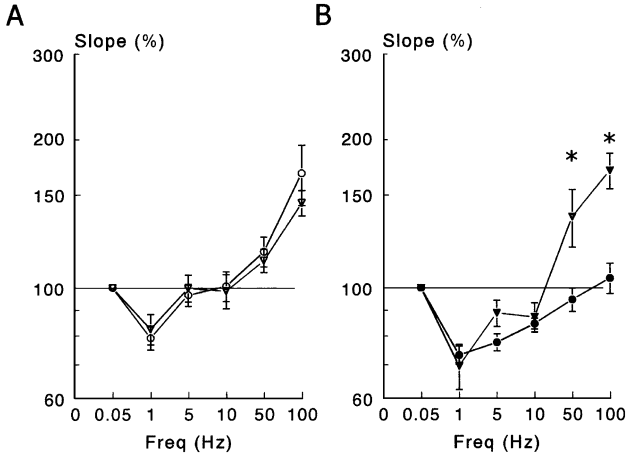

Fig. 3. Effects of treatment with the Ca^{2+} channel antagonist nimodipine on hippocampal synaptic plasticity in aged nondiabetic and diabetic rats. In this experiment, we set out to determine the effects of 2 months of nimodipine treatment on hippocampal synaptic plasticity in aged non-diabetic and diabetic rats. The experimental procedures were exactly the same as in the aged animals from the experiment that is depicted in Figs. 1 and 2 (for a detailed description, see Kamal et al., 2000). Rats were 22 months of age when nimodipine treatment commenced. Diabetes was induced 3 days prior to the first day of nimodipine treatment. Nimodipine (a gift from Bayer, Elberfeld, Germany) was injected intraperitoneally at a dose of 20 mg kg^{-1} once every 48 h. At this dosage, nimodipine was previously shown to improve peripheral nerve function in diabetic rats (Kappelle et al., 1994). Nimodipine is also known to protect against certain aspects of brain ageing in rodents (Batuecas et al., 1998; Disterhoft et al., 1996). After 2 months of treatment, hippocampal slices were prepared as described previously (Kamal et al., 2000), and placed in a recording chamber filled with artificial cerebrospinal fluid. Field excitatory postsynaptic potentials (fEPSPs) were recorded in the stratum radiatum with glass microelectrodes. Stimulation electrodes were placed on the afferent fibres of the stratum radiatum of the CA1 region of the hippocampus (Kamal et al., 2000). (A) Hippocampal slices from non-diabetic aged animals [untreated (○), $n=6$ at each frequency; nimodipine-treated (▽), $n=5$). LFS (1 Hz) induced depression of the fEPSP, whereas HFS (50 and 100 Hz) induced potentiation. Two months of nimodipine treatment did not reverse the age-related changes in plasticity. (B) Hippocampal slices from diabetic aged animals [untreated (●), $n=6$ at each frequency; nimodipine-treated (▼), $n=5$]. LFS (1, 5 and 10 Hz) induced depression of the fEPSP. LTP could not be induced in slices from untreated diabetic rats. Nimodipine treatment from the onset of diabetes prevented the diabetes-attributable deficit in LTP at 50 and 100 Hz ($*P<0.05$ versus the untreated diabetic group). Data are means ± S.E.M. (Kamal, Biessels and Gispen, unpublished observations).

Ca^{2+} homeostasis in diabetic neurones in part may be related to the accelerated ageing of the brain.

5. Conclusions

We have reviewed herein clinical and experimental data on the effects of diabetes on the brain and have explored the hypothesis that effects of diabetes and ageing on the brain may interact. Due to the ageing of the western population, the prevalence of diabetes and the combination of diabetes and advanced age is expected to increase considerably. Diabetes appears to be an important risk factor for significant cognitive decline and dementia in the elderly. The challenge for the next decades will be to unravel the complex interaction between the mechanisms of ageing and diabetes. Further insight into this interaction may lead to the development of preventive measures or treatment strategies that may be of relevance to the growing population of diabetic patients and to the elderly in general. Preliminary studies in experimental models of diabetes and ageing provide evidence that treatment aimed at the pathogenetic factors described above may be fruitful. Treatment with, for example, antioxidants (Biessels et al., 2001) or Ca^{2+} channel antagonists (Fig. 3), may restore deficits in synaptic plasticity in STZ-diabetic rats.

Acknowledgements

The research described in this review was supported by grant 96125H from the Dutch Diabetes Foundation. The research of Geert Jan Biessels is also supported by grant 2000D030 from the Dutch Heart Association.

References

Adachi, T., Ohta, H., Hirano, K., Hayashi, K., Marklund, S.L., 1991. Non-enzymic glycation of human extracellular superoxide dismutase. Biochem. J. 279, 263–267.

Anderer, P., Pascual-Marqui, R.D., Semlitsch, H.V., Saletu, B., 1998. Differential effects of normal aging on sources of standard N1, target N1 and target P300 auditory event-related brain potentials revealed by low resolution electromagnetic tomography (LORETA). Electroencephalogr. Clin. Neurophysiol. 108, 160–174.

Araki, Y., Nomura, M., Tanaka, H., Yamamoto, H., Yamamoto, T., Tsukaguchi, I., 1994. MRI of the brain in diabetes mellitus. Neuroradiology 36, 101–103.

Arezzo, J.C., 1997. The use of electrophysiology for the assessment of diabetic neuropathy. Neurosci. Res. Commun. 21, 13–23.

Artola, A., Bröcher, S., Singer, W., 1990. Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in the rat visual cortex. Nature 347, 69–72.

Barnes, C.A., 1994. Normal aging: regionally specific changes in hippocampal synaptic transmission. Trends Neurosci. 17, 13–18.

Batuecas, A., Pereira, R., Centeno, C., Pulido, J.A., Hernandez, M., Bollati, A., Bogonez, E., Satrustegui, J., 1998. Effects of chronic nimodipine on working memory of old rats in relation to defects in synaptosomal calcium homeostasis. Eur. J. Pharmacol. 350, 141–150.

Beckman, K.B., Ames, B.N., 1998. The free radical theory of aging matures. Physiol. Rev. 78, 547–581.

Bell, D.S., 1994. Stroke in the diabetic patient. Diabetes Care 17, 213–219.

Bellush, L.L., Rowland, N.E., 1989. Stress and behavior in streptozotocin diabetic rats: biochemical correlates of passive avoidance learning. Behav. Neurosci. 103, 144–150.

Bellush, L.L., Reid, S.G., North, D., 1991. The functional significance of biochemical alterations in streptozotocin-induced diabetes. Physiol. Behav. 50, 973–981.

Bennett, R.G., Hamel, F.G., Duckworth, W.C., 2000. Insulin inhibits the ubiquitin-dependent degrading activity of the 26S proteasome. Endocrinology 141, 2508–2517.

Biessels, G.J., Gispen, W.H., 1996. The calcium hypothesis of brain aging and neurodegenerative disorders: significance in diabetic neuropathy. Life Sci. 59, 379–387.

Biessels, G.J., Kappelle, A.C., Bravenboer, B., Erkelens, D.W., Gispen, W.H., 1994. Cerebral function in diabetes mellitus. Diabetologia 37, 643–650.

Biessels, G.J., Kamal, A., Ramakers, G.M., Urban, I.J., Spruijt, B.M., Erkelens, D.W., Gispen, W.H., 1996. Place learning and hippocampal synaptic plasticity in streptozotocin-induced diabetic rats. Diabetes 45, 1259–1266.

Biessels, G.J., Kamal, A., Urban, I.J., Spruijt, B.M., Erkelens, D.W., Gispen, W.H., 1998. Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: effects of insulin treatment. Brain Res. 800, 125–135.

Biessels, G.J., Smale, S., Duis, S.E.J., Kamal, A., Gispen, W.H., 2001. The effect of gamma-linolenic acid–alpha-lipoic acid on functional deficits in the peripheral and central nervous system of streptozotocin-diabetic rats. J. Neurol. Sci. 182, 99–106.

Bleys, R.L., Cowen, T., Groen, G.J., Hillen, B., 1996. Perivascular nerves of the human basal cerebral arteries: II. Changes in aging and Alzheimer's disease. J. Cereb. Blood Flow Metab. 16, 1048–1057.

Bliss, T.V., Collingridge, G.L., 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361, 31–39.

Brownlee, M., 2000. Negative consequences of glycation. Metabolism 49, 9–13.

Bucala, R., Tracey, K.J., Cerami, A., 1991. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. J. Clin. Invest. 87, 432–438.

Candy, S.M., Szatkowski, M.S., 2000a. Neuronal excitability and conduction velocity changes in hippocampal slices from streptozotocin-treated diabetic rats. Brain Res. 863, 298–301.

Candy, S.M., Szatkowski, M.S., 2000b. Chronic hyperglycaemia increases neuronal sensitivity to high potassium in hippocampal slices from streptozotocin-treated diabetic rats. Neurosci. Lett. 279, 105–108.

Cassar, M., Jones, M.G., Szatkowski, M., 1998. Reduced adenosine uptake accelerates ischaemic block of population spikes in hippocampal slices from streptozotocin-treated diabetic rats. Eur. J. Neurosci. 10, 239–245.

Cencetti, S., Lagi, A., Cipriani, M., Fattorini, L., Bandinelli, G., Bernardi, L., 1999. Autonomic control of the cerebral circulation during normal and impaired peripheral circulatory control. Heart 82, 365–372.

Chabot, C., Massicotte, G., Milot, M., Trudeau, F., Gagne, J., 1997. Impaired modulation of AMPA receptors by calcium-dependent processes in streptozotocin-induced diabetic rats. Brain Res. 768, 249–256.

Costagliola, C., 1990. Oxidative state of glutathione in red blood cells and plasma of diabetic patients: in vivo and in vitro study. Clin. Physiol. Biochem. 8, 204–210.

Cowen, T., Thrasivoulou, C., 1990. Cerebrovascular nerves in old rats show reduced accumulation of 5-hydroxytryptamine and loss of nerve fibres. Brain Res. 513, 237–243.

Craft, S., Asthana, S., Newcomer, J.W., Wilkinson, C.W., Matos, I.T., Baker, L.D., Cherrier, M., Lofgreen, C., Latendresse, S., Petrova, A., Plymate, S., Raskind, M., Grimwood, K., Veith, R.C., 1999. Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. Arch. Gen. Psychiatry 56, 1135–1140.

Cryer, P.E., Fisher, J.N., Shamoon, H., 1994. Hypoglycemia. Diabetes Care 17, 734–755.

de la Torre, J.C., 2000. Critically attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer's pathogenesis. Neurobiol. Aging 21, 331–342.

de Mendonca, A., Ribeiro, J.A., 1994. Endogenous adenosine modulates long-term potentiation in the hippocampus. Neuroscience 62, 385–390.

Di Luca, M., Ruts, L., Gardoni, F., Cattabeni, F., Biessels, G.J., Gispen, W.H., 1999. NMDA receptor subunits are modified transcriptionally and post-translationally in the brain of streptozotocin-diabetic rats. Diabetologia 42, 693–701.

Di Mario, U., Morano, S., Valle, E., Pozzessere, G., 1995. Electrophysiological alterations of the central nervous system in diabetes mellitus. Diabetes Metab. Rev. 11, 259–278.

Disterhoft, J.F., Thompson, L.T., Moyer, J.R., Mogul, D.J., 1996. Calcium-dependent after-hyperpolarization and learning in young and aging hippocampus. Life Sci. 59, 413–420.

Donald, M.W., Williams Erdahl, D.L., Surridge, D.H.C., Monga, T.N., Lawson, J.S., Bird, C.E., Letemendia, F.J.J., 1984. Functional correlates of reduced central conduction velocity in diabetic subjects. Diabetes 33, 627–633.

Duckrow, R.B., Beard, D.C., Brennan, R.W., 1987. Regional cerebral blood flow decreases during chronic and acute hyperglycemia. Stroke 18, 52–58.

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

Dyck, P.J., Kratz, K.M., Karnes, J.L., Litchy, W.J., Klein, R., Pach, J.M., Wilson, D.M., O'Brien, P.C., Melton, L.J., 1993. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology 43, 817–824.

Facchini, F.S., Hua, N.W., Reaven, G.M., Stoohs, R.A., 2000. Hyperinsulinemia: the missing link among oxidative stress and age-related diseases? Free Radic. Biol. Med. 29, 1302–1306.

Finkel, T., Holbrook, N.J., 2000. Oxidants, oxidative stress and the biology of ageing. Nature 408, 239–247.

Flood, J.F., Mooradian, A.D., Morley, J.E., 1990. Characteristics of learning and memory in streptozocin-induced diabetic mice. Diabetes 39, 1391–1398.

Forloni, G., 1993. Beta-amyloid neurotoxicity. Funct. Neurol. 8, 211–225.

Foster, T.C., 1999. Involvement of hippocampal synaptic plasticity in age-related memory decline. Brain Res. Brain Res. Rev. 30, 236–249.

Frolich, L., Blum-Degen, D., Bernstein, H.G., Engelsberger, S., Humrich, J., Laufer, S., Muschner, D., Thalheimer, A., Turk, A., Hoyer, S., Zochling, R., Boissl, K.W., Jellinger, K., Riederer, P., 1998. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J. Neural Transm. 105, 423–438.

Gagne, J., Milot, M., Gelinas, S., Lahsaini, A., Trudeau, F., Martinoli, M.G., Massicotte, G., 1997. Binding properties of glutamate receptors in streptozotocin-induced diabetes in rats. Diabetes 46, 841–846.

Garner, M.H., Bahador, A., Sachs, G., 1990. Nonenzymatic glycation of Na, K-ATPase. Effects on ATP hydrolysis and K+ occlusion. J. Biol. Chem. 26739, 15058–15066.

Gavin III, J.R., Alberti, K.G.M.M., Davidson, M.B., DeFronzo, R.A., Drash, A., Gabbe, S.G., Genuth, S., Harris, M.I., Kahn, R., Keen, H., Knowler, W.C., Lebovitz, H., Maclaren, N.K., Palmer, J.P., Raskin, P., Rizza, R.A., Stern, M.P., 1997. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 20, 1183–1197.

Gispen, W.H., Biessels, G.J., 2000. Cognition and synaptic plasticity in diabetes mellitus. Trends Neurosci. 23, 542–549.

Gold, A.E., Deary, I.J., Jones, R.W., O'Hare, J.P., Reckless, J.P., Frier, B.M., 1994. Severe deterioration in cognitive function and personality in five patients with long-standing diabetes: a complication of diabetes or a consequence of treatment? Diabetes Med. 11, 499–505.

Gsell, W., Conrad, R., Hickethier, M., Sofic, E., Frolich, L., Wichart, I., Jellinger, K., Moll, G., Ransmayr, G., Beckmann, H., et al., 1995. Decreased catalase activity but unchanged superoxide dismutase activity in brains of patients with dementia of Alzheimer type. J. Neurochem. 64, 1216–1223.

Hall, K.E., Sima, A.A.F., Wiley, J.W., 1995. Voltage-dependent calcium currents are enhanced in dorsal root ganglion neurones from the bio bred/Worchester diabetic rat. J. Physiol. (London) 486, 313–322.

Hamel, F.G., Bennett, R.G., Harmon, K.S., Duckworth, W.C., 1997. Insulin inhibition of proteasome activity in intact cells. Biochem. Biophys. Res. Commun. 234, 671–674.

Hamel, F.G., Bennett, R.G., Duckworth, W.C., 1998. Regulation of multicatalytic enzyme activity by insulin and the insulin-degrading enzyme. Endocrinology 139, 4061–4066.

Harik, S.I., LaManna, J.C., 1988. Vascular perfusion and blood–brain glucose transport in acute and chronic hyperglycemia. J. Neurochem. 51, 1924–1929.

Havrankova, J., Schmechel, D., Roth, J., Brownstein, M., 1978. Identification of insulin in rat brain. Proc. Natl. Acad. Sci. U.S.A. 75, 5737–5741.

Honda, Y., Honda, S., 1999. The daf-2 gene network for longevity regulates oxidative stress resistance and Mn-superoxide dismutase gene expression in *Caenorhabditis elegans*. FASEB J. 13, 1385–1393.

Hoyer, S., 1998. Is sporadic Alzheimer disease the brain type of non-insulin dependent diabetes mellitus? A challenging hypothesis. J. Neural. Transm. 105, 415–422.

Huang, W.C., Juang, S.W., Liu, I.M., Chi, T.C., Cheng, J.T., 1999. Changes of superoxide dismutase gene expression and activity in the brain of streptozotocin-induced diabetic rats. Neurosci. Lett. 275, 25–28.

Ikebuchi, M., Kashiwagi, A., Asahina, T., Tanaka, Y., Takagi, Y., Nishio, Y., Hidaka, H., Kikkawa, R., Shigeta, Y., 1993. Effect of medium pH on glutathione redox cycle in cultured human umbilical vein endothelial cells. Metabolism 42, 1121–1126.

Jakobsen, J., Nedergaard, M., Aarslew Jensen, M., Diemer, N.H., 1990. Regional brain glucose metabolism and blood flow in streptozocin-induced diabetic rats. Diabetes 39, 437–440.

Jennings, P.E., Jones, A.F., Florkowski, C.M., Lunec, J., Barnett, A.H., 1987. Increased diene conjugates in diabetic subjects with microangiopathy. Diabetes Med. 4, 452–456.

Johnson, P.C., Brenedel, K., Meezan, E., 1982. Thickened cerebral cortical capillary basement membranes in diabetics. Arch. Pathol. Lab. Med. 106, 214–217.

Johnson, T.E., Cypser, J., de Castro, E., de Castro, S., Henderson, S., Murakami, S., Rikke, B., Tedesco, P., Link, C., 2000. Gerontogenes mediate health and longevity in nematodes through increasing resistance to environmental toxins and stressors. Exp. Gerontol. 35, 687–694.

Junker, U., Jaggi, C., Bestetti, G., Rossi, G.L., 1985. Basement membrane of hypothalamus and cortex capillaries from normotensive and spontaneously hypertensive rats with steptozotocin-induced diabetes. Acta Neuropathol. (Berlin) 65, 202–208.

Kalaria, R.N., 1996. Cerebral vessels in ageing and Alzheimer's disease. Pharmacol. Ther. 72, 193–214.

Kaleeswari, R., Thombre, D.P., Chakrabarty, A.S., 1986. Acute effect of streptozotocin induced diabetes on bar pressing for food reward in albino rats. Indian J. Physiol. Pharmacol. 30, 319–321.

Kalmijn, S., Feskens, E.J.M., Launer, L.J., Stijnen, T., Kromhout, D., 1995. Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. Diabetologia 38, 1096–1102.

Kamal, A., Biessels, G.J., Urban, I.J.A., Gispen, W.H., 1999. Hippocampal synaptic plasticity in streptozotocin-diabetic rats: impairment of long-term potentiation and facilitation of long-term depression. Neuroscience 90, 737–745.

Kamal, A., Biessels, G.J., Duis, S.E.J., Gispen, W.H., 2000. Learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: interaction of diabetes and ageing. Diabetologia 43, 500–506.

Kappelle, A.C., Biessels, G., Bravenboer, B., Van Buren, T., Traber, J., de Wildt, D.J., Gispen, W.H., 1994. Beneficial effect of the Ca2+ antago-

nist, nimodipine, on existing diabetic neuropathy in the BB/Wor rat. Br. J. Pharmacol. 111, 887–893.
Khachaturian, Z.S., 1994. Calcium hypothesis of Alzheimer's disease and brain aging. Ann. N. Y. Acad. Sci. 747, 1–11.
Khardori, R., Soler, N.G., Good, D.C., DevlescHoward, A.B., Broughton, D., Walbert, J., 1986. Brainstem auditory and visual evoked potentials in type 1 (insulin-dependent) diabetic patients. Diabetologia 29, 362–365.
Kimura, T., Takamatsu, J., Ikeda, K., Kondo, A., Miyakawa, T., Horiuchi, S., 1996. Accumulation of advanced glycation end products of the Maillard reaction with age in human hippocampal neurons. Neurosci. Lett. 208, 53–56.
Knudsen, G.M., Gobel, U., Paulson, O.B., Kuschinsky, W., 1991. Regional density of perfused capillaries and cerebral blood flow in untreated short-term and long-term streptozotocin diabetes. J. Cereb. Blood Flow Metab. 11, 361–365.
Kops, G.J., Burgering, B.M., 1999. Forkhead transcription factors: new insights into protein kinase B (c-akt) signaling. J. Mol. Med. 77, 656–665.
Kostyuk, E., Pronchuk, N., Shmigol, A., 1995. Calcium signal prolongation in sensory neurones of mice with experimental diabetes. NeuroReport 6, 1010–1012.
Kostyuk, E., Svichar, N., Shishkin, V., Kostyuk, P., 1999. Role of mitochondrial dysfunction in calcium signalling alterations in dorsal root ganglion neurons of mice with experimentally-induced diabetes. Neuroscience 90, 535–541.
Kristian, T., Siesjo, B.K., 1996. Calcium-related damage in ischemia. Life Sci. 59, 357–367.
Kumagai, A.K., 1999. Glucose transport in brain and retina: implications in the management and complications of diabetes. Diabetes Metab. Res. Rev. 15, 261–273.
Kumar, J.S., Menon, V.P., 1993. Effect of diabetes on levels of lipid peroxides and glycolipids in rat brain. Metabolism 42, 1435–1439.
Lagnado, M.L.J., Crowe, R., Lincoln, J., Burnstock, G., 1987. Reduction of nerves containing vasoactive intestinal polypeptide and serotonin, but not neuropeptide Y and catecholamine in cerebral blood vessels of the 8-week streptozotocin-induced diabetic rat. Blood Vessels 24, 169–180.
Landfield, P.W., 1994. Increased hippocampal Ca2+ channel activity in brain aging and dementia. Hormonal and pharmacologic modulation. Ann. N. Y. Acad. Sci. 747, 351–364.
Langan, S.J., Deary, I.J., Hepburn, D.A., Frier, B.M., 1991. Cumulative cognitive impairment following recurrent severe hypoglycaemia in adult patients with insulin-treated diabetes mellitus. Diabetologia 34, 337–344.
Lartaud, I., Bray-des-Boscs, L., Chillon, J.M., Atkinson, J., Capdeville-Atkinson, C., 1993. In vivo cerebrovascular reactivity in Wistar and Fischer 344 rat strains during aging. Am. J. Physiol. 264, H851–H858.
Leibson, C.L., Rocca, W.A., Hanson, V.A., Cha, R., Kokmen, E., O'Brien, P.C., Palumbo, P.J., 1997. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. Am. J. Epidemiol. 145, 301–308.
Levy, J., Gavin, J.R., Sowers, J.R., 1994. Diabetes mellitus: a disease of abnormal cellular calcium metabolism? Am. J. Med. 96, 260–273.
Lin, K., Dorman, J.B., Rodan, A., Kenyon, C., 1997. daf-16: an HNF-3/forkhead family member that can function to double the life-span of *Caenorhabditis elegans*. Science 278, 1319–1322.
Lowery, J.M., Eichberg, J., Saubermann, A.J., LoPachin, R.M.J., 1990. Distribution of elements and water in peripheral nerve of streptozocin-induced diabetic rats. Diabetes 39, 1498–1503.
Lunetta, M., Damanti, A.R., Fabbri, G., Lombardo, M., Di Mauro, M., Mughini, L., 1994. Evidence by magnetic resonance imaging of cerebral alterations of atrophy type in young insulin-dependent diabetic patients. J. Endocrinol. Invest. 17, 241–245.
Makar, T.K., Rimpel-Lamhaouar, K., Abraham, D.G., Gokhale, V.S., Cooper, A.J.L., 1995. Antioxidant defense systems in the brains of type II diabetic mice. J. Neurochem. 65, 287–291.
Malenka, R.C., Nicoll, R.A., 1999. Long-term potentiation—a decade of progress? Science 285, 1870–1874.
Mankovsky, B.N., Metzger, B.E., Molitch, M.E., Biller, J., 1997. Cerebrovascular disorders in patients with diabetes mellitus. J. Diabetes Complications 10, 228–242.
Manolio, T.A., Kronmal, R.A., Burke, G.L., Poirier, V., O'Leary, D.H., Gardin, J.M., Fried, L.P., Steinberg, E.P., Bryan, R.N., 1994. Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. Stroke 25, 318–327.
Margineanu, D.G., Niespodziany, I., Wulfert, E., 1998. Hippocampal slices from long-term streptozotocin-injected rats are prone to epileptiform responses. Neurosci. Lett. 252, 183–186.
Mayer, G., Nitsch, R., Hoyer, S., 1990. Effects of changes in peripheral and cerebral glucose metabolism on locomotor activity, learning and memory in adult male rats. Brain Res. 532, 95–100.
Mayhan, W.G., Simmons, L.K., Sharpe, G.M., 1991. Mechanism of impaired responses of cerebral arterioles during diabetes mellitus. Am. J. Physiol. 260, H319–H326.
Meltzer, C.C., Cantwell, M.N., Greer, P.J., Ben Eliezer, D., Smith, G., Frank, G., Kaye, W.H., Houck, P.R., Price, J.C., 2000. Does cerebral blood flow decline in healthy aging? A PET study with partial-volume correction. J. Nucl. Med. 41, 1842–1848.
Messier, C., Gagnon, M., 1996. Glucose regulation and cognitive functions: relation to Alzheimer's disease and diabetes. Behav. Brain Res. 75, 1–11.
Miles, W.R., Root, H.F., 1922. Psychologic tests applied in diabetic patients. Arch. Intern. Med. 30, 767–777.
Mooradian, A.D., Smith, T.L., 1992. The effect of experimentally induced diabetes mellitus on the lipid order and composition of rat cerebral microvessels. Neurosci. Lett. 145, 145–148.
Mooradian, A.D., Perryman, K., Fitten, J., Kavonian, G.D., Morley, J.E., 1988. Cortical function in elderly non-insulin dependent diabetic patients. Behavioral and electrophysiologic studies. Arch. Intern. Med. 148, 2369–2372.
Moore, S.A., Bohlen, H.G., Miller, B.G., Evan, A.P., 1985. Cellular and vessel wall morphology of cerebral cortical arterioles after short-term diabetes in adult rats. Blood Vessels 22, 265–277.
Moreo, G., Mariani, E., Pizzamiglio, G., Colucci, G.B., 1995. Visual evoked potentials in NIDDM: a longitudinal study. Diabetologia 38, 573–576.
Morrison, P.D., Mackinnon, M.W., Bartrup, J.T., Skett, P.G., Stone, T.W., 1992. Changes in adenosine sensitivity in the hippocampus of rats with streptozotocin-induced diabetes. Br. J. Pharmacol. 105, 1004–1008.
Mrak, R.E., Griffin, S.T., Graham, D.I., 1997. Aging-associated changes in human brain. J. Neuropathol. Exp. Neurol. 56, 1269–1275.
Mukherjee, B., Mukherjee, J.R., Chatterjee, M., 1994. Lipid peroxidation, glutathione levels and changes in glutathione-related enzyme activities in streptozotocin-induced diabetic rats. Immunol. Cell Biol. 72, 109–114.
Nanri, M., Miyake, H., Murakami, Y., Matsumoto, K., Watanabe, H., 1998. Chronic cerebral hypoperfusion-induced neuropathological changes in rats. Nihon Shinkei Seishin Yakurigaku Zasshi 18, 181–188.
Ngezahayo, A., Schachner, M., Artola, A., 2000. Synaptic activity modulates the induction of bidirectional synaptic changes in adult mouse hippocampus. J. Neurosci. 20, 2451–2458.
Ogg, S., Paradis, S., Gottlieb, S., Patterson, G.I., Lee, L., Tissenbaum, H.A., Ruvkun, G., 1997. The fork head transcription factor DAF-16 transduces insulin-like metabolic and longevity signals in *C. elegans*. Nature 389, 994–999.
Ott, A., Stolk, R.P., Van Harskamp, F., Pols, H.A., Hofman, A., Breteler, M.M., 1999. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurology 53, 1937–1942.
Pacifici, R.E., Salo, D.C., Davies, K.J., 1989. Macroxyproteinase (M.O.P.): a 670 kDa proteinase complex that degrades oxidatively denatured proteins in red blood cells. Free Radic. Biol. Med. 7, 521–536.
Parisi, V., Uccioli, L., 2001. Visual electrophysiological responses in persons with type 1 diabetes. Diabetes Metab. Res. Rev. 17, 12–18.

Pekiner, C., Cullum, N.A., Hughes, J.N., Hargreaves, A.J., Mahon, J., Casson, I.F., 1993. Glycation of brain actin in experimental diabetes. J. Neurochem. 61, 436–442.

Pelligrino, D.A., Miletich, D.J., Albrecht, R.F., 1992. Diminished muscarinic receptor-mediated cerebral blood flow response in streptozotocin-treated rats. Am. J. Physiol. 262, E447–E454.

Peress, N.S., Kane, W.C., Aronson, S.M., 1973. Central nervous system findings in a tenth decade autopsy population. Prog. Brain Res. 40, 473–483.

Picton, T.W., 1992. The P300 wave of the human event-related potential. J. Clin. Neurophysiol. 9, 456–479.

Pitsikas, N., Algeri, S., 1992. Deterioration of spatial and nonspatial reference and working memory in aged rats: protective effect of life-long calorie restriction. Neurobiol. Aging 13, 369–373.

Popovic, M., Biessels, G.J., Isaacson, R.L., Gispen, W.H., 2001. Learning and memory in streptozotocin-induced diabetic rats in a novel spatial/object discrimination task. Behav. Brain Res. 122, 201–207.

Pozzessere, G., Valle, E., de-Crignis, S., Cordischi, V.M., Fattapposta, F., Rizzo, P.A., Pietravalle, P., Cristina, G., Morano, S., di-Mario, U., 1991. Abnormalities of cognitive functions in IDDM revealed by P300 event-related potential analysis. Comparison with short-latency evoked potentials and psychometric tests. Diabetes 40, 952–958.

Qiu, W.Q., Walsh, D.M., Ye, Z., Vekrellis, K., Zhang, J., Podlisny, M.B., Rosner, M.R., Safavi, A., Hersh, L.B., Selkoe, D.J., 1998. Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. J. Biol. Chem. 273, 32730–32738.

Reske-Nielsen, E., Lundbaek, K., Rafaelsen, O.J., 1965. Pathological changes in the central and peripheral nervous system of young long-term diabetics. Diabetologia 1, 233–241.

Robertson, S., Cameron, N.E., Cotter, M.A., 1992. The effect of the calcium antagonist nifedipine on peripheral nerve function in streptozotocin-diabetic rats. Diabetologia 35, 1113–1117.

Rosen, P., Nawroth, P.P., King, G., Moller, W., Tritschler, H.J., Packer, L., 2001. The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a congress series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. Diabetes Metab. Res. Rev. 17, 189–212.

Rubin, M.J., Bohlen, H.G., 1985. Cerebral vascular autoregulation of blood flow and tissue PO_2 in diabetic rats. Am. J. Physiol. 249, H540–H546.

Ryan, C.M., 1988. Neurobehavioral complications of type I diabetes. Examination of possible risk factors. Diabetes Care 11, 86–93.

Ryan, C.M., Geckle, M.O., 2000. Circumscribed cognitive dysfunction in middle-aged adults with type 2 diabetes. Diabetes Care 23, 1486–1493.

Ryan, C.M., Williams, T.M., 1993. Effects of insulin-dependent diabetes on learning and memory efficiency in adults. J. Clin. Exp. Neuropsychol. 15, 685–700.

Ryle, C., Leow, C.K., Donaghy, M., 1997. Nonenzymatic glycation of peripheral and central nervous system proteins in experimental diabetes mellitus. Muscle Nerve 20, 577–584.

Sabri, O., Hellwig, D., Schreckenberger, M., Schneider, R., Kaiser, H.J., Wagenknecht, G., Mull, M., Buell, U., 2000. Influence of diabetes mellitus on regional cerebral glucose metabolism and regional cerebral blood flow. Nucl. Med. Commun. 21, 19–29.

Sauter, A., Goldstein, M., Engel, J., Ueta, K., 1983. Effect of insulin on central catecholamines. Brain Res. 260, 330–333.

Schmidt-Kastner, R., Freund, T.F., 1991. Selective vulnerability of the hippocampus in brain ischemia. Neuroscience 40, 599–636.

Schnedl, W.J., Ferber, S., Johnson, J.H., Newgard, C.B., 1994. STZ transport and cytotoxicity. Specific enhancement in GLUT2-expressing cells. Diabetes 43, 1326–1333.

Schulingkamp, R.J., Pagano, T.C., Hung, D., Raffa, R.B., 2000. Insulin receptors and insulin action in the brain: review and clinical implications. Neurosci. Biobehav. Rev. 24, 855–872.

Schwartz, M.W., Baskin, D.G., Kaiyala, K.J., Woods, S.C., 1999. Model for the regulation of energy balance and adiposity by the central nervous system. Am. J. Clin. Nutr. 69, 584–596.

Segovia, G., Porras, A., Del Arco, A., Mora, F., 2001. Glutamatergic neurotransmission in aging: a critical perspective. Mech. Ageing Dev. 122, 1–29.

Shafrir, E., 1997. Diabetes in animals: contribution to the understanding of diabetes by study of its etiopathology in animal models. In: Porte, J.R.D., Sherwin, R.S. (Eds.), Ellenberg and Rifkin's Diabetes Mellitus; Theory and Practice. Appleton & Lange, Stamford, pp. 301–348.

Simpson III, R.E., Phillis, J.W., Buchannan, J., 1990. A comparison of cerebral blood flow during basal, hypotensive, hypoxic and hypercapnic conditions between normal and streptozotocin diabetic rats. Brain Res. 531, 136–142.

Singh, R., Barden, A., Mori, T., Beilin, L., 2001. Advanced glycation end-products: a review. Diabetologia 44, 129–146.

Smith, M.A., Sayre, L.M., Monnier, V.M., Perry, G., 1995. Radical AGEing in Alzheimer's disease. Trends Neurosci. 18, 172–176.

Soininen, H., Puranen, M., Helkala, E.L., Laakso, M., Riekkinen, P.J., 1992. Diabetes mellitus and brain atrophy: a computed tomography study in an elderly population. Neurobiol. Aging 13, 717–721.

Stewart, R., Liolitsa, D., 1999. Type 2 diabetes mellitus, cognitive impairment and dementia. Diabet. Med. 16, 93–112.

Stolk, R.P., Breteler, M.M.B., Ott, A., Pols, H.A.P., Lamberts, S.W.J., Grobbee, D.E., Hofman, A., 1997. Insulin and cognitive function in an elderly population—the Rotterdam Study. Diabetes Care 20, 792–795.

Strachan, M.W.J., Deary, I.J., Ewing, F.M.E., Frier, B.M., 1997. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. Diabetes Care 20, 438–445.

Tang, Y.P., Shimizu, E., Dube, G.R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G., Tsien, J.Z., 1999. Genetic enhancement of learning and memory in mice. Nature 401, 63–69.

Tekkok, S., Krnjevic, K., 1999. Diabetes mellitus preserves synaptic plasticity in hippocampal slices from middle-aged rats. Neuroscience 91, 185–191.

ter Laak, M.P., Hamers, F.P.T., Verhage, M., Gispen, W.H., 1997. Calcium homeostasis in intact dorsal root ganglia of diabetic and control rats. J. Peripher. Nerv. Syst. 2, 306.

The Diabetes Control and Complications Study Group, 1993. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N. Engl. J. Med. 329, 977–986.

Thrasivoulou, C., Cowen, T., 1995. Regulation of rat sympathetic nerve density by target tissues and NGF in maturity and old age. Eur. J. Neurosci. 7, 381–387.

Toyoda, K., Fujii, K., Takata, Y., Ibayashi, S., Fujikawa, M., Fujishima, M., 1997. Effect of aging on regulation of brain stem circulation during hypotension. J. Cereb. Blood Flow Metab. 17, 680–685.

Troni, M., Carta, Q., Cantello, R., Caselle, M.T., Rainero, I., 1984. Peripheral nerve function and metabolic control in diabetes mellitus. Ann. Neurol. 16, 178–183.

Van Dam, P.S., Van Asbeck, B.S., Erkelens, D.W., Marx, J.J.M., Gispen, W.H., Bravenboer, B., 1995. The role of oxidative stress in neuropathy and other diabetic complications. Diabetes Metab. Rev. 11, 181–192.

Vanhanen, M., Soininen, H., 1998. Glucose intolerance, cognitive impairment and Alzheimer's disease. Curr. Opin. Neurol. 11, 673–677.

Vanhanen, M., Koivisto, K., Karjalainen, L., Helkala, E.L., Laakso, M., Soininen, H., Riekkinen, P., 1997. Risk for non-insulin-dependent diabetes in the normoglycaemic elderly is associated with impaired cognitive function. NeuroReport 8, 1527–1530.

Vinik, A.I., Holland, M.T., Le Beau, J.M., Liuzzi, F.J., Stansberry, K.B., Colen, L.B., 1992. Diabetic neuropathies. Diabetes Care 15, 1926–1975.

Vlassara, H., Brownlee, M., Cerami, A., 1983. Excessive non enzymatic glycosylation of peripheral and central nervous system myelin components in diabetic rats. Diabetes 32, 670–674.

Voitenko, N.V., Kostyuk, E.P., Kruglikov, I.A., Kostyuk, P.G., 1999. Changes in calcium signalling in dorsal horn neurons in rats with streptozotocin-induced diabetes. Neuroscience 94, 887–890.

Voitenko, N.V., Kruglikov, I.A., Kostyuk, E.P., Kostyuk, P.G., 2000. Effect

of streptozotocin-induced diabetes on the activity of calcium channels in rat dorsal horn neurons. Neuroscience 95, 519–524.

Watt, J.A., Pike, C.J., Walencewicz-Wasserman, A.J., Cotman, C.W., 1994. Ultrastructural analysis of beta-amyloid-induced apoptosis in cultured hippocampal neurons. Brain Res. 661, 147–156.

Wautier, J.L., Wautier, M.P., Schmidt, A.M., Anderson, G.M., Hori, O., Zoukourian, C., Capron, L., Chappey, O., Yan, S.D., Brett, J., 1994. Advanced glycation end products (AGEs) on the surface of diabetic erythrocytes bind to the vessel wall via a specific receptor inducing oxidant stress in the vasculature: a link between surface-associated AGEs and diabetic complications. Proc. Natl. Acad. Sci. U.S.A. 91, 7742–7746.

Wohaieb, S.A., Godin, D.V., 1987. Alterations in tissue antioxidant systems in the spontaneously diabetic (BB Wistar) rat. Can. J. Physiol. Pharmacol. 65, 2191–2195.

Wolff, S.P., Dean, R.T., 1987. Glucose autoxidation and protein modification. Biochem. J. 245, 243–250.

Wolff, S.P., Jiang, Z.Y., Hunt, J.V., 1991. Protein glycation and oxidative stress in diabetes mellitus and ageing. Free Radic. Biol. Med. 10, 339–352.

Wredling, R., Levander, S., Adamson, U., Lins, P.E., 1990. Permanent neuropsychological impairment after recurrent episodes of severe hypoglycaemia in man. Diabetologia 33, 152–157.

Yagihashi, S., 1995. Pathology and pathogenetic mechanisms of diabetic neuropathy. Diabetes Metab. Rev. 11, 193–225.

Yan, S.D., Chen, X., Fu, J., Chen, M., Zhu, H., Roher, A., Slattery, T., Zhao, L., Nagashima, M., Morser, J., Migheli, A., Nawroth, P., Stern, D., Schmidt, A.M., 1996. RAGE and amyloid-β peptide neurotoxicity in Alzheimer's disease. Nature 382, 685–691.

Yang, S.N., Tang, Y.G., Zucker, R.S., 1999. Selective induction of LTP and LTD by postsynaptic [Ca2+]i elevation. J. Neurophysiol. 81, 781–787.

Ylikoski, A., Erkinjuntti, T., Raininko, R., Sarna, S., Sulkava, R., Tilvis, R., 1995. White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. Stroke 26, 1171–1177.

Zhao, W., Chen, H., Xu, H., Moore, E., Meiri, N., Quon, M.J., Alkon, D.L., 1999. Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. J. Biol. Chem. 274, 34893–34902.

Ziegler, O., Guerci, B., Algan, M., Lonchamp, P., Weber, M., Drouin, P., 1994. Improved visual evoked potential latencies in poorly controlled diabetic patients after short-term strict metabolic control. Diabetes Care 17, 1141–1147.

Zucker, R.S., 1989. Short-term synaptic plasticity. Annu. Rev. Neurosci. 12, 13–31.