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REVIEW PAPER

Neuroactive Steroids and Sex-Dimorphic Nervous Damage Induced by Diabetes Mellitus

Silvia Giatti[1] · Silvia Diviccaro[1] · Roberto Cosimo Melcangi[1]

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Abstract
Diabetes mellitus is a metabolic disease where improper glycaemic control may induce severe complications in different organs. In this review, we will discuss alterations occurring in peripheral and central nervous system of patients with type 1 (i.e., insulin dependent diabetes mellitus,) or type 2 diabetes (i.e., non-insulin dependent diabetes mellitus), as well as related experimental models. A particular focus will be on the role exerted by neuroactive steroids (i.e., important regulators of nervous functions) in the nervous damage induced by diabetes. Indeed, the nervous levels of these molecules are affected by the pathology and, in agreement, their neuroprotective effects have been reported. Interestingly, the sex is another important variable. As discussed, nervous diabetic complications show sex dimorphic features in term of incidence, functional outcomes and neuroactive steroid levels. Therefore, these features represent an interesting background for possible sex-oriented therapies with neuroactive steroids aimed to counteract nervous damage observed in diabetic pathology.

Keywords Diabetic peripheral neuropathy · Diabetic encephalopathy · Sex difference · Myelin · Neuroprotection

Introduction

Patients with type 1 (i.e., insulin dependent diabetes mellitus) or type 2 diabetes (i.e., non-insulin dependent diabetes mellitus) have increased risk of developing a number of severe health problems, including damage in the central (CNS) and peripheral (PNS) nervous system. Here, we review some of the main consequences of diabetes mellitus in the human nervous system as well as in animal models with a particular focus on the role exerted by neuroactive steroids (i.e., important regulators of the nervous function) and sex.

Diabetic Peripheral Neuropathy

An important complication of the diabetes mellitus is represented by the damage in the PNS (i.e., diabetic peripheral neuropathy). As reported, this occurs in more than 50% of type 1 and type 2 diabetic patients (Zochodne 2007). In particular, functional and structural changes in peripheral nerves, such as alterations in nerve conduction velocity (NCV), axonal degeneration, paranodal demyelination and loss of myelinated fibers are reported in these patients (Sugimoto et al. 2000; Vinik et al. 2000). In addition, as shown in an experimental model of type 1 diabetes (e.g., rats raised diabetic by injection with streptozotocin, STZ), peripheral nerve alterations are represented by myelin invaginations in the axoplasm (infoldings) and myelin evaginations in the Schwann cell cytoplasm (outfoldings) as well as alterations in myelin compaction such as abnormally wide incisures and abnormal separation of myelin lamellae (Veiga et al. 2006). Important myelin components, such as proteins (i.e., myelin protein zero, P0, and peripheral myelin protein 22, PMP22) and lipids (i.e., phospholipids, fatty acids, and cholesterol content), are also strongly affected by diabetes mellitus (Leonelli et al. 2007; Cermenati et al. 2012).

Alteration in myelin structure may impair axonal physiology. Indeed, distal axons present a dying-back process due to impaired regeneration ability, sensory/motor abnormalities (e.g., decrease of Na^+, K^+-ATPase activity), and impaired nociceptive threshold linked to the loss of intraepidermal nerve fiber (IENF) density (Bianchi et al. 2004; Biessels et al. 1999; Lauria et al. 2005; Yagihashi 1997).

✉ Roberto Cosimo Melcangi
roberto.melcangi@unimi.it

[1] Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milano, Italy

This pathological picture appears to be largely due to hyperglycemia, that deregulates many metabolic pathways resulting in production of neurotoxic intermediates and reactive oxygen species (ROS) (Fernyhough 2015; Zychowska et al. 2013).

Moreover, hyperglycemia mediates phenotypic changes in mitochondrial biology affecting their function, biogenesis, and regenerative capacity (Fernyhough 2015). The outcome is the exhaustion of the ATP supply for energy consuming processes in neurons such as excitation, ion flux, plasticity, and axonal transport of organelles or cargoes, which in turn contribute to the distal axonopathy observed in diabetes mellitus (Fernyhough et al. 2010; Cashman and Hoke 2015).

Mitochondrial dysfunctions, such as a decrease in the respiratory chain complex IV, has been observed in IENF and subpapillary dermal fibers of diabetic patients, prior to significant fiber loss (Casanova-Molla et al. 2012). Reduced respiratory chain activity together with a downregulation of mitochondrial respiratory chain complexes I and IV expression have been also observed in dorsal root ganglia (DRG) of STZ-diabetic rats and db/db mice (i.e., an experimental model of type 2 diabetes), at the advanced stage of the disease (Chowdhury et al. 2010; Roy Chowdhury et al. 2012). In addition, in a mouse model of type 1 diabetes, prolonged hyperglycemia leads to accumulation of small fragmented mitochondria in DRG probably as a consequence of altered mitochondrial dynamics, such as fission and fusion and/or trafficking (Edwards et al. 2010; Vincent et al. 2010). Aberrant mitochondrial trafficking and dynamics can further deplete the distal nerve fiber of ATP supply for axonal transport. These events might be part of a vicious circle mechanism that ultimately leads to axonal degeneration.

Neuropathic pain is also observed in diabetic peripheral neuropathy. Indeed, the symptomatology could be ascribed to peripheral sensory nerve hyperexcitability (Chen and Levine 2001, 2003; Chen and Pan 2002) as well as increase of the release of glutamate associated with hyperactivity of the post-synaptic glutamate receptor (Tomiyama et al. 2005; Malcangio and Tomlinson 1998; Calcutt and Chaplan 1997). Neuropeptides and neuroinflammation are also included in the mechanisms responsible for painful neuropathy. For instance, in response to substance P, microglia and astrocytes secrete proinflammatory cytokines that contribute to the development and maintenance of central sensitization and pain by amplifying the noxious neurotransmission (Milligan and Watkins 2009; Watkins and Maier 2003).

Diabetic Encephalopathy

The association of diabetes mellitus with cognitive deficits and increased risk of dementia, stroke, cerebrovascular, and Alzheimer disease (AD), as well as psychiatric disorders it is now very clear (Biessels and Reijmer 2014; Gispen and Biessels 2000; Riederer et al. 2017; Rani et al. 2016; Baglietto-Vargas et al. 2016). In particular, a common feature of type 2 diabetes and AD seems to be brain insulin resistance, such as failure of brain cells to respond to insulin that results in impairments in synaptic, metabolic, and immune response functions (Baglietto-Vargas et al. 2016; Arnold et al. 2018; Rani et al. 2016). Moreover, accumulation of beta-amyloid and hyperphosphorylated tau (i.e., AD related proteins) in type 2 diabetes, not only induces neuronal degeneration, but it has also a role in pancreatic beta-cell dysfunction (Bharadwaj et al. 2017). In addition to this, dysregulation of glucose homeostasis and hypothalamic–pituitary–adrenal axis, obesity, hyperleptinemia, neuroinflammation, impaired neurotransmission, oxidative stress, apoptosis, and mitochondrial dysfunction may distrupt neuronal homeostasis causing diabetes-associated cognitive decline (Gaspar et al. 2016; Cardoso et al. 2017; Sadeghi et al. 2016; Riederer et al. 2017). Moreover, other mechanisms may be involved in diabetic encephalopathy. Indeed, swollen synaptic boutons and fragmentation of neurofilaments within the axons (Hernandez-Fonseca et al. 2009), swelling of axons and dendrites (Zhou et al. 2013), alterations of myelin membranes (Hernandez-Fonseca et al. 2009), and its components (i.e., lipids and proteins) (Pesaresi et al. 2010a; Kawashima et al. 2007; Cermenati et al. 2017) and impairment of axonal transport (Baptista et al. 2013) have been reported. Furthermore, an interaction between microglia and neurons has been also recently proposed. Indeed, neurons, in response to hyperglicemia, release factors involved in signalling pathways, such as CX3CL1, p38MAPK, purinergic, and CD200/CD200R, that potentially activate microglial cells (Liu et al. 2018).

Neurobehavioral decline has been demonstrated in experimental model of type 1 diabetes. For instance, STZ-treated rats showed a deficit in learning and memory as well as impairment of hippocampal long-term potentiation (Biessels et al. 1998, 1996). These features have been proposed to be related with pre- as well as post-synaptic changes in hippocampus (Kamal et al. 2006). In addition, STZ injection in CD1 mice induced cognitive decline mainly due to white matter abnormalities and atrophy (Toth et al. 2006).

Sex Dimorphic Features

Diabetic Peripheral Neuropathy

The incidence of damage induced by diabetes mellitus in the peripheral nervous system is higher in men (i.e., the ratio male/female is 2.9) (Basit et al. 2004; Booya et al. 2005). In addition, diabetic peripheral neuropathy develops earlier in men than in women (Aaberg et al. 2008). Muscle weakness

and atrophy (Kiziltan and Benbir 2008), as well as motor nerve conduction abnormalities and ulnar nerve involvement are also more frequently observed in males than in females (Kiziltan and Benbir 2008; Kiziltan et al. 2007). Accordingly, men express lower amplitudes and conduction velocities and longer latencies with respect to female patients (Albers et al. 1996). On the contrary, neuropathic pain and negative sensory symptoms are more frequent in females than in males (Kiziltan and Benbir 2008). Similar results have been obtained also in experimental models, such as STZ-treated rats (Joseph and Levine 2003). However, in the same experimental model other parameters, such as NCV, Na^+,K^+-ATPase activity, expression of myelin proteins, thermal sensitivity, and production of ROS were similarly affected in male and female rats (Pesaresi et al. 2011a). Interestingly, after 1 month of diabetes in STZ rat model, axonal transport and mitochondrial function were observed to be affected in a sex-dimorphic way (Pesaresi et al. 2018). Indeed, gene expression and axonal protein contents of kinesin family members involved in the axonal transport, such as KIF1A and KIF5B, and the axonal content of KIF5B and Myosin Va were affected in males but not in females. Interestingly, sex specific alteration of KIF1A might account for sexual dimorphism in pain and analgesia mentioned above (Kiziltan and Benbir 2008; Joseph and Levine 2003). Indeed, this motor protein has a role in mediating the signaling pathway responsible for sensory function in the PNS (Tanaka et al. 2016).

The expression of peroxisome proliferator-activated receptor gamma co-activator-1 alpha (PGC-1α, i.e., a transcriptional co-activator coordinating the expression of multiple mitochondrial proteins involved in mitochondrial biogenesis), respiratory chain complex IV (i.e., oxidative phosphorylation), ATP levels, and key regulators of mitochondrial fission/fusion (e.g., mitofusin 2 and dynamin-1-like protein) were also affected, after 1 month of diabetes, in male but not in female diabetic rats (Pesaresi et al. 2018). A possible hypothesis may be that the observed downregulation of PGC-1α in diabetic males is related with the decrease in the levels of the respiratory chain complex IV, which may secondarily result in ATP decline, contributing to impaired bioenergetics in neurons leading to neuronal injury. Moreover, these data, may suggest that mitochondrial respiratory chain from female rats is not affected by diabetes in an early stage of the disease. Indeed, female mitochondria have higher electron transport chain activity and ATP production (Guevara et al. 2011; Escames et al. 2013) and, as observed in the brain of young mice, females have higher NADH-linked respiration than males (Gaignard et al. 2015). Therefore, what reported in short-term diabetic model could be related to the sex differences in mitochondrial respiratory function.

A sex dimorphism has been also observed in diabetic peripheral neuropathy occurring in BTBR *ob*/*ob* mice (i.e., an experimental model of type 2 diabetes). As reported, even if the motor and sensory NCV deficits are similar in male and female animals, males exhibited greater IENF loss than females (O'Brien et al. 2016). These findings may be related with a more robust increase in metabolic perturbations (i.e., hypertriglyceridemia) observed in male animals (O'Brien et al. 2016; Hudkins et al. 2010).

Diabetic Encephalopathy

Damage induced by diabetes in CNS also shows sex dimorphic features. For instance, young subjects with type 1 diabetes, perform poorly in school compared to healthy classmates, showing reduced performance and intelligence quotient. This decline was only observed in diabetic boys, and not in girls, diagnosed before the age of six (Schoenle et al. 2002). In addition, as demonstrated in patients with type 2 diabetes a gender difference was also observed in hippocampal volume. Indeed, female patients have smaller hippocampal volumes (Hempel et al. 2012). Moreover, diabetic encephalopathy is associated with other neurological events (Jacobson et al. 2002; Biessels et al. 2002, 2008; Gispen and Biessels 2000; Kodl and Seaquist 2008) showing sex differences in term of incidence, progression and severity, such as cognitive deficits and increased risk of dementia, stroke, cerebrovascular disease, AD and psychiatric disorders, (e.g., depression and eating disorders) (Andersen et al. 1999; Fratiglioni et al. 1997; Farace and Alves 2000; Niemeier et al. 2007; Marcus et al. 2008; Simonds and Whiffen 2003; Kaye 2008; Policardo et al. 2015). Observations supporting a sex difference in diabetic encephalopathy have been also obtained in experimental models of type 1 and type 2 diabetes. For instance, as reported in STZ model, Na^+,K^+-ATPase in cerebellum shows different sex dimorphic features in acute and prolonged diabetes. Indeed, this enzyme, which has a critical role in the maintenance of intracellular sodium homeostasis, showed in acute diabetes (i.e., 8 days after STZ injection), a decrease of alpha 1 subunit in male but not in female rats. On the contrary, a long-term diabetes (i.e., 16 weeks) showed a decrease of this subunit exclusively in females (Kalocayova et al. 2017). As reported in the genetic model of type 2 diabetes (i.e., db/db mouse), experimental stroke (i.e., unilateral common carotid artery ligation combined with system hypoxia) shows, in male animals, a higher mortality and bigger infarction size (Vannucci et al. 2001). However, ischemic brain injury, when assessed in another experimental model of type 2 diabetes, presents a brain damage more marked in females than in males. Indeed, using KKAy mouse model, female animals showed a much larger ischemic area as well as cerebral NADPH oxidase

activity in comparison to what observed in male animals (Sakata et al. 2011).

Observations obtained in KKAy mice have also indicated that females, in comparison to male animals, showed impaired cognitive function, greater insulin resistance, lower expression of peroxisome proliferators-activated receptor gamma and higher superoxide production (Sakata et al. 2010).

As reported in a non-obese model that spontaneously develops type 2 diabetes early in life (i.e., Goto-Kakizaki rats), middle-aged females, in comparison to male animals, were less vulnerable to oxidative damage and less prone to the accumulation of AD-like neuropathological markers (Candeias et al. 2017).

Neuroactive Steroids in Diabetes Mellitus

Levels, Synthesis and Neuroprotective Effects

It is well known that steroid hormones (i.e., molecules produced by peripheral steroidogenic glands) can affect nervous function. On the other hand, a more recent concept is that also the nervous system is able to produce these compounds that, due to their functions and origin, are defined neurosteroids. Indeed, since the first identification of local steroid synthesis in nervous system by Baulieu and collaborators (Baulieu and Robel 1990), different research groups described, both in PNS and in CNS, the production of pregnenolone (PREG), progesterone (PROG), dehydroepiandrosterone (DHEA), testosterone (T) and 17beta-estradiol (17β-E) (Tsutsui 2012; Melcangi et al. 2008; Giatti et al. 2015). Moreover, the nervous system is also able to convert some of these compounds in metabolites that, thanks to their ability to bind with different receptors, may exert different functions when compared to their precursors. For example, the enzyme 5alpha-reductase (5α-R) converts PROG into dihydroprogesterone (DHP), which, in turn, may be further metabolized in tetrahydroprogesterone, also known as allopregnanolone (3α,5α-THP) or into isopregnanolone (3β,5α-THP) by the action of 3alpha- (3α-HSOR) or 3beta-hydroxysteroid oxidoreductase (3β-HSOR), respectively. Similarly, T may be converted, by the enzyme 5α-R, into dihydrotestosterone (DHT), and then, by 3α-HSOR or 3β-HSOR into 5alpha-androstane-3alpha,17beta-diol (3α-diol) or 5alpha-androstane-3beta,17beta-diol (3β-diol), respectively (Melcangi et al. 2008; Giatti et al. 2015). As stated above, these metabolic conversions highly affect the mechanism of action of these steroids. Indeed, while PROG and its 5α-reduced metabolite (i.e., DHP) are able to bind to the classical PROG receptor, 3α,5α- and 3β,5α-THP can exert their effects by the GABA-A receptor. In particular, while 3α,5α-THP activates this ionotropic receptor (Belelli and Lambert 2005; Lambert et al. 2003, 2009), its isomer (i.e., 3β,5α-THP) antagonizes the effect of 3α,5α-THP on it (Melcangi et al. 2008).

Also T metabolism has a deep impact on the mechanism of action of this neuroactive steroid. Indeed, T and DHT bind to the classical androgen receptor, but the further metabolites of DHT, 3α-diol and 3β-diol, may act by interaction with GABA-A receptor and ERβ, respectively (Handa et al. 2008; Melcangi et al. 2008). Moreover, T may be also converted by the enzyme aromatase (ARO) into 17β-E, that is able to interact with both isoforms of estrogen receptor (i.e., ERα and ERβ).

Steroids that are able to affect nervous function, irrespectively by their origin (i.e., from peripheral glands or nervous system), are defined as neuroactive steroids.

Several neurodegenerative and psychiatric disorders, including diabetes mellitus, affect the levels of neuroactive steroids (Melcangi et al. 2014, 2016). Indeed, type 1 diabetic patients and, more frequently type 2 diabetic patients, show low free T levels in plasma (van Dam et al. 2003; Giatti et al. 2018; Chandel et al. 2008; Liu et al. 2013). As reported, in an animal model of type 1 diabetes (i.e., STZ-rat), a decrease in PREG, PROG, DHP, T and 3α-diol levels was detected after 3 months of disease in plasma and cerebral cortex; in this brain area also a decrease in 3α,5α-THP, 3β,5α-THP and DHT levels was observed (Pesaresi et al. 2010b). Levels of neuroactive steroids are also affected in the sciatic nerve. However, in this case only a decrease in the levels of PREG, T, DHT and 3α-diol was observed (Pesaresi et al. 2010b).

Recently, it has been observed that 1 month of diabetes may already alter the cerebral levels of neuroactive steroids. For instance, it has been reported that even if only the levels of few steroids are decreased in plasma (e.g., 3β,5α-THP, T and 3α-diol) the situation in hippocampus shows a more dramatic picture. Indeed, reduced levels of PREG, PROG, 3α,5α-THP, T, DHT and 3α-diol, coupled to an increase in 3β,5α-THP levels, were observed in this brain area (Romano et al. 2017). Interestingly, the reduction in PREG, which is the first steroid produced in mitochondria from the precursor cholesterol, in the hippocampal structure but not in plasma, may suggest that neurosteroidogenic process is impaired by short-term diabetes. Further observations have supported this hypothesis. Indeed, proteins involved in this first step of steroidogenesis present a reduced gene expression in diabetic hippocampus. In particular, decreased levels of the steroidogenic acute regulatory protein, which is involved in the translocation of cholesterol into mitochondria, and of the enzyme cytochrome P450 side chain cleavage, that cuts cholesterol lateral chain to produce PREG, were observed. Interestingly, also alterations of cholesterol homeostasis and mitochondrial dysfunction were reported, further supporting impaired neurosteroidogenesis in this brain area (Romano et al. 2017). Interestingly, further recent observations obtained in cerebral cortex have indicated that an impaired

neurosteroidogenesis also occurred in this brain area but with subtle differences in comparison to what observed in the hippocampus (e.g., the expression of cytochrome P450 side chain cleavage was unmodified, a different effect on cholesterol homeostasis and a milder impact on mitochondrial compartment) (Romano et al. 2018). Thus, short-term diabetes has specific effects on neurosteroidogenesis depending on the brain areas considered (Romano et al. 2017, 2018).

As mentioned above diabetes mellitus shares some neuropathological hallmarks with AD (Takeda et al. 2011). In agreement, in this neurodegenerative disease has been reported impaired insulin and insulin-like growth factor pathways (Steen et al. 2005). Moreover, in AD patients (Marx et al. 2006) as well as in an animal model of the disease (i.e., 3xTg-AD mice) impaired levels of neuroactive steroids have been reported (Caruso et al. 2013). Collectively, these results may suggest that neuroactive steroid alteration could be consider as a common factor underpinning the cognitive deficits that are present both in AD and diabetes mellitus.

In agreement with the observed changes in neuroactive steroid levels induced by neurodegeneration (Melcangi et al. 2016, 2014), neuroprotective effects exerted by these molecules have been also reported in many experimental models of neurodegeneration (Giatti et al. 2015), including diabetes mellitus (Giatti et al. 2018). In particular, an important target of these neuroprotective effects is represented by the myelin compartment. For instance, PROG and its metabolite, DHP, are able to counteract the decreased expression of myelin proteins (i.e., P0 and PM22) (Leonelli et al. 2007) and the increase in the number of fibers with myelin infoldings (Veiga et al. 2006) observed in the sciatic nerve of STZ-rat. Similar effects has been also recently reproduced in an ex-vivo model of hyperglycemia (i.e., dorsal root ganglia cultures exposed to high levels of glucose) (Giatti et al. 2018). Not only PROG and its metabolites, but also androgens may exert neuroprotective effects. For instance, DHT was able to stimulate the low expression of P0 observed in the sciatic nerve of STZ-rat (Roglio et al. 2007).

Neuroactive steroids are also able to counteract the effects of diabetes on lipid components of the peripheral myelin. For instance, in STZ-model, DHP, by promoting fatty acid desaturation altered by diabetes, reduces myelin structural alterations in rat sciatic nerve (Mitro et al. 2014) and restores the lipid profile of myelin in rat cerebral cortex (Cermenati et al. 2017).

In addition, treatment in STZ model with neuroactive steroids exerts a variety of other protective effects. For instance, PROG treatment was able to counteract in brain, spinal cord and sciatic nerve, the increased expression of vascular endothelial growth factor (i.e., a marker of angiogenesis), interleukin-6 (i.e., a marker for inflammation), CD11, NG2, COX2 and matrix metalloproteinase-2 (i.e., markers of tissue injury) observed in diabetic animals (Atif et al. 2017). 3α,5α-THP improves NCV, thermal threshold and skin innervation density, while its precursor, DHP, in addition to these parameters, also improves alterations in Na^+,K^+-ATPase activity (Leonelli et al. 2007). Similar effects are also exerted by T derivatives (Roglio et al. 2007). For instance, 3α-diol, counteracts impairment of NCV, thermal sensitivity and skin innervation density while, its precursor DHT, in addition to these parameters, also improves Na^+,K^+-ATPase activity (Roglio et al. 2007). Moreover, DHEA prevents neuronal and vascular dysfunction (Yorek et al. 2002). Neuroactive steroids have also neuroprotective effects on neuropathic pain occurring in diabetes mellitus. For instance, in STZ model, DHT counteracts the effect of diabetes on mechanical nociceptive threshold while 3α-diol was effective on tactile allodynia (Calabrese et al. 2014). A PROG metabolite, such as 3α,5α-THP, also exerts protective effects. Indeed, in STZ model, this neuroactive steroid ameliorates diabetic-induced thermal hyperalgesia and prevent cell apoptosis in spinal cord (Afrazi et al. 2014).

Several clinical observations indicate that type 2 diabetes increases the risk of dementia and brain atrophy in older women (Mehlig et al. 2014; Moran et al. 2013; Carcaillon et al. 2014; Espeland et al. 2015b, a). However, the effects exerted by neuroactive steroids in experimental model of type 2 diabetes have been poorly considered so far. For instance, in the obese Zucker rats it has been reported that DHEA severely reduced daily food intake by promoting the increased release of serotonin, one of the feeding-inhibitory transmitter (Leibowitz 1987) from the hypothalamus (Abadie et al. 1993).

A therapeutic alternative to the treatment with neuroactive steroids might be the use of pharmacological tools able to increase steroidogenesis. Up to now two different molecules have been considered (i.e., activators of liver X receptor, LXR, and activators of translocator protein, TSPO). Indeed, activation of LXR, a nuclear receptor controlling cholesterol homeostasis (Cummins and Mangelsdorf 2006), by GW3965 or activation of TSPO, a key protein favoring cholesterol entrance into the mitochondria, by Ro5-4864 was able to increase the levels of neuroactive steroids in the sciatic nerve of STZ rat and to exert neuroprotective effects (Cermenati et al. 2010; Giatti et al. 2009). Interestingly, in the same experimental model, these two ligands also restore to control levels, the neuroactive steroids in spinal cord, in cerebellum and in cerebral cortex (Mitro et al. 2012). Between, these two therapeutic strategies, activation of LXR seems to be the most promising. Indeed, the treatment with GW3965, differently from Ro5-4864 treatment, did not induce significant changes in plasma levels of neuroactive steroids (Mitro et al. 2012). Thus, it may selectively increase the levels of these molecules in the nervous system

avoiding possible endocrine side effects due to increased plasma steroid levels.

Changes Depending on the Sex and Sex Specific Effects

As described above, sex is an important variable in nervous damage induced by diabetes mellitus. In agreement, also neuroactive steroid levels in PNS and CNS are controlled in a sex dimorphic way. This concept is true not only in healthy animals, but also in many neurodegenerative and psychiatric disorders, including diabetes mellitus (Melcangi et al. 2016). For instance, 3 months of diabetes in STZ-rats induced a decrease in the levels of PREG, T and its derivatives (i.e., DHT and 3α-diol) present in the male sciatic nerve, while the levels of PROG, 3α,5α-THP and 3β,5α-THP are decreased only in female animals (Pesaresi et al. 2010b). The levels of PROG are sex-dimorphic in the cerebellum with a decrease of its levels only in females. The CNS levels of DHP and its metabolites (i.e., 3α,5α-THP and 3β,5α-THP) are also impaired in a sex-different way. Thus, the levels of DHP and 3α,5α-THP in the cerebellum and spinal cord are, respectively, decreased only in males, while those of 3β,5α-THP levels were decreased only in the cerebellum of females (Pesaresi et al. 2010b). The levels of T and its metabolites (i.e., DHT and 3α-diol) levels are only decreased in spinal cord, cerebellum and cerebral cortex of male (Pesaresi et al. 2010b). Further observations indicate that also the expression of ARO is affected by long-term diabetes (i.e., after 3 months) in a sex-dimorphic way. Thus, the expression of this enzyme was increased both in sciatic nerve and in the hippocampus of female but not of male animals (Burul-Bozkurt et al. 2010).

Recent results have also indicated that short-term diabetes (i.e., after 1 month) in STZ model is already able to affect in a sex-dimorphic way the levels of neuroactive steroids present in rat sciatic nerve. As reported, an increase of 3α,5α-THP and a decrease of T and DHT occurred in males but not in females (Pesaresi et al. 2018).

Sex-dimorphic changes of neuroactive steroids have been also reported in an experimental model of type 2 diabetes. Indeed, data obtained in Goto-Kakizaki rats, showed that an increase of DHEA and T associated with a decrease of 17β-E occurred in female brain; decrease in the levels of 17β-E also occurred in female plasma. On the contrary, in male animals only an increase of T occurred in brain and that was associated with a decrease in the density of ERα (Candeias et al. 2017).

The finding that neuroactive steroids are affected in a sex-dimorphic way by diabetes may provide a possible background for the development of new sex-oriented therapies based on these molecules to be applied in diabetic peripheral neuropathy and/or diabetic encephalopathy. Up to now, DHEA has identified as a possible sex specific neuroprotective agent for diabetic peripheral neuropathy. Indeed, in female, but not in male STZ animals, castration was able to significantly counteract molecular and functional alterations observed in diabetic peripheral neuropathy (Pesaresi et al. 2011a). These neuroprotective effects were due to an increase in the levels of DHEA and its metabolites (i.e., T and DHT) directly in the sciatic nerve of female diabetic rats (Pesaresi et al. 2011a). In agreement, treatment with DHEA in intact diabetic animals was more effective in females than in males (Pesaresi et al. 2011b).

Sex specific neuroprotective effects have been observed in an experimental model of type 2 diabetes (i.e., KKAy mouse). In these animals a protective effect on the brain by 17β-E treatment has been ascertained. Indeed, female animals exhibit a more severe ischemic brain damage after stroke in comparison to male animals and 17β-E treatment induced an attenuation of oxidative stress specifically in the female brain (Sakata et al. 2011).

Conclusions

Diabetic peripheral neuropathy and diabetic encephalopathy are two neurological disorders often present in type 1 and type 2 diabetic patients. Accordingly, in addition to the well-known effects on peripheral sex steroid production, diabetes mellitus also impairs the levels of important regulators of the nervous function, such as the neuroactive steroids. As summarized in this review, observations obtained in experimental models have indicated that treatment with neuroactive steroids or with pharmacological tools (e.g., LXR or TSPO ligands) able to increase their levels may counteract many alterations observed in diabetic peripheral neuropathy and diabetic encephalopathy (i.e., in myelin compartment, neuronal parameters and neuropathic pain).

In this scenario, an important issue is represented by sex. Indeed, nervous damage induced by diabetes mellitus shows sex differences in term of incidence, functional outcomes and neuroactive steroid environment. Thus, these sex dimorphic features may provide a possible background to design sex-specific therapeutic intervention based on neuroactive steroid molecules.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have not conflict of interest for this manuscript.

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