Experimental models of PD and the occurrence of non-motor symptoms

Robust animal models to study specific NMS in PD remain a key unmet need. Experimental models of PD have been extensively used to evaluate the effects of dopaminergic neurons loss and dopamine replacement therapies on motor symptoms. These models have invariably focused on destruction of the nigrostriatal pathway through the use of toxins (eg.6-hydroxydopamine (OHDA) and rotenone in rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates) and as such not reflecting the widespread pathological changes that occur in PD underpinning the origins of NMS. The same models have been used to look at non-motor symptoms of PD but not to the same extent and not in a manner that has led to major improvement in therapeutic intervention. Indeed, since most non-motor symptoms in PD show only partial responsiveness to dopaminergic medication, it is highly likely that their origin lies mainly in the degeneration of non-dopaminergic nuclei in the brain, including the locus coeruleus, raphe nuclei and dorsal motor nucleus of the vagus. This is an area, where so far, there has been little effort to produce models of non-motor symptoms of PD outside of basal ganglia and it may explain the lack of progress in understanding their pathological basis and devising strategies for treatment.

In Table 2, we illustrate some non-motor symptoms that have been detected in the various animal models. In addition, there is some information stemming from genetic modifications in mice reflecting over-expression of wild type α-synuclein or the mutated form or expression of other proteins implicated in familial PD (eg. parkin). However, in these examples it should be borne in mind that such transgenic animals do not usually show patterns of pathological change that reflect events in PD in man.

Some of the non-motor symptoms reported require additional commentary because of their clinical relevance. For example, it is clear that MPTP treated primates (low dose, chronic treatment) exhibit changes in executive function and visuo-spatial awareness that reflect the early cognitive changes that are seen in PD and that may have a component related to altered limbic and cortical dopaminergic function. This is one of the few areas where drug manipulation has been used to reverse cognitive symptoms and to look at novel therapeutic approaches (eg. nicotinic agonists).[25] In a similar manner, sleep abnormalities have been demonstrated in MPTP treated primates and alteration in sleep patterns, including Rapid eye movement sleep, now offer an opportunity to evaluate the pharmacological potential for controlling one aspect of sleep disturbance in PD.[25] At the other end of the spectrum, there is a large literature on pain and sensory pathways revolving around basal ganglia but most of this has been undertaken outside of the context of PD. Neuropsychiatric effects (apathy, anxiety, depression) of lesioning the nigrostriatal pathway are reported but the relevance to PD seems unclear and the nature of the testing which commonly involves motor tasks gives rise to some concern. Alterations in bladder and bowel function result from loss of striatal dopaminergic transmission. For example, both 6-OHDA lesioned rats and MPTP treated monkeys develop bladder hyperreflexia which occurs in PD in man. This has been shown to be responsive to dopaminergic drug treatment (notably D1 agonists) and offers an opportunity for further pharmacological intervention. Very recently, both bladder and bowel dysfunction in MPTP treated primates has been associated with local changes in isolated

tissue responsiveness and the integrity of neurotransmitter and neuromodulator control. Again, this shows the potential for investigating the basis of autonomic change in PD and its treatment. Interestingly, in mice, intragastric administration of the toxin rotenone induces alpha-synuclein accumulation, oxidative stress and inflammation in the dorsal motor nucleus vagus after 1.5 month highlighting the role of the enteric nervous system and NMS in PD and a possible model showing progression of pathology.[27] A novel model of PD in minipigs, the Göttingen minipig is a strain specifically designed for research and this model is developed through the intracerebroventricular infusion of proteasome inhibitors, producing not only dopaminergic, but also noradrenergic deficits, as is the case in human PD. Further studies addressing NMS such as cognition using specific positron emission tomography tracers are now under way in this model. [28]

The problem of animal models for NMS in PD:

While the clinical phenomenology of non-motor symptoms of PD and the development of validated rating scales has seen major advances in understanding their evolution and progression, the use of experimental models to assist in understanding pathogenesis and potential approaches to treatment has lagged behind. Opportunities are offered by existing dopaminergic animal models, some of which are now gathering momentum but others, such as the investigation of dopamine dysregulation syndromes/compulsive behaviours and dopamine agonist withdrawal syndromes, are in their infancy. The role of non-dopaminergic degenerative changes in the evolution of non-motor symptoms in PD remains a key unmet need, although feasible.

Clinical investigation has shown that the diverse non-motor symptoms of PD do not have a single underlying cause (eg. sleep disturbance, sensory/pain abnormalities, depression). This makes preclinical investigation difficult as no single model will mirror such complexity and without a focus, model development becomes impractical. From the preclinical scientists' perspective, there is a need for clinicians to identify which specific non-motor symptoms the focus should reflect. Non motor subtyping in humans should aid this concept although many clinicians feel that the preclinical scientists should first come up with a model that shows the overall pathology of PD and its progression. However, this does not seem likely in the near future.