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The Role of the Neuropeptide Substance P in the Pathogenesis of Parkinson's Disease

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1. Introduction

Parkinson's disease (PD) was first described by James Parkinson in 1815 as "shaking palsy syndrome". Today, it is the second most common neurodegenerative disorder, with a lifetime risk of 1 in 45 of developing the debilitating disease and currently affecting 1% of the population over the age of 65 (G. Alves, et al., 2008).

PD is characterized by a slow and progressive loss of the pigmented dopaminergic neurons of the substantia nigra pars compacta (SNc). This loss of dopaminergic neurons is often accompanied by a loss of the noradrenergic pigmented neurons of the locus ceruleus, and in the later stages of the disease, both the cholinergic neurons of the nucleus basalis of Meynert and the serotoninergic neurons of the dorsal raphe nucleus may also degenerate (Marey-Semper, et al., 1995). In remaining DA neurons proteinaceous cytoplasmic inclusions called Lewy bodies (LBs) are found. They are filamentous in nature and predominantly contain alpha-synuclein and ubiquitin proteins (Bennett, 2005). Although LBs are also found in other diseases, such as diffuse Lewy body dementia and incidental Lewy body disease, they are considered to be the pathological hallmark of PD (Greenfields, 1992).

The dopaminergic neurons of the SNc are part of the basal ganglia (BG), an integral part of the brain that ensures smooth execution of movement. Accordingly motor symptoms such as resting tremor, bradykinesia, akinesia, rigidity and postural instability are most common. Degeneration of dopaminergic neurons is slow, with progressive loss of about 5% per year (Blum, et al., 2001), suggesting that a therapy could halt or slow down the progression of the disease, but to date no known neuroprotective therapy exists. Instead, current treatment involves managing patients' symptoms. Normally this treatment is L-DOPA, the precursor to DA. The rationale for this therapy is to restore DA levels to near normal and therefore restore normal function of the basal ganglia for a period of time. Unfortunately, following prolonged use many patients fail to maintain a good response and often experience "wearing off" effects, which is a reduction in the length of time that L-DOPA effectively alleviates symptoms (Krasnova, et al., 2000). Furthermore, motor complications like dyskinesia, or involuntary movements, occur in approximately 50-80% of PD patients who have been on L-DOPA for more than 5-10 years. These side effects are often more debilitating than the original motor deficits (Chen, et al., 2004).

In addition to the loss of dopaminergic neurons, there is also a reduction in the expression of the neuropeptide, substance P (SP), an important neurotransmitter in the BG, which is essential for proper execution of function. However, this loss of SP has been observed in

animal and human studies under conditions that represented end-stage PD. We suggest that this late loss of SP content is an event secondary to dopamine neuronal death. In the early phase of the disease, we propose that SP expression may actually be increased, and that this increase in SP may contribute to dopaminergic cell death through its effects on inflammatory processes and blood brain barrier (BBB) dysfunction. This review critically analyses the evidence that SP contributes to the pathogenesis of PD.

2. The basal ganglia

The BG is a group of nuclei located within the midbrain whose primary function is the smooth execution of movement. Apart from the substantia nigra, which also contains the pars reticulta (SNr), the BG nuclei include the striatum (caudate/putamen), the globus pallidus, both internal (GPi) and external segments (GPe), and the subthalamic nucleus (STN). Although the thalamus is not strictly part of the BG, it is fundamental to its function. In order for the BG to function correctly, it requires the two main signalling pathways, the direct and indirect pathway, to act in concert.

The direct signalling pathway involves an excitatory glutamatergic signal being sent from the cortex to striatal GABAergic projection neurons that project to the GPi and SNr resulting in inhibition of these nuclei. These nuclei also send inhibitory GABAergic signals, the inhibition of GPi/SNr neurons results in decreased inhibitory output to the thalamus. Consequently, the activity of thalamic neurons are increased causing excitatory glutamatergic signals to be sent back to the cortex, reinforcing cortical activity. The direct pathway therefore provides positive feedback for the cortex to allow movement (Silkis, 2001). Alternatively, the indirect pathway involves an excitatory signal being sent from the cortex to striatal inhibitory GABAergic neurons that project to the GPe, resulting in increased inhibition of the GPe neurons. As these neurons send an inhibitory GABAergic signal to the STN, the inhibition of these neurons leads to increased glutamatergic excitatory output from the STN. Subsequently, the STN sends excitatory signals to the inhibitory GPi and SNr neurons increasing their inhibitory output to the thalamus ensuring inhibition of the thalamic neurons and thus inhibition of cortical activity. The indirect pathway is therefore involved in negative feedback to the cortex and inhibition of the posture keeping the limb there (Sil'kis, 2002). These signalling pathways are kept in balance to ensure the almost simultaneous inhibition of the original position and initiation of the new required movement.

The direct and indirect signalling pathways are kept in balance by the dopaminergic input from the SNc to the striatum, known as the nigrostriatal pathway. The striatal GABAergic projection neurons express both DA receptors, namely D1 and D2 (Yelnik, 2002), although there are higher numbers of D1 receptors on the projections neurons involved in the direct pathway and D2 receptors for the indirect pathway (Aizman, et al., 2000). Through binding to D1 receptors, DA increases cAMP production, thereby reinforcing the activity of the direct pathway. In contrast, when DA binds to D2 receptors, cAMP production is reduced, creating a reversal of the activity of the nuclei within the indirect pathway and a decrease in its activity. As the indirect pathway is involved in negative feedback to the cortex, DA causes increased activity of the cortical neurons and reinforcement of cortical activity (van der Stelt and Di Marzo, 2003). Thus, the release of striatal DA within the nigrostriatal pathway of the BG allows fine-tuning of movement control and smooth execution of movement.

2.1 Basal ganglia function in Parkinson's disease

The initial loss of dopaminergic neurons in early PD does not decrease striatal DA activity due to pre- and post-synaptic compensatory responses of the dopaminergic system. These include upregulation of D1 and D2 dopamine receptor expression, which have a lower threshold for activation than normal, and an increase in activity of the surviving dopaminergic neurons (Deumens, et al., 2002). These compensatory mechanisms are able to sustain normal activity until approximately 50% of DA neurons and 80% of the total striatal DA is lost. Once this threshold level of striatal DA is reached, the direct and indirect signalling pathways become imbalanced producing a subsequent increase in the indirect signalling pathway and a decrease in the direct signalling pathway (Contreras-Vidal and Stelmach, 1996, Wardas, et al., 2003). Although these pathways also control the limbic system, the deficiency of DA in PD is heterogenous and DA is predominantly lost in the putamen area of the striatum, which is mainly involved in motor function of the BG. Therefore, PD is a hypokinetic disorder where the decreased activity of the direct pathway and increased activity of the indirect pathway results in a lack of movement as the common symptom (Silkis, 2001).

The BG does not only contain classical neurotransmitters such as glutamate, GABA and DA, but it also involves neuropeptides such as SP, neurokinin A (NKA) and the opioids enkephalin and dynorphin that act together for the fine-tuning of BG pathways (Graybiel, 1990, Hauber, 1998). These neurotransmitters can be segregated into the two pathways, with SP, NKA and dynorphin located in the GABAergic projection neurons of the direct pathway, whereas enkephalin is found within the striatal GABAergic projections neurons of the indirect pathway. Accordingly, in PD the change in activity of signalling pathways creates abnormal levels of these neurotransmitters. Changes in SP may be particularly important with respect to PD.

3. Substance P

Substance P was first discovered in 1934 by Gaddum and Schild, as the active principle in a stable dry powder. In 1936, Von Euler suggested the peptidergic nature of SP as its activity was stopped following digestion with trypsin, although later it was discovered that the degradation of SP was due to chymotrypsin as SP is trypsin-resistant (Leeman and Ferguson, 2000). Consequently it became part of the tachykinin family of which NKA and neurokinin B (NKB) are also members. Tachykinins are located in capsaicin-sensitive neurons, also known as primary sensory neurons, within the CNS, peripheral tissue and non-neuronal cells including endothelial cells and inflammatory cells (Hokfelt, et al., 2001). Within the brain there is a heterogeneous distribution of SP, with higher levels found in the grey matter. The highest concentration of SP is actually found within the SN (Ribeiro-da-Silva and Hokfelt, 2000), where SP immunoreactivity in the SNc is 25% higher than that in the SNr (Sutoo, et al., 1999). Also, within the BG SP expression is high within the internal segment of the globus pallidus.

Tachykinins share a common terminal sequence, Phe-X-Gly-Leu-Met-NH2, where X is Phe or Val (Harrison and Geppetti, 2001, Saria, 1999). This sequence is essential for their biological activity and thus there is a certain amount of cross reactivity amongst the tachykinin receptors and their ligands (Gerard, et al., 1991, Khawaja and Rogers, 1996). Each tachykinin has varying affinities for the tachykinin receptors, with SP having the greatest affinity for the tachykinin NK1 receptor (NK_1), NKA to NK_2 and NKB to NK_3 tachykinin receptors.

Tachykinin receptors have a rhodopsin-like membrane structure comprising of 7 hydrophobic transmembrane domains connected by extra- and intracellular loops and coupled to G-proteins (Harrison and Geppetti, 2001). NK_1 and NK_3 receptors are mainly found in the CNS, but are also present in peripheral tissues (Otsuka and Yoshioka, 1993). Throughout the brain, greatest NK_1 receptor immunoreactivity is found in the striatum, nucleus accumbens, hippocampus, hypothalamus and the raphe nuclei (Harrison and Geppetti, 2001), whereas NK_3 receptors are most abundant in the cortex and on glial cells (Yip and Chahl, 2000). In contrast, NK_2 receptors are widely distributed in the peripheral nervous system (PNS) especially in the smooth muscle of the respiratory, gastrointestinal and urinary tracts (Maggi, 1995).

SP binds to the hydrophobic ligand-binding pocket within the extracellular loops of the NK_1 receptor causing rapid internalisation of the ligand and its receptor (Harrison and Geppetti, 2001). Ligand binding stimulates the activity of adenylate cyclase and the conversion of adenosine triphosphate (ATP) to adenosine monophosphate, which inturn activates phospholipase C_B (PLC_B) (Saria, 1999). Activation of PLC_B results in an increased turnover of intracellular inositol 1,4,5-triphosphate and a subsequent elevation of intracellular calcium (Ca^{2+}) (Gerard, et al., 1991). The NK_1 receptor has a 5' untranslated region containing a cyclic AMP (cAMP) binding protein that responds to elevated levels of cAMP and Ca^{2+} by increasing gene transcription of SP (Saria, 1999). This creates a positive feedback loop for SP production and release. Conversely, SP may also block potassium channels causing membrane depolarisation and/or activate NK_1 autoreceptors to inhibit its own release (Harrison and Geppetti, 2001).

SP is synthesized from the preprotachykinin (PPT)-A gene, which also encodes NKA, neuropeptide K (NPK) and neuropeptide Y (NPY), the latter two being elongated versions of NKA (Hokfelt, et al., 2001). Alternative splicing of the PPT-A gene results in 3 distinct mRNAs: α-PPT-A, β-PPT-A and γ-PPT-A. Although all 3 PPT-A mRNAs encode for SP (Harrison and Geppetti, 2001), α-PPT-A mRNA is the main isoform of mRNA in the brain, whereas α- and γ-PPT-A mRNA are primarily expressed within the periphery (Severini, et al., 2002). NKB is encoded by the PPT-B gene and like PPT-A gene is conserved amongst species (Hoyle, 1998).

Synthesis of SP occurs within ribosomes in cell bodies of the dorsal root ganglia before it is packaged into large dense core vesicles with processing enzymes called convertases, which cleave at Lys-Arg, Arg-Arg or Arg-Lys bonds to release the active form of SP (Severini, et al., 2002). When stimulated, SP-containing vesicles undergo retrograde axonal transport to the terminal endings in both the CNS and PNS, where they undergo final enzymatic processing and post-translational enzymatic modifications such as C-terminal amidation (Hokfelt, et al., 2000). As previously mentioned, SP release is triggered by a small rise in intracellular Ca^{2+}, which will increase the pH within the vesicle resulting in alkinisation and release of SP by exocytosis (Otsuka and Yoshioka, 1993). NK_1 receptors are also synthesized and then anterogradely transported along axons to peripheral and perhaps central terminals. Thus, upon release SP can activate the postsynaptic NK_1 receptors (Malcangio and Bowery, 1999).

3.1 Substance P regulation of basal ganglia function

Substance P is important in regulating the function of the SN and BG (Bell, et al., 1998, Maubach, et al., 2001) where it acts as an excitatory neurotransmitter (Napier, et al., 1995). Like in other areas of the brain, SP is released in the BG due to an elevation in Ca^{2+} (Otsuka

and Yoshioka, 1993). Once released, it may bind to NK_1 receptors located on striatal interneurons to increase the firing rate and depolarise membrane potentials causing the release of other BG neurotransmitters such as GABA, glutamate and acetylcholine (Aosaki and Kawaguchi, 1996, Bailey, et al., 2004, Kemel, et al., 2002).

It is now known that NK_1 receptors are also located on 90% of DA neurons in the SNc (L-W. Chen, et al., 2004). However, earlier studies reported that there was an absence of NK_1 receptors in the SN and a mismatch between SP and NK_1 in this region (Humpel and Saria, 1993). This mismatch in the expression and binding of SP in the SN was subsequently thought to be due to the rapid internalisation of the SP/NK_1 complex following SP binding resulting in NK_1 being mainly located intracellularly (Levesque, et al., 2007). Accordingly, through binding to NK_1 receptors on dopaminergic neurons, SP can directly cause the release of DA within the striatum (Galarraga, et al., 1999, Orosz and Bennett, 1990, Reid, et al., 1990a, Reid, et al., 1990b). Moreover, as DA receptors are located on SP-containing striatal projection neurons, DA or DA agonists can potentiate SP release within the SN (Humpel and Saria, 1993). Therefore, SP and DA within the BG are modulated through a positive feedback mechanism. Accordingly, an injection of SP into the BG induces behavioural effects such as sniffing, rearing, grooming and increased motor activity in rats by promoting striatal DA release (Saria, 1999). However in PD, the loss of striatal DA interrupts this positive feedback mechanism and therefore a reduction in striatal SP gene transcription and SP protein content within the SN has been observed.

3.2 Substance P expression in Parkinson's disease

Post-mortem immunohistochemical studies have shown that there is a loss of SP content in the striatum and SN in PD brains (De Ceballos and Lopez-Lozano, 1999, Mauborgne, et al., 1983, Nisbet, et al., 1995, Sivam, 1991, Tenovuo, et al., 1984). Along with this loss of SP, there is also a significant deficit of NK_1 receptors in the putamen and GP of PD patients compared to aged matched controls (Fernandez, et al., 1994). Moreover, in a case of idiopathic PD, where the person died shortly after diagnosis from an unrelated cause, LBs were observed in surviving SP-containing neurons of the pedunculopontine tegmental nucleus, suggesting that these SP neurons were affected early in PD (Gai, et al., 1991).

Decrease in SP has also been extensively studied in the 6-OHDA rodent and MPTP non-human primate models of PD. Like in human PD, there is a decrease in SP content in the SN and striatum in these animal models (Bannon, et al., 1995, Schwarting and Huston, 1996). However, in a study by Orosz and Bennet in 1990 using the 6-OHDA rat model of PD, it was shown that although there was a decline in SP-immunoreactivity and SP mRNA in tissue levels of the SN, there was a rise in SP-immunoreactivity in the extracellular space of the SN. Subsequently, it was suggested that this rise was a compensatory mechanisms for the loss of intracellular SP (Orosz and Bennett, 1990). This was the first study to show an increase in extracellular SP during PD. Due to the tissue loss of SP, 6-OHDA animals were given replacement SP treatment into either the lateral ventricle or directly into the SN restoring striatal DA content (Krasnova, et al., 2000). Additionally, pre-treatment with SP assisted the recovery from a 6-OHDA lesion. The authors suggested that this was due to prolonged changes in SP release that helped to negate the tissue loss of SP caused by 6-OHDA (Nikolaus, et al., 1997). Thus basal levels of SP are fundamental for proper function.

In the non-human primate MPTP model of PD, which represents the model most similar to human PD, it was shown that there was a reduction in striatal SP gene expression and that

this deficiency in SP correlated with the degree of motor symptoms present (Wade and Schneider, 2001). However when primates were treated with L-DOPA the decrease in SP gene expression was reversed (Herrero, et al., 1995).

It is important to note that these studies have all been undertaken in post-mortem tissue or in models that replicate the end stage of the disease. Therefore, the SP changes observed may be a secondary effect due to the loss of DA input into the striatum and the activation of the direct pathway. Indeed, research in our laboratory has shown that SP may actually be increased in the early stages of PD. In nigrostriatal organotypic cell culture, 6-OHDA treatment caused an immediate and prolonged elevation in SP content that was significantly correlated with lactate dehydrogenase content, a marker of cell death. Furthermore, the 6-OHDA induced cell death was prevented by treatment with an NK_1 receptor antagonist (Thornton, et al., 2010).

Subsequent *in vivo* studies using the rodent striatal 6-OHDA model also measured SP content in the striatum and SN at days 3 and 7 following lesioning using an enzyme-linked immunosorbent assay (ELISA) method, which determines SP content from a standardized amount of protein (Figure 1). Despite the difference in SP content between the hemispheres in sham (control) animals, there was an apparent increase in SP content in the contralateral (left) and ipsilateral (right) striatum at both 3 and 7 days following 6-OHDA administration. However, SP content was not elevated within the SN until day 7 following 6-OHDA striatal lesions. Dopaminergic neuronal loss as assessed by tyrosine hydroxylase immunoreactivity was also not apparent at day 3 but had begun by day 7 and was significant by day 14 post-lesion. Nonetheless, a small loss of striatal DA terminals was observed by day 3. These results suggest that increased SP expression may contribute to the loss of dopaminergic terminals and neurons, however dopaminergic cell loss must also have initiated an increase in SP content within the SN. Furthermore, as the majority of dopaminergic degeneration occurs from day 7 to 14, the rise in SP content may act to potentiate this cell loss.

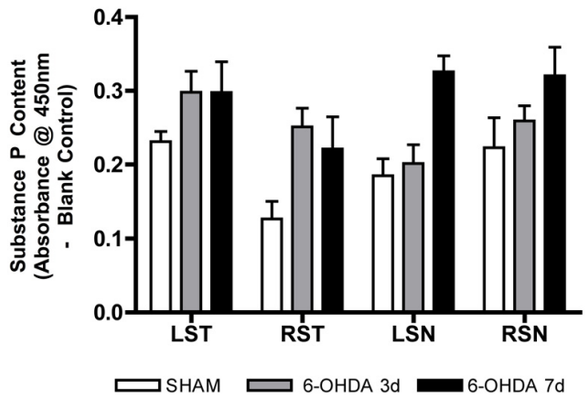

Fig. 1. Using an ELISA method, substance P content was semi-quantified within the striatum and substantia nigra following 6-OHDA intrastriatal injections. Results are displayed as mean+SEM (n=5/group).

Substance P has been associated with cell loss and functional deficits in other brain pathologies such as traumatic brain injury and stroke (Donkin, et al., 2009, R. J. Turner, et al., 2006). This detrimental effect of SP was credited to its ability to induce BBB breakdown

and the subsequent genesis of cerebral oedema (R. Turner and Vink, 2007). Although cerebral oedema does not occur in PD, a decrease in BBB integrity has recently been linked to dopaminergic cell loss and the progression of PD (Bartels, et al., 2008, Kortekaas, et al., 2005). Moreover, SP has been shown to play an integral role in the inflammatory response within both the peripheral and central nervous systems (R.V. Alves, et al., 1999). Recently, neuroinflammation has also received much interest for its potential role in DA degeneration and disease progression. We therefore hypothesize that SP may be involved in dopaminergic cell death in early PD by promoting neuroinflammation and BBB dysfunction.

4. Potential role for substance P in dopaminergic degeneration in PD

4.1 Inflammatory processes

Two of the main inflammatory cells within the brain are microglia and astrocytes. Resting microglia are important for maintaining cellular homeostasis, and once activated are involved in the removal of cellular debris (Mosley, et al., 2006, Rock and Peterson, 2006). However, activated microglia produce proinflammatory trophic factors and cytokines such as interleukin-1 (IL-1), IL-2, IL-6 and tumour necrosis factor-α (TNF-α), all of which are potentially cytotoxic (Blum, et al., 2001). Chronic activation of microglia and therefore prolonged expression of cytokines can be especially damaging to neurons. Indeed, activated microglia have been observed in post-mortem PD tissue and in experimental models long after the induction of PD (Depino, et al., 2003, Marinova-Mutafchieva, et al., 2009, McGeer and McGeer, 2008). Moreover, in human cases and animal models of PD a rise in these proinflammatory factors and cytokines has been demonstrated in the SN, striatum and cerebrospinal fluid (CSF) (Jenner and Olanow, 1998, Liu and Hong, 2003).

Activated microglia can also generate reactive oxygen species (ROS) such as hydrogen peroxide and superoxide (O_2^-) through activation of NADPH oxidase (Wu, et al., 2003). Under normal conditions this is important for the microglial role in brain immune surveillance and ability to kill foreign organisms that enter the brain. However, excessive production of ROS can result in oxidative damage to proteins, lipids and DNA, resulting in dopaminergic cell death (reviewed by (Mosley, et al., 2006)). In addition, microglia contain inducible NOS (iNOS), enabling the secretion of nitric oxide (NO). NO can react with ROS to form reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$), which is more stable than O^{2-} and can cross cell membranes and thus can be more damaging to cells than ROS. Indeed, by-products of oxidative damage are found in the SN of PD brains at post-mortem (Marsden and Olanow, 1998).

Usually, the SN contains large numbers of microglia compared to other areas of the brain. This is consistent with dopaminergic neurons already being in a state of oxidative stress due to the production of ROS during normal DA metabolism, making these neurons particularly vulnerable to insults (Berretta, et al., 2005, Liu and Hong, 2003, Olanow, et al., 2004). Moreover, oxidative damage by ROS and RNS is exacerbated in PD due to a deficiency of glutathione and superoxide dismutase, two of the main antioxidant enzymes that scavenge ROS, RNS and reduce H_2O_2 to its non-reactive state (Canals, et al., 2001).

Apart from causing damage to cellular structures, RNS and ROS may also cause mitochondrial dysfunction. In PD, a 30 to 40% decrease in complex I (NADH dehydrogenase) activity of the electron transport chain (ETC) is observed in mitochondria within the SN (Blum, et al., 2001, Squire, et al., 2003). The ETC, through oxidative phosphorylation, produces ATP, an important energy source for cell organelles, enzymes

and transport systems. Thus, mitochondrial dysfunction causes a bioenergetic deficit that leads to membrane depolarisation, disruption of Ca^{2+} homeostasis and further production of free radicals and ROS (Shults, 2004). Specifically, a reduction in ATP causes impairment of the mitochondrial membrane potential, and subsequent opening of the mitochondrial permeability transition pore. Pore opening stimulates the release of mitochondrial proteins, such as cytochrome c and apoptosis-inducing factor, that trigger apoptosis (Rego and Oliveira, 2003). Consistent with this, DA neurons are thought to die via apoptotic cell death cascades in PD (Olanow and Tatton, 1999).

With the loss of ATP production, there is also a consequential loss of the magnesium blockade of N-methyl-D-aspartate (NMDA) receptors, resulting in elevated levels of glutamate and NO (Q. Chen, et al., 1996). Dopaminergic neurons in the SN are rich in functional NMDA glutamate receptors and therefore affected by any change in glutamate levels (Olanow and Tatton, 1999). Glutamate, an excitatory amino acid, causes an increase in intracellular Ca^{2+} resulting in FR production, mitochondrial damage and activation of degradative enzymes. These enzymes, including proteases, endonucleases and phospholipases, result in degradation of plasma membranes, the cytoskeleton and nuclear material and subsequent cell death. This deleterious cascade of events, known as glutamate excitotoxicity, is also a major contributor to cell loss in PD (Beal, 1992).

Notably, production of ROS and RNS during inflammation and mitochondrial dysfunction are critically linked since activation of microglia can lead to mitochondrial dysfunction, and vice versa (Di Filippo, et al., 2010). The combined effects of these disease mechanisms in dopaminergic degeneration are further reinforced in experimental models of PD as the complex 1 inhibitor rotenone causes DA degeneration and microglial activation following either systemic or intracerebral administration (Gao, et al., 2003). Additionally, MPTP and 6-OHDA models also demonstrate both mitochondrial dysfunction and an exacerbated inflammatory response (Blum, et al., 2001, Chung, et al., 2010a).

Activation of microglia is not only a vicious cycle whereby the degeneration of neurons stimulates further microglial activation (Raivich, et al., 1999), it may also precede DA degeneration (Wojtera, et al., 2005). Activated microglia may prematurely phagocytose damaged DA neurons that may not have gone on to degenerate as evidence by the fact that phagocytotic CD68 positive microglia are observed prior to caspase-3 positive apoptotic DA neurons in the 6-OHDA model of PD (Marinova-Mutafchieva, et al., 2009).

The astrocytic response in PD has received less attention than microglia for its potential role in the pathogenesis of PD. Nevertheless, in all animal models of PD, there is an increase in glial fibrillary acidic protein immunoreactivity in both the striatum and SN, with the presence of reactive, hypertrophic astrocytes (Depino, et al., 2003, Takagi, et al., 2007). Furthermore, a 30% increase in these reactive astrocytes within the SN was seen in PD tissue at post-mortem (Wu, et al., 2003). However, activation of astrocytes may be both beneficial, through secretion of neurotrophic substances such as glial derived nerve factor and brain derived nerve factor, and detrimental through secretion of pro-inflammatory cytokines (Brahmachari, et al., 2006, Hirsch, 2000). These cytokines stimulate the activation of additional microglia or astrocytes, thereby further exacerbating the inflammatory response and tissue damage previously described for microglia (Chauhan, et al., 2008, Raivich, et al., 1999). In reactive astrocytes, myeloperoxidase produces RNS and damage to DA neurons (Choi, et al., 2005). However, the presence of astrocytes may be also beneficial as the density of astrocytes is low in the SNc compared to the ventral tegmental area, an area much less susceptible to DA damage in clinical and experimental models of PD. Nonetheless, reactive

astrocytes are thought to contribute to disease progression, although their exact role remains controversial (Chung, et al., 2010b).

The CNS immune response in PD can result in apoptosis of neurons by causing mitochondrial dysfunction and production of cytokines. An increase in cytokines, especially TNFα, can initiate apoptosis through binding at the tumour necrosis factor-α receptor 1 (TNFαR1), a known cell death receptor located on dopaminergic cell bodies in the SN (Mladenovic, et al., 2004).

4.1.1 Substance P and inflammation

Substance P and its NK_1 receptor have long been known to be important mediators of CNS inflammation (Harrison and Geppetti, 2001, Martin, et al., 1992). SP binding at NK_1 receptors expressed on microglia and astrocytes may directly result in the activation of these glial cells in the CNS (Mantyh, et al., 1989, Marriott, 2004). SP can also cause the indirect activation of astrocytes and microglia through its ability to promote cytokine and NO production, as they are able to modulate the activation of each other during the inflammatory response (Brahmachari, et al., 2006, Rodrigues, et al., 2001). Furthermore, pro-inflammatory cytokine production, for example, Il-1β can upregulate the expression of NK_1 receptors on glial cells (Guo, et al., 2004). Due to its ability to modulate the inflammatory response, SP may play a critical role in inflammation-induced damage. Indeed, in bacterial diseases of the CNS, SP/NK_1 interactions exacerbate the glial immune responses through both initiating and progressing the subsequent inflammation (Chauhan, et al., 2008).

In vitro studies also have increased our understanding of the signal transduction pathways induced by SP in microglia and astrocytes and resulting in pro-inflammatory cytokine production. SP can stimulate the secretion of TNF-α from microglia and astrocytes following treatment with the endotoxin lipopolysaccharide (LPS) (Luber-Narod, et al., 1994). The presence of NK_1 receptors could not be demonstrated on microglia, therefore suggesting that this effect was mediated via the SP induced release of IL-1 from astrocytes, causing TNF-α release from both glial cell populations. However, the authors concede that their methods may have not have detected NK_1 receptors. Subsequent studies have shown functional NK_1 receptors expressed on murine microglia *in vitro* (Rasley, et al., 2002). The production of pro-inflammatory cytokines from glial cells has been shown to occur following the translocation of NF-κβ. SP by binding to NK_1 activated the NF-κβ pathway stimulating cytokine production (Lieb, et al., 1997). Moreover, SP has also been shown to induce IL-6 production by activating p39 MAPK pathway (Fiebich, et al., 2000).

The role of inflammation in dopaminergic cell loss is further confirmed by the efficacy of anti-inflammatory agents in PD as they have been shown to slow down disease progression (Qian, et al., 2010). A meta-analysis of peer reviewed data between 1966 and 2008 indicated NSAIDs may be slightly protective in PD through their ability to halt the pro-inflammatory response, prevent cyclooxygenase activity and scavenge ROS and RNS (Samii, et al., 2009). Furthermore, Minocycline, a microglial inhibitor, has advanced to phase III clinical trials (Tansey and Goldberg, 2010). These promising results suggest that inhibiting SP signalling through antagonism of the NK_1 receptor may reduce the inflammatory response in PD, thus offering a novel therapeutic target to slow the progression of PD.

4.2 Blood brain barrier dysfunction

Recently, BBB dysfunction has been implicated in the pathophysiology of PD. In clinical PD, p-glycoprotein function, a marker of BBB integrity, was reduced suggesting a loss of barrier

integrity (Bartels, 2008; Kortekaas 2005). The authors suggested that this loss of barrier function may contribute to the progression of PD. In the SN the BBB is known to be weaker than in other brain regions and consequently is easily disrupted (Ionov, 2008). Notably, dopaminergic neurons demonstrate a greater vulnerability to barrier breakdown. In a study by Rite and collegues (2007), intracerebral injection of vascular endothelium growth factor (VEGF) into the SN and striatum caused BBB breakdown as assessed by fluorescently tagged FITC-albumin infiltration. This resulted in dopaminergic terminal degeneration and apoptotic markers, caspase-3 and TUNEL expression in DA neurons. In contrast, injection of VEGF into the hippocampus caused no apparent apoptosis of hippocampal neurons (Rite, et al., 2007).

A correlation between BBB breakdown, the astrocytic and microglial response and dopaminergic degeneration has been previously described (Tomas-Camardiel, et al., 2004). In experimental models of PD, barrier dysfunction has been reported in MPTP, 6-OHDA and rotenone models of PD (Carvey, et al., 2005, Chao, et al., 2009, Ravenstijn, et al., 2008) and has also been observed in our own studies (unpublished). Further evidence for the BBB and CNS inflammation contributing to dopaminergic cell death is that mesenchymal stem cell (MSC) transplantation was found to be protective to DA neurons in the MPTP model of PD (Chao, et al., 2009). MSC transplantation reduced microglial activation and restored BBB function as reflected in reduced FITC-labelled albumin leakage, and returned expression of tight junction proteins, claudin 1 and 5 expression back to basal levels. The authors attributed this beneficial effect of MSCs expression of TGF-β1, which has an anti-inflammatory effect.

BBB dysfunction may also result in damage to DA neurons by allowing the influx of peripheral immune cells, such as blood borne macrophages, T-lymphocytes and leukocytes into the brain (Hunot, et al., 1999, Kortekaas, et al., 2005). Similar to CNS immune cells, peripheral immune cells secrete cytokines following the translocation of transcription factor NF-κβ. Accordingly, PD patients challenged with LPS had significantly exacerbated release of cytokines / chemokines from peripheral borne macrophage cells as compared to healthy controls (Reale, et al., 2009). Blood inflammatory cells such as neutrophils may also infiltrate through the disrupted BBB and activate microglia. Indeed, increased neutrophil infiltration, greater BBB permeability and decreased astrocyte numbers in SNc are thought to contribute to selective DA degeneration (Ji, et al., 2008). Furthermore, a study by Brochard and colleagues has shown that peripheral immune cells such as CD4+ T leukocytes are involved in MPTP induced cell death in mice while CD4+ null mice have reduced DA degeneration (Brochard, et al., 2009).

Thus, the infiltration and production of pro-inflammatory cytokines by peripheral cells can activate resident brain immune cells such as microglia. Therefore, not only do peripheral immune cells directly injure dopaminergic neurons, they can also indirectly activate microglia and astrocytes to further exacerbate inflammatory and cell death cascades. These results suggest that peripheral cytokine production and infiltration across the BBB may contribute to PD pathogenesis.

4.2.1 Substance P and blood brain barrier dysfunction

Along with its known role in modulating the peripheral immune response, SP is an important regulator of BBB integrity and can potentiate barrier breakdown through neurogenic inflammation. Neurogenic inflammation is a neurally elicited local

inflammatory response characterised by vasodilation, protein extravasation and tissue swelling, which can be induced by certain types of injury or infection (Vink, et al., 2003). It is caused by a release of calcitonin-gene related peptide (CGRP) and SP from primary sensory nerve fibers surrounding blood vessels with subsequent activation of NK_1 receptors on endothelial cells (Lever, et al., 2003). CGRP, the most potent vasodilator, increases blood flow, bringing cytokines and inflammatory mediators to the area (Woie, et al., 1993), whereas SP binding to NK_1 receptors increases vessel permeability, leading to plasma extravasation and BBB breakdown (Hokfelt, et al., 2001). Neurogenic inflammation has been well described in the periphery but has also recently been reported to occur in the CNS (Nimmo, et al., 2004, R. Turner and Vink, 2007).

Another mechanism whereby SP may affect BBB permeability is through histamine. SP instigates the release of histamine from mast cells, to further increase vessel permeability and extravasation (R.V. Alves, et al., 1999). Thus, SP plays a central role in mediating extravascular migration of inflammatory cells into inflamed tissue (Harrison and Geppetti, 2001). Interestingly in PD, patients demonstrate elevated plasma histamine levels (Coelho, et al., 1991) and intranigral injection of histamine results in DA cell death and glial cell activation (Vizuete, et al., 2000).

5. Conclusion

We conclude that SP may be involved in the pathogenesis of PD, particularly in relation to inflammation and BBB breakdown. We suggest that the reported loss of SP expression in PD may be a secondary effect due to the decrease in striatal dopamine and therefore the loss of the SP/dopaminergic positive feedback mechanism. In contrast, SP may actually be increased within the BG *early* in PD and induce nigral BBB breakdown through neurogenic inflammation, as well as contribute to local inflammatory responses. Therefore, treatment with a NK_1 receptor antagonist may be a novel neuroprotective agent to slow the progression of PD.

6. References

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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

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