Hippocampal synaptic plasticity and glutamate receptor regulation: influences of diabetes mellitus

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Abstract

Diabetes mellitus is an endocrine disorder of carbohydrate metabolism resulting primarily from inadequate insulin release (Type 1 insulin-dependent diabetes mellitus) or insulin insensitivity coupled with inadequate compensatory insulin release (Type 2 non-insulin-dependent diabetes mellitus). Previous studies involving behavioural and electrophysiological analysis indicate that diabetes mellitus induces cognitive impairment and defects of long-term potentiation in the hippocampus. Considered to be an important mechanism of learning and memory in mammals, long-term potentiation is known to require regulation of the glutamate receptor properties. According to many studies, defects of long-term potentiation in the hippocampus of diabetic animals are due to abnormal glutamate receptors. We review here the changes in glutamate receptors that may account for modifications of long-term potentiation in various models of diabetes mellitus. As glutamate receptors are also involved in the appearance of neurodegenerative states, we discuss the possibility that deficits in long-term potentiation during chronic diabetes might arise from dysfunction of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors in early stages of the disease. This review addresses the possible role of hyperglycaemia and insulin in regulating these receptors.
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1. Introduction

According to projections, over 200 million people worldwide will be diagnosed to suffer from diabetes by the year 2010 (Mandrup-Poulsen, 1998) while the number of Americans diagnosed with diabetes is projected to increase by 165% over the next 50 years (Boyle et al., 2001). In Canada alone, there is an estimated incidence of 60,000 diagnosed cases of diabetes every year, and 25,000 deaths annually are attributed to diabetes-related complications. While the symptoms of diabetes can be controlled by insulin replacement, drugs, diet and exercise, its long-term complications can lead to devastating consequences, such as cardiovascular diseases as well as renal and ocular disorders. Complications of the peripheral nervous system also are known to be very common in diabetic patients (Ametov et al., 2003;

Brown and Asbury, 1984; Dyck et al., 1993), and a substantial body of evidence has demonstrated that diabetes may have negative impacts on the central nervous system (Biessels et al., 2002; Gispen and Biessels, 2000; McCall, 1992; Ryan and Geckle, 2000a). People with diabetes, especially older adults, apparently face a greater risk of vascular dementia, with large population studies detecting an association between diabetes mellitus, depression and Alzheimer's disease (Anderson et al., 2001; Leibson et al., 1997; Ott et al., 1999; Gasparini et al., 2002). Following a population of over 6000 for up to 6 years, Ott et al. (1999) found that the risk of dementia is nearly doubled in diabetic subjects, an effect that cannot be accounted only through vascular factor. According to the Honolulu–Asia Aging Study, association between diabetes and Alzheimer disease is especially strong among carriers of the apolipoprotein E epsilon 4 allele (Peila et al., 2002).

Several observations indicate that diabetes mellitus might be accompanied by a certain erosion of brain function. For example, impaired performance in global memory, attention, abstract reasoning and visual-motor tasks are recog-

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nized to be more frequent in the diabetic population (Franceshi et al., 1984; Ryan et al., 1985; Ryan et al., 1993) Data from the longitudinal Atherosclerosis Risk in Communities study indicate that diabetes mellitus is positively linked to cognitive decline over a period of 6 years in middle-aged people (age 47 to 57 years) (Knopman et al., 2001). Studies have revealed an association between Type 1 diabetes and cognitive difficulties, particularly in diabetic individuals who have early onset of the disorder (Northam et al., 2001; Ryan et al., 1985, 1993). For instance, small deficits in attention, executive skills and processing speed have been reported in studies of children with Type 1 diabetes. Six years after the onset of disease, children with Type 1 diabetes performed more poorly than control subjects on measures of attention, processing speed, long-term memory, and executive skills. These neuropsychological defects of children with Type 1 diabetes were consistent with dysfunction of anterior and medial temporal brain regions and correlated with the history of hypoglycemic episodes (Northam et al., 2001). However, these results must be placed in perspective as there is no evidence that neuropsychological deficits often reported in children with Type 1 diabetes are related with lower academic performance of these children over time (McCarthy et al., 2002, 2003). Large-scale epidemiological investigations have found poorer learning and memory performance to be also associated with Type 2 diabetes, impaired glucose tolerance and/or hyperinsulinaemia (Biessels et al., 2002; Gispen and Biessels, 2000). According to recent reports, cognitive alterations observed during Type 2 diabetes appear to require the interaction of aging factors with diabetes (Knopman et al., 2001; Ryan and Geckle, 2000a,b) and based on calculations in a group of elderly women with Type 2 diabetes, Grodstein et al. (2001) of Harvard Medical School estimated that having diabetes is equivalent to aging 4 years in terms of cognitive performance. Recent investigations have indicated that diabetes-induced changes of brain properties might, in fact, share many properties with brain ageing (Artola et al., 2002; Biessels et al., 2002; Kamal et al., 2003).

From an electrophysiological perspective, reduced amplitudes and prolonged latencies of evoked potential components have been described in the central nervous system of adults with both Type 1 and Type 2 diabetes mellitus (Di Mario et al., 1995; Suzuki et al., 2000). Intriguing animal experiments suggest that cognitive dysfunctions during diabetes may be associated with significant changes in the integrity of the hippocampus, a brain region considered to mediate memory formation in mammals. The present review focuses mainly on diabetes-induced alterations in hippocampal function and includes a survey of the modifications occurring in the glutamatergic system during both Type 1 and Type 2 diabetes mellitus. Particular attention is given to modulation of alpha-amino-3-hydroxy-5-methylisoxazole-propionate (AMPA) and *N*-methyl-D-aspartate (NMDA) subtypes of glutamate receptors as well as synaptic plasticity in the hippocampus of animal models presenting manifestations of diabetes mellitus.

2. Long-term potentiation in animal models of diabetes mellitus

Along with many observations in diabetic individuals, animal-based experiments indicate that cognitive dysfunctions during diabetes are associated with significant changes in the integrity of the hippocampus. At the behavioural level, streptozotocin-diabetic rodents exhibit impairments in hippocampal-mediated memory processes, such as during shock avoidance and spatial water maze learning (Biessels et al., 1996). Consistently, several morphological experiments performed on streptozotocin-treated rats suggest that cognitive impediments elicited by diabetes might result from a reduced number of apical branch points as well as decreased total length of apical dendrites of CA_3 pyramidal neurons (Magarinos and McEwen, 2000). An additional line of evidence indicates that these brain alterations are linked to electrophysiological dysfunctions in area CA_1 of the hippocampus. In fact, and based on numerous electrophysiological experiments, diabetes-induced abnormalities of the brain and behaviour could originate from defects in expression of long-term potentiation in hippocampal slices (see Biessels et al., 2002). Long-term potentiation is a form of synaptic plasticity considered by many to be an important electrophysiological device subserving learning and memory processes (Baudry and Lynch, 2001; Baudry and Massicotte, 1992; Massicotte and Baudry, 1991). It occurs when a particular group of synapses in the hippocampus (or in some other areas) receives strong and sustained or rhythmic inputs. Synaptic physiology is altered in such a way that subsequent inputs of equivalent magnitude to presynaptic cells will generate significantly increased responses from postsynaptic cells (see Fig. 1).

Glutamate receptors, which are major excitatory receptors within the central nervous system, are the object of particular attention by the scientific community since their regulation appears to be crucial for controlling synaptic operation during learning and memory (Baudry and Lynch, 2001; Malinow and Malenka, 2002; Manabe et al., 1992; Massicotte, 2000). Glutamate receptors have been shown to control excitatory synaptic transmission at glutamatergic synapses, but their excessive activation has been demonstrated to be potently toxic for the brain. NMDA and non-NMDA (kainate and AMPA) receptors are two families of ionotropic receptors activated by glutamate. Among several functions, AMPA receptors have been demonstrated to mediate most excitatory responses in the brain, while NMDA receptors have been implicated in the appearance of long-term potentiation in several brain regions (Dingledine et al., 1999). In the area CA_1 of the hippocampus, it is now well documented that induction of long-term potentiation requires sufficient dendritic depolarization to activate
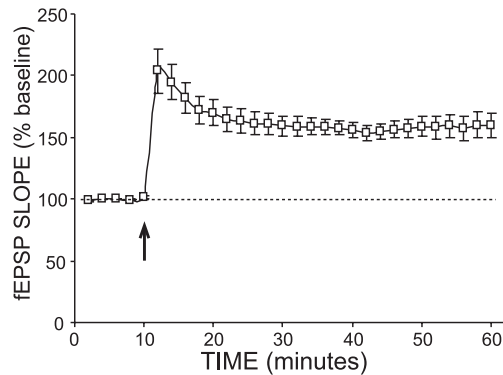
Fig. 1. LTP formation in area CA_1 of hippocampal slices. Field excitatory postsynaptic potentials (fEPSPs) were recorded in the stratum radiatum of CA_1 pyramidal cells in hippocampal slices. The slope of the response exhibited approximately 100% potentiation following theta burst stimulation (10 trains of four 100-Hz pulses given at 5 Hz; see arrow) which slowly decayed during the first 10 min. In most slices, the potentiation remained stable with a 60% increase. The values obtained during the period preceding theta burst stimulation were averaged to derive baseline values. Each point represents the mean ± S.E.M. of eight different experiments in which the responses of control slices were measured before and after theta burst stimulation.

the NMDA subtype of glutamate receptors to produce Ca^{2+} influx into postsynaptic structures (Artola et al., 1990; Baudry and Lynch, 2001). This rise in Ca^{2+} concentration is critical for the generation of synaptic potentiation, and several hypotheses implicating both pre- and postsynaptic processes have been advanced to explain expression of long-term potentiation in various brain regions. At the presynaptic level, changes in synaptic efficacy during long-lasting potentiation may be caused by alterations in the amount of transmitter release, which requires the existence of retrograde messengers generated by postsynaptic neurons and acting on presynaptic terminals (Bliss and Collingridge, 1993). Diabetes has been shown to affect neurotransmitter synthesis or release in several brain regions (Bitar et al., 1985; Chu et al., 1986; Lackovic et al., 1990; Welsh and Wecker, 1991), and it can be argued that the impaired ability of streptozotocin-treated rats to generate synaptic potentiation in the hippocampus is related to alteration at the presynaptic level, which possibly involves a reduction of transmitter release from glutamatergic neurons. However, this interpretation is certainly not consistent with a study revealing that streptozotocin-induced diabetes is associated with a selective decrease of physiological responses mediated by the AMPA subtype of glutamate receptors, without changes of synaptic responses mediated by NMDA receptors in the CA_1 field of the hippocampus (Chabot et al., 1997). If a decline in transmitter release were to occur in area CA_1 of the hippocampus of diabetic rats, one would expect the synaptic responses mediated by both NMDA and AMPA receptors to change in the same direction. Differences in the ratio of paired-pulse responses following induction of long-term potentiation in the hippocampus have been interpreted by several investigators as the

differential expression of various forms of long-lasting changes in synaptic function in terms of presynaptic transmitter release mechanisms (Staubli et al., 1990; Zucker, 1989). In fact, it is generally admitted that paired-pulse facilitation, a phenomenon due to presynaptic enhancement of transmitter release during a second pulse given 50–250 ms after the first stimulation is altered by most conditions interfering with transmitter release mechanisms. Employing this experimental approach, Biessels et al. (1996, 2002) found that paired-pulse facilitation was not modulated by streptozotocin administration, reinforcing the notion that chronic diabetes in rats does not interfere with presynaptic properties but rather with postsynaptic mechanisms (i.e. regulation of AMPA receptors) contributing to maintenance of long-term potentiation. Indeed, this scenario is supported by recent electrophysiological experiments indicating that streptozotocin-induced diabetes in rats is associated with biophysical abnormalities of AMPA receptors (Vaithianathan et al., 2003).

Long-term depression of synaptic function is another form of activity-dependent synaptic plasticity that has been proposed to control learning and memory. In contrast to long-term potentiation, synaptic depression is a long-lasting decrease in the efficacy of synaptic transmission which occurs after the application of a low-frequency train of synaptic activity (Artola et al., 1990, 1996). In area CA_1 of the hippocampus, long-term depression is triggered by an increase in the level of postsynaptic Ca^{2+} concentration, an effect resulting from NMDA receptor stimulation. The levels of postsynaptic Ca^{2+} influx achieved by different degrees of NMDA receptor activation during tetanic stimulation are thought to evoke opposing changes in protein phosphorylation; high levels of Ca^{2+} influx activate protein kinases necessary for synaptic potentiation, and low-Ca^{2+} influx prompts protein phosphatases necessary for long-term depression (Malenka, 1994; O'Dell and Kandel, 1994; Wang and Kelly, 1996). In particular, various studies have focused on the role of endogenous phosphatases for the expression of long-term depression in hippocampal slices, including Ca^{2+}-independent phosphatase-1 and the Ca^{2+}/calmodulin-dependent phosphatase calcineurin (Mulkey et al., 1993, 1994). After 6–8 weeks of streptozotocin-elicited diabetes, we observed that, in contrast to synaptic potentiation, expression of long-term depression was not affected in area CA_1 of the hippocampus (Chabot et al., 1997). However, studies implying a longer period of diabetes indicate that induction of long-term depression can be facilitated in area CA_1 of streptozotocin-diabetic rats. This augmentation in synaptic depression appears to be dependent on stimulus frequency, suggesting that abnormal NMDA receptor stimulation and/or activation of Ca^{2+}-dependent mechanisms involved in formation of long-term depression are altered in chronic streptozotocin-diabetic rats (Kamal et al., 1999, 2000). As in long-term potentiation, there is increasing evidence that expression of synaptic depression is mediated by modification of postsynaptic

currents evoked by the AMPA subtype of glutamate receptors (Malinow and Malenka, 2002). In this regard, enzymes participating in phospholipid and arachidonic acid metabolisms were reported to influence the AMPA response as well as formation of long-term depression in the area CA_1 of the hippocampus (Massicotte, 2000; St-Gelais et al., in press) and, as alterations of arachidonic acid metabolisms were found to be affected in streptozotocin-diabetic animals (Rosello-Catafau et al., 1994a,b), we cannot yet totally exclude a possible interaction of diabetes with AMPA receptor regulation during expression of long-lasting depression of synaptic function.

3. Brain glutamate receptor abnormalities in streptozotocin-induced diabetes in rats

It is believed that the functional changes in the hippocampus of diabetic animals might involve reorganization of postsynaptic receptors participating in glutamatergic synaptic transmission (Biessels et al., 2002; Gispen and Biessels, 2000). In fact, modulation of the AMPA subtype of glutamate receptors is widely assumed to be an important component of glutamatergic synaptic transmission as well as expression of long-term potentiation in the hippocampus. For instance, increased [^{3}H]AMPA binding in the hippocampus correlates well with heightened synaptic responses after formation of synaptic potentiation (Bernard et al., 1994; Gagné et al., 1998; Maren et al., 1993; Tocco et al., 1992). The exact biochemical mechanisms underlying alterations in AMPA receptor properties are still a matter of debate, but a large number of experiments support the notion that activation, by Ca^{2+} ions, of protein kinases and proteases could be critical for expression of long-term potentiation (Baudry and Lynch, 2001; Malinow and Malenka, 2002; Song and Huganir, 2002). Several arguments have also been advanced to support the hypothesis that activation of Ca^{2+}-dependent lipases may be part of the molecular mechanisms involved in long-term potentiation. NMDA receptor activation has been found to generate long-lasting enhancement of endogenous phospholipase A_2 activity, and various inhibitors of this enzymatic system have been shown to block formation of synaptic potentiation in area CA_1 of the hippocampus (for review, see Massicotte, 2000). On the other hand, incubation of hippocampal tissues with Ca^{2+} or exogenous phospholipase A_2 has been reported to increase, similarly to long-term potentiation, AMPA receptor binding (Dev et al., 1997, 1998; Lapierre et al., 2000) without altering the binding of ligands to the NMDA receptor complex (Massicotte, 2000).

Work over the past decades has shown that memory and long-term potentiation impairments in diabetic animals might be due to abnormalities in postsynaptic glutamatergic receptors (Chabot et al., 1996; Massicotte et al., 1991, 1992). Using quantitative autoradiographic analysis, we discovered that defects are correlated with reduced [^{3}H]AMPA binding in various brain regions of streptozotocin-injected rats (Chabot et al., 1997; Gagné et al., 1997); an effect probably caused by a decrease in receptor conformation. The streptozotocin-induced decline of [^{3}H]AMPA binding differs between various brain structures being more pronounced in the striatum, cerebral cortex, and hippocampus while almost no reduction is seen in the cerebellum. It is of interest that up-regulation of AMPA receptor binding resulting from endogenous phospholipase A_2 activation is also virtually absent in hippocampal preparations originating from diabetic rats. We have presented evidence suggesting that phospholipase A_2-induced modifications of AMPA receptor properties could be a necessary step for changes in postsynaptic operation during long-term potentiation, and the diminished capacity of this lipase to modulate AMPA receptor properties would provide a simple explanation for the defect in synaptic plasticity observed during diabetes (Chabot et al., 1997). It should be noted that abnormalities in AMPA receptor regulation by phospholipase A_2 have also been noted in the early stages of brain development and after kainic acid-induced seizure in adult rats, two situations in which expression of long-term potentiation is impaired in the hippocampus (Baudry et al., 1991; Chabot et al., 1996; Massicotte et al., 1991). The mechanisms involved in the decline in AMPA receptor regulation by phospholipase A2 are not yet known. The phospholipid concentration of membranes was previously found to be affected by diabetes and therefore phospholipase A_2 treatment could produce very different disturbances in the lipid environment of AMPA receptors in control versus streptozotocin-treated rats (Makar et al., 1995; Mooradian et al., 1990). Another possible explanation could be that streptozotocin treatment differentially modifies the expression of various genes coding for AMPA receptors. In the brain, AMPA receptor subunits (GluR1–4) are coded by multiple genes, and it has been postulated that the AMPA receptor is a heteromeric molecule composed of a combinational arrangement of different subunits (Dingledine et al., 1999). Then, it can be proposed that the significant impairment of AMPA receptor modulation by Ca^{2+} and phospholipase A_2 may reflect the differential expression of receptor subunits in various hippocampal structures of diabetic rats.

Western blots performed on hippocampal membranes have revealed that the decrease in [^{3}H]AMPA binding is possibly associated with changes in the properties of a glutamate receptor subunit, GluR1 (Gagné et al., 1997). In fact, the marked diminution in AMPA receptor binding and GluR1 subunits may be important factors contributing to down-regulation in AMPA receptor and defects of synaptic plasticity in streptozotocin-treated rats, as previous work has shown that AMPA receptors devoid of the GluR1 subunit are not competent to express long-term potentiation in area CA1 of the hippocampus (Vanderklish et al., 1992). It should be remembered that decrease in GluR1 immunoreactivity may also be reproduced by treatment of brain sections with Ca^{2+}-dependent proteases (Bi et al., 1996,

1998), suggesting that changes in immunological properties during diabetes mellitus might not necessarily be due to the differential expression of AMPA receptor subunits. Indeed, the elucidation of factors regulating GluR1 immunoreactivity could have important consequences for our understanding of the mechanisms underlying deficits of long-term potentiation and impaired modulation of AMPA receptors in streptozotocin-treated rats.

NMDA receptor expression and phosphorylation also have been reported to be down-regulated in postsynaptic densities from the brain of chronic streptozotocin-induced diabetic rats (Di Luca et al., 1999; Gardoni et al., 2002). For instance, NR2B subunit immunoreactivity of NMDA receptors, Ca^{2+}-calmodulin-dependent protein kinase II (CaM-KII) and Tyrosine-dependent phosphorylation of the NR2A/B subunits were found to be decreased 4 months after the induction of diabetes in streptozotocin-treated rats. Moreover, alphaCaMKII autophosphorylation and its association with the NMDA receptor complex were abnormal in streptozotocin-injected rats compared with age-matched controls. Likewise, NMDA currents in hippocampal pyramidal neurons monitored by intracellular recording were shown to be altered in these diabetic animals (Gardoni et al., 2002). Of course, from a functional point of view, this observation indicates that the impairment of synaptic plasticity in streptozotocin-diabetic rats can be linked to an inappropriate level of NMDA receptor stimulation required for the induction phase of long-term potentiation. It is noteworthy that a decline in the NMDA-independent form of long-term potentiation in the CA_3 field of the hippocampus was also reported in streptozotocin-diabetic rats (Kamal et al., 1999). In contrast to synaptic potentiation in area CA_1 of the hippocampal slices, the expression of long-term potentiation in the CA_3 sector appears to be dependent on presynaptic mechanisms rather than changes in AMPA receptor-mediated function (Staubli et al., 1990). Therefore, it is possible that plasticity deficits detected in diabetic rats, depending of the brain area, might differentially affect pre- or postsynaptic mechanisms involved in expression of synaptic plasticity.

4. The glutamatergic system in spontaneously diabetic animals

It should be remembered that, apart from their involvement in synaptic plasticity and memory, NMDA and AMPA receptor systems are also suspected to be involved in neurodegeneration following a wide range of neurological insults, including ischemia, trauma and epileptic seizures (Lipton and Rosenberg, 1994). Overactivation of these receptors is recognized to participate in the initiation of cell damage by increasing intracellular Ca^{2+} concentration in neurons, thereby leading to the generation of free radicals and the activation of proteases, phospholipases and endonucleases and the transcriptional activation of specific cell death programs (Schreiber and Baudry, 1995; Siesjö et al.,

1995). On the other hand, a number of recent studies have shown that insulin can rapidly alter NMDA receptor activation as well as interact with AMPA receptor trafficking between the plasma membrane and the intracellular compartment in cultured hippocampal neurons (Liu et al., 1995; Man et al., 2000; Skeberdis et al., 2001). In this context, it might be possible that mechanisms underlying diabetic neuropathies may be initiated in early stages of the disease as a consequence of abnormal glutamate receptor properties. Such a possibility is indeed relevant to the clinical situation, since excessive activation of glutamate receptors is a characteristic feature of brain damage during stroke and ischemia (McCall, 1992), conditions that are exacerbated by hyperglycemic states and diabetes (Mandrup-Poulsen, 1998).

Relatively little is known about the regulation of glutamate receptors in the early stages of diabetes mellitus. In vitro receptor autoradiography and immunoblotting experiments have demonstrated that AMPA and NMDA receptor properties can be altered in the early stages of diabetes in non-obese diabetic mice, a genetic model of insulin-dependent (Type 1) diabetes (Valastro et al., 2002). Binding experiments indicate that diabetes in this mouse model is associated with the up-regulation of [^{3}H]glutamate binding to NMDA receptors, an effect possibly due to an increase in the maximal number of NMDA binding sites (Fig. 2). In support of this contention, it was discovered that the levels of NR2A (but not NR1) subunits are augmented in crude synaptosomal fractions prepared from non-obese diabetic mice (Valastro et al., 2002). From the functional point of view, experiments performed on recombinantly expressed NMDA receptors have revealed that NR2 composition strongly influences the electrophysiological characteristics of NMDA receptor subtypes (Dingledine et al., 1999). NR2A-containing receptor channels differ from other channel subtypes showing fast deactivation and prominent Ca^{2+}-dependent desensitization (Medina et al., 1995). Interestingly, NR2A appears to be necessary for formation of long-term potentiation at several synapses, emphasizing the functional significance of studies revealing NR2A up-regulation in synaptic membranes from non-obese diabetic mice (Ito et al., 1997; Michaelis, 1998). The finding that NR2A concentrations are increased in synaptic membranes in these diabetic mice raises the intriguing possibility that the expression of abnormal NMDA receptors during diabetes may have functional as well as pathological consequences. This contention is concordant with a recent study reporting up-regulation of both NMDA and AMPA receptors in thoracic spinal cord sections in early stages of diabetes of obese-diabetic ob/ob mice, another model in which diabetes develops spontaneously and closely resembles the Type 2 (insulin-independent) condition (Li et al., 1999).

The literature reports increased lipid peroxidation products and remarkable changes in free radical scavenger system enzymes in diabetic patients and different organs from diabetic animals (Biessels et al., 2002; Rosen et al.,
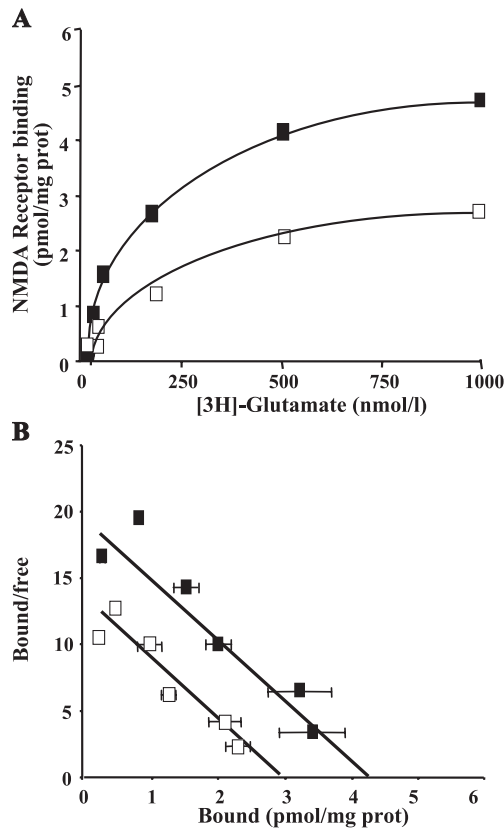
Fig. 2. Binding properties of NMDA receptors in the cortex formation of NOD mice. Saturation curve (A) and Scatchard plots (B) of [³H]glutamate binding to NMDA sites in the parieto-temporal cortex of control (open squares) and NOD mice (closed squares) sections. NMDA receptor binding was determined using [³H]glutamate concentrations from 20 nmol/l to 1 μmol/l, and nonspecific binding was defined in the presence of 5 mmol/l of glutamate. The data are presented as Scatchard plots (bound/free) and analyzed by the Inplot program from GrafPad to generate K_d and B_{max}; bound values are means ± S.E.M. of values obtained with eight different measurements for the cerebral region examined. The saturation binding curve and the saturation plots are representative of experiments done on four different animals (reproduced from Valastro et al., 2002).

2001). Moreover, several lines of evidence point toward NMDA receptor overactivation as a central event that could lead to oxidative stress and ultimately to neuronal damage during various neurodegenerative conditions (Choi and Rothman, 1990; Michaelis, 1998). Of course, future studies will be required to determine whether defects of synaptic plasticity in non-obese diabetic mice involve NMDA-induced toxicity in the hippocampus and/or differences in oxidative stress. As mentioned previously, the activation of NMDA receptors is an important component for induction of long-term potentiation. During high-frequency stimulation, transient hyperactivity of NMDA receptors is responsible for appearance of long-term potentiation in numerous brain pathways known to be involved in learning and memory processes. Consequently, it is arguable that deficits in synaptic plasticity in the early stages of diabetes might reflect pre-existing expression of synaptic potentiation (the so-called occlusion effects) rather

than increased sensitivity to excitotoxicity. In this context, diabetes should lead to stimulation of silent synapses in the hippocampus, a feature normally required for expression of long-term potentiation in this brain region. More precisely and, based on several electrophysiological studies, expression of long-term potentiation appears to involve the uncovering of functional AMPA receptors that, prior to potentiation, are either not present in postsynaptic membranes or are "silent" electrophysiologically (Isaac et al., 1995; Liao et al., 1995). Such modifications of AMPA responses might be caused by an increase in the number of receptors or in their conformation (Hayashi et al., 2000; Massicotte, 2000; Shi et al., 1999; Song and Huganir, 2002). The observation that AMPA receptor affinity is enhanced in the early stages of diabetes in the hippocampus of non-obese diabetic mice supports this suggestion. Taken together, these observations are consistent with the possibility that brain glutamate receptor properties can be modified in diabetic subjects (Valastro et al., 2002). Of course, identifying the mechanisms by which biochemical and electrophysiological changes in glutamatergic properties are exerted in the early stages of diabetes may provide important clues about the cellular events responsible for diabetes-induced neuropathies.

5. Hyperglycaemia and the glutamatergic system

Clinical and experimental studies have revealed that altered glucose status might be an important factor controlling learning and memory processes (Messier and Gagnon, 1996). Within this context, one obvious question remaining to be answered is whether abnormalities of the glutamatergic system during diabetes result in variations of brain glucose. Hyperglycaemia is a defining characteristic of diabetes mellitus, and it is likely that the link between diabetes and hippocampal vulnerability might be mediated by the family of metabolic derangements associated with elevated blood glucose levels. For example, chronic hyperglycaemia may affect brain integrity by triggering the development of advanced glycation products which are known to cause pathological damage to various tissues, including the hippocampus. Damage to central nervous system could also be induced by hyperglycaemia via other possible pathways. Increased aldose reductase activity, with a corresponding accumulation of sorbitol, depletion of neural myo-inositol, and alterations of Na-K ATPase activity, might readily disrupt the transport of nutrients to the brain (Biessels et al., 2002).

Recent findings demonstrate that, in Otsuka Long Evans Tokushima Fatty rats, which lack the cholecystokinin-A receptor because of a genetic abnormality, several properties of Type 2 diabetes are developing over time. From a behavioural perspective, the results indicate that the Otsuka Long Evans Tokushima Fatty rats showed a spatial memory deficit, hypoactivity and anxiety due, at

least in part, to the lack of cholecystokinin-A receptors (Li et al., 2002). In Zucker diabetic fatty rats, another animal model presenting several aspects of Type 2 diabetes, performance of the Morris water maze task and level in long-term potentiation were found not to be affected after 5–9 weeks of diabetes (Bélanger et al., in preparation). Like streptozotocin-diabetic rats, this animal model exhibits severe hyperglycaemia which generates significant peripheral damage and dysfunctions (for instance, cataract and heart apoptosis). Given these results, it appears that hyperglycaemia is possibly not the only factor contributing to diabetes-induced impairment in memory formation and synaptic plasticity. This apparent discrepancy between our recent results in this model and those obtained in streptozotocin-diabetic rats could be related to the differential activity of antioxidant defense mechanisms. In particular, it is recognized that the activities of superoxide dismutase and catalase, two major enzymes involved in brain detoxification, are reduced in the streptozotocin-diabetic model, whereas brain superoxide dismutase is increased in Type II diabetic animals (Biessels et al., 2002). Recently, we discovered that the binding properties of the NMDA subtype of glutamate receptors are altered in Zucker diabetic fatty rats. After 5–9 weeks of diabetes, ligand binding autoradiography indicates that [^{3}H]glutamate binding to NMDA receptors in area CA$_1$ of the hippocampus is reduced in Zucker rats (data not shown). The reduction of NMDA receptor binding in these rats suggests that, in this model, hyperglycaemia could have biochemical consequences which favor down-regulation of NMDA receptor function. Of course, the characteristic effect, i.e. decreased NMDA binding and no changes in expression of long-term potentiation in area CA$_1$ of the hippocampus, indicates that in Zucker diabetic fatty rats the modifications of NMDA receptors are not sufficient to alter synaptic plasticity. However, it cannot be excluded that this down-regulation in NMDA receptor could limit neurodegenerative processes in this animal model and then prevent cognitive and electrophysiological defects. This intriguing possibility that NMDA-induced cell damage might be reduced in Type 2 diabetes requires further investigation.

It should be remembered that, in contrast to Type 1 diabetes, Type 2 diabetes is not necessarily associated with insulin deficiency. In Zucker diabetic fatty rats, after 5–9 weeks of diabetes, systemic insulin levels are increased compared to control animals (Schmidt et al., 2003). Insulin has been proposed to play an important role in protecting patients against the development of peripheral neuropathies during chronic Type 2 diabetes. One of the key differences between Type 1 and Type 2 diabetes is the high vulnerability of Type 1 patients to progressive disruption of the paranodal ion-channel barrier. This change, which does not occur in Type 2 diabetes, has been associated with more severe conduction defects in Type 1 diabetic rats. In streptozotocin-diabetic rats, local unilateral application of insulin to the sciatic nerve results in an enhanced number of myelinated fibres and in the prevention of slowing conduction in treated nerves (Sima and Sugimoto, 1999; Yagihashi, 1995). Thus, it is conceivable that insulin might be involved in maintaining electrophysiological integrity as well as cognitive function in Zucker rats, and that its deficiency may play an important role in Type 1 diabetic impairment of hippocampal function. However, clinical observations in human suggest that in the central nervous system, hyperinsulinaemia in itself, in the absence of hyperglycaemia, is associated with accelerated cognitive decline in the elderly (Biessels et al., 2002). Of course, this observation suggest that insulin may possess differential effects on the central and peripheral system and further investigations of the mechanisms underlying glutamate receptor regulation during Type 2 diabetes might thus provide interesting information concerning the influence of insulin on this neurotransmitter system during diabetes.

6. Overall conclusion

Behavioural, electrophysiological and neurochemical studies indicate that diabetes mellitus is capable of altering brain function. In particular, animal models reproducing several aspects of Type 1 and Type 2 diabetes have been shown to represent valuable tools for exploring cellular and molecular brain dysfunctions during diabetic conditions. Abnormal regulation of glutamatergic receptors appears to play an important role in diabetes-induced impairment in synaptic plasticity and may therefore contribute to the development of cognitive defects in diabetic patients. However, a number of issues still remain to be clarified. Biochemical experiments in non-obese diabetic mice suggest that up-regulation of NMDA receptors is associated with the early stages of diabetes mellitus. There is, of course, a need for further studies on how these changes in NMDA receptor properties may accentuate glutamate toxicity. Preliminary investigations in experimental models of Type 2 diabetes and NMDA receptors provide evidence that hyperinsulinaemia might be capable of limiting NMDA-mediated toxicity, and this possibility should be addressed in greater detail. Diabetes appears to be an important risk factor for the development of various neuropathological conditions, and future experiments dealing with glutamate receptor regulation could help in understanding brain vulnerability in diabetic patients.

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