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Diabetes, adult neurogenesis and brain remodeling: New insights from rodent and zebrafish models

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ABSTRACT

The prevalence of diabetes rapidly increased during the last decades in association with important changes in lifestyle. Diabetes and hyperglycemia are well-known for inducing deleterious effects on physiologic processes, increasing for instance cardiovascular diseases, nephropathy, retinopathy and foot ulceration. Interestingly, diabetes also impairs brain morphology and functions such as (1) decreased neurogenesis (proliferation, differentiation and cell survival), (2) decreased brain volumes, (3) increased blood-brain barrier leakage, (4) increased cognitive impairments, as well as (5) increased stroke incidence and worse neurologic outcomes following stroke. Importantly, diabetes is positively associated with a higher risk to develop Alzheimer disease. In this context, we aim at reviewing the impact of diabetes on neural stem cell proliferation, newborn cell differentiation and survival in a homeostatic context or following stroke. We also report the effects of hyper- and hypoglycemia on the blood-brain barrier physiology through modifications of tight junctions and transporters. Finally, we discuss the implication of diabetes on cognition and behavior.

Introduction

Hyperglycemia is defined as a high blood glucose concentration (> 1.26 g/L in fasting conditions) reflecting a failure in energy homeostasis and/or in glucose sensing. It can result from chronic disorder of insulin secretion and/or resistance (diabetes) or from acute stress. In the context of diabetes, chronic hyperglycemia leads to severe complications such as cardiovascular diseases, diabetic nephropathy, foot ulceration, retinopathy, and nerve damage. More and more evidences document the impact of metabolic disorders such as diabetes and obesity on the central nervous system (CNS). Diabetes is notably linked to changes in the blood-brain barrier (BBB) physiology of cerebral microvessels (barrier and transport functions). Furthermore, diabetic patients display lower brain volumes, and they increase their vulnerability to cognitive deficits and/or behavioral alterations.

This review aims at further documenting the impact of diabetes/hyperglycemia on the CNS. After introducing the main experimental models of type 1 and type 2 diabetes (T1D and T2D), we will describe the impact of diabetes on neurogenesis, stroke and brain remodeling, as well as its impact on BBB physiology, on cognitive functions and behavior in mammals. Finally, we will discuss the use of zebrafish as an emerging model for studying the impact of diabetes on neurogenesis and brain remodeling.

Part 1: Insights of rodents and mammals

Models of type 1 and type 2 diabetes in rodents

The main models of type 1 diabetes (T1D) in the literature are non obese diabetic (NOD) mice and streptozotocin (STZ)-induced diabetic rodent models. NOD mice spontaneously develop T1D due to immune cell infiltration in the pancreatic islets, leading to the destruction of the insulin-synthesizing β cells. Despite divergences in the immune response of NOD mice and T1D subjects, NOD mice remain a representative model of human T1D. Another model for inducing T1D in animals is the injection of drugs such...
as alloxan or streptozotocin, 2 toxic glucose analogs. These compounds accumulate in pancreatic β-cells through the glucose transporter GLUT2 and lead to their destruction. It consequently impairs insulin synthesis and secretion and results in increased blood glucose levels.

Several models have been also developed for studying T2D in rodents. For example, db/db mice and zucker diabetic fatty (ZDF) rats are models of T2D and obesity in which the leptin receptor is deficient due to a point mutation. These rodents display high levels of fasted blood glucose. The Goto-Kakizaki (GK) rats are a well-characterized model of non-obese Wistar rats that spontaneous develop T2D. High fat diets (HFD) also allow the development of T2D in mice and rats.

**Diabetes impairs adult neurogenesis in rodents**

Adult neurogenesis is a physiologic process involving the proliferation of adult neural progenitors, the genesis of newborn neurons, their differentiation, their migration, and their functional integration into neural networks. Such a process is spatially and temporally controlled by a wide variety of intrinsic and extrinsic factors including transcriptional regulators and hormones. In the brain of mammals, including humans, adult neurogenesis is mainly detected in 2 regions of the brain: the subventricular zone (SVZ) of the lateral ventricle and the subgranular region of the dentate gyrus (DG) of the hippocampus. Hippocampal adult neurogenesis appears to be important for learning and memory processes.

**Diabetes impairs brain cell proliferation in neurogenic regions**

To investigate the impact of diabetes on brain cell proliferation, several studies have used BrdU (5-bromo-2’-deoxyuridine) injection/detection as well as immunohistochemistry using antibodies raised against well-characterized proliferative markers such as PCNA (Proliferative Cell Nuclear Antigen) and Ki-67. In NOD mice, brain cell proliferation was reported to be significantly decreased in the DG compared with their control littermates. Similarly, using STZ-induced T1D models of mice and rats, accumulating data show that diabetes results in a decreased cell proliferation in the DG by performing BrdU and Ki-67 stainings. Interestingly, only 6 days after STZ injection, diabetic mice already displayed a lower number of proliferative cells in the DG.

In a similar way, T2D models mainly exhibit a decrease in brain cell proliferation in the DG, as shown in db/db mice and in HFD mice and rats. Interestingly, HFD impairs neurogenesis in young rats (when intake started at weaning) but not when it started in adults as revealed by performing DCX-immunostaining, a marker of newly generated neurons. It suggests that the hippocampus would be more sensitive to HFD during a critical period of development. In striking contrast, other studies described an increase in hippocampal cell proliferation in both db/db and HFD mice as well as in GK rats, while another work shows the absence of effects of the diabetic status on cell proliferation of the DG. To our knowledge, fewer studies investigate the impact of diabetes on brain cell proliferation in the SVZ. Six week-old GK rats and their respective controls had a similar pattern of neural progenitor proliferation in the SVZ, while 18 week-old GK rats displayed a strong increase in dividing neural progenitors compared with controls. Proliferation of the SVZ striatal wall of the lateral ventricle was also reported to be not impacted in HFD rats (Rivera et al., 2011), while a drastic decrease in cell proliferation was observed after only 20 days of treatment STZ-injected mice reported. Such discrepancies could be attributed to differences in the age of the animals, the duration and the gravity of the diabetic status, and also the species used.

Taken together, these data tend to show that T1D and T2D mainly induce a significant decrease in cell proliferation of the subgranular zone of the DG (Fig. 1).

**Diabetes impairs brain cell differentiation in neurogenic regions**

Although most studies show that diabetes impairs brain cell proliferation in neurogenic niches, the picture appears more contrasted by investigating the effects of diabetes on neural differentiation. Different studies using BrdU experiments and co-staining with mature and immature neuronal markers (i.e. doublecortin -DCX-, Tuj-1/β-III tubulin) have documented the negative impact of diabetes on neuronal differentiation. For instance, the number of DCX-positive cells in the granule cell layer did not show statistically
significant differences between experimental groups.\textsuperscript{32} However, in STZ-treated mice and rats, a significant decrease in newly generated neurons was observed.\textsuperscript{24,33,34} T2D models of mice (HFD) and rats (ZDF) also display a reduced neuronal differentiation.\textsuperscript{26,35} However, few studies reported no change in neuronal differentiation under type 1 and type 2 diabetic status.\textsuperscript{22,28,36} and in striking contrast, a 2-fold increase in neuronal differentiation was reported in GK rats at 4 months of age compared with controls, assuming a compensatory mechanism induced by neuronal damage.\textsuperscript{37}

In addition, STZ models of mice and rats as well as HFD rats and db/db mice, display a consistent decreased in dendritic density and branching.\textsuperscript{10} For instance, the dendritic length of pyramidal cells from the prefrontal cortex, the occipital cortex, and the hippocampus of T1D rats was decreased (from 20%
to 45%) as well as their density (from 36% to 58%) compared with controls.\textsuperscript{38} Such an inhibition of synapticogenesis was also reinforced in HFD model in rats and db/db mouse.\textsuperscript{30,36}

Taken together, these data highlight the fact that diabetes impairs neuronal differentiation (Fig. 1), including decreased hippocampal dendritic density and branching leading to an overall decrease in hippocampal volume.\textsuperscript{39} Such data probably argue in favor of a link between diabetes and cognitive impairment,\textsuperscript{10} given that the hippocampus is involved in memory processes.

**Diabetes impairs brain cell survival**

Most studies documented that T1D and T2D result in a decreased survival of newborn cells,\textsuperscript{10} except in GK rats for which no significant difference was observed in cell survival 3 weeks after BrdU injection, while proliferation was impacted.\textsuperscript{37} STZ models of rat have shown that diabetes increases neuronal death through apoptotic mechanisms in the hippocampus.\textsuperscript{40} For instance, the number of TUNEL-positive neurons was increased,\textsuperscript{41-43} and the expression of pro-apoptotic protein such as Caspase-3 and Bax was upregulated.\textsuperscript{44-46} Taken together, these data highlight that diabetes impairs neuronal survival by increasing Caspase-3 expression and activity, and apoptotic gene regulators\textsuperscript{40} (Fig. 1).

**Hyperglycemia, stroke and injury-induced neurogenesis in rodents and humans**

**Hyperglycemia and stroke**

Hyperglycemia is an independent factor of poor outcome after acute ischemic stroke (AIS). There is a strong association between admission blood glucose levels and intracerebral hemorrhage following thrombolytic therapy (recombinant tissue plasminogen activator, rtPA) after stroke.\textsuperscript{47} Fig. 2 shows the increase of hemorrhagic transformation following middle cerebral artery occlusion (MCAO) in mouse. Recently, hyperglycemia was shown to be independently associated with worse outcome at 3 months after mechanical therapy (thrombectomy) in AIS patients.\textsuperscript{48} The mechanisms by which hyperglycemia affects ischemic tissues include glutamate accumulation, intracellular acidosis, BBB disruption accompanied by an increased matrix metalloprotease (MMP) activity, brain edema formation, and inhibited plasma fibrinolysis.\textsuperscript{49-52}

There is only few data showing deleterious effects of hyperglycemia in very early reperfusion.\textsuperscript{53} In clinical conditions, the detrimental effect of acute hyperglycemia was shown to be higher after early (< 3 hours) than after delayed or no reperfusion.\textsuperscript{54} These findings support the notion that acute hyperglycemia was sufficient to increase infarct volume and that this detrimental effect was also dependent on the time of reperfusion.

In a model of MCAO in db/db mice, increased mortality, infarct volume and cerebral edema were reported relative to db/+ mice. This was associated with a worsened neurologic status.\textsuperscript{55} Wound healing was reported to be impaired after cerebral ischemia and hypoxia in db/db mice, potentially due to a decreased inflammatory response in diabetic conditions.\textsuperscript{56} db/db mice had also increased brain hemorrhage and displayed more severely injured white matter than nondiabetic mice after MCAO. MMP-9 as well as apoptotic markers were upregulated in db/db mice and in primary cortical neuron culture.\textsuperscript{57} In a different model of hypoxia (8% O2) and ischemia (carotid ligation), gelatinase activity (MMP-2 and 9) was more increased in the infarcted hemisphere of db/db relative to db/+ mice, suggesting a protease-mediated alteration of the BBB.\textsuperscript{58} Other mechanisms such as increased autophagy may participate in the aggravation of the brain insult under diabetic conditions as shown in a STZ-induced diabetes model in mice.\textsuperscript{59} In a similar model, microangiopathy associated with diabetes was shown to impact on post-stroke remodeling (vasoreactivity was abolished and the angiogenesis was delayed).\textsuperscript{60} After ischemic stroke, a decreased vascularization is also noticed in the
ischemic cortex and striatum of diabetic rats compared with control. In addition, they displayed increased swelling and number of astrocytic processes highlighting that the healing process is impaired. Beyond microvessels diabetic conditions also affect the proliferation and survival of oligodendrocyte progenitor cells that potentially reduce the white matter response to ischemia. Whereas epigenetic modifications may occur during diabetes and participate in aggravating ischemia-reperfusion consequences, hyperglycemia induced by stress even in nondiabetic condition is sufficient to worsen ischemic stroke outcome.

**Hyperglycemia and injury-induced neurogenesis**

Interestingly, neurogenesis plays a crucial role in cerebral recovery occurring after stroke; the formation of new neurons in the SVZ and in the DG being promoted in such a pathological condition. Severe hyperglycemia leads to a strong decrease in injury-induced proliferation in the SVZ of rats following MCAO. The downregulation of CREB phosphorylation and the decrease of BDNF expression appear to be involved in the injury-induced neurogenesis impairment in a hyperglycemic context. In the same line of evidences, diabetes inhibits BDNF expression in the hippocampus and decreases the survival and the differentiation of the newly generated neurons after ischemia in rats. Such adverse effects of hyperglycemia in reactive neurogenesis were also highlighted by in vitro ischemia of adult rats neural stem cells in which, hyperglycemia promotes apoptosis and decreases proliferation. Hyperglycemia is also known to promote the production of ROS and free radicals and could thus promote their formation in the ischemic brain, leading to an increased cell death.

**Hyperglycemia and blood-brain barrier in rodents and humans**

The BBB plays a key role in maintaining the CNS homeostasis. The BBB separates the peripheral blood circulation from the brain parenchyma. On the one hand, the BBB prevents detrimental substances to enter the brain, and on the other hand, the BBB will facilitate nutrients and oxygen passage in the CNS. The BBB is also involved in the water and electrolyte equilibrium in the brain interstitial fluid. The particular structure and the specific properties of the vessels composing the BBB are responsible for the different functions of the BBB. Structurally, the BBB is characterized by the presence of tight junctions, and it has also specific transporters and electric properties. Endothelial dysfunction is a hallmark of diabetes; it has been linked to T2D and to insulin resistance in experimental and clinical studies, and during the onset of cerebral ischemia, the role of endothelial cells composing the BBB is critical. The vasculature appears also as an important component of the neurogenic niches given that endothelial cells regulate neural stem cell activity through diffusible signal that are not clearly identified.

**Transporters**

**Glucose transporters.** As recently reviewed, many experimental studies report a downregulation of BBB glucose transporters in hyperglycemic animals, however other works did not reveal significant changes in the BBB glucose transporters expression in DM. In hypoglycemia conditions, glucose transporters such as glut1, glut4 or SGLT-1 (Na+/glucose co-transporter) have been reported to be upregulated.

**Efflux transporters.** Glycemic changes have also been studied on the ABC family transporters, which includes the P-glycoprotein (Pgpp) and multidrug resistance-related proteins (MRPs). These transporters play a key role in brain homeostasis and mediate active efflux of many potential toxicants including lipophilic compounds. In the hCMEC/D3 BBB cellular model, acute hypoglycemic exposure upregulated BBB endothelial expression of P-glycoprotein, breast cancer resistance protein (BCRP) and MRP1 and 4 proteins, while acute hyperglycemic exposure induced BCRP activity. Repeated hyperglycemic episodes upregulate P-glycoprotein activity. In rat model of diabetes (STZ), contradictory results have been reported in the brain with no change or a decrease of P-glycoprotein expression. Actually, the modulation of efflux transporters expression in the brain is region dependent, with an increase of P-glycoprotein expression in the hippocampus and in the striatum and a decrease in the cerebral cortex of the diabetic rats when compared with control. For BCRP, a decrease in the cortex of diabetic rats has been described. It is likely that other transporter may be
affected in diabetes as expression of transporters such as L-type amino acid transporter 1 (LAT1), have been described to be affected in an inflammatory environment.84

**Tight junctions and integrity**

Variation of glycemia affects tight junction (VE-cadherin, claudin, zona-occludens (ZO)) and permeability on endothelial cells mimicking the BBB. Hyperglycemia promotes cerebral-barrier dysfunction through activation of PKC-β and consequent stimulations of oxidative stress and tight junction dissolution.85 Hyperglycemia increases VE-cadherin and decreases claudin 5 expression, while hypoglycemia modify ZO-1 localization and also decreases claudin 5 expression and increases the permeability of the BBB.76

Taken together, these data highlight the impact of hypo- and hyperglycemia on the integrity of the BBB and its physiology (Fig. 3). It also suggests that under pathological condition (diabetes), the microenvironment regulating neural stem cell activity could be disturbed, impairing neurogenesis and favoring neurodegeneration. Such links between metabolic disorders (diabetes and obesity) and BBB disruption could favor cognitive impairment and modulation of feeding neuronal networks.

**Diabetes, neurotransmission, cognitive impairment and behavior in rodents and humans**

The brain is a glucose-dependent organ, which can be damaged by both hypoglycemia and hyperglycemia.86 In the hippocampus, diabetes leads to a reduced hippocampal volume due to a decrease in dendritic branching.10 The membrane potential, the membrane input resistance, and membrane time constant, remain unaffected in diabetes.10 Still in the hippocampus, the basal neurotransmission appears to be uncertain: (1) long-term potentiation (LTP), a cellular mechanism implied in learning and memory, is affected in CA1 neurons of the hippocampus in STZ and HFD treated rodents, (2) LTP appears to be impacted by both the duration and the severity of diabetes.87,88 The impairment of LTP in the different diabetic models results in cognitive impairments observed through different neurologic tests (Y-maze, Morris water maze, novel recognition test). Functional MRI studies showed a dysfunction in glucose metabolism in patient having Alzheimer disease and also in small subcortical structures in patients with Parkinson disease.89,90

Besides showing significantly more cognitive deficits, T1D and T2D patients display equally more behavioral alterations such as depression, related to their condition.4,10 In fact, depression is a risk factor for developing diabetes as glycemic control is affected by lifestyle (e.g. self-care, exercise, diet,
medication outlet) which is often neglected in the case of depression. Metabolic defects and neuropsychiatric diseases consequently appear to be linked.\textsuperscript{92} Through ATP generation, glucose is the main source of energy for the brain and a tight glucose regulation is required for a suitable brain homeostasis, as well as neurotransmitter biosynthesis.\textsuperscript{93} As an illustration, a significant increase in acetylcholinesterase activity was observed in the hippocampus of diabetic rats induced by high fat diet followed by STZ injection. These rats showed reduced glutamate levels in their hippocampus and increased GABA levels in their hippocampus and cortex compared with normal animals. They also display altered performance in various behavioral tests such as Morris water maze, open field and elevated plus maze. A prolonged uncontrolled hyperglycemia and impaired insulin function resulted in cognitive deficits and altered behaviors.\textsuperscript{94}

However, glucose is not only a nutrient, but also an input for neuronal circuits located in the hypothalamus (e.g. VMH, ARC, PVN) and containing pro-opiomelanocortin (POMC), melanin concentrating hormone (MCH), and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons.\textsuperscript{95-97} These neuronal populations are involved in energy storage/expenditure and food intake.\textsuperscript{98,99} Numerous study have proved that (1) mice lacking MCH are hypophagic and lean, (2) direct injection of NPY into the hypothalamus of rats stimulates food intake, (3) mice lacking the POMC-derived peptides become obese and present defective adrenal development, (4) activation of AgRP neurons in mice induced voracious feeding.\textsuperscript{100-104} Interestingly, it was recently demonstrated that the non-nutritive sweetener sucralose promoted food intake via a NPY-dependent mechanism, supporting a link between synthetic sweetener consumption and metabolic dysregulations.\textsuperscript{105} Consequently, disruption of such feeding neural networks could result in an increased risk to develop diabetes.

**Part 2: Zebrafish as an emerging model for studying the impact of diabetes on neurogenesis and brain remodeling**

In few years, zebrafish became a recognized model for studying adult neurogenesis and brain repair mechanisms. In contrast to mammals, the brain of adult zebrafish maintains a lot of neurogenic niches across the whole brain.\textsuperscript{21} Such a strong neurogenic capacity is due to the persistence of (a) radial glial cells, acting like neural stem cells, and of (b) further committed progenitors (neuroblasts).\textsuperscript{106} Teleost fish also display a strong capability for brain regeneration.\textsuperscript{19,107,108} Zebrafish is also a common model for investigating a wide variety of physiologic and physiopathological processes including metabolic syndrome and diabetes.\textsuperscript{109-113} T2D has been developed by immersing fish in water supplemented with D-glucose,\textsuperscript{109,111,114} and T1D has been set up by STZ intraperitoneal (ip) injection.\textsuperscript{109} Acute hyperglycemia can be also mimicked by intraperitoneal injection of D-glucose.\textsuperscript{112} Consequently, zebrafish appear as interesting models for investigating the role of metabolic disorders such as diabetes on the CNS.

The impact of hyperglycemia on the blood-brain and blood-retinal barriers has been assessed in zebrafish. In our experimental conditions, we recently demonstrated that acute hyperglycemia (2.5 g/kg of body weight) leads to impaired expression of genes involved in the establishment of blood-brain barrier (claudin 5a, z01a and 1b).\textsuperscript{112} In addition, Alvarez and colleagues also showed that the blood-retinal barrier is compromised in glucose-treated (110mM; 30 days) fish.\textsuperscript{115}

Recent data also implies hyperglycemia in the disruption of neurogenic processes as well as in memory process in zebrafish. Chronic hyperglycemia induced by putting fish in water supplemented with D-glucose (111mM, 14 days) impairs brain cell proliferation along the neurogenic niches.\textsuperscript{34} In the same line of evidences, mechanical injury of the zebrafish telencephalon under such chronic hyperglycemia conditions leads to impaired injury-induced stem cell proliferation at 7 days post-injury.\textsuperscript{34} Until now, the impact of acute and chronic hyperglycemia has not yet been assessed for newborn cell migration and cell survival under homeostatic and regenerative conditions. Last but not least, chronic hyperglycemia (111mM; 14 days) has been shown to impair memory in zebrafish through increased acetylcholinesterase activity.\textsuperscript{116}

Taken together, these data show that diabetes impairs blood-brain and -retinal barriers, constitutive and regenerative neurogenesis as well as cognitive functions in zebrafish, similar to what was shown in mammals. It consequently highlights the use of zebrafish as a model for investigating the impact of hyperglycemia on the CNS and for screening therapeutically molecules to restore impaired functions.
Conclusion

Most studies using different models of diabetes tend to show that diabetes impairs neurogenic processes including neural stem cell proliferation, neuronal differentiation and survival. Hyperglycemia is also a risk factor for stroke and a predictor of bad neurologic outcomes, impairing notably the injury-induced neurogenic process. In addition, diabetes is associated with morphological and functional changes of the CNS. In the ADNI cohort, T2D patients displayed a lower brain volume and a disturbed brain glucose metabolism compared with non-diabetic participants. Another study involving 614 patients with T2D has shown a significant association between the duration of diabetes and an increase in abnormal gray and white matters. Interestingly, diabetes is implied in cognitive impairment. Indeed, T1D patients exhibit mainly modest, but sometimes severe, cognitive impairments. In contrast, T2D patients display more consistently moderate cognitive impairments in verbal memory tasks and complex information processing. An increasing number of data and epidemiological studies also link diabetes and Alzheimer disease, T2D being associated with an almost 2-fold increased risk of dementia. By modifying the BBB physiology, diabetes/hyperglycemia could disturb the microenvironment of neural stem cell niches and impairs neural stem cell activity and newborn cell survival. Diabetes consequently disturbs brain functions and homeostasis leading to cognitive impairment and impaired feeding behavior reinforcing its deleterious impact through a vicious circle.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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