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Brain Alterations in Autoimmune and Pharmacological Models of Diabetes Mellitus: Focus on Hypothalamic-Pituitary-Adrenocortical Axis Disturbances

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Key Words

Type 1 diabetes · Streptozotocin · Nonobese diabetic mice · Hypothalamus · Hippocampus · Vasopressin · Hypothalamic-pituitary-adrenal axis · Glucocorticoids · Astrocytes · Neurogenesis

Abstract

Type 1 diabetes (T1D) is linked to an 'encephalopathy' explained by some features common to the aging process, degenerative and functional disorders of the central nervous system. In the present study we describe a manifest hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in two different experimental mouse models of T1D including the pharmacological one induced by streptozotocin and the spontaneous NOD (nonobese diabetic mice). The high expression of hypothalamic hormones like oxytocin and vasopressin were part to this alteration, together with elevated adrenal glucocorticoids and prominent susceptibility to stress. In the hippocampus of diabetic animals a marked astrogliosis, often associated with neural damage, was present. Dentate gyrus neurogenesis was also affected by the disease: proliferation and differentiation measured by bromodeoxyuridine immunodetection were significantly reduced in both experimental models used. Several facts, including changes associated with chronic hyperglycemia, hyperstimulation of the HPA axis, increased levels of circulating glucocorticoids in combination with brain inflammation and low production of new neurons, contribute to emphasize the impact of diabetes on the central nervous system.

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Diabetes mellitus is the most common serious metabolic disorder in humans. Ninety percent of diabetic individuals have type 2 diabetes (T2D, non-insulin-dependent), while 5–10% have type 1 diabetes (T1D, insulin-dependent). T1D begins usually earlier in life than T2D and has important short-term and long-term consequences. The incidence of both types of diabetes continues to increase worldwide, affecting younger people and causing a medical and socioeconomic burden [1, 2]. Diabetic complications result in both acute and chronic metabolic and vascular disturbances that lead to clinically relevant end-organ damage in eyes, kidneys, heart, blood vessels, nerves and central nervous system (CNS). Depending on the duration of diabetes and the quality of metabolic control, the development of these complications can be managed but only partially prevented by insulin treatment.

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In diabetic patients, regardless of the type, CNS deficits have been reported in neuropsychological and neurophysiological studies, reporting a poor performance in cognitive functions, in particular learning and memory and complex information processing [3, 4]. Even if the deficits are generally modest, they can occasionally be severe and undoubtedly diabetic patients present an enhanced risk of depression, stroke, dementia and Alzheimer's disease [5–9]. It has even been stated that diabetes is linked to an 'encephalopathy' characterized by slowly progressive, clinically significant cognitive deficits which are paralleled by brain neurophysiological and neuroradiological changes [10].

Streptozotocin (STZ)-induced diabetes in adult rodents and nonobese diabetic mice (NOD) is a well-accepted experimental model of T1D [11, 12]. In the STZ-induced model, numerous reports emphasize structural and functional abnormalities especially located in the hippocampus, such as impaired long-term potentiation, synaptic alterations, neurodegeneration and neuronal loss [7, 13–16]. Deficient cognitive function, particularly in the water maze test, was also well established [17]. Moreover, several studies explored potential diabetes-induced alterations of the hypothalamus, a cerebral structure that is physiologically under the negative hippocampal regulation. Indeed, hypothalamic lesions were reported in rats with long-term STZ-induced diabetes [18].

The NOD mouse represents a rare spontaneous model whose clinical and pathophysiological features make it suitable for studying human T1D [19, 20]. Clinical onset of diabetes is preceded by a latent (prediabetic) period during which T cell infiltration (insulitis) of the pancreas develops. Then, insulitis leads to extensive β-cell destruction, lack of insulin secretion and marked hyperglycemia. However, not all NOD mice become diabetic and the incidence of diabetes is higher in females than in males. Depending on the colony, hyperglycemia starts in females from around 12 weeks of age and 80% of them will have become diabetic by 6 months of age. Diabetes in NOD mice is characterized by polydipsia, glycosuria, reduced body weight, hyperglycemia and ketoacidosis. Without insulin treatment diabetic NOD mice die after 4–8 weeks [19–21]. Before our brain studies in this spontaneous T1D model, there was no study available, except the downregulation of the blood-brain glucose transport in hyperglycemic NOD mice [22].

Marked Hyperactivity of the Hypothalamic-Pituitary-Adrenal Axis Associated with Diabetes

In patients, T1D correlates with moderate disturbances in the hypothalamic-pituitary-adrenal (HPA) response to different tests. In most studies, exaggerated plasmatic cortisol levels have been found, but normal ACTH response to CRH [23]. A prominent HPA axis hyperactivity has also been repeatedly noted in the STZ-induced model in rodents: adrenal glucocorticoids are elevated, associated in some cases with insulin resistance, because of the antagonistic effects of glucocorticoids on insulin action [24–27]. Moreover, a high expression of hypothalamic hormones such as arginine vasopressin (AVP) and oxytocin (OT) was described in the paraventricular nucleus (PVN) of both STZ-treated rats [28] and NOD mice [29]. In this strain, the PVN content of AVP and OT neuropeptides was higher in NOD diabetic mice than in nondiabetic NOD or control mice. In addition, the AVP mRNA expression measured by in situ hybridization was significantly upregulated in the magnocellular and parvocellular portions of the diabetic NOD PVN. These changes in neurohormone expression were not caused by water loss, because diabetic mice were neither hypernatremic nor dehydrated [29]. This OT and AVP upregulation might therefore reflect a high-stress condition in this strain during the diabetic state.

Deleterious Effects of T1D on Hippocampal Functionality: Various Mechanisms Involved Including HPA Axis Dysfunction

Astrogliosis

Induction of glial fibrillary acidic protein (GFAP), an astrocyte intermediate filament cytoskeletal protein, is considered to be the main indicator of astroglial activation caused by stress, aging, CNS injury, and neurodegeneration [30, 31]. Astrogliosis is often associated with neural damage or distress as a secondary reaction [32].

The close connection between astrocytes and the blood-brain barrier makes them early sensors of variations of glucose homeostasis. Astrocytes can communicate with neurons, leading to neuroprotection by increasing glucose uptake, metabolism and transport. On the one hand, they are sensitive to hypoglycemia, which can occur during insulin treatment [33, 34]. On the other hand, they can be targets of hyperglycemia that is able to induce neurotoxic effects via augmented oxidative stress, polyol pathway and protein glycation [10].

Concerning glucocorticoids, they are abundantly presented in limbic areas and their effects are mediated by mineralocorticoid and glucocorticoid receptors, [35]. Indeed, astrocyte abnormalities have been described in the hippocampus of STZ rats. In these rats, hippocampal damage causing hyperreactivity to stress and involving both astrocytes and neurons was observed [15]. In STZ-treated mice, we also described an important increase in the number of hippocampal GFAP+ astrocytes and in the GFAP+ cellular area [34]. Moreover, astrocytes were positive for apolipoprotein E, a marker of ongoing neuronal dysfunction [36, 37]. Interestingly, these features are common to stress response and aging. In NOD mice, quite unexpectedly, we showed that hippocampal astrogliosis was an early feature of the NOD genetic background, because it was present during the prediabetic stage in NOD mice and in lymphocyte-deficient NOD scid mice that do not become diabetic [34]. However, after onset of diabetes, the number of GFAP+ cells increased significantly in the stratum radiatum area of NOD hippocampus.

The study of the kinetics of events in NOD and NOD scid mice highlighted the early appearance of the hippocampal astrocyte reaction in a possible relationship with a period of hyperinsulinemia and corresponding low glucose levels that can activate the HPA axis. First, high levels of plasmatic insulin have been associated with negative effects on hypothalamic control centers [38]. Second, NOD pups showed an absence of a stress-hyporesponsive period before weaning, particularly after interleukin-1 induction [39]. Therefore, manifest susceptibility to stress could originate early in life [19–21]. The hyperinsulinism noted at crucial moments of brain development like birth and after weaning may be related to priming effects for late stress effects at the time of clinical diabetes.

Impaired Adult Hippocampal Neurogenesis

More than 40 year ago, Altman and Das [40, 41] provided the first evidence of adult neurogenesis in two discrete zones in the dentate gyrus (DG) of the hippocampus: the subventricular zone and the subgranular zone. In these zones, a process of generating functionally integrated neurons from progenitor cells occurs [42–45]. During generation of new neurons in the brain, some steps can be clearly identified: proliferation, including neuronal fate and specification of progenitors; migration through the granular cell layer; maturation and functional integration into neuronal circuits. Depending on physiological conditions, a large proportion of the newly generated cells die after the proliferation step and survival and integration are a critical peak of this process. Newly generated hippocampal cells have been implicated in learning and memory processes [44].

Multiple and several factors and conditions are able to modulate the production of new neurons in the adult brain, including strain, gender, hormones, neurotransmitters, neuropeptides, environment, new challenges, physical activity, learning, and dietary restriction. Extraordinarily, stress, alcohol and/or drug abuse, inflammation, degenerative diseases, aging and also diabetes are strongly associated with low neurogenesis in the DG [46–51].

In STZ-treated rodents, DG proliferation and differentiation, which were assessed by detection of proliferation-associated markers and/or labeling with bromodeoxyuridine (BrdU), were significantly reduced [52–54]. This deficit was prevented by the administration of antidepressants or sexual hormones such as estrogens with known neuroprotective effects. In NOD female mice, hippocampal neurogenesis was strongly decreased compared with two control strains (C57BL/6 and BALB/c). As observed for astrogliosis, this alteration was present early during the prediabetic period. As illustrated in figure 1, the number of BrdU+ cells (measured 2 h after BrdU injection) was always significantly lower in the NOD DG than in that of age-matched C57BL/6 or BALB/c mice. Even if as assumed, the proliferation rate diminishes with age, the spontaneous diabetic strain exhibited less BrdU+ cells before (5 and 8 weeks of age) and after (12 weeks of age, at the onset of hyperglycemia) [52]. Concerning DG cell survival, overtly diabetic NOD mice showed a dramatic decrease in the number of BrdU+ cells (here BrdU was injected 21 days before killing) compared with non-diabetic NOD or control age-matched strains. Interestingly, DG cell survival was also significantly lower in prediabetic NOD mice than in age-matched control strains. However, confocal computerized quantification of double immunocytochemistry studies showed that diabetes was not linked to changes in the proportion of new cells exhibiting a neuronal or glial phenotype [52].

Among the potential causes linked to low ability in neurogenesis in diabetic animals, an influence of anomalies of glucose homeostasis could be noted. Low basal nonfasting glycemia values correlating with transient hyperinsulinemia during the prediabetic period in the NOD mice have been reported [39]. On the other hand, Suh et al. [55] confirmed a close relationship between hypoglycemia and progenitor cell loss in rat DG and long-term potentiation impairment was also associated with low glucose levels [56]. Conversely, during adulthood or even in pregnancy, evident hyperglycemia can exert its own

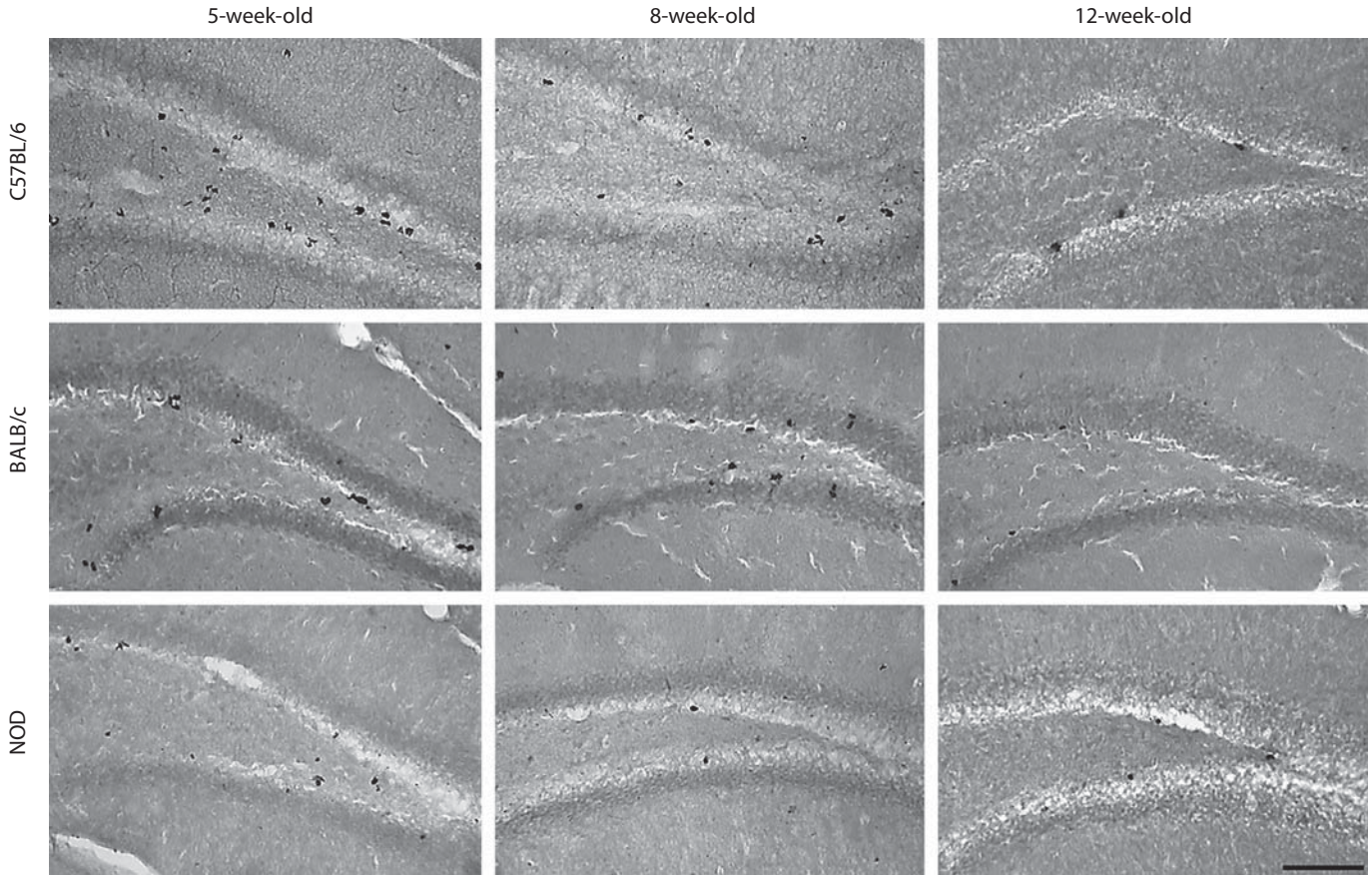

Fig. 1. BrdU+ cells in dentate gyrus of female C57BL/6, BALB/c and NOD strains at 5, 8 and 12 weeks of age counterstained with cresyl violet. BrdU was administered 2 h before killing. The scale bar corresponds to 100 μm. Note the decrease of dentate gyrus proliferation with age. Regardless of age NOD mice exhibited less BrdU+ cells than age-matched control strains. At 12 weeks of age, overt diabetes correlates with depressed proliferation.

Table 1. Brain parameters, HPA axis status and plasmatic glucose condition in control strain, nondiabetic NOD, diabetic NOD, and STZ-induced diabetes

	C57BL/6	Nondiabetic, NOD	Diabetic, NOD	STZ-induced diabetes
DG cell proliferation	high [16, 49, 71]	ND	low [52]	low [16, 53, 54]
DG survival	high [16]	medium [52]	low [52]	low [16]
Hippocampal astrocytosis	no [34, 37]	++ [34]	+++ [34]	+++ [37]
Brain inflammatory status	no	prone [69]	prone [69]	+ oxidative stress, leukocyte endothelial adhesion [37]
HPA axis status				
Corticosterone response to stress	low [72, 73]	high [70, 73]	high [70, 73]	high [70, 73]
PVN; AVP and/or OT	low [29]	ND	high [29]	high [28]
Corticosensitivity or corticoresistance	CS [63, 73]	CR [70, 73]	CR [70, 73]	CS [73]
Glycemic status	normal [70, 73]	lower values [70, 73]	hyperglycemia [70, 73]	hyperglycemia [10, 15, 16, 37]

CS = Corticosensitivity; CR = corticoresistance.

effects influencing brain functionality and development [7, 57].

Glucocorticoids might also be at play. Indeed, they are thought to play an important role in many aspects of normal brain development and have been implicated in neuronal maturation and survival [58–60]. Evidence from a number of species suggests that exposure to glucocorticoids, at a critical stage of development, can permanently alter neuroendocrine function and behavior [61, 62].

Concluding Remarks

The pathogenesis of the so-called 'diabetic encephalopathy' is complex and multifactorial: the toxic effects of high levels of plasmatic glucose include increased oxidative stress, nonenzymatic protein glycation, disturbed Ca^{2+} homeostasis and in turn is connected to impaired blood flow, vascular reactivity and angiopathy. At the neural level, the consequences of this condition comprise changes in neurotrophic molecules and diverse neuromodulators, including insulin.

As previously shown, transient hypoglycemia and chronic hyperglycemia trigger deep changes in specific gene transcription within neurons of the hypothalamus and hippocampus that could be associated with the development of secondary brain complications. The upregulation of hypothalamic OT and AVP evidently is in close association with diabetic nephrology, abnormal HPA activity and high stress condition in diabetic subjects. The role of endogenous glucocorticoids, absolutely coupled to stress response, is highlighted taking into account the elevated levels in diabetic patients and rodents. However, the degree of possible corticoresistance of a given individual or a given strain should be kept in mind [63]. Normally, corticosteroids have a strong negative regulatory effect on adult neurogenesis and they are central candidates to mediate in the damaged hippocampal function. Along this line, it was recently reported that, when normal physiological levels of corticosterone are maintained in diabetic animals, it is possible to prevent changes in hippocampal plasticity and function, suggesting that cognitive impairment in diabetes could be glucocorticoid-mediated [64]. Also, unpublished results from our laboratory showed that the administration of the specific glucocorticoid receptor antagonist RU486 is able to prevent the decreased hippocampal proliferation in STZ-treated mice.

The contribution of neuroimmune interactions cannot be neglected. In the aging brain, there is increased microglia reactivity suggestive of an ongoing inflammatory response accompanying low rates of neurogenesis [65]. This age-related increase of brain inflammation might be linked to decreased corticosensitivity associated with aging [66]. LPS-induced inflammation is deleterious for hippocampal neurogenesis and inflammatory blockade can restore it [67]. Cytokines and their receptors, abundantly expressed in the hipocampal region, are involved in brain neurodegenerative diseases, and also in depression [68]. Interestingly, the prediabetic NOD mice are quite sensitive to the induction of experimental acute encephalomyelitis, suggesting an inflammatory predisposition [69] linked to early corticoresistance [63]. The NOD strain also exhibited a greater sensitivity to the behavioral effects of interleukin-1 than controls showing an altered behavior [70].

In conclusion, CNS effects of diabetes result, among other disorders, in cognitive dysfunction, cerebrovascular diseases and a high risk of Alzheimer's disease. The HPA axis appears to be highly stimulated, with high levels of circulating glucocorticoids. Diabetic subjects are in general more susceptible to the effects of stress and depression. In experimental models, a marked astrogliosis is present in the hippocampus. The potential for neurogenesis is powerfully reduced but modulation with different agents is still possible, even if the exact role of the adult-generated neurons still has to be determined. Table 1 summarizes the features related to the different steps of neurogenesis, brain inflammatory status, and HPA-associated items among other important points in control, nondiabetic and diabetic NOD and STZ-induced diabetes. Many of these features are also present in physiological aging and/or pathological conditions.

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