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Dopaminergic Dysfunction in Experimental Hepatic Encephalopathy

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1. Introduction

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that appears as a consequence of acute or chronic liver dysfunction. Ammonia is considered central to its pathogenesis, but the factors contributing to the neurological dysfunction the disorder entails remain unclear (Butterworth et al., 2002). In humans with HE, it has been suggested that the basal ganglia may be selectively affected (Spahr et al., 2002), and lesions detected by magnetic resonance in the basal ganglia of such patients (Spahr et al., 2000; Burkhard et al., 2003) have been associated with movement disorders (Layrargues, 2001; Spahr et al., 2002; Weissenborn & Kolbe, 1998). The mechanisms by which liver failure leads to abnormal motor function are not clear, but the symptoms described in HE patients (Spahr et al., 2002) are similar to those of Parkinson's disease (PD).

In patients with chronic HE, the neurological symptoms resemble those observed in chronic hyperammonaemia in the rat resulting from portacaval anastomosis (PCA) - PCA is used as an experimental model of HE since it induces chronic hyperammonaemia (Audet & Butterworth, 1998; Bodega et al., 1991). Rats exposed to PCA show motor deficits (Cauli et al., 2006; Martin, 1986; Steindl et al., 1996) which might be associated with degeneration and/or dysfunction of the dopaminergic system. Since it is well known that motor deficits in PD are due to the dysfunction of the nigrostriatal system, the aim of this chapter is to analyse whether its dysfunction occurs in the PCA model of chronic HE, and to discuss what its consequences might be.

2. The nigrostriatal system

The nigrostriatal pathway projects from the substantia nigra (SN) to the basal ganglia and is involved in motor control (Smith and Bolam, 1990). The SN is the brain region in which the main dopaminergic (DAergic) pathway supplies dopamine (DA) to the striatum. The DAergic neurons of the midbrain have traditionally been described as those nerve cells positioned in the mesencephalon that possess the ability to synthesise, package, release, and reuptake the neurotransmitter dopamine. In the normal brain, DAergic midbrain neurons in the SN pars compacta (SNc) synthesise dopamine, which is immediately taken up and stored in synaptic vesicles. Under normal conditions, the efficient sequestration of

dopamine by these vesicles provides a major means of protecting DAergic neurons from the harmful effects of dopamine oxidation. Striatal delivery of DA by midbrain DAergic SNc neurons is vital for motor control. Dysfunctional DAergic neurotransmission between the SNc and the dorsal striatum causes several prominent movement disorders, such as that seen in PD. In patients with this disease, the DAergic projections to the striatum deteriorate, and the decline in DAergic modulation of the basal ganglia leads to muscle control problems (Gauthier & Sourkes, 1982).

Tyrosine hydroxylase (TH) is the rate-limiting enzyme in dopamine synthesis, making it a major marker of DAergic neurons. In the production of catecholamines, L-tyrosine is converted to L-dopamine by TH. TH expression is regulated by many factors, e.g., growth factors, hormones and ion-channels, which can induce changes in nigrostriatal DAergic neurotransmission. A positive relationship between the activity of adult SNc neurons and the expression of TH has recently been reported (Aumann et al., 2011).

There is increasing evidence of functional diversity as well as plasticity within the population of DAergic midbrain neurons; indeed, this diversity may extend to the molecular level (Korotkova et al., 2004). Further, DAergic midbrain neurons are not homogeneously affected by neurodegenerative diseases, but rather show differences in their relative vulnerability, especially with respect to cell death. The DAergic neurons in the SNc deteriorate selectively in PD and those that project to the dorsolateral striatum are substantially more vulnerable (Damier et al., 1999). Often no symptoms appear until approximately 60% of the DAergic cells in the SNc have died (Gaig & Tolosa, 2009).

To date, no studies have described the neurotoxic effects of hyperammonaemia on nigral DAergic cells *in vivo*, and it is unsure whether the down-regulation of TH expression leads to the disturbance of DAergic neurotransmission in chronic hyperammonaemia following PCA. Our group has shown that PCA leads to a reduction in the number of TH-immunoreactive neurons in the SN (Fig. 1), as well as causing a reduction in TH expression in the TH-positive neurons of this area. The loss of TH-positive neurons might be attributable to their sensitivity to high circulating ammonia concentrations, which are induced by PCA (Bodega et al., 1991).

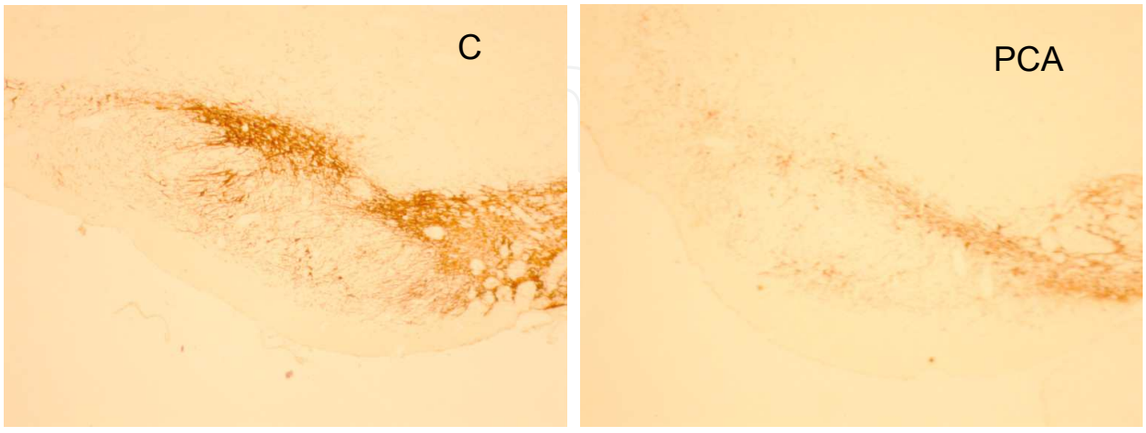

Fig. 1. TH immunoreactivity in the substantia nigra of control (C) and PCA-exposed rats (PCA). Note the reduction in TH expression in PCA rats, as well as in the number of TH+ neurons.

It is well known that ammonia plays an important role in the pathophysiology of HE. Certainly, an increase in the ammonia concentration can affect numerous cellular processes that might contribute towards the neurological deficits associated with the disease, and it has been proposed that the ammonia levels in blood correlate with the severity of HE symptoms (Ong et al., 2003). Since PCA leads to a reduction in TH immunoreactivity in the SN and the dorsal striatum, a specific susceptibility of nigral DAergic neurons to hyperammonaemic conditions during PCA exposure might be inferred. There is a possible diversity of response within the DAergic SNc population since functionally and biochemically distinct sub-populations of SNc DAergic neurons have been described (Hajos & Greenfield, 1993; Korotkova et al., 2004; Liss & Roeper, 2008). This phenomenon of differential vulnerability of DA neurons towards degeneration is well documented in PD; some of the DA cell groups in the midbrain are particularly affected by neurodegenerative process while others are relatively spared of its effects (Damier et al., 1999). Since a relationship between TH expression and activity in adult SNc neurons has been described (Aumann et al., 2011), it seems reasonable to conclude that an increase in ammonia levels in PCA and/or hyperammonaemia can lead to reduced TH expression in SNc cells, and that this might contribute towards the vulnerability of DAergic cells - and therefore to their reduced activity. In fact, the presence of acid-sensitive ion channels has been described in DAergic neurons, which are also sensitive to ammonium ions (Pidoplichko & Dani, 2006). Recently, it has been shown that ammonium chloride treatment reduces the number of TH-positive DAergic neurons in the medaka fish, causing the selective loss of DAergic neurons and the appearance of Lewy body-like inclusions (Matsui et al., 2010). Together, these observations suggest DAergic neurons to be particularly sensitive to increased levels of ammonia, as occurs following PCA.

There is very good evidence that the loss of TH-immunoreactivity in the SN is a good marker for the death of nigral DAergic neurons in neurodegenerative diseases. Although it is generally assumed that neuronal cell death is minimal in liver failure, recent studies have shown severe neuronal dysfunction and neuronal cell death to occur in end-stage liver failure (Butterworth, 2007). To date, no selective loss of DAergic neurons has been described in PCA, although, as mentioned above, a reduced number of TH-positive neurons are seen in PCA exposed rats.

In addition to the reduced number of TH-positive neurons in the SN, TH-positive nerve terminals within the striatum are significantly reduced in PCA-treated rats compared to controls; this might suggest dysfunctional neurotransmission. The smaller number of TH-positive neurons might in turn affect the innervation of the striatum, which agrees with the fact that TH staining in the striatum shows lower expression in PCA-exposed rats than in controls. These differences suggest an imbalance in the proper functioning of the striatum and might underlie the behavioural deficits observed in long-term PCA-exposed rats.

The presence of extrapyramidal signs and symptoms in patients with end-stage chronic liver failure might suggest dysfunctional DAergic neurotransmission between the SNc and the dorsal striatum (the nigrostriatal pathway). The striatal content of dopamine is reduced in encephalopathic animals after bile duct ligation, which is consistent with results observed in patients with cirrhosis (Galvez-Gastélum et al., 2011). This could be due to dopamine-accelerated metabolism and/or a reduction in TH.

2.1 Dopamine and glutamate interactions in the nigrostriatal system

There is evidence that the brain dopamine system is under glutamatergic regulatory influence. Nigral DAergic neurons possess glutamate receptors (Chatha et al., 2000; Testa et al., 1994) and receive glutamatergic input from the neurons of the subthalamic nucleus (Groenewegen & Berendse, 1990; Kita & Kitai, 1987). These DAergic neurons degenerate when exposed to excitotoxic glutamate (Alexi et al., 2000; Tapia et al., 1999). *In vitro* studies have shown that DAergic neurons are preferentially affected by glutamate toxicity. DAergic neurons exposed to glutamate for 24 h were more vulnerable than non-DAergic neurons exposed to chronic glutamate-induced toxicity (Izumi et al., 2009), leading to selective DAergic neuronal death.

The glutamatergic modulation of DA release in SN DAergic neurons appears to be associated with increased DA release in the striatum (Morari et al., 1998). The rat dorsal striatum receives DAergic projections from the SN and glutamatergic projections from the cortex. Glutamatergic receptors are located on DAergic terminals and dopamine receptors on glutamatergic presynaptic endings. This anatomic arrangement implies that dopamine and glutamate may act in concert to regulate the activity of striatal neurons (Kulagina et al., 2001). Through the activation of ionotropic glutamate receptors, glutamate regulates the basal extracellular dopamine concentration in the striatum (Borland & Michael, 2004; Kulagina et al., 2001). In contrast, the inhibitory role of DA in the modulation of glutamate release is well established and in the striatum DA acts via the activation of dopamine D2 receptors. It would seem that the overstimulation of glutamate receptors on nigral DAergic neurons may be involved in the progression of neurodegenerative diseases. It is known that the balance between glutamate and dopamine is disturbed when DAergic nigrostriatal neurons degenerate in the course of PD (Starr, 1995). However, it is not clear to what extent dopamine and glutamate interact with each other in hyperammonaemic situations. The densities of postsynaptic dopamine D2 receptors are reduced in the pallidum of HE patients (Mousseau et al., 1993) and it has recently been described that the binding site densities of dopamine receptors (D1 and D2) are down-regulated in the putamen (Palomero-Gallagher et al., 2006). These alterations of dopamine D2 receptor sites are indicative of DAergic synaptic dysfunction (Watanabe et al., 2008). This suggests that the nature of the dopamine-glutamate interaction varies depending on the receptor subtype involved and the experimental conditions employed.

Under hyperammonaemic conditions, high extracellular concentrations of glutamate can cause neurodegeneration by excessive stimulation of the post-synaptic glutamate receptors. Glutamate receptors are reduced in PCA-treated rats (Suárez et al., 1997). In addition, the increased extracellular brain concentrations of glutamate in experimental HE are due, in part, to the failure of astrocytic glutamate transporters (Knecht et al., 1997; Suárez et al., 2000). Their down-regulation has important consequences on the amount of extracellular glutamate since astrocytes are the brain cells that metabolise ammonia and glutamate via glutamine synthetase (GS). Thus, the activity of the enzyme glutamine synthetase, the glutamine/glutamate cycle and the brain's capacity to eliminate toxic substances, all influence the toxicity of increased ammonium levels.

3. Astrogliosis in the nigrostriatal system

In response to almost any kind of CNS injury, astrocytes change their appearance (at different times post-injury) and undergo a characteristic hypertrophy of their processes, a condition known as astrogliosis. One of the hallmarks of this phenomenon is the up-regulation of the intermediate filament protein glial fibrillary acidic protein (GFAP). Increased GFAP expression is also seen in neurodegenerative diseases (Eng & Ghirnikar, 1994; Johansson et al., 2007). Both astrogliosis and increased GFAP in the SN in neurodegenerative diseases are associated with the reduction of TH and the progressive degeneration of DAergic neurons (McGeer & McGeer, 2008). In experimental models of PD, DAergic cells show reduced TH immunoreactivity, whereas reactive astrocytes show increased GFAP reactivity (Gomide et al., 2005; Reinhard et al., 1988). It has recently been postulated that glial cells are responsible for the progression of PD since more astrocytes are affected over the course of the disease (Halliday & Stevens, 2011).

The importance of astrocytes in neurodegenerative diseases, particularly HE, is well accepted (Butterworth, 2003; Norenberg, 1998). As mentioned above, astrocytes metabolise ammonia and glutamate through GS (review in Suárez et al., 2002). The principal neuropathological finding in HE is modified astrocyte morphology, which has been used as a marker of HE. Changes in astrocytes include nuclear enlargement, chromatin peripheral margination and prominent nucleoli; these changes are found mainly in the basal ganglia of patients dying of the disease (Norenberg, 1981).

It is well known that astrocytes perform a number of important functions including the regulation of the extracellular concentration of neurotransmitters, the promotion of synapse formation, and the promotion of neuronal survival. GFAP expression in the brain has been studied in both experimental and human chronic liver failure, in which it is reported reduced or increased depending on the brain region in question (Norenberg, 1987; Sobel et al., 1981; Suárez et al., 1998). The basis for these regional brain differences remains unknown. Although it is not known precisely why basal ganglia have a high affinity for ammonia, astrocytes show increased GFAP immunoreactivity in the striatum during the prolonged elevation of ammonia following PCA (Suárez et al., 2009).

Interactions have been reported between DAergic neurons and mesencephalic astrocytes *in vitro*, and it has been postulated that mesencephalic astrocytes may exert a morphogenetic effect on DAergic neurons (Denis-Donini et al., 1984). We showed astrocyte activation in the nigrostriatal pathway, which parallels the PCA-induced loss of DAergic neurons and terminals after PCA. The normal function of astrocytes was compromised following PCA, as evidenced by the increased GFAP expression in the SN, which was accompanied by neuronal dysfunction. Also, astrocytes in the striatum of PCA-exposed rats expressed increased GFAP immunoreactivity compared to controls (Fig. 2). These data reinforce the results of neuropathologic and molecular studies which indicate that HE in both acute and chronic liver failure is primarily a disorder of astroglial cells, and add support to the idea that HE is a classic example of a primary gliopathy (Butterworth, 2010; Norenberg, 1987).

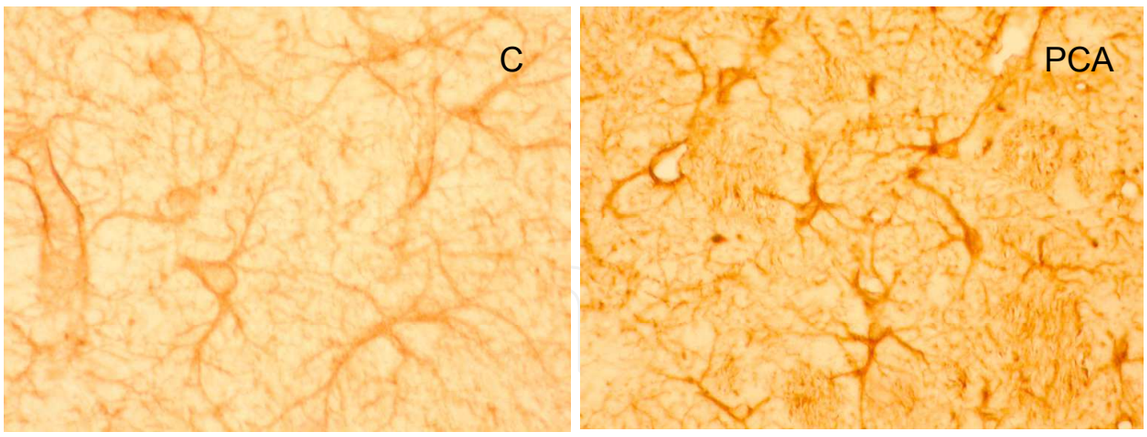

Fig. 2. GFAP immunoreactivity in the striatum of control (C) and PCA-exposed rats (PCA). Note the increase in GFAP expression in PCA rats.

4. α-synuclein in the nigrostriatal system

α-synuclein is a normally soluble, neuronal protein found in the synaptic terminals (Maroteaux & Sheller, 1991; Sidhu et al., 2004). There is growing evidence that it is an important regulator of DAergic transmission; certainly, it participates in the life cycle of dopamine from its synthesis through to its storage, release and reuptake (Al-Wandi et al., 2010; Chadchankar et al., 2011; Liu et al., 2008; Shidu et al., 2004; Yavich et al., 2004). However, very little is known about the mechanisms, signalling pathways or transcriptional elements that regulate α-synuclein expression. The overexpression of α-synuclein may, however, lead to degenerative processes (Goedert, 2001; Kirik et al., 2002; Lee & Trojanowski, 2006). It can inhibit TH expression (Lo Bianco et al., 2002; Niu et al., 2009; Yu et al., 2004) and TH activity (Luo et al., 2007; Peng et al., 2005; Perez et al., 2002) in DAergic cells, and impair dopamine release (Nemari et al., 2010; Pelkonen et al., 2010). Indeed, studies on transgenic animals and gene-transfected DAergic cells have shown that overexpression is accompanied by the degeneration and even death of these cells as well as the formation of α-synuclein-positive intracellular inclusions (Lo Bianco et al., 2002; Masliah et al., 2000; Xu et al., 2002; Yamada et al., 2004). In fact, the abnormal aggregation of α-synuclein is thought to cause neurodegeneration (Cookson, 2009; Dawson & Dawson, 2003; Ma et al., 2003; Tofaris & Spillantini, 2005). Once aggregation begins the normal physiological functions regulated by this protein can be severely compromised (Shidu et al., 2004). α-synuclein has been shown to form aggregates or insoluble fibrils finally leading to pathological deposits such as those seen in PD, in dementia with Lewy bodies (DLB), and in MSA (Duda et al., 2000; Goedert, 2001; Spillantini et al., 1998; Trojanowski & Lee, 2001; Wakabayashi et al., 2007). Experimental PD models show increased α-synuclein expression and aggregation as well as DAergic neuron degeneration/loss (Cannon & Greenamyre, 2010; Chesselet, 2008; Khodr et al., 2011), accompanied by motor deficit (Khodr et al., 2011).

The pathological involvement of α-synuclein in HE has never before been investigated. *In vitro* studies have shown that cultured astrocytes exposed to ammonia produce α-synuclein mRNA (Bodega et al., 2006). Our group studied the modifications of α-synuclein

conformation in PCA-treated rats and found that PCA clearly affected α-synuclein expression in the cerebellum (Suárez et al., 2010). It has been postulated that the structure of α-synuclein is extremely sensitive to its environment, and studies with the SH-SY5Y human DAergic cell line have shown that ammonium chloride treatment can induce the formation of α-synuclein inclusions (Matsui et al., 2010). This is in agreement with our other observations that indicate that chronically high ammonia levels in PCA-exposed rats induce α-synuclein expression in the nigrostriatal pathway. Although the precise mechanisms of the upregulation of α-synuclein are unknown, previous evidence (Lo Bianco et al., 2002; Gomide et al., 2005; Luo et al., 2007; Niu et al., 2009; Peng et al., 2005; Perez et al., 2002) suggests that the overexpression of α-synuclein in the nigrostriatal system may contribute to the reduced TH expression in PCA-exposed rats and to the degeneration of DAergic neurons. DAergic neurons might be more vulnerable to chronic hyperammonaemia in the presence of α-synuclein, supporting the idea of the latter's importance in the pathogenesis of HE. The vulnerability of SN neurons in which α-synuclein is overexpressed has been associated with the loss of DAergic neurons in a rat model of PD (Yamada et al., 2004).

α-synuclein has been reported to accumulate in the neuronal cytoplasm and processes in the brains of patients with PD and DLB (Polymeropoulos et al., 1997; Zarranz et al., 2004), and recently it has been shown that most aggregates are located at the presynapses in the form of very small deposits (Schulz-Schaeffer, 2010). This would impair synaptic plasticity in the basal ganglia prior to neurodegeneration (Kurz et al., 2010).

Although α-synuclein is not normally expressed by glial cells in the adult brain, α-synuclein-immunoreactive inclusions have been reported in these cells in patients with PD, DLB and MSA (Duda et al., 2000; Piao et al., 2000; Spillantini et al., 1998; Wakabayashi et al., 1998, 2000). Exposure to extracellular α-synuclein aggregates can lead to astroglial activation; studies *in vitro* have shown that α-synuclein treatment can directly cause GFAP reactivity in human astrocytes (Koob et al., 2010), and experimental *in vivo* studies with α-synuclein mutant mice have indicated that the number of GFAP-positive astrocytes increases in the brainstem (Gu et al., 2010).

Astrocytes, however, are not known to synthesize α-synuclein (Mori et al., 2002). It has been suggested that α-synuclein is released from neurons into the extracellular space (Borghi et al., 2000; Lee et al., 2005) and accumulates there – something seen in the brains of patients with PD (Lee, 2008). In PD, the altered α-synuclein molecule can, however, be taken up and accumulated by astrocytes (Braak et al., 2007; Lee et al., 2010), leading to the progression of the disease (Halliday & Stevens, 2011). In PCA-treated rats, the increase in α-synuclein expression is concomitant with the increase in GFAP expression in the striatum (Suárez et al., 2009). It is possible that astroglial activation is caused by increased α-synuclein production associated with the markedly elevated ammonia levels observed in PCA-treated animals.

5. Nitric oxide in the nigrostriatal system

Nitric oxide (NO) has been implicated in the pathogenesis of several CNS diseases. It is well known that increased extracellular glutamate leads to an increased inflow of Ca^{2+} into post-synaptic neurons, the activation of nitric oxide synthases (NOS), and the formation of NO.

Nitric oxide is a key modulator of neuronal activity in the dorsal striatum and is thought to play an important role in different complex processes, including the control of motor function (West et al., 2002). In the striatum, NOS, the enzyme involved in the synthesis of NO, has been selectively found in a scattered population of interneurons (Vincent & Kimura, 1992). The level of neuronal NOS (nNOS) is increased in neurodegenerative diseases in which disorders of the basal ganglia have been described (Aguilera et al., 2007; Pérez-Severiano et al., 2002). Increased NO (via nNOS activity) can be harmful to surrounding cells in neurodegenerative processes mediated by glutamate. Striatal nNOS-producing neurons are particularly vulnerable to glutamate (Calabresi et al., 2000; Mitchell et al., 1999); they receive asymmetric synapses from glutamatergic afferents (Vuillet et al., 1989) and express glutamate receptors (Kawaguchi, 1997), which play a primary role in stimulating nNOS activity. The glutamate receptor activation of nNOS-producing neurons induces NO formation in the striatum (Bogdanov & Wurtman, 1997) and, in turn, NO increases glutamate release (Trabace & Kendrick, 2000).

In addition to glutamatergic inputs, striatal nNOS-expressing interneurons are innervated by DAergic terminals (Fujiyama & Masuko, 1996; Hidaka & Totterdell, 2001). Striatal NOS interneurons express dopamine D1/5 receptors (Rivera et al., 2002), and dopamine D1 receptor activation stimulates striatal NO synthesis. In addition, the glutamatergic activation of the NMDA receptors stimulates nNOS activity and NO production (Garthwaite, 2008) in a manner likely to be modulated by reciprocal dopamine D1-NMDA glutamate receptor interactions; the latter play a critical role in regulating striatal nNOS interneuron activity (Hoque et al., 2010). Further, *in vitro* and *in vivo* studies have shown that NO modulates dopamine and glutamate release in the striatum (Bogdanov & Wurtman, 1997; Hanbauer et al., 1992; Lin et al., 1995; Sandor et al., 1995; Shibata et al., 1996). These findings indicate that interactions between striatal DAergic, glutamatergic, and nitrergic systems play a significant role in the regulation of striatal function (Hoque et al., 2010; West et al., 2002).

In recent years, it has been suggested that nitrosative stress is involved in the pathophysiological cascade in HE (Bemeur et al., 2010); nitrosative stress is potentially lethal to neurons and occurs in the brain in both acute and chronic liver failure (Larsen et al., 2001; Schliess et al., 2002). NOS activity is increased in the brains of portacaval shunted rats (Rao et al. 1995). The number of nNOS-positive neurons increases in the striatum of PCA-treated rats (Fig. 3), and the astrocytes of the striatum express nNOS as well as inducible NOS (iNOS) (Suárez et al., 2009). The induction of iNOS in astrocytes may contribute to neuronal damage in chronic neurodegenerative disorders since glial cells can synthesise large amounts of NO (Dawson & Dawson, 1998). Certainly, iNOS stimulates DAergic neurodegeneration in an animal model of PD (Liberatore et al., 1999). Thus, the induction of iNOS in reactive astrocytes may generate toxic levels of NO, contributing to the induction of neuronal damage associated with chronic hyperammonaemia in PCA-exposed rats/patients with HE.

The NO produced by activated astrocytes can be harmful to neurons since it reacts with superoxide to generate peroxynitrite (Catania, 2001), a molecule that contributes to cell death. Nitrotyrosine (NT) is a relatively stable marker for peroxynitrite production (Gow et al., 1996) and has been proposed a valuable indicator of pathological levels of NO and peroxynitrite (Beckman, 1996). When our group analysed nitrotyrosine expression in PCA-rats showing NT expression in the nigrostriatal pathway, a significant increase was

observed in NT immunoreactivity in some of the cell bodies in the SN. NT expression in the astroglial cells occurred in the upper part of the striatum and colocalised with GFAP (Suárez et al., 2009). Therefore, the DAergic system might be particularly susceptible to NO neurotoxicity, which may contribute to the dysfunction of DAergic neurons after PCA exposure.

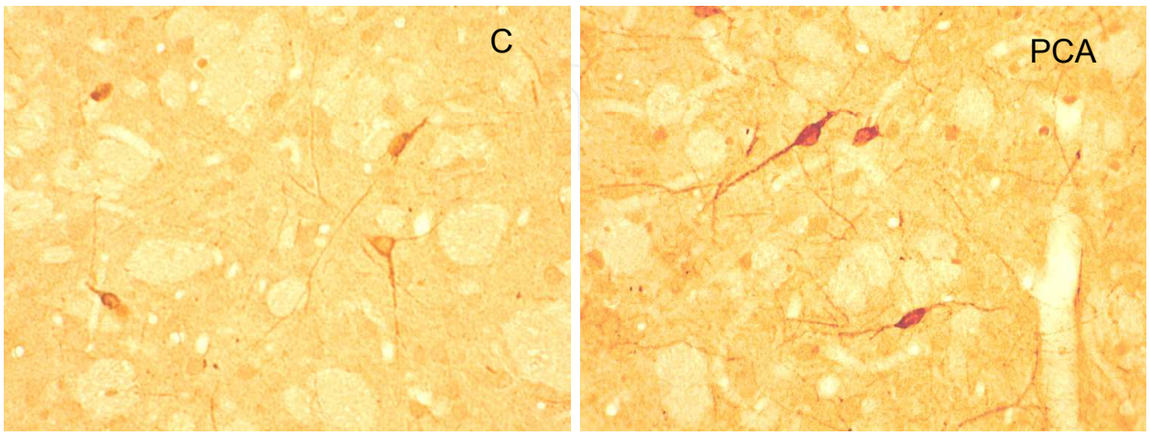

Fig. 3. nNOS immunoreactivity in the striatum. In controls (C), nNOS-immunoreactive neurons were homogeneously distributed in the striatum. In PCA exposed brains, the number of nNOS+ neurons was increased and immunolabeled neurons presented intensified immunoreactivity and thickened processes.

Although NO plays a crucial role in the integration of glutamate and DA transmission, the role of NO in modulating neurotransmitter interaction in the striatum following PCA and/or hyperammonaemia remains somewhat unclear. The involvement of NO in HE pathogenesis is supported by the observations that nNOS and iNOS expressions are upregulated in experimental HE. This evidence strongly supports the hypothesis that the excessive production of NO in the DAergic pathway contributes towards the neuronal dysfunction observed after PCA. Experimental evidence for cerebral nitrosative stress in experimental models of HE involving acute or chronic liver failure suggests it is involved in the pathophysiological cascade responsible for the disease (Bemeur et al., 2010). In patients with HE, NO levels correlate with the presence and severity of HE (Papadopoulos et al., 2010).

6. Conclusions

This work analyses whether chronic hyperammonaemia affects the activity of SN neurons and the regulation of TH expression following PCA. The neurones and astrocytes in the nigrostriatal system show different responses to PCA; neuronal TH decreases and astroglial GFAP increases in both the SN and the striatum. This may be related to different cellular susceptibilities to increased ammonia levels in both types of cell, which contributes to the progress of DAergic neurodegeneration. Since the DAergic neurons in the SN that project to the dorsolateral striatum are substantially more vulnerable to hyperammonaemic conditions, the dysfunction and/or loss of SN DAergic neurons following PCA might be attributed to the overexpression of α-synuclein as well as to the activation of nearby

astroglia. As in PD, dysfunctional DAergic neurotransmission between the SNc and the dorsal striatum (the nigrostriatal pathway) might be the cause of the movement disorders observed in PCA-exposed rats as well as in HE patients. Different elements can initiate a cascade of events in the cell body, inducing DAergic neuron degeneration and ultimately HE. These events may include α-synuclein overexpression, astroglial activation and nitrosative stress.

In summary, chronic moderate hyperammonaemia, similar to that seen in HE patients, induces DAergic dysfunction in DA neurons via a reduction in TH immunoreactivity, astroglial activation via an increase in GFAP, the overexpression of α-synuclein in DAergic cells, and increased nNOS, iNOS and NT expression in the nigrostriatal system. These changes underlie the harmful effects of chronic hyperammonaemia on motor and cognitive function.

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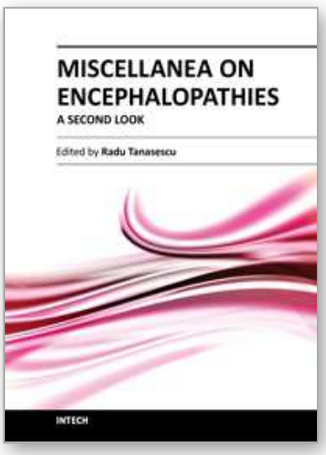

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