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Is Parkinson's disease an autoimmune disorder of endogenous vasoactive neuropeptides?

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Summary Parkinson's disease (PD) is a motor disease including disorders of mobility, fine tremor, rigidity and posture caused by a relentless deterioration of dopaminergic cells in the substantia nigra (SN). Disorders of affect and a range of other symptoms including fatigue, cognitive dysfunction and mental confusion, sleep disorder and addictions are also seen as other CNS sites are also affected. Idiopathic and genetic causes together with inflammatory and degenerative disorders of ageing have been postulated as contributing to PD.

Autoimmunity affecting certain vasoactive neuropeptides (VNs) has been postulated as contributing to certain fatigue-related conditions in humans and may be consistent with compromise of receptors associated with VNs and including receptors for vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP).

Pro-inflammatory responses are seen in PD patients consistent with apoptotic neurodegeneration. Involvement of the Th1 directed cytokine interferon-gamma has been demonstrated and Th2 directed cytokines such as IL-10 protect against inflammation-mediated degeneration of dopaminergic neurons in the SN. Nitric-oxide dysregulation is also postulated in PD by fostering dopamine depletion via nitric-oxide synthase (iNOS).

Both PACAP and VIP have neuroprotective effects in PD models by inhibiting the production of inflammatory mediators. PACAP specifically protects against the neurotoxicity induced by rotenone as well as protecting against oxidative stress-induced apoptosis. These findings suggest that a defect in VN function may act adversely on SN cells and hence contribute to a clinical presentation consistent with PD. The conclusion drawn from these findings is that PD may be an autoimmune disorder of VNs, specifically PACAP and VIP. Possibly unusual or anatomically specific receptors for these VNs may be involved. If proven, this hypothesis would have significant implications for immunological and pharmacological treatment and prevention of PD.

Introduction

Autoimmunity affecting vasoactive neuropeptides (VNs) has been postulated as contributing to certain fatigue-related conditions in humans [1]. This hypothesis was suggested to account for the multi-faceted and confusing symptomatology of some fatigue-related conditions e.g. chronic fatigue-syndrome/myalgic encephalomyelitis (CFS/ME) and fibromyalgia (FM). The constellation of symptoms associated with these conditions is compatible with compromise of receptors associated with VNs and

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include the receptors for vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP). These receptors are class II G protein-coupled receptors (GPCRs) which couple primarily to the adenylate cyclase (AC)-cyclic AMP pathway [2]. As VNs activate AC they have a key role in converting ATP to cyclic AMP (cAMP), hence setting balance levels for ATP and cAMP. Importantly ATP is critical for cell survival and cAMP has a central role in neurological metabolism including influencing blood—brain barrier permeability, coordination of neuroregulatory pathways, and protecting against neuronal apoptosis. Importantly for therapeutic contexts cAMP effects are maintained by phosphodiesterase inhibitors.

Parkinson's disease (PD) is a serious motor disease including disorders of mobility, fine tremor, rigidity and posture caused by a relentless deterioration of dopaminergic cells in the substantia nigra (SN) [3]. However it also includes disorders of affect and a range of other symptoms including fatigue, cognitive dysfunction and mental confusion, sleep disorder and addictions suggesting pathology of frontal lobe and other CNS sites. Idiopathic and genetic causes together with inflammatory and degenerative disorders of ageing have been postulated as contributing to PD [4].

Autoimmunity and apoptosis in Parkinsons's disease

Autoimmunity has been suggested in PD [5] including humoral immunity [6]. Experimental autoimmune nigral damage in guinea pigs causes degeneration of dopaminergic neurons suggesting an autoimmune process [7]. Pro-inflammatory responses are seen along with decreased expression of neurotrophins in nigrostriatal neurons and cerebrospinal fluid (CSF) of PD patients consistent with apoptotic neurodegeneration [8]. Involvement of the Th1 directed cytokine interferon-gamma has been demonstrated [9]. Moreover Th2 directed cytokines such as IL-10 protect against inflammation-mediated degeneration of dopaminergic neurons in the SN [10]. Nitric-oxide dysregulation is also postulated in PD by fostering dopamine depletion via inducible nitric-oxide synthase (iNOS) [11].

Interestingly these inflammatory and apoptotic findings are not confined to the CNS. Apoptotic markers have been found in lymphocytes of PD patients [12] which might suggest a common pathomechanism involving apoptotic pathways and receptors expressed outside the CNS. Moreover mitochondrial survival is largely determined by cytochrome c and the Bcl-2 family of proteins which may either facilitate or oppose apoptosis. Other apoptotic pathway agents include certain caspases. Apoptosis involving both neurons and microglia may contribute to PD neuronal loss [13] and mitochondrial factors appear to play a key role [14].

Animal models developed to simulate PD in rats include application of the natural pesticide rotenone, which targets the SN through toxicity associated with calpain and caspase-3 upregulation with neuronal death accompanied by astrogliosis and microgliosis [15]. However these models may not entirely represent the neurodegenerative condition of PD [16] and may reflect changes only in rats and not mice [17]. Nevertheless significant changes in tyrosine hydroxylase-positive neurons can arise from relatively short duration, low dose exposures of rats to rotenone [18].

Loss of SN cells is thus believed to be through dysregulated apoptotic mechanisms involving Bcl-2 and p53 pathways. In humans, Bcl-x(L), an anti-apoptotic member of the Bcl-2 family, is up-regulated in PD [19] possibly suggesting effort to counter-apoptotic events. Similarly p53 inhibitors preserve dopamine neurons and motor function in experimental parkinsonism [20]. Activation of apoptotic JNK pathways in PD models is also described [21]. PACAP has been shown to oppose-apoptotic JNK/SAPK/p38 pathways in hippocampal cells [22]. PACAP also regulates iNOS expression in macrophages [23] and microglia [24]. Hence compromise of PACAP or one of its receptor sub-types within the PAC1R family could have a direct link to these apoptotic findings in a range of tissue cells.

Is Parkinson's disease linked to vasoactive neuropeptides?

Receptors for VNs exhibit a number of specific subtypes which continue to be discovered and mapped. It is possible that autoimmunity may affect different sub-types in different anatomical regions. Thus it may be possible that VN receptor sub-types specific for the SN may be involved. PACAP activates receptors of PAC1R, VPAC1R and VPAC2R families, and PACAP has been identified widely in the brain including the SN as well as in other organs and blood cells [25]. PACAP has been shown to be effective in treatment in rat models of PD [26]. Both PACAP and VIP have neuroprotective effects in PD models by inhibiting the production of inflammatory mediators [27]. PACAP specifically protects against the neurotoxicity induced by

rotenone [28] as well as protecting against oxidative stress-induced apoptosis [29].

In a murine model for PD, Delgado and Ganea [30] note that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) activates microglia and promotes dopaminergic neuronal loss. These pathologies are significantly decreased by VIP thus suggesting that VIP may be useful in treatment of neuropathological conditions such as PD. Turning this evidence around, these findings might suggest that a defect in specific VN function could act adversely on SN cells and, perhaps in concert with other environmental factors, contribute to a clinical presentation consistent with PD. This would have significant implications for immunological [31] and pharmacological [32] treatment and prevention of PD possibly including anti-idiotypic antibodies and phosphodiesterase inhibitors.

Conclusion

Autoimmunity has been postulated as being implicated in PD although no definitive pathway has been identified to date. The premise adopted in this paper is that PD-inflammatory and apoptotic pathways may be instigated by VN autoimmunity. Pathways for ATP and cAMP control would conceivably be deregulated and this outcome would be consistent with VN failure. The conclusion drawn from these findings is that PD may be an autoimmune disorder of VNs such as VIP and PACAP. Possibly unusual or anatomically specific receptors for VIP and PACAP may be involved. If proven, this hypothesis would have significant implications for treatment and prevention of PD.

References

[1] Staines DR. Postulated vasoactive neuropeptide autoimmunity in fatigue-related conditions: a brief review and hypothesis. Clin Devel Immunol 2006;13(1):25—39.

[2] Martin B, Lopez de Maturana R, Brenneman R, Walent T, Mattson MP, Maudsley S. Class II G protein-coupled receptors and their ligands in neuronal function and protection. Neuromol Med 2005;7(1—2):3—36.

[3] Ferreri F, Agbokou C, Gauthier S. Recognition and management of neuropsychiatric complications in Parkinson's disease. CMAJ 2006;175(12):1545—52.

[4] McGeer PL, McGeer EG. Inflammation and the degenerative diseases of aging. Ann NY Acad Sci 2004;1035:104—16.

[5] Abramsky O, Litvin Y. Autoimmune response to dopamine-receptor as a possible mechanism in the pathogenesis of Parkinson's disease and schizophrenia. Perspect Biol Med 1978;22(1):104—14.

[6] Orr CF, Rowe DB, Mizuno Y, Mori H, Halliday GM. A possible role for humoral immunity in the pathogenesis of Parkinson's disease. Brain 2005;128(part 11):2665—74.

[7] Le WD, Engelhardt J, Xie WJ, Schneider L, Smith RG, Appel SH. Experimental autoimmune nigral damage in guinea pigs. J Neuroimmunol 1995;57(1—2):45—53.

[8] Nagatsu T, Mogi M, Ichinose H, Togari A. Changes in cytokines and neurotrophins in Parkinson's disease. J Neural Transm Suppl 2000;60:277—90.

[9] Mount MP, Lira A, Grimes D, Smith PD, Faucher S, Slack R, et al. Involvement of interferon-gamma in microglial-mediated loss of dopaminergic neurons. J Neurosci 2007;27(12):3328—37.

[10] Arimoto T, Choi DY, Lu X, Liu M, Nguyen XV, Zheng N, et al. Interleukin-10 protects against inflammation-mediated degeneration of dopaminergic neurons in substantia nigra. Neurobiol. Aging, in press.

[11] Blandini F, Cosentino M, Mangiagalli A, Marino F, Samuele A, Rasini E, et al. Modifications of apoptosis-related protein levels in lymphocytes of patients with Parkinson's disease. The effect of dopaminergic treatment. J Neural Transm 2004;111(8):1017—30.

[12] Tatton WG, Chalmers-Redman R, Brown D, Tatton N. Apoptosis in Parkinson's disease: signals for neuronal degradation. Ann Neurol 2003;53(Suppl 3):S61—70.

[13] Kannan K, Jain SK. Oxidative stress and apoptosis. Pathophysiology 2000;7(3):153—63.

[14] Ebadi M, Sharma SK. Peroxynitrite and mitochondrial dysfunction in the pathogenesis of Parkinson's disease. Antioxid Redox Signal 2003;5(3):319—35.

[15] Samantaray S, Knaryan VH, Guyton MK, Matzelle DD, Ray SK, Banik NL. The parkinsonian neurotoxin rotenone activates calpain and caspase-3 leading to motoneuron degeneration in spinal cord of Lewis rats. Neuroscience 2007;146(2):741—55.

[16] Hoglinger GU, Oertal WH, Hirsch EC. The rotenone model of parkinsonism—the five years inspection. J Neural Transm Suppl 2006(70):269—72.

[17] Richter F, Hamann M, Richter A. Chronic rotenone treatment induces behavioural effects but no pathological signs of parkinsonism in mice. J Neurosci Res 2007;85(3):681—91.

[18] Luo C, Rajput AH, Akhtar S, Rajput A. Alpha-synuclein and tyrosine hydroxylase-expression in acute rotenone toxicity. Int J Mol Med 2007;19(3):517—21.

[19] Hartmann A, Mouatt-Prigent A, Vila M, Abbas N, Perier C, Faucheux BA, et al. Increased expression and redistribution of the anti-apoptotic molecule Bcl-xL in Parkinson's disease. Neurobiol Dis 2002;10(1):28—32.

[20] Duan W, Zhu X, Ladenheim B, Yu QS, Guo Z, Oyler J, et al. p53 inhibitors preserve dopamine neurons and motor function in experimental parkinsonism. Ann Neurol 2002;52(5):597—606.

[21] Klintworth H, Newhouse K, Li T, Choi WS, Faigle R, Xia Z. Activation of c-Jun N-terminal protein kinase is a common mechanism underlying paraquat- and rotenone- induced dopaminergic cell apoptosis. Toxicol Sci 2007;97(1):149—62.

[22] Dohi K, Mizushima H, Nakajo S, Ohtaki H, Matsunaga S, Aruga T, et al. Pituitary adenylate cyclase-activating polypeptide (PACAP) prevents hippocampal neurons from apoptosis by inhibiting JNK/SAPK and p38 signal transduction pathways. Reg Pept 2002;109(1—3):83—8.

[23] Delgado M, Munoz-Elias EJ, Gomariz RP, Ganea D. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide prevent inducible nitric-oxide synthase transcription in macrophages by inhibiting NF-kappa B and IFN

regulatory factor 1 activation. J Immunol 1999;162(8): 4685—96.
[24] Delgado M. Inhibition of interferon (IFN) gamma-induced Kak-STAT1 activation in microglia by vasoactive intestinal peptide: inhibitory effect on CD40, IFN-induced protein-10, and inducible nitric-oxide synthase expression. J Biol Chem 2003;278(30):27620—9.
[25] Kausz M, Murai Z, Arimura A, Koves K. Distribution of pituitary adenylate cyclase-activating polypeptide (PACAP) immunoreactive elements in the brain stem of rats studied by immunohistochemistry. Neurobiology (Bp) 1999;7(1): 19—31.
[26] Reglodi D, Tamas A, Lubics A, Szalontay L, Lengvari I. Morphological and functional effects of PACAP in 6-hydroxydopamine-induced lesion of the substantia nigra in rats. Reg Pept 2004;123(1—3):85—94.
[27] Dejda A, Sokolowska P, Nowak JZ. Neuroprotective potential of three neuropeptides PACAP, VIP and PHI. Pharmacol Rep 2005;57(3):307—20.
[28] Wang G, Qi C, Fan GH, Zhou HY, Chen SD. PACAP protects neuronal differentiated PC12 cells against the neurotoxicity induced by a mitochondrial complex 1 inhibitor, rotenone. FEBS Lett 2005;579(18):4005—11.
[29] Vaudry D, Pamantung TF, Basille M, Rouselle C, Fournier A, Vaudry H, et al. PACAP protects cerebellar granule neurons against oxidative stress-induced apoptosis. Eur J Neurosci 2002;15(9):1451—60.
[30] Delgado M, Ganea D. Neuroprotective effect of vasoactive intestinal peptide (VIP) in a mouse model of Parkinson's disease by blocking microglial activation. FASEB J 2003;17(8):944—6.
[31] Staines DR. Therapeutic and preventive interventions for postulated vasoactive neuropeptide autoimmune fatigue-related disorders. Med Hypotheses 2005;65(4):797—803.
[32] Staines DR. Phosphodiesterase inhibitors may be indicated in the treatment of postulated vasoactive neuropeptide autoimmune fatigue-related disorders. Med Hypotheses 2006;66(1):203—4.