Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 490 (2004) 159–168
www.elsevier.com/locate/ejphar

Cerebral dysfunction in type 1 diabetes: effects of insulin, vascular risk factors and blood-glucose levels

Augustina M.A. Brands[a,b], Roy P.C. Kessels[a,c], Edward H.F. de Haan[a,c], L. Jaap Kappelle[a], Geert Jan Biessels[a,*]

[a] *Department of Neurology, G03.228, University Medical Center, PO Box 85500, 3508 GA Utrecht, The Netherlands*
[b] *Department of Neuropsychology, Hofpoort Hospital, Woerden, The Netherlands*
[c] *Helmholtz Research Institute, Utrecht University, The Netherlands*

Accepted 27 February 2004

Abstract

Type 1 diabetes can lead to several well-described complications such as retinopathy, nephropathy and peripheral neuropathy. Evidence is accumulating that it is also associated with gradually developing end-organ damage in the central nervous system. This relatively unknown complication can be referred to as 'diabetic encephalopathy' and is characterised by electrophysiological and neuroradiological changes, such as delayed latencies of evoked potentials, modest cerebral atrophy and (periventricular) white matter lesions. Furthermore, individuals with type 1 diabetes may show performance deficits in a wide range of cognitive domains. The exact mechanisms underlying this diabetic encephalopathy are only partially known. Chronic metabolic and vascular changes appear to play an important role. Interestingly, the differences in the 'cognitive profile' between type 1 and type 2 diabetes also suggest a critical role for disturbances of insulin action in the central nervous system.

Keywords: Type 1 diabetes; Diabetic encephalopathy; Cognition; Insulin; Cerebrovascular alteration; Hypoglycaemia

1. Introduction

Diabetes mellitus is a common metabolic disease. Prevalence of diabetes in adults was estimated to be 4% in 1995 and is expected to rise to over 5% by the year 2025 worldwide (King et al., 1998). This implies an increase of the number of adults with diabetes from 135 million in 1995 to 300 million in 2025 (King et al., 1998). Diabetes is characterised by hyperglycaemia due to defects in the secretion of, or resistance to insulin, or both (American Diabetes Association, 2002). The most common form is type 2 diabetes, in which resistance to insulin is accompanied by an inadequate compensation in the secretion of insulin. Type 1 diabetes is caused by an absolute shortage in the production of insulin due to the destruction of pancreatic β cells (American Diabetes Association, 2002). This type of diabetes, which was previously defined as Insulin Dependent Diabetes Mellitus, is not as common as type 2 diabetes; only 5–10% of the patients with diabetes has type 1 diabetes.

Patients with type 1 diabetes are treated with exogenous insulin. Unfortunately, even with repeated injections, or subcutaneously implanted insulin pumps, these treatments cannot fully compensate for the tightly regulated insulin secretions of a normally functioning pancreas. Therefore, individuals with type 1 diabetes may experience fluctuations in blood glucose levels throughout the day, ranging from low blood glucose levels (i.e. hypoglycaemia) to high blood glucose levels (i.e. hyperglycaemia). These fluctuations depend upon the timing, type, dose of insulin administration, the quantity and nutritional content of food ingested, and the amount of physical activity. Since normal cerebral functioning is dependent upon sufficient levels of continuous circulating glucose, these fluctuations can affect functioning of the brain.

It is well known that both type 1 and type 2 diabetes can lead to several complications, such as retinopathy, nephropathy and peripheral neuropathy, and the characteristic clinical signs and symptoms as well as the techniques to diagnose these complications are well established (American

* Corresponding author. Tel.: +31-30-250-9111; fax: +31-30-254-2100.
E-mail address: G.J.Biessels@med.uu.nl (G.J. Biessels).

0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.02.053

Diabetes Association, 2002). Already in 1922, it was recognised that diabetes may also affect cognition (Miles and Root, 1922). Today, there is substantial evidence that acute hypo- and hyperglycaemia have disruptive effects on the central nervous system (CNS) (Weinger and Jacobson, 1998), although relatively less is known about the slowly developing end-organ damage to the CNS that may present itself by electrophysiological and structural changes and impairment of cognitive functioning. These cerebral complications of both type 1 and type 2 diabetes may be referred to as 'diabetic encephalopathy', a concept introduced several decades ago (Reske-Nielsen et al., 1965). Since then many different features of these complications have been identified and important leads into the pathophysiology are emerging. However, the clinical characteristics remain heterogeneous. In this review, we will provide an overview of the available data and the questions that remain to be answered. First, we will look into the clinical characteristics and the risk factors that have been implicated in altered CNS functioning in type 1 diabetes. In the last sections, we will explore the possible mechanisms that may underlie diabetic encephalopathy.

2. Long-term effects on the brain

2.1. Neurophysiological changes

Evoked potentials are frequently used to evaluate CNS physiology. The electrophysiological response of specific CNS structures to visual, auditory or somatosensory stimuli are called visual evoked potentials, brainstem auditory evoked potentials and somatosensory evoked potentials respectively (Di Mario et al., 1995). In the brainstem auditory evoked potentials, five waves can be distinguished (I–V). The latency of wave I is determined by the peripheral components of the acoustic system and the interpeak latencies I–III and III–V reflect signal conduction in the pons and midbrain, respectively. In patients with type 1 diabetes, the latencies of wave I and the interpeak latencies I–III and III–V of the brainstem auditory evoked potentials, may be increased (e.g. Khardori et al., 1986; Pozzessere et al., 1988, 1991; Toth et al., 2001; Dejgaard et al., 1991). The visually evoked P100 wave is thought to be generated in the visual cortex (Chiappa and Ropper, 1982). Its latency is also delayed in type 1 diabetes (Pietravalle et al., 1993; Pozzessere et al., 1988, 1991; Ziegler et al., 1994a,b; Collier et al., 1988; Das et al., 2001). Studies on somatosensory evoked potentials have provided more variable results. Increased latencies have been reported, although significant conduction delays were mostly limited to peripheral components of the somatosensory pathways (Collier et al., 1988; Pietravalle et al., 1993; Bax et al., 1995; Das et al., 2001).

The evoked potential approach is also used to explore cognitive brain functions in humans. In this case, the evoked potential components are known as 'endogenous'. Among these, the P300 (or P3) wave has been identified as a late cortical neurophysiological event reflecting the activity of cognitive and mnemonic functions in humans (Polich et al., 1983; Surwillo, 1984).

The latencies of event related potentials, such as the P300, are generally reported to be increased in patients with type 1 diabetes mellitus (e.g. Pozzessere et al., 1991; Kramer et al., 1998; Howorka et al., 2000, but see Ziegler et al., 1994a,b).

It is not clear to what extent the established electrophysiological alterations correlate with the level of hemoglobin A1c (HbA1C) values as an index of the level of metabolic control. Interestingly, abnormal visual evoked potentials have been demonstrated to be partly reversible, since a tight 3-day blood glucose regimen has resulted in a significant decrease of visual evoked potentials latencies in patients with diabetes, although they remained significantly longer than in healthy participants (Ziegler et al., 1994a,b).

The relation between these changes in CNS function and the duration of diabetes is not yet fully understood. Studies using evoked potentials may show abnormalities in the early course of type 1 diabetes that can be assessed before other complications (Seidl et al., 1996; Pozzessere et al., 1989, 1991; Pietravalle et al., 1993; Donald et al., 1984) or cognitive dysfunction (Dejgaard et al., 1991) develops. These studies show that subclinical CNS dysfunction is common in type 1 diabetes and can be detected by using (endogenous) evoked potential latencies. The exact time after disease onset at which these abnormalities develop and whether certain interventions, such as tight metabolic control, can prevent or even reverse these abnormalities are questions that remain to be answered.

2.2. Neuroradiological changes in the brain

Only few neuroradiological studies have been performed in patients with type 1 diabetes, some involving a case-control design, some comparing patients to reference values. Both central and peripheral atrophy has been reported in a case-control study (Lunetta et al., 1994) and in a number of studies comparing patients to reference values (Araki et al., 1994; Perros et al., 1997). Some authors do not interpret this as a distinct characteristic of the disease itself, since most magnetic resonance imaging (MRI) results in type 1 diabetic patients are well within normal range (Chabriat et al., 1994). It has been suggested that the radiological appearance of the brain in patients with diabetes resembles that of normal ageing, but appears to develop at a younger age than in non-diabetic participants (Araki et al., 1994).

Atrophy may be linked to a history of severe hypoglycaemic episodes, since only patients who had experienced multiple severe hypoglycaemic episodes showed cortical atrophy (Perros et al., 1997). These findings need confirmation in future studies.

Focal lesions mostly involve the subcortical white matter (Perros et al., 1997; Dejgaard et al., 1991; Ferguson et al., 2003a,b). For example, high-intensity periventricular white-

matter lesions, particularly small punctuate white matter lesions, periventricular caps, or pencil thin rims were present in one third of the scans in a study by Ferguson et al. They found these to be related to the presence of background retinopathy (Ferguson et al., 2003a,b).

2.3. Cognitive functioning

2.3.1. Cognitive performance in patients compared to healthy controls

Individuals with type 1 diabetes have repeatedly been reported to show modest performance deficits in a wide range of neuropsychological tests compared with non-diabetic controls. Already in 1922, a study on cognitive performance was conducted (Miles and Root, 1922). In the last decades, over 20 studies have compared cognitive functioning in type 1 diabetic patients with non-diabetic controls. In 16 of these studies, data were presented in such a way that standardised effect sizes could be calculated with respect to the distinct cognitive domains (see Table 1).

In total, data of over 850 patients and 600 controls are available. Detailed analysis is in preparation (Brands et al., in preparation). Although the different studies vary widely with respect to patient characteristics and psychometric tests used, Table 1 shows that patients with type 1 diabetes perform worse on a variety of neuropsychological tests. A majority of the studies show negative effects on general cognitive ability (i.e., intellectual functioning), psychomotor speed, attention, delayed memory and mental flexibility. Contrary to results from studies on type 2 diabetes (Strachan et al., 1997; Stewart and Liolitsa, 1999), learning and immediate memory seem to be less inflicted. Also, the pattern of impairments varies between studies, possibly due to the relatively subtle nature of the deficits or to the heterogeneity of the studied samples. In general, the magnitude of the cognitive deficits is relatively modest in Cohen's terminology (Cohen, 1988), that is within one half standard deviation of the control group, or an equivalent effect size of less than 0.5. However, analysis of the studies in Table 1 does shows that cognitive impairment can be objectively demonstrated with the help of sensitive neuropsychological tests in type 1 diabetic patients. It is important to note that even mild forms of cognitive dysfunction might hamper everyday activities, since they can be expected to present problems in more demanding situations and may, for example, negatively affect academic performance (McCarthy et al., 2002) or vocational success. Severe impairments have been reported in case studies as well (Gold et al., 1994). The question arises whether this inter-study variation is due to the fact that a small effect is measured over a large group (i.e., insufficient statistical power), or that specific subgroups are at risk for greater deterioration. Since most of the aforementioned studies have small sample sizes it is difficult to assess individual risk factors for this reported cognitive decline. Still we would like to highlight some of the possible relevant risk factors.

2.3.2. Are recurrent episodes of severe hypoglycaemia deleterious?

The issue whether or not repeated episodes of severe hypoglycaemia result in permanent mild cognitive impairment has been debated extensively in the literature. Several studies report a relation between recurrent episodes of severe hypoglycaemia and (mild) cognitive deficits (e.g. Gold et al., 1994; Langan et al., 1991; Sachon et al., 1992; Wredling et al., 1990; Hershey et al., 1997; Lincoln et al., 1996), but this is not confirmed by others (e.g. (Kramer et al., 1998; The DCCT Research Group, 1996; Reichard et al., 1996; Ryan and Williams, 1993).

The studies that found evidence of mild cognitive impairment after recurrent episodes of severe hypoglycaemia were cross-sectional studies. Two large prospective studies did not find a relation between recurrent episodes of severe hypoglycaemia and cognitive decline. The Diabetes Control and Complications Trial (The DCCT Research Group, 1996) was a longitudinal study with an average follow-up of 6.5 years, that examined the effect of intensive treatment of diabetes mellitus on microvascular complications in 1441 patients with type 1 diabetes. Intensive treatment delayed the onset and magnitude of long-term complications, such as neuropathy and retinopathy, compared with conventional treatment. Although this type of treatment caused a threefold increase in the risk of episodes of severe hypoglycaemia, it was not associated with cumulative neuropsychological impairment. These findings are consistent with the results of the 5-year longitudinal Stockholm Diabetes Intervention Study (Reichard et al., 1991). Although the issue is still unresolved, the results of these studies suggest that the negative effects of recurrent episodes of severe hypoglycaemia on cognitive functioning are limited.

2.3.3. Duration of diabetes and the presence of other complications

In general, the development of complications such as retinopathy, neuropathy and nephropathy is determined by the duration of diabetes and the level of metabolic control. Several studies demonstrate an association between these complications and cognitive performance (Ryan et al., 1993; Skenazy and Bigler, 1984; Ferguson et al., 2003a,b). This suggests that the brain is susceptible to the same processes that underlie these other complications. Detailed information on the relation between diabetes duration, metabolic control and cognition is not yet available, in particular studies on elderly patients are missing. This is important since it has been suggested that the elderly are particularly vulnerable for the effects of diabetes on the brain. In addition, similarities have been found in the pathophysiology of cerebral ageing and diabetic complications (Biessels et al., 2002a,b).

2.3.4. Disease onset in early childhood

In general, studies involving children who developed diabetes before the age of 5 suggest that these children are at

Table 1
Cognitive performance in type 1 diabetes compared to healthy controls

No.	Study		Study characteristics		Cognitive domains							
		Mean age patients (S.D.)	*N* patients/ *N* controls	Patient characteristics	General cognitive ability	Psychomotor speed	Attention	Working memory	Learning and immediate memory	Delayed memory	Mental flexibility	Perception
1	Franceschi et al. (1984)	26 (5)	37/26	Poor metabolic control	− − −	−	−	−	− −			+
2a	Skenazy et al., 1984	28 (5)	20/24	Visually impaired	−							
2b	Skenazy et al., 1984	32 (6)	19/24	Non vis. imp	− − −	− − − −					− − −	− −
3	Grill et al., 1990[a]	37 (7)	6/5	Good metabolic control		− − −		+++			+/−	
4a	Widom and Simonson, 1990[a]	27 (6)	8/10	Poor metabolic control		− −	− − −				−	
4b	Widom and Simonson, 1990[a]	22 (3)	9/10	Good control		− −	+/−				++	
5	Dejgaard et al., 1991	44 (9)	20/120	Long duration	− − −	+/−		+/−	++	− −	− − −	
6	Pozzessere et al., 1991	33 (12)	16/16	Normal neurological examination				− − −				
7	Blackman et al., 1992[a]	30 (6)	14/10	Poor metabolic control		− −						
8a	Ryan et al., 1992	36 (6)	34/19	males	−	− −	− −	+/−	+	++	+	− −
8b	Ryan et al., 1992	36 (6)	41/56	females	− −	− − −	− −	−	− −	− −	− −	− − −
9	Wirsen et al., 1992[a]	Median 25	10/12	Males, no complications	+/−	+/−	++	++	+++		− −	
10a	Sachon et al., 1992	41 (13)	30/25	Frequent hypo		− − − −	− − −	− − −	− − −	− − − −	− − − −	
10b	Sachon et al., 1992	34 (10)	25/25	No hypo		− − − −	− − −	− −	− −	−	− − −	
11	Deary et al., 1993	40 (7)	100/100	Onset after age 19	− −							
12	Ryan et al., 1993	34 (6)	142/100	Onset before age 17	− −	− − −	− −			+/−	− −	− − −
13a	Ryan et al., 1993	33 (6)	41/41	female	− −	− − −	− − −	++	− −	− −	− −	− −
13b	Ryan et al., 1993	33 (5)	41/41	Male	− −	− − −	− − −	+	+/−	++	− −	− − −
14a	Maran et al., 1995[a]	36 (3)	8/8	Hypo unaware		− − − −						
14b	Maran et al., 1995[a]	32 (4)	10/8	Hypo aware		− − − −						
15a	Hershey et al., 1997	26 (7)	26/21	Severe hypo	− − − −	− − −	− −		− −	− −	− −	−
15b	Hershey et al., 1997	23 (8)	12/21	No severe hypo	− − −	− − −	+/−		− −	− −	+	− −
16	Kramer et al., 1998	36 (13)	108/108	Good control	+/−	− −						

+++: 0.5≤ES<1.0.
++: 0.2≤ES<0.5.
+: 0.1<ES<0.2.
+/−: 0.1<ES<−0.1.
−: −0.2<ES<−0.1.
− −: −0.5<ES<−0.2.
− − −: −1.0<ES<−0.5.
− − − −: ES<−1.0.

[a] A study design was to measure the effect of acute hypoglycaemia, but subjects were tested at euglycaemia before hypoglycaemia was induced.

risk for the development of cognitive impairment, particularly with respect to visuo-spatial abilities, motor function, attention and memory (Ryan et al., 1985a,b; Rovet et al., 1987; Golden et al., 1989; Rovet and Alvarez, 1997; Bjorgaas et al., 1997) and for impairments in overall intelligence (Ryan et al., 1985a,b).

It is important to consider the possibility that the developing brain is more vulnerable for the effect of diabetes. Ryan et al. (1985a,b) found that 24% of adolescents with diabetes that was diagnosed before the age of 5 show neuropsychological deficits compared with 6% of those diagnosed later, and 6% of controls. Of course, one must take into consideration that multiple school and classroom absences, family disruptions and other psychosocial problems associated with chronic illness may interfere with learning and with accurate cognitive assessment (Ryan et al., 1985a,b).

2.3.5. Psychiatric comorbidity in diabetes mellitus

The prevalence of psychiatric disorders, in particular depression and anxiety disorders which are known to have a negative effect on cognition, is increased in type 1 diabetes (Anderson et al., 2001; Gavard et al., 1993; Peyrot and Rubin, 1997; Popkin et al., 1988; Roy et al., 1994). In a recent meta-analysis, odds ratios and prevalence of depression were estimated for both type 1 and 2 diabetes, from 42 studies having a combined sample size of 21,351 subjects (Anderson et al., 2001). The main conclusion is that diabetes doubles the odds ratio. A difference in the prevalence of depression in type 1 compared to type 2 diabetes could not be established. This increased prevalence of depression might result from an inability to cope with the stresses associated with diabetes, but alterations in serotonin and dopamininergic activity, could also be involved (Broderick and Jacoby, 1988; Lackovic et al., 1990). Disturbances in glucocorticoid metabolism may play an additional role, since several authors have mentioned a relation between type 1 diabetes and a dysregulation of the hypothalamic–pituitary–adrenal axis activity (Roy et al., 1991; Prestele et al., 2003).

In all, the relation between cognition and depression in type 1 diabetes is complex. On the one hand, the co-occurrence of depression could influence cognitive performance negatively, on the other hand depression and cognitive dysfunction could each be a different expression of the same underlying encephalopathy. hypothalamic–pituitary–adrenal axis dysfunction could be a modulating factor in this process.

2.3.6. Genetic risk factors for cognitive decline especially in women?

The possible contribution of genetic risk factors for cognitive decline in type 1 diabetes is only just beginning to be explored. The ε4 allele of the apolipoprotein-E (APOE) gene is associated with cognitive decline and Alzheimer's disease (Wilson et al., 2002; Strittmatter et al., 1993) and with poor outcome following various cerebral insults (Friedman et al., 1999). The apolipoprotein-E genotype may also impair aspects of cognitive ability in type 1 diabetes (Ferguson et al., 2003a,b). Especially type 1 diabetic women with APOE ε4 performed less well on tests of non-verbal intellectual ability and executive functioning, such as planning and concept shifting, compared with type 1 diabetic women without the APOE ε4 allele (Ferguson et al., 2003a,b). Confirmation of these data is necessary in order to draw further conclusions.

3. Possible underlying mechanisms

Multiple pathogenic factors appear to be involved in the pathogenesis of cerebral dysfunctioning in type 1 diabetes. The relative contribution of different factors will vary between individuals, depending on characteristics such as age, sex, amount of glycaemic control and co-morbidity.

3.1. Mechanisms of hyperglycaemia induced damage

Hyperglycaemia leads to an increased level of glucose in the brain (Sredy et al., 1991; Knudsen et al., 1989) that, as in peripheral tissues, is shunted through the so-called "polyol pathway", by which excess glucose is converted to sorbitol and fructose (Greene et al., 1987). Concentrations of sorbitol and fructose in the brain of diabetic rodents are indeed increased, but to a lesser extent than in peripheral nerves (Sredy et al., 1991; Knudsen et al., 1989). Increased sorbitol has been linked to alterations in phosphoinositide and diacylglycerol metabolism (Bhardwaj et al., 1999), which, together with alterations in Ca^{2+} homeostasis (Biessels et al., 2002a,b), affects the activity of protein kinases in the brain. In diabetic rats the activities of protein kinases A and C were shown to be increased (Bhardwaj et al., 1999) and that of calcium/calmodulin dependent protein kinase II decreased (Di Luca et al., 1999).

Another potentially "toxic" effect of elevated glucose levels is an enhanced formation of advanced glycation end products (Brownlee, 1992). Increased amounts of advanced glycation end products have been demonstrated in the brain and spinal cord of diabetic rats (Vlassara et al., 1983; Ryle et al., 1997), albeit at lower levels than in peripheral nerves (Ryle et al., 1997), Finally, toxic effects of glucose are mediated through an imbalance in the generation and scavenging of reactive oxygen species (Van Dam and Bravenboer, 1997). Increased concentrations of the by-products of lipid peroxidation, indicative of oxidative damage, have been demonstrated in the cerebral microvasculature and brain tissue of diabetic rats (Mooradian, 1995; Kumar and Menon, 1993). Furthermore, the activities of superoxide dismutase and catalase, enzymes involved in the antioxidant defence of the brain, are decreased (Kumar and Menon, 1993; Makar et al., 1995).

3.2. Cerebrovascular alterations

Diabetes is associated with both structural and functional alterations of the cerebral vascular system, which increases the risk of stroke (Mankovsky et al., 1997; Beckman et al., 2002), and may also affect cognitive functioning.

Atherosclerotic disease is the main manifestation of structural alterations of the large extra- and intracranial arteries in diabetic patients (Reske-Nielsen et al., 1965; Mankovsky et al., 1997). Age, duration of diabetes, male gender, triglycerides and nephropathy are important determinants of atherosclerosis, assessed by ultrasonographic measurement of carotid intima-media wall thickness (Frost and Beischer, 1998, 2003).

Structural abnormalities at the microvascular level include thickening of capillary basement membranes and decreased capillary density, as has been shown in brain autopsy studies of diabetic patients (Johnson et al., 1982; Reske-Nielsen et al., 1965).

Functional alterations in the cerebral vascular system that have been associated with type 1 diabetes include regional alterations in cerebral blood flow and disturbances of vascular reactivity. Cerebral blood flow has been reported to be decreased (Keymeulen et al., 1995), with some degree of regional variation (MacLeod et al., 1994; Rodriguez et al., 1993). Others, however, report increased cerebral blood flow in diabetic subjects (Grill et al., 1990), and it has been suggested that the decrease in blood flow that is reported in studies that use positron emission tomography (Keymeulen et al., 1995; MacLeod et al., 1994) possibly reflects an artefact, due to concomitant atrophy (Sabri et al., 2000). Still, since cerebral atrophy is generally modest in subjects with type 1 diabetes, other factors are likely to be involved in these variable results and this issue needs further investigation.

Studies on cerebrovascular reactivity in type 1 diabetes provide more consistent results. The increase in blood flow after administration of a dilatory stimulus, such as acetazolamide administration (Fulesdi et al., 1997) or carbon dioxide inhalation (Griffith et al., 1987; Dandona et al., 1978) is impaired in diabetic subjects. This impairment appears to be most pronounced in subjects with a long duration of diabetes and in subjects with other complications, such as retino- and nephropathy (Fulesdi et al., 1997). Cerebral vasoreactivity and accompanying changes in blood flow are important compensatory mechanisms during conditions such as hypoglycaemia, hypotension, hypoxia and hypercapnia. Loss of these compensatory mechanisms may therefore have detrimental effects on the brain.

The exact relation between these vascular alterations and cognitive functioning in patients with type 1 diabetes has not been studied in detail. However, in animal models of diabetes, improvement of cerebral blood flow by chronic treatment with an angiotensin converting enzyme inhibitor is associated with an improvement of cognitive functioning (Manschot et al., 2003).

3.3. The role of severe hypoglycaemic episodes

Severe and prolonged hypoglycaemia may provoke brain damage through uncontrolled release of excitatory amino acids like glutamate and aspartate, which trigger calcium influx, leading to activation of proteolytic enzymes, thereby causing neuronal damage (Perros and Frier, 1997). Experimental studies have clearly shown that the severity of the resulting brain damage is dependent on the duration of the hypoglycaemic coma (Auer, 1986). Irreversible brain damage in rats occurred only after a period of at least one hour of flat electro-encefalogram (EEG) (Auer, 1986). These findings suggest that despite the acute energy failure in the brain associated with hypoglycaemia, there might be a period during which the CNS is resistant to hypoglycaemia-induced damage (Chabriat et al., 1994). This ‘‘brain-damage-free period’’ is in contrast with the immediate brain damage caused by hypoxia or ischaemia. This may be due to the use of alternative non-glucose fuels such as amino acids and ketone bodies, in order to maintain the cellular energy state for a limited period (Chabriat et al., 1994).

Rheological changes are another mechanism by which severe hypoglycaemia can affect the brain. Hypoglycaemia and its associated counterregulatory hormonal responses are associated with an acute rise in haematocrit and blood viscosity which can alter capillary blood flow (Frier and Hilsted, 1985). It has been suggested that tissues affected by microangiopathy are particular vulnerable to this process (Frier and Hilsted, 1985). Interestingly, the patients in the DCCT study, which found no association between the frequency of severe hypoglycaemia and cognitive impairment, did not have advanced microvascular complications at study entry (The Diabetes Control and Complications Trial Research Group, 1993). Future studies should determine whether patients with established microvascular disease are indeed more sensitive to the adverse effects of hypoglycaemia on the brain.

3.4. The role of insulin in the brain

Insulin receptors are widely distributed in the brain. Classically, the CNS was thought to be an insulin-insensitive tissue, but in the late 1970s it was demonstrated that insulin receptors were present throughout the CNS (Havrankova et al., 1979). In animal studies, it has been demonstrated that insulin signalling through its cerebral receptors influences the regulatory processes associated with food intake, body weight, and it also seems to affect higher cognitive functions. A high number of insulin receptors is present in the hippocampus, a brain structure critically implicated in memory function, especially the long-term consolidation of information (Freychet, 2000; Park, 2001). It has been suggested that insulin can modulate memory function by several mechanisms. For instance, insulin is thought to promote glucose utilisation in specific brain areas, such as the hippocampus, and glucose has been

reported to facilitate memory function (Park, 2001). An alternative, yet indirect effect of insulin-stimulated glucose uptake in neurons may be to enhance the activity of neurotransmitters such as acetylcholine, which is important for the consolidation of information in memory (Park, 2001).

The question arises how alterations in insulin metabolism associated with type 1 diabetes and its treatment, affect insulin signalling in the brain. The levels of circulating insulin in the systemic circulation are increased in most patients with type 1 diabetes, which is largely caused by the site of administration of exogenous insulin. Under physiological conditions, insulin is produced in the pancreas, released into the portal circulation and passes the liver, where it exerts an important part of its metabolic effects. In type 1 diabetes, endogenous production of insulin in the pancreas is virtually abolished, and exogenous insulin is administered subcutaneously, and is taken up by the systemic circulation. Consequently, insulin levels in the systemic circulation are increased, up to 200% above control values, in patients with type 1 diabetes treated with subcutaneous injections (Nijs et al., 1990).

To exert its effects on the brain, insulin has to be transported across the blood–brain barrier, bind to cerebral insulin receptors and convey its signal through an intracellular signalling cascade. Each of these processes may be affected by diabetes. Transport of insulin across the blood–brain barrier, for example, was shown to be increased in hyperglycaemic, hypoinsulinaemic rodent models of type 1 diabetes (Banks et al., 1997), whereas it is decreased in hyperinsulinaemic, hyperglycaemic rat models of type 2 diabetes (Baskin et al., 1985). Binding of insulin to receptors in brain tissue of hyperglycaemic, hypoinsulinaemic diabetic animals does not differ from controls (Havrankova et al., 1979; Marks and Eastman, 1989), whereas it appears to be decreased in the brains of hyperinsulinaemic, hyperglycaemic rats (Figlewicz et al., 1985). Insulin signalling may be disturbed both in type 1 and type 2 diabetes, as type 1 diabetes is also associated with some degree of insulin resistance, albeit to a lesser degree than in type 2 diabetes (DeFronzo et al., 2003; Pedersen and Beck-Nielsen, 1987).

Given these variable results in animal models, the nature of the relation between hyperinsulinaemia and cognitive function in type 1 or type 2 diabetes in humans is at this stage unclear. These animals studies do indicate, however, that different degrees of hyperglycaemia, hyperinsulinaemia and insulin resistance are associated with clear-cut differential effects on insulin action in the brain. Differences in insulin action in the brain between patients with type 1 and type 2 diabetes may therefore explain part of the distinctive cognitive profiles of these two conditions. Acquisition of information over time (i.e., learning) and consolidation of information for long-term storage, for example, seem to be relatively spared in type 1 diabetes compared with type 2 diabetes. These two cognitive domains are critically dependent on the hippocampus (Squire and Alvarez, 1995). This structure has a relatively high density of insulin receptors and may therefore be extra vulnerable for defects in insulin action. Further studies are required to investigate this hypothesis.

4. Conclusions and directions for future research

Type 1 diabetes can lead to slowly developing end-organ damage resulting in cerebral dysfunction. Diabetic encephalopathy seems to be a heterogeneous disorder characterised by cognitive impairments, electrophysiological and structural changes, and depression or anxiety disorders. A reliable diagnosis of diabetic encephalopathy in individual patients, however, is to date very difficult. There are no specific diagnostic criteria available yet, and the level of cognitive decline might be compensated for by the individual patient, hence manifesting themselves only in cognitively demanding situations. Specific therapeutic interventions or preventive measures are not yet available. This stresses the need for further research into the underlying mechanisms. In this respect, it is most important to further explore the differences between type 1 and type 2 diabetes. Analysis of the available studies on cognitive function in diabetes indicates that type 1 and type 2 diabetes are characterised by distinctive patterns of cognitive impairment. The central issue that needs further clarification is whether these distinctive patterns are due to differences in aetiology between the two types of diabetes, specifically focusing on the role of insulin in the brain, or due to the fact that studies in type 2 diabetes, in contrast to those in type 1 diabetes, were mostly performed with patients over the age of 50.

Acknowledgements

The research of Ineke Brands is partially supported by grant 2001.00.023 from the Dutch Diabetes Foundation. The research of Geert Jan Biessels is supported by grant 2001.00.023 from the Dutch Diabetes Foundation and grant 2000D030 from the Dutch Heart Association.

References

American Diabetes Association, 2002. Standards of medical care for patients with diabetes mellitus. Diabetes Care 25, 213–229.

Anderson, R.J., Freedland, K.E., Clouse, R.E., Lustman, P.J., 2001. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 24, 1069–1078.

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

Auer, R.N., 1986. Progress review: hypoglycemic brain damage. Stroke 17, 699–708.

Banks, W.A., Jaspan, J.B., Kastin, A.J., 1997. Effect of diabetes mellitus on the permeability of the blood–brain barrier to insulin. Peptides 18, 1577–1584.

Baskin, D.G., Stein, L.J., Ikeda, H., Woods, S.C., Figlewicz, D.P., Porte, D.J., Greenwood, M.R., Dorsa, D.M., 1985. Genetically obese

Zucker rats have abnormally low brain insulin content. Life Sci. 36, 627–633.
Bax, G., Lelli, S., Grandis, U., Cospite, A.M., Paolo, N., Fedele, D., 1995. Early involvement of central nervous system type I diabetic patients. Diabetes Care. 18, 559–562.
Beckman, J.A., Creager, M.A., Libby, P., 2002. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 287, 2570–2581.
Bhardwaj, S.K., Sandhu, S.K., Sharma, P., Kaur, G., 1999. Impact of diabetes on CNS: role of signal transduction cascade. Brain Res. Bull. 49, 155–162.
Biessels, G.J., ter Laak, M.P., Hamers, F.P., Gispen, W.H., 2002a. Neuronal Ca(2+) disregulation in diabetes mellitus. Eur. J. Pharmacol. 447, 201–209.
Biessels, G.J., van der Heide, L.P., Kamal, A., Bleys, R.L.A.W., Gispen, W.H., 2002b. Ageing and diabetes: implications for brain function. Eur. J. Pharmacol. 441, 1–14.
Bjorgaas, M., Gimse, R., Vik, T., Sand, T., 1997. Cognitive function in Type 1 diabetic children with and without episodes of severe hypoglycaemia. Acta Paediatr. 86, 148–153.
Blackman, J.D., Towle, V.L., Sturis, J., Lewis, G.F., Spire, J.P., Polonsky, K.S., 1992. Hypoglycemic thresholds for cognitive dysfunction in IDDM. Diabetes 41, 392–399.
Broderick, P.A., Jacoby, J.H., 1988. Serotonergic function in diabetic rats: psychotherapeutic implications. Biol. Psychiatry 24, 234–239.
Brownlee, M., 1992. Glycation products and the pathogenesis of diabetic complications. Diabetes Care. 15, 1835–1843.
Chabriat, H., Sachon, C., Levasseur, M., Grimaldi, A., Pappata, S., Rougemont, D., Masure, M.C., De Recondo, A., Samson, Y., 1994. Brain metabolism after recurrent insulin induced hypoglycaemic episodes: a PET study. J. Neurol. Neurosurg. Psychiatry 57, 1360–1365.
Chiappa, K.H., Ropper, A.H., 1982. Evoked potentials in clinical medicine (First of two parts). N. Engl. J. Med. 306, 1140–1150.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Erlbaum, Hillsdale, NJ.
Collier, A., Reid, W., McInnes, A., Cull, R.E., Ewing, D.J., Clarke, B.F., 1988. Somatosensory and visual evoked potentials in insulin-dependent diabetics with mild peripheral neuropathy. Diabetes Res. Clin. Pract. 5, 171–175.
Dandona, P., James, I.M., Newbury, P.A., Woollard, M.L., Beckett, A.G., 1978. Cerebral blood flow in diabetes mellitus: evidence of abnormal cerebrovascular reactivity. Br. Med. J. 2, 325–326.
Das, T., Kundu, S., Mazumdar, A.K., Mukhopadhyay, S.C., 2001. Studies on central nervous system function in diabetes mellitus. J. Indian Med Assoc. 99, 84, 86–87, 89.
Deary, I.J., Crawford, J.R., Hepburn, D.A., Langan, S.J., Blackmore, L.M., Frier, B.M., 1993. Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. Diabetes 42, 341–344.
DeFronzo, R.A., Hendler, R., Simonson, D., 2003. Insulin resistance is a prominent feature of insulin-dependent diabetes. Diabetes 31, 795–801.
Dejgaard, A., Gade, A., Larsson, H., Balle, V., Parving, A., Parving, H.H., 1991. Evidence for diabetic encephalopathy. Diabet. Med. 8, 162–167.
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.
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.
Ferguson, S.C., Blane, A., Perros, P., McCrimmon, R.J., Best, J.J., Wardlaw, J., Deary, I.J., Frier, B.M., 2003a. Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. Diabetes 52, 149–156.
Ferguson, S.C., Deary, I.J., Evans, J.C., Ellard, S., Hattersley, A.T., Frier, B.M., 2003b. Apolipoprotein-e influences aspects of intellectual ability in type 1 diabetes. Diabetes 52, 145–148.
Figlewicz, D.P., Dorsa, D.M., Stein, L.J., Baskin, D.G., Paquette, T., Greenwood, M.R., Woods, S.C., Porte, D.J., 1985. Brain and liver insulin binding is decreased in Zucker rats carrying the 'fa' gene. Endocrinology 117, 1537–1543.
Franceschi, M., Cecchetto, R., Minicucci, F., Smizne, S., Baio, G., Canal, N., 1984. Cognitive processes in insulin-dependent diabetes. Diabetes Care 7, 228–231.
Freychet, P., 2000. Insulin receptors and insulin actions in the nervous system. Diabetes/Metab. Res. Rev. 16, 390–392.
Friedman, G., Froom, P., Sazbon, L., et al., 1999. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. Neurology 52, 244–248.
Frier, B.M., Hilsted, J., 1985. Does hypoglycaemia aggravate the complications of diabetes? Lancet 2, 1175–1177.
Frost, D., Beischer, W., 1998. Determinants of carotid artery wall thickening in young patients with Type 1 diabetes mellitus. Diabet. Med. 15, 851–857.
Frost, D., Beischer, W., 2003. Progression of the carotid artery intima-media thickness in young patients with type 1 diabetes. Diabetes Care 26, 545.
Fulesdi, B., Limburg, M., Bereczki, D., Michels, R.P., Neuwirth, G., Legemate, D., Valikovics, A., Csiba, L., 1997. Impairment of cerebrovascular reactivity in long-term type 1 diabetes. Diabetes 46, 1840–1845.
Gavard, J.A., Lustman, P.J., Clouse, R.E., 1993. Prevalence of depression in adults with diabetes. Diabetes Care 16, 1167–1178.
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? Diabet. Med. 11, 499–505.
Golden, M.P., Ingersoll, G.M., Brack, C.J., Russell, B.A., Wright, J.C., Huberty, T.J., 1989. Longitudinal relationship of asymptomatic hypoglycemia to cognitive function in IDDM. Diabetes Care 12, 89–93.
Greene, D.A., Lattimer, S.A., Sima, A.A., 1987. Sorbitol, phosphoinositides, and sodium–potassium–ATPase in the pathogenesis of diabetic complications. N. Engl. J. Med. 316, 599–606.
Griffith, D.N., Saimbi, S., Lewis, C., Tolfree, S., Betteridge, D.J., 1987. Abnormal cerebrovascular carbon dioxide reactivity in people with diabetes. Diabet. Med. 4, 217–220.
Grill, V., Gutniak, M., Bjorkman, O., Lindqvist, M., Stone-Elander, S., Seitz, R.J., Blomqvist, G., Reichard, P., Widen, L., 1990. Cerebral blood flow and substrate utilization in insulin-treated diabetic subjects. Am. J. Physiol. 258, E813–E820.
Havrankova, J., Roth, J., Brownstein, M.J., 1979. Concentrations of insulin and insulin receptors in the brain are independent of peripheral insulin levels. Studies of obese and streptozotocin-treated rodents. J. Clin. Invest. 64, 636–642.
Hershey, T., Craft, S., Bhargava, N., White, N.H., 1997. Memory and insulin dependent diabetes mellitus (IDDM): effects of childhood onset and severe hypoglycemia. J. Int. Neuropsychol. Soc. 3, 509–520.
Howorka, K., Pumprla, J., Saletu, B., Anderer, P., Krieger, M., Schabmann, A., 2000. Decrease of vigilance assessed by EEG-mapping in type I diabetic patients with history of recurrent severe hypoglycaemia. Psychoneuroendocrinology 25, 85–105.
Johnson, P.C., Brenedel, K., Meezan, E., 1982. Thickened cerebral cortical capillary basement membranes in diabetics. Arch. Pathol. Lab. Med. 106, 214–217.
Keymeulen, B., Jacobs, A., de Metz, K., de Sadeleer, C., Bossuyt, A., Somers, G., 1995. Regional cerebral hypoperfusion in long-term type 1 (insulin-dependent) diabetic patients: relation to hypoglycaemic events. Nucl. Med. Commun. 16, 10–16.
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.
King, H., Aubert, R.E., Herman, W.H., 1998. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 21, 1414–1431.
Knudsen, G.M., Jakobsen, J., Barry, D.I., Compton, A.M., Tomlinson, D.R., 1989. Myo-inositol normalizes decreased sodium permeability of the blood–brain barrier in streptozotocin diabetes. Neuroscience 29, 773–777.
Kramer, L., Fasching, P., Madl, C., Schneider, B., Damjancic, P., Waldhausl, W., Irsigler, K., Grimm, G., 1998. Previous episodes of hypoglycemic coma are not associated with permanent cognitive brain dysfunction in IDDM patients on intensive insulin treatment. Diabetes 47, 1909–1914.
Kumar, J.S., Menon, V.P., 1993. Effect of diabetes on levels of lipid peroxides and glycolipids in rat brain. Metabolism 42, 1435–1439.
Lackovic, Z., Salkovic, M., Kuci, Z., Relja, M., 1990. Effect of long-lasting diabetes mellitus on rat and human brain monoamines. J. Neurochem. 54, 143–147.
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.
Lincoln, N.B., Faleiro, R.M., Kelly, C., Kirk, B.A., Jeffcoate, W.J., 1996. Effect of long-term glycemic control on cognitive function. Diabetes Care 19, 656–658.
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.
MacLeod, K.M., Hepburn, D.A., Deary, I.J., Goodwin, G.M., Dougall, N., Ebmeier, K.P., Frier, B.M., 1994. Regional cerebral blood flow in IDDM patients: effects of diabetes and of recurrent severe hypoglycaemia. Diabetologia 37, 257–263.
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.
Mankovsky, B.N., Metzger, B.E., Molitch, M.E., Biller, J., 1997. Cerebrovascular disorders in patients with diabetes mellitus. J. Diabetes Complicat. 10, 228–242.
Manschot, S.M., Biessels, G.J., Cameron, N.E., Cotter, M.A., Kamal, A., Kappelle, L.J., Gispen, W.H., 2003. Angiotensin converting enzyme inhibition partially prevents deficits in water maze performance, hippocampal synaptic plasticity and cerebral blood flow in streptozotocin-diabetic rats. Brain Res. 966 AB, 274–282.
Maran, A., Lomas, J., Macdonald, I.A., Amiel, S.A., 1995. Lack of preservation of higher brain function during hypoglycaemia in patients with intensively-treated IDDM. Diabetologia 38, 1412–1418.
Marks, J.L., Eastman, C.J., 1989. Effect of starvation on insulin receptors in rat brain. Neuroscience 30, 551–556.
McCarthy, A.M., Lindgren, S., Mengeling, M.A., Tsalikian, E., Engvall, J.C., 2002. Effects of diabetes on learning in children. Pediatrics 109, E9.
Miles, W.R., Root, H.F., 1922. Psychologic tests applied in diabetic patients. Arch. Intern. Med. 30, 767–777.
Mooradian, A.D., 1995. The antioxidative potential of cerebral microvessels in experimental diabetes mellitus. Brain Res. 671, 164–169.
Nijs, H.G., Radder, J.K., Poorthuis, B.J., Krans, H.M., 1990. Insulin resistance in type 1 (insulin-dependent) diabetes: dissimilarities for glucose and intermediary metabolites. Diabetes Res. 15, 15–19.
Park, C.R., 2001. Cognitive effects of insulin in the central nervous system. Neurosci. Biobehav. Rev. 25, 311–323.
Pedersen, O., Beck-Nielsen, H., 1987. Insulin resistance and insulin-dependent diabetes mellitus. Diabetes Care 10, 516–523.
Perros, P., Frier, B.M., 1997. The long-term sequelae of severe hypoglycemia on the brain in insulin-dependent diabetes mellitus. Horm. Metab. Res. 29, 197–202.
Perros, P., Best, J.J.K., Deary, I.J., Frier, B.M., Sellar, R.J., 1997. Brain abnormalities demonstrated by magnetic resonance imaging in adult IDDM patients with and without a history of recurrent severe hypoglycemia. Diabetes Care 20, 1013–1018.
Peyrot, M., Rubin, R.R., 1997. Levels and risks of depression and anxiety symptomatology among diabetic adults. Diabetes Care 20, 585–590.
Pietravalle, P., Morano, S., Cristina, G., Mancuso, M., Valle, E., Annulli, M.A., Tomaselli, M., Pozzessere, G., Di Mario, U., 1993. Early complications in type 1 diabetes: central nervous system alterations preceded kidney abnormalities. Diabetes Res. Clin. Pract. 21, 143–154.
Polich, J., Howard, L., Starr, A., 1983. P300 latency correlates with digit span. Psychophysiology 20, 665–669.
Popkin, M.K., Callies, A.L., Lentz, R.D., Colon, E.A., Sutherland, D.E., 1988. Prevalence of major depression, simple phobia, and other psychiatric disorders in patients with long-standing Type I diabetes mellitus. Arch. Gen. Psychiatry 45, 64–68.
Pozzessere, G., Rizzo, P.A., Valle, E., Mollica, M.A., Meccia, A., Morano, S., di-Mario, U., Andreani, D., Morocutti, C., 1988. Early detection of neurological involvement in IDDM and NIDDM. Multimodal evoked potentials versus metabolic control. Diabetes Care 11, 473–480.
Pozzessere, G., Rizzo, P.A., Valle, E., Mollica, M.A., Sanarelli, L., Morano, S., Pietravalle, P., di-Mario, U., Morocutti, C., 1989. A longitudinal study of multimodal evoked potentials in diabetes mellitus. Diabetes Res. 10, 17–20.
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.
Prestele, S., Aldenhoff, J., Reiff, J., 2003. The HPA-axis as a possible link between depression, diabetes mellitus and cognitive dysfunction. Fortschr. Neurol. Psychiatr. 71, 24–36.
Reichard, P., Britz, A., Rosenqvist, U., 1991. Intensified conventional insulin treatment and neuropsychological impairment. BMJ 303, 1439–1442.
Reichard, P., Pihl, M., Rosenqvist, U., Sule, J., 1996. Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. Diabetologia 39, 1483–1488.
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.
Rodriguez, G., Nobili, F., Celestino, M.A., Francione, S., Gulli, G., Hassan, K., Marenco, S., Rosadini, G., Cordera, R., 1993. Regional cerebral blood flow and cerebrovascular reactivity in IDDM. Diabetes Care 16, 462–468.
Rovet, J., Alvarez, M., 1997. Attentional functioning in children and adolescents with IDDM. Diabetes Care 20, 803–810.
Rovet, J.F., Ehrlich, R.M., Hoppe, M., 1987. Intellectual deficits associated with early onset of insulin-dependent diabetes mellitus in children. Diabetes Care 10, 510–515.
Roy, M., Collier, B., Roy, A., 1991. Dysregulation of the hypothalamo–pituitary–adrenal axis and duration of diabetes. J. Diabetes Complicat. 5, 218–220.
Roy, M., Collier, B., Roy, A., 1994. Excess of depressive symptoms and life events among diabetics. Compr. Psychiatry 35, 129–131.
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.
Ryan, C., Longstreet, C., Morrow, L., 1985a. The effects of diabetes mellitus on the school attendance and school achievement of adolescents. Child Care Health Dev. 11, 229–240.
Ryan, C., Vega, A., Drash, A., 1985b. Cognitive deficits in adolescents who developed diabetes early in life. Pediatrics 75, 921–927.
Ryan, C.M., Williams, T.M., Orchard, T.J., Finegold, D.N., 1992. Psychomotor slowing is associated with distal symmetrical polyneuropathy in adults with diabetes mellitus. Diabetes 41, 107–113.

Ryan, C.M., Williams, T.M., Finegold, D.N., Orchard, T.J., 1993. Cognitive dysfunction in adults with type 1 (insulin-dependent) diabetes mellitus of long duration: effects of recurrent hypoglycaemia and other chronic complications. Diabetologia 36, 329–334.

Ryle, C., Leow, C., 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.

Sachon, C., Grimaldi, A., Digy, J.P., Pillon, B., Dubois, B., Thervet, F., 1992. Cognitive function, insulin-dependent diabetes and hypoglycaemia. J. Intern. Med 231, 471–475.

Seidl, R., Birnbacher, R., Hauser, E., Bernert, G., Freilinger, M., Schober, E., 1996. Brainstem auditory evoked potentials and visually evoked potentials in young patients with IDDM. Diabetes Care 19, 1220–1224.

Skenazy, J.A., Bigler, E.D., 1984. Neuropsychological findings in diabetes mellitus. J. Clin. Psychol. 40, 246–258.

Squire, L.R., Alvarez, P., 1995. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr. Opin. Neurobiol. 5, 169–177.

Sredy, J., Sawicki, D.R., Notvest, R.R., 1991. Polyol pathway activity in nervous tissues of diabetic and galactose-fed rats: effect of dietary galactose withdrawal or tolrestat intervention therapy. J. Diabetes Complicat. 5, 42–47.

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

Strachan, M.W., Deary, I.J., Ewing, F.M., 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.

Strittmatter, W.J., Saunders, A.M., Scmechel, D., et al., 1993. Apolipoprotein E: high-avidity binding to β-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 90, 1977–1981.

Surwillo, W.W., 1984. P300 latency and digit span. Psychophysiology 21, 708–709.

The DCCT Research Group, 1996. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. Ann. Intern. Med. 124, 379–388.

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

Toth, F., Varkonyi, T.T., Kiss, J.G., Rovo, L., Lengyel, C., Legrady, P., Jori, J., Czigner, J., 2001. Brainstem auditory-evoked potential examinations in diabetic patients. Scand. Audio 1. Suppl., 156–159.

Van Dam, P.S., Bravenboer, B., 1997. Oxidative stress and antioxidant treatment in diabetic neuropathy. Neurosci. Res. Commun. 21, 41–48.

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

Weinger, K., Jacobson, A.M., 1998. Cognitive impairment in patients with type 1 (insulin-dependent) Diabetes Mellitus. CNS Drugs 9, 233–252.

Widom, B., Simonson, D.C., 1990. Glycemic control and neuropsychologic function during hypoglycemia in patients with insulin-dependent diabetes mellitus. Ann. Intern. Med. 112, 904–912.

Wilson, R.S., Bienias, J.L., Berry-Kravis, E., Evans, D.A., Bennett, D.A., 2002. The apolipoprotein E e2 allele and decline in episodic memory. J. Neurol. Neurosurg. Psychiatry 73, 672–677.

Wirsen, A., Tallroth, G., Lindgren, M., Agardh, C.D., 1992. Neuropsychological performance differs between type 1 diabetic and normal men during insulin-induced hypoglycaemia. Diabetic Med. 9, 156–165.

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.

Ziegler, D., Langen, K.J., Herzog, H., Kuwert, T., Muhlen, H., Feinendegen, L.E., Gries, F.A., 1994a. Cerebral glucose metabolism in type 1 diabetic patients. Diabet. Med. 11, 205–209.

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